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Original Article

Radiation dose is associated with prognosis of small cell lung cancer with superior vena cava syndrome

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Abstract: Approximately 10% of small cell lung cancer (SCLC) cases develop superior vena cava syndrome (SVCS). Many SCLC patients with SVCS have relatively limited disease, requiring curative rather than palliative treatment. Besides chemotherapy, radiotherapy is important for treating SCLC with SVCS. We retrospectively evaluated the influence of radiotherapy dose on the prognosis of 57 patients with SCLC with SVCS treated with concurrent chemoradiotherapy. The mean biological equivalent radiation dose was 71.5 Gy. We administered etoposide/cisplatin as sequential and concurrent chemotherapy. All patients received at least one cycle of concurrent chemotherapy. All patients had partial or complete response; SVCS-associated symptoms were reduced in 87.7% (50/57) of patients within 3-10 days after treatment. Radiation dose did not affect 2-year local control (74.2% vs. 80.8%). Patients who received high-dose radiation had a lower 2-year overall survival rate than those who received low-dose radiation (11.6 vs. 33%; $P = 0.024$). The high dose group median survival was 15.0 months (95% confidence interval [CI]: 11.2-19.0) compared with 18.7 months (95% CI: 13.9-23.6) in the low dose group. Grade 3/4 neutropenia occurred in 22/26 high dose patients (84.6%) and 21/31 low dose patients (67.7%). In the high dose group, 30.8% of patients had grade 3/4 esophagitis compared with 19.4% of low dose patients. Only 29.0% of low dose patients received < 4 cycles of chemotherapy in the first 12 weeks after treatment began compared with 46.2% of high dose patients. Concurrent chemoradiotherapy is a tolerable modality for treating stage IIIA/IIIB SCLC with SVCS. Moderate-dose radiotherapy is preferable.

Keywords: Small cell lung cancer, superior vena cava syndrome, radiotherapy

Introduction

Small cell lung cancer (SCLC) accounts for 20-25% of lung cancer that is the leading cause of cancer-related deaths worldwide [1]. Compared with other cell types of lung cancers, SCLC is one of the most aggressive malignancies, and approximately 10% of SCLC develop superior vena cava syndrome [2]. SVCS is a series of symptoms and signs caused by superior vena cava obstruction that includes dyspnea, facial swelling, orthopnea, and jugular vein distention, etc. Although SVCS is not life-threatening in most cases [3], SVCS-related symptoms lead to severe discomfort and greatly reduce the quality of life of a patient. Therefore, treatment should be administered as soon as possible. SCLC is sensitive to both radiation and chemotherapy. Thus, either chemotherapy or radiotherapy can be used as the first-line treatment [4, 5]. However, both higher local recurrence in patients who receive chemotherapy only and distant metastases that develop easily during/after radiotherapy in patients who receive radiotherapy only lead to poor overall survival [6]. The modality of radiotherapy combined with chemotherapy might be optimal for SCLC presenting with SVCS, especially for SCLC without distant metastases. Previous studies reported an obvious difference with regard to the radiotherapy fraction, but it did not have an impact on local control [7, 8]. The role, dose, and timing of radiotherapy in SCLC with SVCS are uncertain. The aim of this study was to explore the influence of radiotherapy dose on the prognosis of SCLC with SVCS.

Table 1. Characteristics of 57 SCLC patients with SVCS

Characteristics	No. (%) of patients	Radiation dose (BED)		
		≤ 70 Gy (n = 31)	> 70 Gy (n = 26)	*P* value[a]
Sex				
Male	46 (80.7)	27	19	0.159
Female	11 (19.3)	4	7	
Age (y)				
> 65	8 (14.0)	6	2	0.191
< 65	49 (86.0)	25	24	
ECOG-PS				
1-2	35 (61.4)	19	16	0.985
3-4	22 (38.6)	12	10	
SIADH				
Yes	9 (15.8)	3	6	0.275
No	48 (84.2)	28	20	
NSE[b]				
Normal	1 (1.8)	0	1	0.456
Elevated	56 (98.2)	31	25	
SVC thrombosis				
Yes	4 (7.0)	2	2	1.000
No	53 (93.0)	29	24	
ChT Cycles[c]				
≥ 4	37 (64.9)	18	19	0.276
< 4	20 (35.1)	13	7	
Stage[d]				
IIIA	21 (36.8)	13	8	0.422
IIIB	36 (63.2)	18	18	
PCI[e]				
Yes	19 (33.3)	10	9	1.000
No	38 (66.7)	21	17	

[a]Chi-square test or Fisher's exact test; $P < 0.05$ was considered statistically significant. [b]Value of neuron-specific enolase (NSE) > three times the upper limit of the cutoff. [c]Chemotherapy cycles within 12 weeks from the beginning of treatment. [d]AJCC (2010). [e]Prophylactic cranial irradiation.

