

Sequential Versus Concurrent Thoracic Radiotherapy in Combination With Cisplatin and Etoposide for N3 Limited-Stage Small-Cell Lung Cancer

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Abstract

At present, concurrent chemoradiotherapy (CRT) is considered the standard treatment of limited-stage small cell lung cancer (LS-SCLC). However, LS-SCLC is highly heterogeneous in the T stage, N stage, and prognosis. Increasing evidence has shown that individual treatment should be considered when treating LS-SCLC patients. The aim of the present study was to explore the optimal combination model of thoracic radiotherapy (TRT) and chemotherapy in N3 LS-SCLC. We retrospectively analyzed 93 N3 LS-SCLC patients treated in the Department of Oncology of Binzhou Medical University Hospital (Shandong, China) between March 2010 and October 2015. A total of 52 (52/93; 55.9%) patients received sequential CRT, and 41 (41/93; 44.1%) patients received concurrent CRT. All patients received 4-6 cycles of chemotherapy and TRT (50-60 Gy). The median follow-up time was 25.4 months (range was 6-65 months). The overall response rate was 88.5% in the sequential CRT group (9.6% complete response rate and 78.8% partial response rate) and 90.2% in the concurrent CRT group (14.6% complete response rate and 75.6% partial response rate). The PFS and OS were 15.4 months and 19.1 months in sequential CRT group, and 16.9 months and 20.5 months in concurrent CRT group. There was no significant difference in treatment response rate, PFS, and OS between sequential and concurrent CRT patients. The most common treatment-related toxicities were nausea/vomiting, neutropenia, and esophagitis. In conclusion, when concurrent CRT is performed in N3 LS-SCLC patients, tolerance to treatment should be fully considered. In our study, sequential CRT and concurrent CRT showed the same efficacy, and sequential CRT demonstrated better tolerance. However, these results require confirmation in future follow-up studies.

Keywords

small cell lung cancer, radiotherapy, chemotherapy, chemoradiotherapy sequence, prognosis

Introduction

Small cell lung cancer (SCLC) accounts for approximately 20-25% of all lung cancer, which is the leading cause of cancer-related deaths worldwide.¹ According to the Veterans Administration's classification system, limited stage small cell lung cancer (LS-SCLC) is confined to the ipsilateral hemithorax and can be safely encompassed within a single radiation portal. Based on the TNM classification system (AJCC 8th Edition), LS-SCLC is generally considered to include T1-4N1-3M0 cases except for T3-4 with multiple lung nodules, which is a group of diseases that display a

wide range of involvement. Since SCLC is prone to metastasis and sensitive to cytotoxic agents, chemotherapy is the basis for LS-SCLC treatment. Several studies have

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Table 1. Characteristics of N3 LS-SCLC Patients.

Characteristics	Sequential patients (n = 52)		Concurrent patients (n = 41)		p-value ^a
	n	%	n	%	
Age (years)					
<60	30	57.7	25	61.0	0.749
≥60	22	42.3	16	39.0	
Gender					
Male	45	86.5	36	87.8	0.856
Female	7	13.5	5	12.2	
Performance status					
0-1	46	88.5	39	95.1	0.784
2	6	11.5	2	4.9	
N3 lymph node regions					
Contralateral mediastinum	47	90.4	35	85.4	0.696
Contralateral hilum	11	21.2	5	12.2	
Supraclavicular	10	19.2	7	17.1	
Cycles of chemotherapy					
4	25	48.1	26	63.4	0.140
5-6	27	51.9	15	36.6	
Prophylactic brain radiation					
Yes	28	53.8	19	46.3	0.420
No	24	46.2	22	53.7	
PTV ^b volume (cm ³)					
≤310	34	65.4	21	51.2	0.168
>310	18	34.6	20	48.8	
Radiation dose (Gy)					
60	49	94.2	35	85.4	0.279
50-60	3	5.8	6	14.6	

^aChi-square test; $P < 0.05$ was considered statistically significant; ^b PTV: Planning target volume.

