The role of higher thoracic irradiation doses in patients with limited stage of small-cell lung cancer – retrospective study

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SUMMARY

Background: *Small-cell lung cancer is highly chemo- and radiosensitive tumor. We evaluated two different radiotherapy doses applied sequentially with chemotherapy in relation to time to progression, progression free survival, and overall survival in patients with limited disease of small cell lung cancer.*

Methods: *From 1998 to 2003, 81 patients were treated for small-cell lung carcinoma. Median age was 57 years (range, 36-77 years) and female: male ratio was 1:4. Patients were initially treated with four cycles of chemotherapy during three weeks (cisplatin 80mg/m^2 IV, day 1 and etoposide 100 mg/m^2 IV, days 1 – 3). One month later, patients received up to 44 Gy, 2 Gy per day, 5 days per week (group I, 41 patients) or above 44 Gy, standard fractionation (group II, 40 patients), to mediastinum and tumor. Range of higher radiotherapy doses was 54 Gy to 64 Gy, standard fractionation. We evaluated if different radiotherapy doses had any influence on time to progression, progression free survival, and overall survival.*

Results: *The median follow up time was 23 months (range, 12-72 months) for both groups of patients (81). The median time to progression in group I of patients (41) was 13 months (range, 11-29 months) while median time to progression in group II of patients (40) was 20 months (min=9, max=60). There was no statistically significant difference in relapse rate between two groups of patients (p>0.05, Fisher test). However, there was difference but not statistically significant in one-year progression free survival (p=0.05, chi square test) between groups, while there was statistically significant difference in two-year progression free survival favoring higher doses of radiotherapy (p<0.05, chi-square test). The median overall survival was 18 months (range, 12-35 months) for group I of patients and 28 months (range, 15-72 months) for group II of patients. There was no statistically significant advantage between two groups of patients for one-year overall survival (p>0.05, chi-square test). However, there was statistically significant difference in overall survival favoring higher radiotherapy doses for two-year overall survival (p<0.05, chi-square test).*

Conclusion: *We found that higher radiotherapy doses had an impact on long-term time to progression, progression free survival, and overall survival (2 years) of patients.*

KEY WORDS: *Small Cell Lung Carcinoma; Radiotherapy; Radiation Dosage; Dose-Response Relationship; Treatment Outcome*

INTRODUCTION

Govindan et al. reported on the incidence of small-lung cell carcinoma (SCLC) using the Surveillance, Epidemiology, and End Results (SEER) database over the past three decades. They report that the incidence of SCLC as a percentage of the number of patients diagnosed with all types of lung cancer decreased from 17.26% in 1986 to 12.95% in 2002. The staging classification suggested by the Veterans Administration Lung Cancer Group (VALG) is widely used, and it divides patients into those with limited-stage disease and those with extensive-stage disease. At presentation, approximately 25% to 30% of patients will have local or regional disease, classified as limited-stage disease (1,2).

In limited-stage SCLC with good performance status, chemotherapy plus thoracic radiotherapy achieved median survival in excess of 17 months and five-year survival rate of 12%–17% (3,4); in extensive stage disease, combination chemotherapy achieved median survival of 7 to 12 months and five-year survival rate of only 1%–2% (5). Despite high responsiveness to initial chemotherapy, >95% of patients with SCLC will die of this disease (3). The use of thoracic radiation has become standard in the combined modality treatment approach to limited-stage small-cell lung cancer. Traditionally, modest total doses of radiation, ranging from 45 to 50 Gy, have been employed because of the observed responsiveness of small cell lung cancer to radiotherapy. However, a review of the literature reveals high rates of local tumor relapse (6-9).

Fried et al. (10) recently reported a meta-analysis regarding the timing of radiotherapy. Early radiotherapy was defined as beginning before 9 weeks since the initiation of chemotherapy and before the third cycle of chemotherapy. Late radiotherapy was defined as beginning 9 weeks or more after the initiation of chemotherapy or after the beginning of the third cycle of chemotherapy. Seven randomized trials with a total of 1,524 patients met the inclusion criteria. Six of the trials favored the use of early radiotherapy, and the overall risk ratio at 2 years was 1.17 (95% CI, 1.02-1.35; p=0.03). Current available data would support an improved survival when the thoracic radiation is delivered early in the course of treatment for patients with limited stage small cell lung cancer (10-13).