Materials and methods

Patients and tumor characteristics

We enrolled 57 SCLC patients with SVCS in this retrospective study (**Table 1**). The patients were treated with chemoradiotherapy at the Department of Oncology at the Affiliated Hospital of Binzhou Medical College, Shandong, China, between January 2004 and December 2009. 57 patients were diagnosed by tissue pathology (including sputum cytology, bronchoscopic biopsy, and supraclavicular lymph node biopsy). All 57 patients underwent computed tomography (CT) examination of the neck, thorax, upper abdomen, and brain for staging and received at least four weeks' radiotherapy. According to the 2010 American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system, the patients had stage IIIA or IIIB ($T_{1-4}N_{2-3}$) SCLC, which could be safely encompassed within a radiation field. The median age was 56.3 years (range, 42-69 years). The ethics committee of the Affiliated Hospital of Binzhou Medical College approved the study. We obtained written informed consent from all patients before treatment. The median follow-up time was 19.6 months (range, 7-50 months).

Therapy

Radiotherapy: All patients received radiotherapy with computed tomography (CT)-based radiation treatment planning. The gross tumor volumes (GTV) of the primary and involved lymph nodes were based on the CT images. Clinical tumor volume 1 (CTV1) included the GTV1 with a 0.5-cm margin and ipsilateral hilar and lymph node stations 2R, 2L, 4R, 4L, and 7. For left lung primary tumors, lymph node stations 5 and 6 were included. CTV2 included the GTV2 with a 0.5-cm margin. Planning tumor volume 1 (PTV1) was defined as CTV1 with a 1-cm margin. PTV2 included CTV2 with a 1-cm margin. In the first phase of radiation, we used the 2-dimensional conformal technique intending to decrease the dosage to the lung; we administered a 3-Gy daily fraction for the first week (five days per week). We used a 2-Gy daily fraction for the next two weeks. We performed the second CT simulation after the first 3-week radiotherapy. GTV2, CTV2, and PTV2 were contoured based on the obtained CT images. Subsequently, radiotherapy was administered once daily to PTV2 (2 Gy per fraction, five days per week). Radiotherapy was typically administered with the first or second cycle of chemotherapy. The mean biological equivalent radiation dose (BED) was 71.5 Gy (55.5-88 Gy). Patients with complete response or good partial response received prophylactic cranial radiation (3 Gy × 10 times or 2.5 Gy × 10 times). For normal lungs, the total volume receiving > 20 Gy (V20) was < 30%. One-third of the heart volume received < 40 Gy.

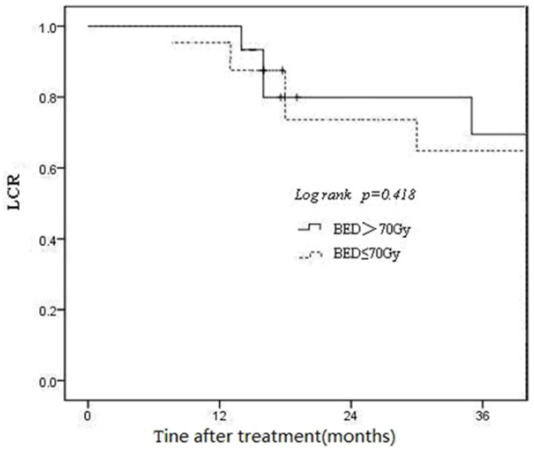

Figure 1. Local control rates (LCR) in high- and low-dose radiation groups (BED > 70 Gy, n = 26; BED ≤ 70 Gy, n = 31).

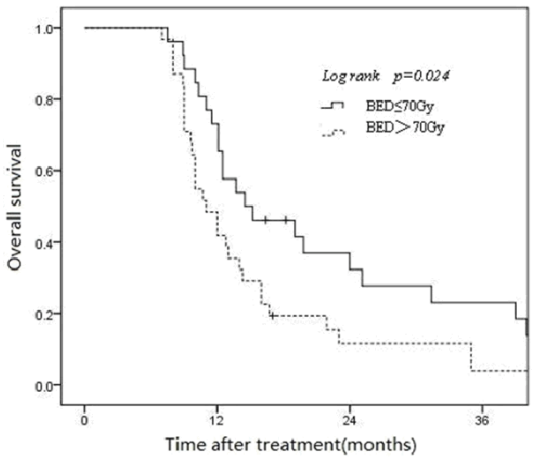

Figure 2. Overall survival in high- and low-dose radiation groups (BED > 70 Gy; n = 26; BED ≤ 70 Gy; n = 31).

The maximum esophageal and spinal cord dose was < 70 Gy and < 49 Gy, respectively.