shown that thoracic radiotherapy (TRT) improves the outcome of LS-SCLC and concurrent chemoradiotherapy (CRT) is superior to sequential CRT, which produced a modest, but significant, long-term benefit (3.9% 3-year OS benefit).²⁻⁴ However, these findings are based on clinical trials involving selected LS-SCLC, some excluding patients with contralateral hilar and supraclavicular lymph node metastasis.^{5,6} Patients with N3 LS-SCLC would require large radiation target volumes of radiotherapy. Large radiation target volumes increase acute and chronic toxicities and sometimes lead to delay of concurrent chemotherapy. A recent study showed that N3 LS-SCLC treated with concurrent CRT still had a lower 3-year survival than heterogeneous LS-SCLC patients.⁷ In addition, our previous work found that patients with high-dose TRT showed a lower 2-year survival than those with low-dose TRT in SCLC patients with superior vena cava syndrome (SVCS, most of them are N3).⁸ Therefore, the prognosis of N3 LS-SCLC remains poor and the best treatment model is unclear. Due to more lymph node regions involvement and the tolerability of treatment, many patients did not receive concurrent CRT and received sequential CRT. The aim of this retrospective study was to explore the optimal combination model of TRT and chemotherapy in N3 LS-SCLC.

Patients and Methods

Patient and Tumor Characteristics

N3 LS-SCLC was defined as LS-SCLC with contralateral mediastinal node metastasis, contralateral hilar node metastasis, and/or supraclavicular (both ipsi- and contralateral) node metastasis. We enrolled 93 N3 LS-SCLC patients in our retrospective study. The patients were treated in the Department of Oncology of Binzhou Medical University Hospital (Shandong, China) between March 2010 and October 2015. All patients were diagnosed by tissue pathology (bronchoscopic biopsy and supraclavicular lymph node biopsy). In all patients, initial staging included computed tomography (CT) examination of the neck/thorax/abdomen, bone scintigraphy, and contrast-enhanced cranial CT (or MRI). PET-CT scan was performed in 17 of the 93 patients. Contralateral mediastinal, contralateral hilar, and supraclavicular lymph node metastasis occurred in 90.4%, 21.2%, 19.2% and 85.4%, 12.2%, 17.1% in sequential group and concurrent group, respectively. A total of 22 (22/93; 23.7%) patients showed 2 or more N3 lymph node region involvement; 52/93 (55.9%) patients received sequential CRT, and 41/93 (44.1%) patients received concurrent CRT. All patients received 4-6 cycles of chemotherapy. The average number of chemotherapy cycles was 5.0 (range 4-6 cycles) in sequential CRT and 4.5 (range 4-6 cycles) in concurrent CRT. TRT consisted of 2 Gy daily in 30 fractions up to 60 Gy. The minimum dose in this study was 50 Gy. The average dose of TRT was 59.6 Gy (range 52-60 Gy) in sequential CRT and 58.6 Gy (range 50-60 Gy) in concurrent CRT. The median patient age was 57.6 years old (range 40-71 years old). The characteristics of the enrolled N3 LS-SCLC patients were shown in Table 1. Age, gender, performance status, involvement of lymph node regions, cycles of chemotherapy, and prophylactic cranial irradiation (PCI) were similar in patients treated concurrently or sequentially. Our study was approved by the Ethics Committee of Binzhou Medical University Hospital (Shandong, China). Due to the retrospective nature of the study, informed consent was waived. The median follow-up time was 25.4 months (range 6-62 months).

Treatments

Chemotherapy consisted of cisplatin and etoposide. Chemotherapy was administered in a 3-week cycle using sequential chemotherapy (100 mg/m² of etoposide was given intravenously on days 1-3 and 25 mg/m² of cisplatin was given intravenously on days 1-3) and was administered in a 4-week cycle using concurrent chemotherapy (80mg/m² of etoposide was given intravenously on days 1-3 and 25 mg/m² of cisplatin was given intravenously on days 1-3). After completing radiotherapy, patients with good performance status continued to receive no more than 2 cycles of chemotherapy. All patients received at least 4 cycles of chemotherapy. Dose adjustment and delay were based on adverse effects. We administered granulocyte colony stimulating factor subcutaneously if the absolute granulocyte count was $<0.5 \times 10^9/L$.

In patients treated with concurrent CRT, TRT was administered at the beginning of the second or third cycles of chemotherapy. In patients that received sequential CRT, TRT was performed after 4 cycles of chemotherapy. During radiation delivery, patients were immobilized with a thermoplastic mask in the supine position and then scanned with a CT slice thickness of 5 mm. All patients received intensity modulated radiotherapy (IMRT). The gross tumor volume (GTV) was based on the planning CT images. Initially involved nodal regions were covered. Clinical tumor volume (CTV) included the GTV with a 7 mm margin. An expansion of 5 mm of the CTV created the planning target volume (PTV). The prescription dose applied to 95% PTV was 60 Gy given in 30 fractions using a fraction dose of 2.0 Gy. Dose constraints of normal tissues included V20 \leq 30% for bilateral lungs, V5 \leq 70% for bilateral lungs, mean lung dose \leq 18 Gy for bilateral lungs, One-third of the heart volume \leq 40 Gy, maximum dose for esophagus \leq 64 Gy, and maximum dose for spinal cord \leq 45 Gy.

