Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Impact of thoracic radiation therapy after chemotherapy on survival in extensive-stage small cell lung cancer: A propensity score-matched analysis

Lei Deng, ZongMei Zhou, ZeFen Xiao, DongFu Chen, QinFu Feng, Jun Liang, JiMa Lv, XiaoZhen Wang, Nan Bi, Xin Wang, Tao Zhang, WenQing Wang & LvHua Wang

National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Keywords
Carcinoma, small cell; chemotherapy; intensity-modulated; lung neoplasm; radiotherapy.

Correspondence
ZongMei Zhou, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Panjiayuannanli 17, Chaoyang District, Beijing 10021, China.
Tel: +86 138 0138 9769
Fax: +86 10 6770 6153
Email: zhouzongmei2013@163.com

Received: 2 December 2018;
Accepted: 13 January 2019.

doi: 10.1111/1759-7714.13001

Thoracic Cancer **10** (2019) 799–806

Abstract

Background: The role of thoracic radiation therapy (TRT) after chemotherapy (CHT) in extensive-stage small cell lung cancer (ES-SCLC) has not been well defined. We investigated whether intensity-modulated radiotherapy (IMRT) improves outcomes in ES-SCLC after CHT compared to CHT alone.

Methods: A total of 292 patients who reached a complete response (CR), partial response (PR), or stable disease (SD) after CHT were assigned into groups: CHT + TRT and CHT alone. Propensity score matching was used to balance patient groups (n = 72 each).

Results: The five-year overall survival (OS: 12.3% vs. 3.6%; $P < 0.001$) and progression-free survival (PFS: 3.2% vs. 1.7%; $P = 0.006$) rates were significantly higher in the CHT + TRT group. This data was confirmed in the matched samples (5-year OS: 10.5% vs. 1.6%, $P < 0.001$; PFS: 4.3% vs. 0.0%, $P = 0.023$). The overall ($P = 0.002$) and locoregional ($P < 0.001$) recurrence rates in the CHT + TRT group were significantly lower than in the CHT group. Univariate analysis showed that response evaluation after CHT and TRT were significant prognostic factors of OS. Multivariate analyses revealed that N Stage 0–1 ($P = 0.02$), > 6 cycles of CHT ($P = 0.042$), CR + PR after CHT ($P < 0.001$), and TRT ($P < 0.001$) were independently associated with longer OS compared to CHT alone.

Conclusion: TRT using IMRT is strongly correlated with improved OS and PFS in ES-SCLC patients reaching CR, PR or SD after CHT. A multicenter, randomized phase III clinical trial is needed to confirm these findings.

Introduction

Small-cell lung cancer accounts for 13–20% of all lung cancers, with approximately two-thirds of patients presenting at a stage of extensive disease.[1,2] Extensive-stage small cell lung cancer (ES-SCLC) is composed of both American Joint Committee on Cancer (AJCC) (7th edition) Stage IV (T any, N any, M 1a/b) and T3–4, which cannot be covered by a tolerable radiation plan because of extensive multiple lung nodules or large tumor/nodal volume.[3] The standard treatment over the past several decades has been four to six cycles of platinum-based chemotherapy (CHT). Survival of ES-SCLC is poor, with median survival ranging from 9 to 12 months and five-year survival of < 2%.[4–6] Increasing dose intensity, alternating drug regimens, and maintenance CHT have also failed to improve overall survival (OS) in recent decades.[3,7,8] In view of the high intrathoracic disease progression of up to 90% within the first year after CHT, thoracic radiation therapy (TRT) has been incorporated into management.[9] TRT has long been administered to improve locoregional tumor control; however, whether TRT provides a clear benefit to survival is controversial.[10–13] This may be a result of the high mortality of suboptimal RT techniques and an ineffective RT dose. Conformal RT, including intensity-modulated radiotherapy (IMRT) and three-dimensional conformal RT have

been widely implemented in recent years and have proven effective in reducing the radiation toxicity to normal tissues in a variety of cancers.[14–16] However, the role of TRT after CHT for ES-SCLC is unclear and requires further investigation. The purpose of this study was to evaluate the role of TRT for patients with ES-SCLC who reached a complete response (CR), partial response (PR), or stable disease (SD) after CHT.

Methods

Eligibility

Medical records of patients with ES-SCLC who were treated at the Cancer Hospital, Chinese Academy of Medical Sciences from January 2007 to December 2012 were retrospectively reviewed. Inclusion criteria were: (i) ES-SCLC confirmed according to AJCC (seventh edition) staging; and (ii) patients achieved CR, PR, or SD after four to six cycles of platinum-based CHT. Exclusion criteria were: (i) a history of malignancy in other sites (previously or at the same time), not including curable non-melanoma skin and cervical carcinoma in situ; (ii) uncontrolled heart disease or myocardial infarction in the past six months; (iii) a history of mental illness; (iv) pregnant or lactating; (v) uncontrolled diabetes, hypertension; (vi) interstitial pneumonia or active pulmonary fibrosis; (vii) active infection; or (viii) prophylactic cranial irradiation (PCI) after CHT. A total of 292 patients were divided into two groups: CHT + TRT, comprising patients administered TRT after CHT; and CHT, comprising a control group of patients administered CHT alone. The Ethics Committee of our institution approved this study.

