

Retrospective Analysis of Chemoradiotherapy for Limited-Stage Small-Cell Lung Cancer

Jong Hoon Lee, M.D.*, Sung Hwan Kim, M.D.*, Su Zy Kim, M.D.*,
Joo Hwan Lee, M.D.*, Hoon Kyo Kim, M.D.[†], and Byoung Yong Shim, M.D.[†]

Departments of *Radiation Oncology and [†]Medical Oncology, St. Vincent's Hospital,
The Catholic University of Korea College of Medicine, Suwon, Korea

Purpose: This study was designed to analyze the outcome and toxicity of thoracic radiation therapy (TRT) and chemotherapy for patients who suffer with limited-stage small-cell lung cancer (LS-SCLC).

Materials and Methods: We retrospectively studied 35 patients with LS-SCLC. TRT was administered once daily (1.8 to 2 Gy per fraction) and it was directed to the primary tumor for a total 50 to 66 Gy in 6 to 7 weeks. The patients received four cycles of etoposide plus cisplatin. TRT was begun on day 1 of the first cycle of chemotherapy in the concurrent arm and after the fourth cycle in the sequential arm.

Results: The median progression-free survival time was 16.5 months (95% confidence interval [CI], 9.0 to 24.1 months) for the sequential arm, and 26.3 months (95% CI, 16.6 to 35.9 months) for the concurrent arm. The 2-year progression-free survival rate was 16.0 percent for the sequential arm and 50.0 percent for the concurrent arm ($p=0.0950$ by log-rank test). Leukopenia was more severe and more frequent in the concurrent arm than in the sequential arm. However, severe esophagitis was infrequent in both arms. The radiotherapy was interrupted more frequently in the concurrent arm than in the sequential arm due to hematologic toxicities ($p=0.001$).

Conclusion: This study suggests that concurrent TRT with etoposide plus cisplatin is more effective for the treatment of LS-SCLC than sequential TRT. However, there is a significant increase in the risk of toxicities, and radiotherapy was frequently interrupted in the concurrent arm due to hematologic toxicities.

Key Words: Chemoradiotherapy, Limited-stage, Small-cell lung cancer

Introduction

Bronchogenic carcinoma is divided into two distinct entities: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC accounts for approximately 20% of all bronchogenic carcinomas,¹⁾ and it follows a more rapid clinical course than NSCLC. However, SCLC is more responsive to chemotherapy and radiotherapy than NSCLC. Staging systems divide small-cell lung cancer into two categories: limited and extensive. Limited-stage small-cell lung cancer (LS-SCLC) is

confined to the hemithorax, clinically, which can be treated by reasonable radiation fields which include all known disease. The main treatment for LS-SCLC is radiotherapy and chemotherapy. The standard chemotherapeutic regimen for SCLC is the two-drug regimen of etoposide and cisplatin (EP). This regimen was first studied in SCLC in the late 1970s,^{2,3)} and its efficacy in treating SCLC is comparable to the previously used standard of cyclophosphamide, doxorubicin, and vincristine (CAV). The wide acceptance of EP regimen over the older CAV regimen mainly results from the absence of toxic effects on intrathoracic organs and the ability to use thoracic radiotherapy concurrently. A meta-analysis of trials comparing chemotherapy alone with combined chemotherapy and thoracic radiotherapy (TRT) found that combined treatment improved survival among patients with LS-SCLC.⁴⁾ But, the optimal method of integrating TRT with chemotherapy remained un-

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Reprint requests to Sung Hwan Kim, M.D., Department of Radiation Oncology, St. Vincent's Hospital, 93-6, Ji-dong, Paldal-gu, Suwon 442-723, Korea

Tel: 031)249-7560, Fax: 031)257-3734

E-mail: kimandre@catholic.ac.kr

defined. To analyze the outcome and toxicity of thoracic radiation therapy and chemotherapy in limited-stage small-cell lung cancer, we evaluated sequential TRT after chemotherapy and concurrent chemotherapy and TRT, retrospectively.