After TRT and chemotherapy, PCI was administered to patients with a complete or partial response. Forty-seven patients received PCI (25 Gy in 10 fractions or 30 Gy in 10 fractions).

Similar percentages of patients received subsequent therapy after disease progression (59.1% in sequential group and 64.7% in concurrent group), including whole brain radiotherapy (WBRT) for brain metastasis and subsequent chemotherapy.

Assessment and Follow-Up

After completion of treatments, patients were evaluated every 3 months during the first 2 years and then every 6 months from the third year. History, physical examination, and CT of the chest and upper abdomen (or ultrasonography) were obtained at every evaluation. Brain magnetic resonance imaging or enhanced CT was performed if there were central nervous system symptoms. Response to treatment was categorized according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1). Toxicities were evaluated by Common Terminology Criteria Adverse Events (CTCAE) version 4.0.

Statistical Analyses

We used SPSS 17.0 (SPSS Inc., Chicago, IL, USA) to perform statistical analyses. Progression-free survival (PFS) and overall survival (OS) were analyzed according to the Kaplan–Meier method and compared by log-rank test. PFS was measured from the date of treatment to the date of the first observation of disease progression or mortality. OS was measured from the date of treatment to the date of death or last follow-up. The response rates of patients were based on the initial follow-up CT. Chi-square test was used for comparisons of categorical data. All *P* values are based on 2-sided tests. A *P*-value of <0.05 indicated a statistically significant difference.

Table 2. Response According to Treatment Regimen.

Characteristics	Sequential patients (n = 52)		Concurrent patients (n = 41)		p-value ^a
	n	%	n	%	
Objective Response	46	88.5	37	90.2	0.783
Complete Response	5	9.6	6	14.6	0.475
Partial Response	41	78.8	31	75.6	
Stable Disease	3	5.8	1	2.4	–
Progressive Disease	3	5.8	3	7.3	–

^aChi-square test; *P* < 0.05 was considered statistically significant.

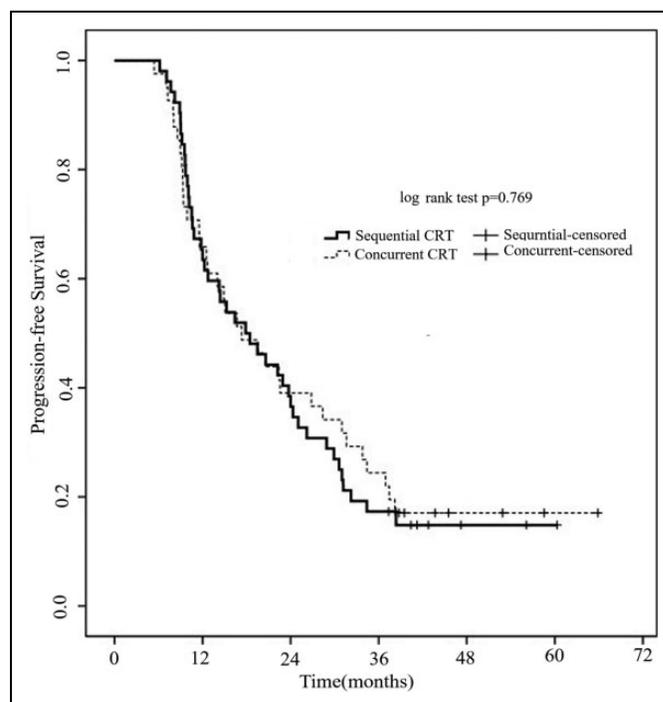


Figure 1. Progression-free survival of patients with N3 LS-SCLC according to treatment regimen. There was no significant difference in the median PFS between sequential group and concurrent group (15.4 vs. 16.9 months; *p* = 0.769).

Results

Treatment Response

Treatment response is described in Table 2. The overall response rate was 88.5% in the sequential CRT group (9.6% complete response rate and 78.8% partial response rate) and 90.2% in the concurrent CRT group (14.6% complete response rate and 75.6% partial response rate). There was no significant difference in treatment response rates between the sequential and concurrent CRT patients.