Chemotherapy

All patients were administered CHT via a platinum-based regimen with a median of five cycles, primarily etoposide + cisplatin (20 mg/m^2 cisplatin from days 1 to 3; 100 mg etoposide from days 1 to 5) or carboplatin + etoposide (500 mg carboplatin for day 1; 100 mg etoposide from days 1 to 5).

Radiotherapy

TRT commenced within seven weeks after CHT, but not within two weeks after CHT or if acute grade 2 or higher toxic effects of CHT were not yet resolved. RT target volumes were defined based on positron emission tomography (PET) or computed tomography (CT) scans obtained at the time of RT planning. The gross tumor volume (GTV) was limited to the post-induction systemic therapy volume to avoid excessive toxicity. The clinical target volume (CTV) was defined as GTV plus 0.8 cm margins and the involved mediastinal node region before CHT. A 0.5 cm three-dimensional expansion of the CTV was used to create the planning target volume (PTV). A total dose of 32–67 Gy was delivered to 95% of the PTV in 25–33 fractions (5 fractions per week) over 5–6.5 weeks using photon beams of 6 MV from a linear accelerator. Organs at risk (OARs), including the bilateral lungs, spinal cord, and heart, were contoured. The dose to the OARs was constrained as follows: the maximal dose to the spinal cord was < 45 Gy, V20 to the bilateral lungs < 28%, V30 to the bilateral lungs < 20%, and V40 to the heart < 30%.

Follow-up

Acute toxicities were scored according to Common Terminology Criteria for Adverse Events version 4.0 and late toxicities were assessed according to Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria.[17] All patients were assessed weekly during treatment and followed up every three to six months for the first two years after treatment, every six to 12 months for the next three years, and every year thereafter. Assessments included: CT scans of the neck, chest, and upper abdomen; ultrasonography of the neck and upper abdomen; nuclear bone scanning; and traditional blood and biochemical tests. PET-CT and fine needle aspiration cytology were performed as required.

Recurrences were defined as locoregional (LRR) or distant. LRRs were defined as recurrences at the supraclavicular, mediastinal regions. Distant metastases were defined as recurrences at other sites. All recurrences were confirmed by a CT or magnetic resonance imaging scan of the corresponding site. Cytology or histology was performed if necessary. Multiple recurrences within a month were considered synchronous. The location and identification date of recurrence were recorded. OS was measured from the first date of treatment to death from any cause, loss to follow-up, or the final follow-up, while progression-free survival (PFS) was measured from the first date of treatment to disease progression, loss to follow-up, or the final follow-up.

Statistical analyses

A chi-square test was used to compare categorical data, with or without correction for continuity. The Kaplan–Meier method was used to calculate the survival rate, and the log-rank method was used to compare survival curves between groups. The Kaplan–Meier method was used for univariate survival analysis to find a correlation between OS and clinical features. A multivariate model was established using the Cox proportional hazards algorithm and

significant variables were determined by backward–forward and stepwise methods. To further adjust unbalanced covariates, a propensity score (PS) matching method was used to create two comparable groups of CHT + TRT and CHT alone. The PS for each patient was estimated with a logit model that included the following variables: number of metastatic organs, liver metastasis, bone metastasis, and response evaluation after CHT. The nearest neighbor matching within a prespecified caliper width without replacement was then used as the matching algorithm to perform 1:1 matching of patients in both groups. The significance level was set as $P < 0.05$. All statistical analyses