Materials and Methods

1. Patients

We analyzed 35 patients in the retrospective study, who had been treated from January 1998 to October 2008 in St. Vincent Hospital. For patients to be eligible the small-cell lung cancer had to be confined to one hemithorax, the ipsilateral supraclavicular fossa, or both. The included patients were grouped according to the TNM staging method. The diagnosis of SCLC was confirmed by the histologic or cytologic findings in all cases. Patients with pleural effusions found on chest films were excluded regardless of cytologic findings. Staging was done by computed tomography (CT) or magnetic resonance imaging (MRI) of chest, abdomen, and brain, and radionuclide bone scanning.

2. Chemotherapy

Chemotherapy was given in a 28-day cycle in the concurrent arm and a 21-day cycle in the sequential arm. The patients received four cycles of chemotherapy. Each three- or four-week cycle consisted of 80 mg of cisplatin per square meter of body-surface area on day 1 and 100 mg of etoposide per square meter on days 1, 2, and 3.

3. Thoracic radiotherapy

TRT was begun on day 1 of the first cycle of chemotherapy in the concurrent arm and after the fourth cycle of chemotherapy in the sequential arm. It was administered once daily (1.8 to 2 Gy per fraction) and directed to the primary tumor for a total 50 to 66 Gy in 6 to 7 weeks. The initial field included the primary disease site, the ipsilateral hilum, the entire width of mediastinum, and the supraclavicular lymph nodes (only if there was tumor involvement). The initial field in the sequential arm was based on the tumor volume after chemotherapy.

4. Prophylactic cranial irradiation

After thoracic radiotherapy, prophylactic cranial irradiation

(PCI) was administered to patients with a complete or near-complete response. PCI consisted of 10 doses of 2.5 Gy to the midplane of the whole brain over a two-week period for a total of 25 Gy.⁵⁾

5. Measurement of response and toxicity criteria

A complete response was defined as the disappearance of all clinical evidence of tumor. A decrease of 50 percent or more in the product of the length and width of any measurable tumor for at least four weeks was counted as a partial response. The disease was considered to have progressed if there was a 25 percent increase in the diameter of the primary tumor. Treatment toxicities were classified in according to the World Health Organization criteria.⁶⁾

6. End points

Overall survival (OS) was measured from the date of histologic or cytologic confirmation to the date of death from any cause or most recent follow-up. Progression-free survival (PFS) was measured from the date of histologic or cytologic confirmation to the date of the first observation of disease progression or death. If the patient survived without evidence of disease progression, progression-free survival was censored at the date of confirmation of no progression.

7. Statistical analysis

Survival distributions were calculated by the Kaplan-Meier method and compared by using log-rank test.^{7,8)} Chi-square test was used for comparisons of categorical data.⁹⁾ Cox's proportional hazards regression model was used to assess the impact on survival of treatment and important demographic factors, such as sex, Eastern Cooperative Oncology Group performance status, age, and stage.¹⁰⁾ All p-values are based on two-sided test.

Results

1. Patient characteristics

Table 1 shows the main characteristics of the 35 patients, of whom 20 received sequential chemoradiotherapy and 15 received concurrent chemoradiotherapy. The median age was 67 years (range, 32 to 79 years) in the sequential arm, and 56 years (range, 30 to 82 years) in the concurrent arm. There are

sixteen (80%) patients of stage IIIB in the sequential arm and eight (53%) patients of stage IIIB in the concurrent arm (p=0.243). Other variables were well balanced between two groups.