Progression-Free Survival and Overall Survival

Figure 1 shows the PFS according to treatment model. The median PFS was 16.2 months (95% CI 12.4–19.2 months) for the entire cohort. There was no significant difference in the

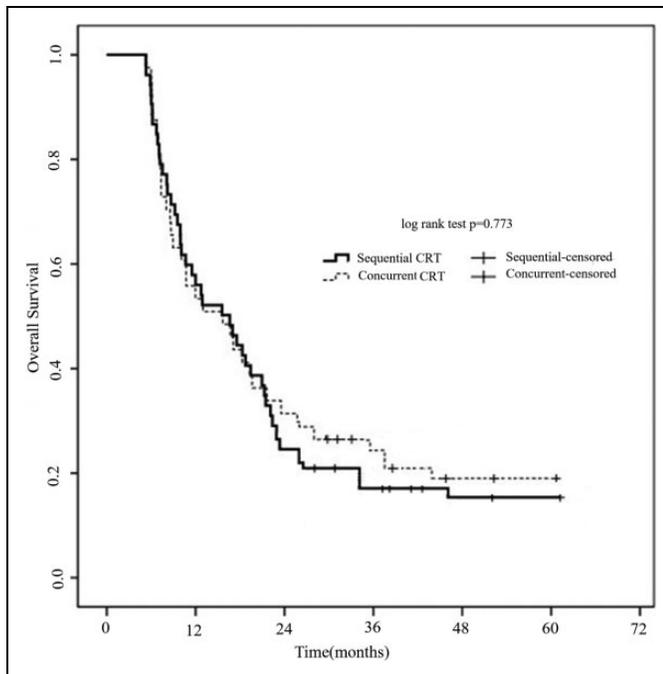


Figure 2. Overall survival of patients with N3 LS-SCLC according to treatment regimen. The 2- and 3-year survival rates were 28.9%, 17.5% for sequential CRT patients and 33.1%, 23.8% for concurrent CRT patients, respectively ($p = 0.773$).

median PFS between sequential group and concurrent groups (15.4 vs. 16.9 months; $p = 0.769$).

Figure 2 shows the OS according to treatment model. The median survival time was 19.1 months for the patients that received sequential CRT (95% CI 14.5-22.3 months) and 20.5 months (95% CI 16.3-25.1 months) for patients with concurrent CRT. The 2- and 3-year survival rates were 28.9%, 17.5% for sequential CRT patients and 33.1%, 23.8% for concurrent CRT patients, respectively ($p = 0.773$).

Patterns of Failure

The patients in sequential group and concurrent group had similar pattern of failure (Table 3). Of the 93 patients in this study, 12 patients in sequential group and 8 patients in concurrent group had the local failure as the first site of failure (27.3% vs. 23.5%; $p = 0.707$). Twenty-four in sequential group and 21 in concurrent group had distant metastasis as the first site of failure (50.0% vs. 55.9%; $p = 0.606$). Twenty-nine patients in this study (32/93, 34.4%) developed brain metastasis (Table 4). Brain metastasis as the first site of failure occurred in 12 patients (7 in sequential group and 5 in concurrent group). Brain metastasis was more common in patients without PCI (43.5% vs. 25.5%; $p = 0.203$). However, there was no significant difference in brain metastasis in sequential and concurrent groups ($p > 0.05$).

Toxicity

Hematologic and nonhematologic toxicities are summarized in Table 5. The most common treatment-related toxicities were

Table 3. Site of First Progression According to Treatment Regimen.

Site	Sequential patients (n = 44)		Concurrent patients (n = 34)		P-value ^a
	n	%	n	%	
Within the thorax	12	27.3	8	23.5	0.707
Outside the thorax	22	50.0	19	55.9	0.606
Within and outside the thorax	10	22.7	7	20.6	0.820
Brain	7	15.9	5	14.7	0.884

^aChi-square test; $P < 0.05$ was considered statistically significant.

Table 4. Brain Metastasis of Patients with or Without PCI^a.