Historically, doses of 40 to 50 Gy delivered in 1.8 to 2.0 Gy daily fractions have been utilized in once-daily radiation schemes with data suggesting a dose response for doses between 30 and 50 Gy (14,15). Phase I trials have been performed suggesting the maximum tolerated dose for once-daily radiotherapy to be in the range of 70 Gy (15). Long-term survival data has been reported from the Cancer and Leukemia Group B. In a phase I trial of 47 patients receiving dose-escalated thoracic radiation, the median survival was an encouraging 24 months (16). In a subsequent phase II experience

(Cancer and Leukemia Group B trial 39,808), (17) 57 patients were treated to 70 Gy in 35 fractions concurrent with carboplatin and etoposide after two prior cycles of paclitaxel and topotecan. The 2-year survival was observed in an encouraging 48%, and the regimen was deemed tolerable with only 16% and 5% of patients experiencing grade 3 and 4 dysphagia, respectively. The strategy of utilizing a once-daily fractionation scheme to 70 Gy continues to be evaluated in combination with novel chemotherapy regimens (18-19). A number of clinical trials have suggested the maximum tolerated dose for hyperfractionated thoracic radiation delivered concurrent with cisplatin and etoposide chemotherapy to be in the range of 40 to 50 Gy (20). Esophagitis is often the dose-limiting toxicity in twice-daily radiation schemes. No randomized trials have been completed that compare the efficacy of high-dose, once-daily radiation (70 Gy) with 45 Gy of hyperfractionated thoracic radiation therapy (21). Because of the increased toxicity and patient inconvenience associated with hyperfractionated radiation, the routine use of this approach in standard practice is often limited to selected patients (22). Additional phase III trials are needed to address the issues of hyperfractionation and the effect of overall treatment time. In Canada, 40 Gy in 3 weeks is still widely used (23). We really do not know that longer treatments or higher doses are better for local control or survival, but we are now able to deliver doses up to 70 Gy in 7 weeks (17) without a clear signal that higher doses are superior. At present, once-daily thoracic radiation doses in the range of 50 Gy to 60 Gy would reflect an accepted standard of care in daily practice (24).

Chemotherapy remains the cornerstone for therapy of SCLC. However, the addition of thoracic radiotherapy to standard chemotherapy has led to improvements in long-term survival in patients with LS – SCLC. Comparison of the 2-year survival rates showed a 5.4% improvement for patients who received radiation therapy. The 5% increase in absolute survival in patients receiving thoracic radiation represents a more than 50% relative improvement in the survival rate observed with chemotherapy alone. Local control rates were doubled from approximately 25% with chemotherapy alone to approximately 50% with the addition of thoracic radiation. Neither study reported the “best” chemotherapy and radiation regimen. However, the use of cisplatin (Platinol) and etoposide (VePesid) (PE) and concurrent thoracic radiation has been associated with the best survival results observed thus far.

The aim of our retrospective study was to evaluate two different radiotherapy (RT) doses applied sequentially with chemotherapy (CT) on time to progression (TTP), progression free survival (PFS), and overall survival (OS) of the patients with limited disease (LD) of small-cell lung cancer (SCLC).

MATERIAL AND METHODS

Eighty-one newly diagnosed patients with histologically confirmed small-cell lung cancer received their initial treatment (combined chemo- and radiotherapy) from 1998 through 2003 at the of Oncology Clinic, Clinical Centre of Montenegro. The patients and tumors characteristics are described in Table 1.

The patients were evaluated for disease stage before the initiation of chemotherapy and chest radiotherapy. Their anamneses were taken and they all had physical examination, complete and differential blood cell count, serum chemistry examination, and urine analysis. Imaging examinations included chest roentgenogram, computed tomography of the chest, magnetic resonance imaging or computed tomography of the head, radionuclide bone scan with radiographs of areas of increased radionuclide uptake, and computed tomography or radionuclide scan of the liver. The patients also underwent fiber-optic bronchoscopy and pulmonary function tests with arterial blood gases. Limited-stage disease was defined as tumor confined to one hemithorax and hilar, mediastinal, and supraclavicular nodes and encompassed within a tolerable radiotherapy portal after completion of the staging evaluation. Patients with extrapulmonary small-cell cancer whose cancer was confined to an anatomic area that could be encompassed within a tolerable radiation portal were also treated with this regimen. The diagnosis of SCLC was based on histologic examination of a bronchial biopsy and/or lymph node metastasis.