2. Treatment delivery and protocol tolerance

Twenty (100%) patients of the sequential arm and fourteen (93%) patients of the concurrent arm completed four cycles of chemotherapy. Seventeen (85%) of twenty patients in the sequential arm and eleven (73%) of fifteen patients in the concurrent arm received planned radiation dose, respectively. The median dose received in the sequential arm was 54 Gy (range, 20 to 60 Gy) and similar to the median dose of 56 Gy (range, 16 to 66 Gy) received in the concurrent arm. The median durations of radiotherapy were 44 days (range, 11 to 51 days)

Table 1. Characteristics of Patients According to Treatment Arm

Characteristics	Sequential arm (N=20)	Concurrent arm (N=15)	p-value
Age			0.345
Median (yr)	67	56	
Range (yr)	32~79	30~82	
Sex			0.700
Male	16	11	
Female	4	4	
Performance status			0.708
0	0	0	
1	4	4	
2	13	10	
3	3	1	
Stage			0.243
II	1	3	
IIIA	3	4	
IIIB	16	8	

Table 2. Tumor Response According to Treatment Arm

Result	Sequential arm (N=20)	Concurrent arm (N=15)	p-value
	No. (%) of patients		
Response			0.420
Complete	7 (35)	9 (60)	
Partial	8 (40)	3 (20)	
Overall	16 (75)	12 (80)	
No change	1 (5)	1 (7)	
Progressive	1 (5)	0 (0)	
Could not be evaluated	3 (15)	2 (13)	

in the sequential arm, and 53 days (range, 16 to 76 days) in the concurrent arm. The radiotherapy duration was prolonged in the concurrent arm because the radiotherapy was interrupted more frequently in the concurrent arm than in the sequential arm (p=0.001). Radiotherapy was interrupted in one (5%) of sequential arm and eight (53%) of concurrent arm over a week mostly due to hematologic toxicities.

3. Tumor response

Table 2 shows tumor response according to treatment arm. The overall response rate was 75% (35% complete response rate and 40% partial response rate) in the sequential arm and 80% (60% complete response rate and 20% partial response rate) in the concurrent arm. The complete response rate of concurrent arm is higher than that of sequential arm. However, there was no significant difference in the overall response rate between the arms.

4. Overall survival and progression-free-survival

The survival analysis of the study was performed in the first of May 2009. The median follow-up period for all patients was 47 months. Fig. 1 shows the estimated survival distribution according to treatment arm. The median survival time was 20 months (95% confidence interval [CI], 13 to 28 months) in the sequential arm, and 28 months (95% CI, 19 to 37 months) in the concurrent arm.

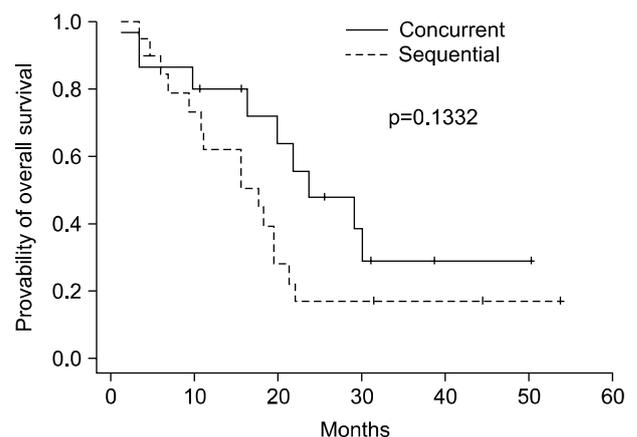


Fig. 1. Overall survival of patients with limited-stage small-cell lung cancer who had sequential chemoradiotherapy or concurrent chemoradiotherapy. The median survival time was 20 months (95% confidence interval [CI], 13 to 28 months) in the sequential arm, and 28 months (95% CI, 19 to 37 months) in the concurrent arm. The 2-year survival rate was 16.8 percent in the sequential arm, and 50.0 percent in the concurrent arm (p=0.1332).

37 months) in the concurrent arm. The 2-year survival rate was 16.8 percent in the sequential arm, and 50.0 percent in the concurrent arm (p=0.1332).