PCI	All patients (n = 93)		Sequential patients (n = 52)		Concurrent patients (n = 41)		P-value
	n	Brain metastasis	n	Brain metastasis	n	Brain metastasis	
Yes	47	13	28	7	19	6	0.621
No	46	19	24	11	22	8	0.515

^aPCI: prophylactic cranial irradiation; ^b Chi-square test; $P < 0.05$ was considered statistically significant.

nausea/vomiting, neutropenia, and esophagitis. Grade 3/4 neutropenia occurred in 25/52 patients (48.1%) received sequential CRT and 30/41 patients (73.2%) received concurrent CRT ($p = 0.015$). Grade 3/4 esophagitis was more frequent in the concurrent group, occurring in 9/41 patients (22.0%) compared with 6/52 patients (11.5%) in sequential group. Two patients in each group developed \geq grade3 radiation pneumonia. In addition, we had a treatment-related death in the concurrent group (radiation pneumonitis combined with pulmonary infection).

Discussion

The PFS and OS were comparable in N3 LS-SCLC patients who received sequential and concurrent CRT treatments. Regardless of the combination model of chemotherapy and radiotherapy, the median survival time of N3 LS-SCLC patients in this cohort was approximately 20 months. However, it was shorter than that of previous studies on LS-SCLC patients with different TNM stages.⁵ Our results were consistent with a recent study of N3 LS-SCLC.⁷ According to previously published results, the prognosis of LS-SCLC is better than ES-SCLC.⁹ Although some studies have found that patients with broader lymph node metastasis showed decreased survival, there are few trials that focus on survival of LS-SCLC with different N staging.^{8,10} It has been gradually recognized that LS-SCLC patients with different T stages and N stages have great heterogeneity in tumor burden, radiation tolerance, and prognosis. Therefore, it has been recommended that TNM staging should be reported in clinical trials.¹¹ A recent study reported that patients with stage I to II

Table 5. Toxic Effects According to Treatment Regimen.

Toxic effects	Sequential patients (n = 52)		Concurrent patients (n = 41)		P-value ^b
	n	%	n	%	
Hematologic toxicities					
Neutropenia					
Grade 1/2	27	51.9	11	26.8	0.015
Grade 3/4	25	48.1	30	73.2	
Thrombocytopenia					
Grade 1/2	35	67.3	22	53.7	0.142
Grade 3/4	15	28.8	18	43.9	
Anemia					
Grade 1/2	34	65.4	23	56.1	0.335
Grade 3/4	11	21.2	12	29.3	
Nonhematologic toxicities					
Nausea/vomiting					
Grade 1/2	37	71.2	33	80.5	0.423
Grade 3/4	12	23.1	7	17.1	
Esophagitis					
Grade 1/2	46	88.5	32	78.0	0.021
Grade 3/4	6	11.5	9	22.0	
Fever					
Yes	1	1.9	2	4.9	0.581
No	51	98.1	39	95.1	

^aChi-square test; $P < 0.05$ was considered statistically significant.

LS-SCLC treated with concurrent CRT had much better outcomes compared with patients that had stage III disease (median OS: 50 vs. 25 months, respectively).⁹ In addition, some evidence has shown that surgical resection improves prognosis in patients with T1-2N0M0 SCLC.^{12,13} We suggest that LS-SCLC patients need more individual treatments regarding the radiation target of TRT, timing of TRT, and intensity of concurrent chemotherapy.

Concurrent CRT is an effective treatment model for malignancies because of spatial cooperation, cytotoxic enhancement, biological cooperation, temporary modulation, and normal tissue protection.¹⁴ Concurrent CRT is widely used in different cancers.^{3,15,16} However, while concurrent CRT improves efficacy, severe toxicities occur more frequently than sequential CRT. Toxicities as a result of concurrent CRT are related to many factors, such as chemotherapeutic drugs, radiation target areas, and radiation dosage. Hence, when concurrent CRT is used to improve therapeutic effect, the influence of patient selection and systemic treatment should be taken into account. SCLC is characterized by rapid growth, early dissemination, and sensitivity to chemotherapy and radiotherapy. Chemotherapy is the fundamental treatment for all patients with SCLC. TRT yields 25-30% reduction in local recurrence and a corresponding 5-7% improvement in 2-year survival for LS-SCLC compared with chemotherapy alone.^{17,18} At present, the standard care for LS-SCLC consists of combined chemotherapy and thoracic radiotherapy, followed by prophylactic cranial irradiation (PCI) for patients who have complete or partial treatment response. Early concurrent TRT results in significant