The eligibility criteria for patient entry included no active second malignancy and an ECOG performance status of 0 to 2. Patients also needed adequate hematologic function, defined as a WBC count greater than 4,000/pL and platelet count greater than 100,000/pL, adequate renal function with a serum creatinine level less than 2.0 mg/dL, and adequate cardiac function, defined as no symptomatic heart disease, no less than fully compensated congestive heart failure, and no significant arrhythmia or myocardial infarction within the past 3 months.

All patients were given chemotherapy with the same drugs (cisplatin and etoposide) followed by chest radiotherapy after the forth cycle of chemotherapy. The initial therapy consisted of etoposide 100 mg/m^2 administered on days 1, 2, and 3, and cisplatin 80 mg/m^2 on day 1; 3 weeks for 4 cycles followed by radiotherapy. Chest irradiation to the primary tumor and involved lymph nodes of mediastinum started 4 weeks after the last cycle of chemotherapy.

The radiotherapy doses were prescribed at midplane for anterior-posterior, posterior-anterior (AP-PA) fields and to specific isodose curves to cover the tumor volume for non AP-PA techniques (3 and 4 fields). All patients’ irradiated tumor volumes were simulated. Tumor volumes were defined by chest radiograph and computed tomography of the chest before initiation of chemotherapy treatment, and the gross tumor volume (GTV) was encompassed by a minimum margin of 1.5 cm throughout the treatment course. Ipsilateral hilum and bilateral mediastinum from thoracic inlet to subcarinal region (5 cm bellow carina) were included. Contralateral hilum or supraclavicular was not included unless involved. Irradiation was administered in one-daily fraction with isocentre technique to a total dose of 44 Gy in 22 fractions (group I) and 54 to 64 Gy in 27 to 32 fractions (group II). All patients were treated on the linear accelerator, Clinac 600C, Varian, X rays with energy of 6 MV.

Statistical methods

The lengths of time until treatment failure – time to progression (TTP) were measured from the date of the end of radiotherapy course. Progression free survival (PFS) was the length of time after radiotherapy treatment in which our patients were living with a disease that did not get worse. Overall survival (OS) was calculated as the length of time until death, irrespective of cause. The values were compared by chi square test and Fisher test. We used the life table method to estimate the probability of treatment failure for the endpoints of PFS and OS.

RESULTS

From 1998 to 2003, 81 patients (65 men and 16 women) were treated in this study. Male: female ratio was 4:1. At the time of study entry, their median age was 57 years (range, 36 to 77). The majority of the patients

Table 1. Patients and tumor characteristics

Total number of patients (81)	Number of patients	Percent of all patients (%)
Gender:		
Male	65	80
Female	16	20
Age range (years):		
30-39	2	2
40-49	18	22
50-59	32	40
60-69	18	22
70- 79	11	14
Median (range):		
57 years (36 – 77 years)		
Performance status (ECOG)*:		
0	28	35
1	43	53
2	10	12
Histopathological status:		
SCLC	81	100
Stage of disease:		
Limited	81	100

*ECOG - Eastern Cooperative Oncology Group

were 50 to 59 years old. All patients had limited-stage of disease. The patients had ECOG status 0 and 1, mostly (88%) (Table 1). All patients completed four cycles of etoposide/cisplatin chemotherapy and the full planned course of chest radiotherapy.

The median follow-up time was 23 months (range, 12-72 months) for both groups of patients. Relapse rate and sites of distant metastases are showed in Table 2 and Figure 1.

The most often combination of metastases' sites was brain and lymph nodes of the neck in 6 patients and brain, liver, and bone metastases in 7 patients. The rest of patients had other combination of distant metastases (bone and brain, liver and bone, liver and lymph nodes). However, there were no statistically significant difference in relapse rate between two groups of patients ($p>0.05$, Fisher test). Brain metastases were observed in 37% of patients in both groups of patients, alone or combined with

Table 2. Relaps rate

	Group I (No/%)	Group II (No/%)
No relapse	1/2	4/10
Extrathoracic relapse	24/59	28/70
Intrathoracic relapse	1/2	4/10
Extrathoracix and intrathoracic relapses	15/37	4/10