Fig. 2 shows the estimated progression-free survival distribution of eligible patients. Progression-free survival in the con-

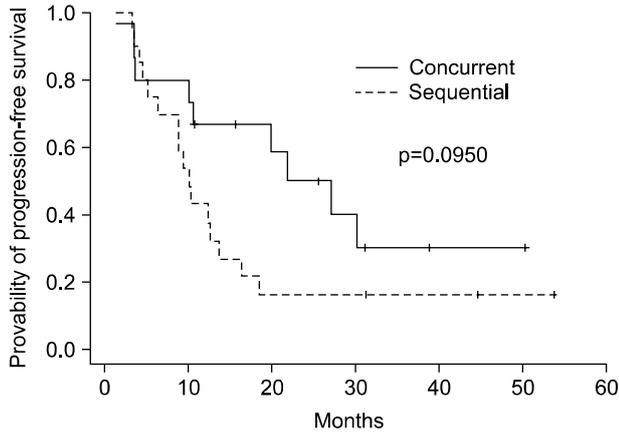


Fig. 2. Progression-free survival of patients with limited-stage small-cell lung cancer who had sequential chemoradiotherapy or concurrent chemoradiotherapy. The median progression-free survival time was 16.5 months (95% confidence interval [CI], 9.0 to 24.1 months) in the sequential arm, and 26.3 months (95% CI, 16.6 to 35.9 months) in the concurrent arm. The 2-year progression-free survival rate was 16.0 percent in the sequential arm, and 48.0 percent in the concurrent arm (p=0.0950).

current arm was superior to that in the sequential arm. The median progression-free survival time was 16.5 months (95% CI, 9.0 to 24.1 months) in the sequential arm, and 26.3 months (95% CI, 16.6 to 35.9 months) in the concurrent arm. The 2-year progression-free survival rate was 16.0 percent in the sequential arm, and 48.0 percent in the concurrent arm (p=0.0950). According to a proportional-hazards regression model, PCI (p=0.018) was associated with longer survival, significantly.

5. Patterns of treatment failure

Nearly all of the recurrences occurred within 24 months

Table 3. The First Site of Disease Progression According to Treatment Arm

Site	Sequential arm (N=20)	Concurrent arm (N=15)	p-value
	No. (%) of patients		
Progression-free	7 (35)	7 (47)	0.511
Locoregional only	3 (15)	2 (13)	0.419
Distant only	4 (20)	4 (27)	0.700
Combined	6 (30)	2 (13)	0.312
Total	20 (100)	15 (100)	

Table 4. Acute Treatment Complications According to Treatment Arm

Complications	Grade						p-value
	0	1	2	3	4	5	
							No. (%) of patients
Hematologic							
Leukopenia							0.008
Sequential	8 (40)	4 (20)	6 (30)	1 (5)	1 (5)	0 (0)	
Concurrent	2 (13)	0 (0)	3 (20)	6 (40)	3 (20)	1 (7)	
Anemia							0.187
Sequential	8 (40)	7 (35)	4 (20)	0 (0)	1 (5)	0 (0)	
Concurrent	2 (13)	5 (33)	7 (47)	1 (7)	0 (0)	0 (0)	
Thrombocytopenia							0.077
Sequential	14 (70)	3 (15)	2 (10)	0 (0)	1 (5)	0 (0)	
Concurrent	5 (33)	4 (27)	6 (40)	0 (0)	0 (0)	0 (0)	
Non-hematologic							
Esophagitis							0.844
Sequential	7 (35)	7 (35)	5 (25)	1 (5)	0 (0)	0 (0)	
Concurrent	6 (33)	5 (33)	4 (27)	1 (7)	0 (0)	0 (0)	
Nausea/Vomiting							0.164
Sequential	17 (85)	2 (10)	1 (5)	0 (0)	0 (0)	0 (0)	
Concurrent	9 (60)	2 (13)	4 (27)	0 (0)	0 (0)	0 (0)	
Pulmonary toxicity							0.900
Sequential	8 (40)	6 (30)	5 (25)	0 (0)	0 (0)	1 (5)	
Concurrent	6 (40)	3 (20)	6 (40)	0 (0)	0 (0)	0 (0)	

after diagnosis. The distribution of the first progression sites was similar in both arms (Table 3). Brain metastasis was experienced as the first progression in 45% of the patients in the sequential arm and 33% in the concurrent arm.