Chemotherapy: The only regimen used was EP (100 mg/m^2 etoposide intravenously on d1-3, 25 mg/m^2 cisplatin intravenously on d1-3). EP was administered in a 3-week cycle as a sequential chemotherapy regimen and in a 4-week cycle as a concurrent chemotherapy regimen. All patients received at least one cycle of concurrent chemotherapy. Dosage modifications and delay were based the adverse effects. We administered granulocyte colony–stimulating factor subcutaneously if the absolute granulocyte count was < 0.5 × 10^9/L to increase it to > 1.5 × 10^9/L. In principle, patients received at least four cycles of chemotherapy.

Follow-up: The beginning of the follow-up period was defined as the last date of chemotherapy treatment. After treatment was completed, patients were evaluated every three months for the first three years, and then every six months. 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. Local recurrence was defined as the appearance of new lesions or increase in the longest diameters of all measured target lesions in the radiation field. Response to treatment was categorized according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Statistical analysis

We used SPSS 13.0 (SPSS Inc., Chicago, IL, USA) to perform statistical analyses. Based on a radiation dose of ≤ 70 Gy or > 70 Gy, we divided patients into high-dose (BED > 70 Gy) and low-dose groups (BED ≤ 70 Gy). Correlations between radiation dose and clinical characteristics (or treatment-induced toxicity) were analyzed using the chi-square test or Fisher's exact probability test. Overall survival was the primary endpoint, which was defined as the interval (in months) between the date of treatment and the date of the last follow-up or mortality. Survival rates were calculated with Kaplan-Meier curves. We compared differences in survival between groups using the log-rank test. A *P*-value < 0.05 indicated a statistically significant difference.

Results

BED and local control

Following treatment, all patients had partial or complete response and relief of SVCS-associated symptoms. There was symptom reduction in 87.7% (50/57) of patients within 3-10 days after treatment. Three patients required up until 29 days after the start of treatment to respond due to the presence of superior vena cava thrombosis. **Figure 1** depicts the local control rates of the two groups. In the high-dose group, the 2-year local control rate was 80.8% (21/26) (95% confidence interval [CI]: 70.7-91.3%) compared with the 74.2% (23/31) (95% CI: 65.5-84.1%) in the low-dose group. As shown in **Figure 1**, radiation dose did not influence local control (*P* = 0.418).

Table 2. Treatment-induced toxicities according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

Toxicities	BED ≤ 70 Gy		BED > 70 Gy		*P* value[a]
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	
Hemoatologic					
Neutropenia	13 (41.9%)	18 (58.1%)	3 (11.5%)	23 (88.5%)	**0.017**
Anemia	19 (61.3%)	3 (9.7%)	18 (69.2%)	3 (11.5%)	1.000
Thrombocytopenia	9 (29.0%)	2 (6.5%)	10 (38.5%)	3 (11.5%)	1.000
Febrile neutropenia	0	4 (12.9%)	0	5 (19.2%)	_
Pneumonitis	2 (6.5%)	0	2 (7.7%)	1 (3.8%)	_
Esophagitis	26 (83.9%)	5 (16.1%)	16 (61.5%)	10 (38.5%)	0.056

[a]Chi-square test or Fisher's exact test; $P < 0.05$ was considered statistically significant. Bold values are statistically significant ($P < 0.05$).

Table 3. Relationship between radiation dose and chemotherapy cycles within 12 weeks after the beginning of treatment

RT[a] dose (BED)	Patients	≤ 4 Cht[b] cycles	≥ 4 Cht cycles	*P* value[c]
> 70	26	12 (46.2%)	14 (53.8)	0.290
≤ 70	31	9 (29.0%)	22 (71.0%)	

[a]Radiotherapy. [b]Chemotherapy. [c]Chi-square test, P < 0.05 was considered statistically significant.

BED and overall survival

Having identified the relationship between radiation dose and local control, we investigated the influence of radiation dose on overall survival. **Figure 2** shows that patients who received high-dose radiation had a lower 2-year overall survival rate than those who received low-dose radiation (11.6% vs. 33%; $P = 0.024$). The median survival time of the high-dose group was 15.0 months (95% CI: 11.2-19.0); that of the low-dose group was 18.7 months (95% CI: 13.9-23.6).

Toxicity

The most common treatment-related toxicities were esophagitis, neutropenia, and radiation pneumonia; **Table 2** summarizes the other main chemoradiation-induced toxicities. Grade 3/4 neutropenia occurred in 22/26 patients (84.6%) in the high-dose group and in 21/31 patients (67.7%) in the low-dose group. Grade 3/4 esophagitis was more frequent in the high-radiation group, occurring in 8/26 patients (30.8%) compared with the 6/31 patients (19.4%) in the low-dose group. Pneumonitis was observed in 3/26 patients (11.5%) who received high-dose radiation and in 2/31 patients (6.5%) who received low-dose radiation.