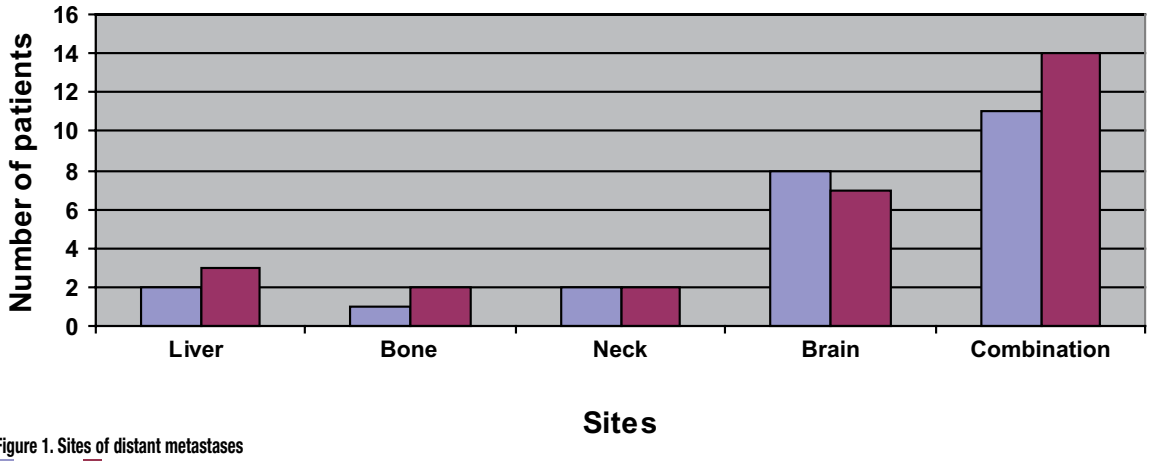

Figure 1. Sites of distant metastases
Group 1, Group 2

other sites of metastases. Whole brain irradiation was performed for these patients with total dose of 30 Gy in 10 fractions.

The most common cause of treatment-related morbidity was combined modality esophagitis in both groups of patients. Four of 41 patients (10%) and 7 of 40 patients (17.5%) had esophagitis (grade 3 toxicity) respectively. In group II of patients, 3 of 40 patients (7.5%) had pneumonitis grade 2 that required administration of corticosteroids. There were no treatment- related deaths in any group of patients.

Of the original 81 patients, 6 patients (7%) from group II were alive and free of cancer at 2 years. The other 75 patients (93%) had relapsed and died.

The median TTP in group I of patients was 13 months (range, 11-29 months) while median TTP in group II of patients was 20 months (range, 9-60 months).

There was difference but not statistically significant in 1 year PFS (p=0.05, chi-square test) while there was statistically significant difference in 2 years PFS favoring higher doses of RT (p<0.05, chi-square test) (Table 3, Figure 2). The median OS was 18 months (range 12-35 months) in group I of patients with two-year survival rate of 5% while median OS was 28 months (range, 15-72 months) in second group of patients with two-year survival rate of 53%. There were no statistically significant advantage in either of the two groups patients regarding one-year OS (p>0.05, chi-square test). However, there were statistically significant difference in OS favoring higher RT doses for two-year OS (p<0.001, chi-square test) (Table 3, Figure 3).

DISCUSSION

Limited-stage small-cell lung cancer remains a therapeutic challenge to medical and radiation oncologists. SCLC is characterized by a more rapid doubling time and higher growth fraction, making either micrometastatic or macrometastatic disease a hallmark of the disease. This aspect of the natural history of SCLC, combined with the initial sensitivity of SCLC to both chemotherapy and radiation therapy, have clearly influenced the therapeutic approach to this disease. The percentage of patients left unstaged has declined (17.9% in 1973 vs. 3.8% in 2002), and the use of combined chemoradiotherapy as primary treatment has increased (34.8% in 1985 vs. 51.9% in 2000) (2).