6. Toxicity

Hematologic and nonhematologic toxicities are summarized in Table 4. Myelosuppression was common in both arms but more severe in the concurrent arm. Leukopenia was much more frequent in the concurrent arm than in the sequential arm ($p=0.008$). Grade 3 esophagitis occurred in two patients in both arms. There was no significant difference in non-hematologic toxicity between the arms. There were 2 treatment-related deaths in both arms (pneumothorax in the sequential arm and sepsis in the concurrent arm).

Discussion and Conclusion

The standard treatment for LS-SCLC is combined modality therapy consisting of TRT and systemic chemotherapy. Chemotherapy and TRT have delivered concurrently, sequentially, or in an alternating manner.^{11,12} Although concurrent use of the two modalities seemed to be more effective, many doxorubicin-based or cyclophosphamide-based regimens could not be combined with full doses of TRT concurrently because of increased pulmonary toxicity. EP is found to be the optimal regimen for combination with concurrent TRT, since it hardly accelerates toxicity at all and there is no recall phenomenon.^{13~15} Comparison of overall- and progression-free survival in this study suggested that concurrent radiotherapy was more advantageous than sequential radiotherapy, but the difference was not statistically significant ($p=0.0950$ for PFS, and $p=0.1332$ for OS). A major reason that this study could not demonstrate a statistically significant result was a small sample size of 35 patients.

In our study, hematologic toxicity was more severe in the concurrent arm, and radiotherapy interruptions due to treatment toxicity occurred more frequently in the concurrent arm. The elder and patients with lower performance score tolerate the aggressive cisplatin-based TRT less well than the younger and those with good performance status. So, fit elderly patients with LS-SCLC must be monitored carefully when they receive combined-modality therapy. The incidence of radiation esophagitis in this study was lower than those previously

reported.¹⁶ In other studies, chemotherapy was administered in 3-week cycle in the concurrent arm. The 4-week cycle of EP seemed to reduce the frequency of radiation esophagitis.

Four randomized trials on the timing of TRT in LS-SCLC have been reported. The Japanese Clinical Oncology Group performed a phase III trial in which LS-SCLC patients were randomized to sequential TRT or concurrent TRT.¹⁷ All 231 patients received four cycles of EP every 3 weeks (sequential arm) or 4 weeks (concurrent arm) and were randomized to receive TRT during the first cycle of chemotherapy in the concurrent arm or after the fourth cycle in the sequential arm. TRT consisted of 45 Gy given in 1.5 Gy fractions twice daily over 3 weeks. Concurrent TRT yielded better survival than sequential arm. The 5-year survival rate for patients treated sequentially was 18.3%, compared with 23.7% for those treated concurrently. A National Cancer Institute of Canada trial compared TRT (40 Gy given in 15 fractions over 3 weeks) applied during cycle 2 versus cycle 6 of an alternation-chemotherapy regimen that included CAV and EP.¹⁸ A survival advantage was seen for the patients randomized to early TRT comparing the patients of late TRT, with median survival time of 16 versus 12 months and 4-year survival rate of 25% versus 15% ($p=0.008$). These two studies indicated that the early administration of TRT with concurrent chemotherapy improved survival, possibly by reducing the chemoresistant clonogens in the primary.