Radiation dose and chemotherapy cycles

The consensus is that concurrent chemotherapy with radiotherapy improves tumor control and overall survival [9], but this treatment pattern always increases the toxicities that reduce patient compliance. The difference in chemotherapy cycles in the first 12 weeks after treatment between the two groups was not statistically significant. However, only 29.0% (9/31) of patients who received low-dose radiation received < 4 cycles of chemotherapy in the first 12 weeks after the beginning of treatment compared with 46.2% (12/26) of patients who received high-dose radiation (**Table 3**).

Discussion

Malignancies cause SVCS by direct extension or compression by the primary tumor or by superior mediastinal lymph node metastasis. The latter is more common in patients with SCLC. The influence of SVCS on outcome is debated. Some studies show that SCLC patients with SVCS have better or poorer outcomes than those without SVCS [2, 10, 11]; others report that SVCS is not an independent prognostic indicator [12]. However, SVCS causes patients much suffering. SVCS severity depends on the location of the obstruction and the rapidity of onset. SVCS can be divided into two types based on the presentation of symptoms: acute and sub-acute. In general, acute SVCS is considered an emergency condition due to the severity of the syndrome and the possibility of complications [12, 13], and treatment should be administered as soon as possible. Treatment

without a confirmed diagnosis can be initiated in patients with rapidly progressive symptoms [14]. As SCLC is sensitive to chemotherapy drugs and radiation, chemotherapy, radiotherapy, or both can be used as the first-line treatment. In patients without thrombosis, improvement is usually seen a few days after the start of treatment. Maddox and colleges reported that chemotherapy, radiotherapy, and chemoradiation could used as palliative treatment to rapidly control the symptoms associated with superior vena cava obstruction [5].

Chemotherapy is the fundamental treatment for all patients with SCLC [15]. Compared with chemotherapy alone, thoracic radiation for limited-stage (LS)-SCLC yields 25-30% reduction in local recurrence and a corresponding 5-7% improvement in 2-year survival [16, 17]. The standard care for LS-SCLC consists of combined chemotherapy and thoracic radiotherapy, followed by prophylactic cranial irradiation for patients who have complete or partial treatment response. Compared to late concurrent or sequential radiotherapy, early concurrent thoracic radiotherapy results in significant improvement in overall survival [18, 19]. Thoracic radiotherapy is typically used in extensive-stage SCLC primarily for symptom palliation [4, 6, 7, 13]. The addition of thoracic radiotherapy in extensive-stage SCLC has potential survival benefit [20]. Despite superior vena cava obstruction, $T_{any}N_{2-3}M_0$ disease is relatively limited compared with distant metastases. The thoracic tumor burden of SCLC patients with SVCS is usually relatively greater, especially in the mediastinum, which renders the GTV in radiation larger. It has been proven that toxicities, including myelosuppression, radiation esophagitis, and radiation pneumonitis, are associated with radiation volume. When radiotherapy is administered with chemotherapy, the radiation volume requires more concentration. Meanwhile, tolerable toxicities are unavoidable when completing a treatment regimen. Numerous studies over the past decades have explored various chemoradiotherapy modalities for SCLC [13, 21-24]. However, the optimal radiotherapy timing, dose, and fractionation regimens remain widely debated. In the present study, the entire course of radiation consisted of two sequential phases. In the first phase, we used a relatively high single-fraction dose to relieve symptoms rapidly. Radiotherapy was administered concurrently with chemotherapy in the first two cycles. In accordance with previous studies [6, 7], we obtained similar results for symptom relief. Twenty years ago, radiotherapy was administered as palliative treatment for SCLC patients with SVCS who were considered late-stage and in emergent condition. Although low-dose radiation relieved the SVCS symptoms efficiently, overall survival was often relatively short [8, 13]. Compared with previous studies [5, 6], the response rate of our study population was higher, as was the 2-year overall survival rate. However, the difference in symptom relief between the two groups was not significant. A possible reason is that high-dose radiation induced more severe toxicities and resulted in reduced chemotherapy intensity. The decreased tolerance of chemotherapy might have been the cause of the shorter overall survival in the high-dose radiation group. Thus, we recommend that thoracic radiotherapy be administered after a few cycles of induction chemotherapy and that the radiation dose should be moderate (BED 50-70 Gy).

In conclusion, moderate-dose radiotherapy combined with chemotherapy is a better treatment modality for stage IIIA/IIIB SCLC with SVCS. This finding should be confirmed with further, large-cohort, prospective studies.

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Disclosure of conflict of interest

None.

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