The treatment of LS-SCLC has evolved significantly over the last two decades with combined-modality therapy now the standard of care (25). In LS-SCLC, combination chemotherapy alone results in poor local control rates, with intra thoracic failures occurring in 75% to 90% of patients (26). The addition of thoracic radiotherapy (TRT) significantly reduced the risk of intra thoracic failures from 60% to 30% but did not consistently result in a survival advantage in individual trials. Pignon et al. evaluated 13 randomized trials including 2,410 patients with LS-SCLC. These studies have investigated the role of thoracic radiotherapy in LS-SCLC. The relative risk (RR) of death in the chemo radiotherapy group compared with the chemotherapy alone group was 0.86 (95% CI, 0.78 to 0.94; P = .001), corresponding to a 14% reduction in mortality and an absolute benefit in overall survival of 5.4% +/- 1.4% at 3 years. There was a trend towards a greater reduction in mortality among younger patients. The 2-year local failure rate of 23%

Table 3. Differences between groups in one-year and two-year PFS and OS

		Year 1 of the treatment end (p)	Year 2 of the treatment end (p)	Two-year PFS and OS (p)
PFS	Group I	42%	2%	p < 0.05
	Group II	65% (p = 0.05)	20% (p < 0.05)	
OS	Group I	98%	5%	p < 0.001
	Group II	100% (p > 0.05)	53% (p < 0.05)	