improvement in overall survival and has led to more severe toxicities compared to late concurrent or sequential radiotherapy.^{2,3,19} However, the timing of TRT is unclear. One study showed that late TRT appeared to be superior to early TRT in terms of complete response and OS in patients with LS-SCLC.²⁰ In our study, concurrent CRT showed a trend toward improving the complete response rate, PFS and OS, but there was no significant difference between sequential group and concurrent group. For N3 LS-SCLC patients, systemic therapy plays a more important role compared with N0-2 patients. The early-starting radiation target volume in N3 LS-SCLC patients is large and treatment-related toxicities are more common and severe, especially with concurrent chemotherapy. Because of intolerance, the intensity of chemotherapy and radiotherapy has to be reduced in some patients. Therefore, the efficacy is sometimes impaired.²¹ Although there was no statistical difference, patients were more likely to receive a substantially reduced radiation therapy volume after 4 cycles of induction chemotherapy in sequential group. In the present study, patients receiving concurrent CRT had fewer chemotherapy cycles than those receiving sequential CRT. Reduced intensity of chemotherapy might offset the advantages of concurrent CRT. In the present study, G3/4 neutropenia and esophagitis were more common in concurrent group than in sequential group.

The patterns of relapse in sequential and concurrent groups were similar, including local progression, extracranial distant metastasis, and brain metastasis. JCOG 9104 showed concurrent CRT had OS superiority on sequential CRT, but local control was the same in both arms.²² Early TRT might attribute survival benefit to early local control that prevents distant spread of the primary tumor. Consistent with a previous study, the sites of first relapse in this study were also similar in the concurrent and sequential groups.²³ Extrathoracic metastasis was the main cause of treatment failure in both groups. Patients without PCI were more likely to develop brain metastasis in the present study. PCI reduced brain metastasis from 43.8% to 25.5%. The difference was not statistically significant, which might be due to the small sample size. PCI is considered as an important component of the treatment of the patients with LS-SCLC.²⁴ Studies have confirmed that WBRT led to neurocognitive dysfunction and worsening quality of life, and even a recent retrospective report indicated that PCI had detrimental effect on the OS of patients with LS-SCLC.²⁵⁻²⁷ With the prolongation of the survival time of the patients with SCLC, both the risk of brain metastasis and neurocognitive toxicity need to be paid more attention to. Hippocampus-sparing WBRT has been proved to reduce the neurological damage caused by PCI. However, sparing the hippocampus during WBRT poses important technical challenges with respect to contouring and treatment planning. So in practice, not all radiotherapy institutes use hippocampus-sparing technology, and some patients refuse PCI because of their fear of neurocognitive toxicity. Nearly half of the patients in this study did not undergo PCI.

There are limitations to this study, including its nature of a retrospective study and its associated biases. A small

percentage of patients underwent PET/CT, which might lead to inaccurate staging. Another limitation is the sample size, especially in patients with contralateral hilar and supraclavicular lymph node metastasis. Therefore, we did not compare the prognosis of N3 LS-SCLC with different lymph node regions. Furthermore, the rate of patients received PCI were relatively low. Although a recent study from Japan showed PCI played a detrimental role in the outcome of patients with LS-SCLC,²⁸ PCI is generally considered as a component of the treatment of patients with LS-SCLC. PFS and OS might be impaired by low PCI rate.

In summary, LS-SCLC is a group of highly heterogeneous tumors, and N3 LS-SCLC is a subcategory with a wider range of involvement. When choosing concurrent CRT, the patient's tolerance should be fully evaluated. In our study, sequential CRT and concurrent CRT demonstrated the same efficacy and sequential CRT had better tolerance in patients with N3 LS-SCLC. This finding should be confirmed in large-cohort, prospective studies.

Abbreviations

CRT	chemoradiotherapy
LS-SCLC	limited-stage small cell lung cancer
TRT	thoracic radiotherapy
SVCS	superior vena cava syndrome
PCI	prophylactic cranial irradiation
IMRT	received intensity modulated radiotherapy
GTV	gross tumor volume
CTV	clinical tumor volume
PTV	planning target volume
WBRT	whole brain radiotherapy
PFS	progression-free survival
OS	overall survival
ES-SCLC	extensive-stage small cell lung cancer

Authors' Note

All persons listed as authors have read the manuscript and given their approval for the submission. Zhenbo Wang and Jinliang Wan participated in the study design and performed the statistical analysis. Haitao Geng, Lei Li, and Changmin Liu collected data and wrote the manuscript. Xinjun Dong collected data, participated in the revision of manuscript. Our study was approved by the Ethics Committee of Binzhou Medical University Hospital (Shandong, China). 2019-LW-018.

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Declaration of Conflicting Interests

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