However, conflicting results have been reported regarding the timing of TRT. In the Cancer and Leukemia Group B study,¹⁹ 426 LS-SCLC patients were treated with cyclophosphamide, and etoposide or doxorubicin, and vincristine and randomized to no radiation therapy (arm 1), radiation therapy starting during cycle 1 of chemotherapy (arm 2), or radiation therapy starting during cycle 4 (arm 3). TRT in both arms was 50 Gy delivered over 6 weeks. There was a survival advantage favoring arms 2 and 3 over the no-irradiation arm, and the best results were achieved in arm 3 ($p=0.0099$). The 5-year survival rates were 3% for chemotherapy alone, 7% for early irradiation, and 13% for delayed radiation therapy. Spiro et al.²⁰ reported an English study of early versus late TRT. The 325 LS-SCLC patients were randomized to early TRT with the second course of chemotherapy or to late TRT with the sixth course of chemotherapy. The chemotherapy was identical in each arm and included six cycles of CAV that alternated

with EP. The TRT dose was 40 Gy given in 15 fractions over 3 weeks. PCI was given to responding patients. Median survival times and 3-year survival rates were 13.5 months and 16% with early TRT versus 15.1 months and 20% with late TRT ($p=0.18$). Sequencing and timing of chemotherapy and TRT are still controversial. A meta-analysis does help make sense of contradictory data.²¹⁾ This study analyzed randomized trial published after 1985 and addressed the timing of TRT relative to chemotherapy in LS-SCLC. The relative risk of survival for early TRT compared with late TRT for all studies was 1.17 (95% CI, 1.02 to 1.35, $p=0.03$), indicating a 5.2% improvement in the 2-year survival for early TRT. This small but significant improvement in 2-year survival for early TRT was similar in overall magnitude to the benefit of adding TRT or PCI to chemotherapy. Potential advantages of concurrent delivery include the shorter overall treatment time, an increase in overall treatment intensity, and potential anticancer synergism between the various therapies. Disadvantages include the heightened risk of toxicity and the inability to assess the antitumor response rate of the chemotherapy alone.

In conclusion, concurrent TRT in combination with etoposide and cisplatin is more efficacious for the treatment of LS-SCLC than etoposide and cisplatin plus sequential TRT. But, treatment complications were also increased.

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제한병기 소세포암 환자의 항암화학방사선요법에 대한 후향적 분석

가톨릭대학교 의과대학 성빈센트병원 방사선종양학교실*, 중앙내과학교실†

이종훈* · 김성환* · 김수지* · 이주환* · 김훈교† · 심병용†

목적: 제한병기 소세포암 환자의 흉부방사선치료 및 항암치료의 성적과 부작용을 분석하고자 연구를 진행하였다.

대상 및 방법: 제한병기 소세포암으로 진단받고 동시항암화학방사선요법 혹은 순차적항암화학방사선요법을 받은 35명의 환자를 후향적으로 조사하였다. 방사선치료선량은 하루 1.8~2 Gy 분할선량으로 원발병소에 총 50~66 Gy 조사하였다. 환자군은 4주기 시스플라틴 및 에토포사이드 복합 항암치료를 받았다. 동시항암화학방사선요법군은 항암 제 1주기 첫 날에 흉부방사선치료를 시작하였고 순차적항암화학방사선요법군은 항암 제 4주기를 마친 후에 흉부방사선치료를 시작하였다.

결과: 순차적항암화학방사선요법군의 무진행생존시간의 중앙값은 16.5개월이었고 동시항암화학방사선요법군의 무진행생존시간의 중앙값은 26.3개월이었다. 동시항암화학방사선요법군의 2년 무진행생존율은 50.0%이었고 순차적항암화학방사선요법군의 2년 무진행생존율은 16.0%이었다($p=0.0950$). 백혈구감소증의 정도와 빈도는 동시항암화학방사선요법군에서 유의하게 높았다. 하지만, 심한 식도염의 빈도는 양군에서 모두 높지 않았다. 동시항암화학방사선요법군은 순차적항암화학방사선요법군에 비하여 빈번하게 혈액학적독성으로 치료가 중단되었다($p=0.001$).

결론: 본 연구에서는 동시항암화학방사선요법이 제한병기 소세포암 치료에서 순차적항암화학방사선요법보다 효과적이었다. 하지만, 동시항암화학방사선요법은 부작용을 유의하게 증가시켰다.

핵심어: 항암화학방사선요법, 소세포암, 제한병기