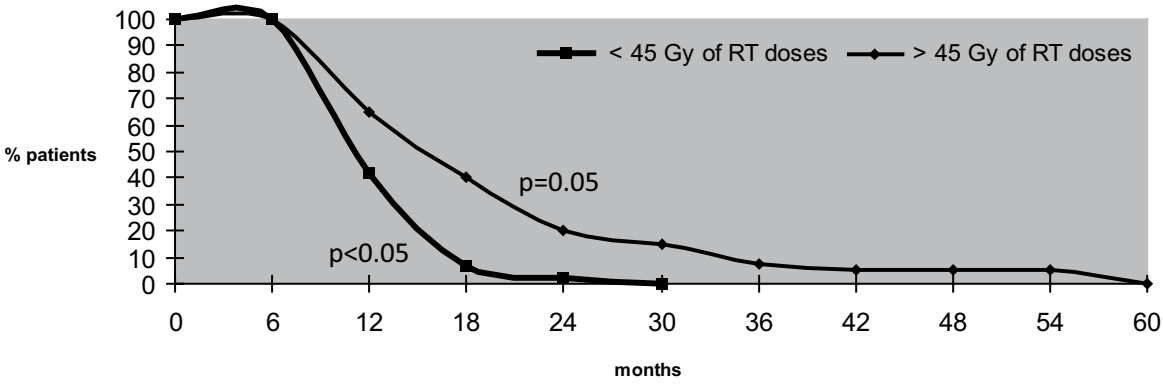

Figure 2. Progression free survival for both groups of patients

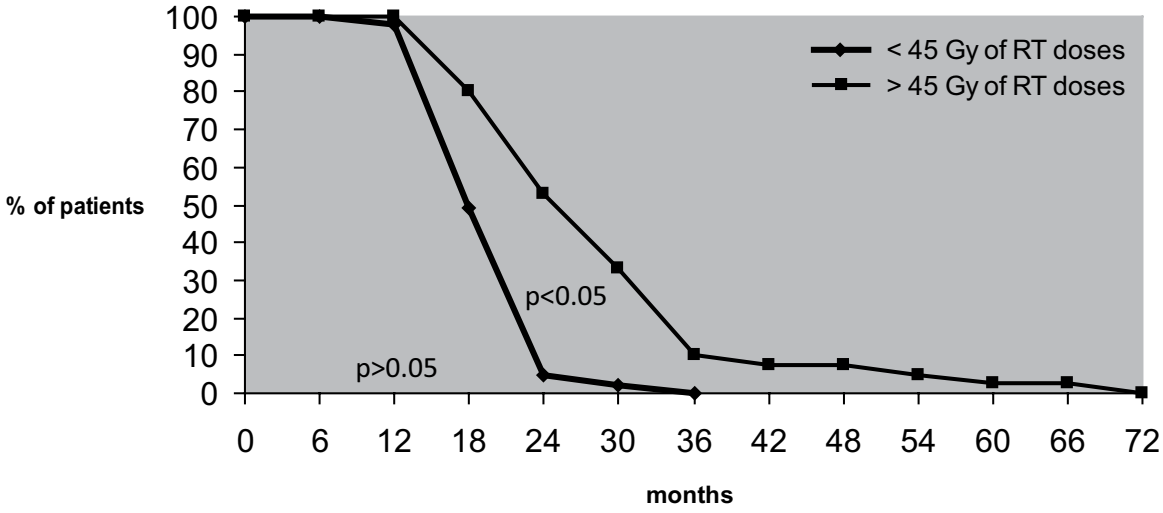

Figure 3. Overall survival for both groups of patients

for irradiated patients vs. 48% for nonirradiated patients remains significant as well (P = .0001). No clear benefit was noted in an indirect comparison of early versus late TRT or sequential versus nonsequential strategies (6-7). Having established TRT as an integral component of the treatment platform for LS-SCLC, many issues remain unresolved regarding the optimal chemo radiotherapy approach. One issue is the dose of TRT. Traditionally, modest doses of TRT (45 to 50 Gy), in daily 1.8- to 2-Gy fractions, were used because of the radiotherapy sensitivity of SCLC (27). Intensifying the radiotherapy dose by accelerating its delivery was one of the initial strategies explored in prospective LS-SCLC trials. Turrisi et al randomly assigned 471 LS-SCLC patients to either 45 Gy in 5 weeks (1.8Gy every day for 25 fractions) or 45 Gy in 3 weeks (1.5 Gy bid for 30 fractions) beginning with the first of four cycles of EP. The 5-year survival rate was 26% with accelerated TRT compared with 16% for conventional TRT. The major toxicity seen with accelerated TRT was a doubling of the grade 3 or 4 esophagitis rate (16% for convention TRT vs. 32% for accelerated TRT); severe pulmonary toxicity was similar on both arms of the trial (approximately 6% grade 3). There was a significant difference in favor of the accelerated TRT arm in overall local tumor control (e.g., local as well as local plus distant recurrence) (21). This data strongly suggested that attempts designed to improve local control could favorably affect the long-term outcome of patients with LS-SCLC. Despite the significant improvement in long-term survival, the adopting of 45 Gy bid as a new standard failed to occur perhaps because of the inconvenience of twice-daily treatment sessions and the increased rate of severe esophageal toxicity seen with this regimen (25, 28,29).

The purpose of our study was the administration of a higher total dose of once-daily TRT to increase the efficacy of treatment. There were no statistically significant advantages between two groups of patients for 1-year PFS (p=0.05, chi square) and OS (p>0.05, chi square). However, there were statistically significant differences in PFS and OS favoring higher RT doses for 2-year PFS (p<0.05, chi square) and OS (p<0.001). Our results were worse than actually trials (in the references 4, 9, 11, 12, 16-19, 22-23, 28) (median TTP = 20 months; two-year PFS was 20%; median OS = 28 months with two-year OS 53%). We suppose that the delay of the initiation of TRT after the fourth cycle of chemotherapy was the reason for these results. The toxicity of our treatment was similar to the toxicity in other studies regarding once-daily TRT with total dose escalation (esophagitis grade 3 in 17.5% patients and pneumonitis grade 2 in 7.5% patients).

The optimal timing of TRT relative to chemotherapy remains controversial. At least five meta-analyses addressing the timing of TRT have recently been published (10, 12, 24). Fried et al., showed an advantage to early (administered within 9 weeks of starting chemotherapy) versus late TRT in terms of survival. This was particularly evident when cisplatin-based chemotherapy regimens and more intensified TRT were used (10). De Ruysscher et al. (11) also reported similar findings with regard to survival when TRT was started within 30 days of chemotherapy initiation. The survival advantage was more pronounced if the TRT was completed in less than 30 days (11, 30-34).

CONCLUSION

Many questions remain about the optimal way to deliver chemoradiotherapy. We found that higher RT doses applied sequentially with CT had influence on long-term TTP, PFS, and OS of our patients (2 years).

The future efforts in this disease should focus on optimizing TRT concerning the optimal doses, fractionation, timing, appropriate target volume, and the use of concurrent vs. sequential protocols. For prophylactic cranial irradiation (PCI), there is some evidence supporting a linear dose-effect relationship, but convincing data on the toxicity/efficacy ratios are still missing.

LS-SCLC has been a model cancer in terms of the potential benefit of combined chemo- radiotherapy strategies in improving patient outcomes. All patients in excellent overall health should be treated aggressively with both radiation and chemotherapy. In addition, the further randomized trials should focus on unraveling the biology of LS-SCLC, which would hopefully lead to more effective systemic therapies.

Conflict of interest

We declare no conflicts of interest.

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