Table 1 Clinical characteristics of patients with ES-SCLC by group

	Before PSM				After PSM			
	Total	CHT	CHT + TRT	*P*	Total	CHT	CHT + TRT	*P*
Characteristic	(*n* = 292)	(*n* = 196)	(*n* = 96)		(*n* = 144)	(*n* = 72)	(*n* = 72)	
Gender								
Men	235 (80.5)	161 (82.1)	74 (77.1)	0.31	115 (79.9)	59 (81.9)	56 (77.8)	0.53
Women	57 (19.5)	35 (17.9)	22 (22.9)		29 (20.1)	13 (18.1)	16 (22.2)	
Age								
< 65	202 (69.2)	135 (68.9)	67 (69.8)	0.87	99 (68.8)	50 (69.4)	49 (68.1)	0.86
≥ 65	90 (30.8)	61 (31.1)	29 (30.2)		45 (31.3)	22 (30.6)	23 (31.9)	
Brain metastasis at diagnosis								
No	246 (84.2)	165 (84.2)	81 (84.4)	0.97	120 (83.3)	63 (87.5)	57 (79.2)	0.18
Yes	46 (15.8)	31 (15.8)	15 (15.6)		24 (16.7)	9 (12.5)	15 (20.8)	
KPS score								
< 80	42 (14.4)	31 (15.8)	11 (11.5)	0.32	23 (16.0)	14 (19.4)	9 (12.5)	0.26
≥ 80	250 (85.6)	165 (84.2)	85 (88.5)		121 (84.0)	58 (80.6)	63 (87.5)	
Smoking status								
No	68 (23.3)	41 (20.9)	27 (28.1)	0.17	43 (29.9)	19 (26.4)	24 (33.3)	0.36
Yes	224 (76.7)	155 (79.1)	69 (71.9)		101 (70.1)	53 (73.6)	48 (66.7)	
SVC syndrome								
No	269 (92.1)	183 (93.4)	86 (89.6)	0.26	131 (91.0)	67 (93.1)	64 (88.9)	0.38
Yes	23 (7.9)	13 (6.6)	10 (10.4)		13 (9.0)	5 (6.9)	8 (11.1)	
T Stage								
1	14 (4.8)	7 (3.6)	7 (7.3)	0.43	9 (6.3)	3 (4.2)	6 (8.3)	0.40
2	100 (34.2)	71 (36.2)	29 (30.2)		57 (39.6)	32 (44.4)	25 (34.7)	
3	85 (29.1)	55 (28.1)	30 (31.3)		36 (25.0)	15 (20.8)	21 (29.2)	
4	93 (31.8)	63 (32.1)	30 (31.3)		42 (29.2)	22 (30.6)	20 (27.8)	
N Stage								
0	6 (2.1)	2 (1.0)	4 (4.2)	0.052	5 (3.5)	1 (1.4)	4 (5.6)	0.15
1	14 (4.8)	12 (6.1)	2 (2.1)		9 (6.3)	7 (9.7)	2 (2.8)	
2	118 (40.4)	73 (37.2)	45 (46.9)		82 (56.9)	38 (52.8)	44 (61.1)	
3	154 (52.7)	109 (55.6)	45 (46.9)		48 (33.3)	26 (36.1)	22 (30.6)	
Number of metastatic organs								
1	141 (48.3)	61 (31.1)	80 (83.3)	< 0.001	112 (77.8)	56 (77.8)	56 (77.8)	1.00
2	77 (26.4)	66 (33.7)	11 (11.5)		22 (15.3)	11 (15.3)	11 (15.3)	
≥ 3	74 (25.3)	69 (35.2)	5 (5.2)		10 (6.9)	5 (6.9)	5 (6.9)	
Liver metastasis								
No	212 (72.6)	124 (63.3)	88 (91.7)	< 0.001	126 (87.5)	62 (86.1)	64 (88.9)	0.61
Yes	80 (27.4)	72 (36.7)	8 (8.3)		18 (12.5)	10 (13.9)	8 (11.1)	
Bone metastasis								
No	218 (74.7)	138 (70.4)	80 (83.3)	0.017	112 (77.8)	56 (77.8)	56 (77.8)	1.00
Yes	74 (25.3)	58 (29.6)	16 (16.7)		32 (22.2)	16 (22.2)	16 (22.2)	
Number of CHT cycles								
≤ 6	273 (93.5)	183 (93.4)	90 (93.8)	0.90	138 (95.8)	69 (95.8)	69 (95.8)	1.00
> 6	19 (6.5)	13 (6.6)	6 (6.3)		6 (4.2)	3 (4.2)	3 (4.2)	
Response evaluation after CHT								
CR + PR	226 (77.4)	146 (74.5)	80 (83.3)	0.090	105 (72.9)	49 (68.1)	56 (77.8)	0.19
SD	66 (22.6)	50 (25.5)	16 (16.7)		39 (27.1)	23 (31.9)	16 (22.2)	

CHT, chemotherapy; CR, complete response; ES-SCLC, extensive-stage small cell lung cancer; KPS, Karnofsky performance status; PSM, propensity score matching; PR, partial response; SD, stable disease; SVC, superior vena cava syndrome; TRT, thoracic radiation therapy.

were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA) and STATA SE version 12.0 (Stata Corp LP, College Station, TX, USA).

Results

Characteristics of patients

A total of 292 patients (235 men and 57 women) were involved in this study: 96 patients in the CHT + TRT and 196 patients in the CHT group. The median age was 60 (range: 19 –81) years. In the CHT + TRT group, all patients received IMRT. The clinical characteristics did not significantly differ between the groups, except there were significantly more patients with only one metastatic organ and fewer patients with bone or liver metastasis in the CHT + TRT compared to the CHT group (Table 1). The PS-matched cohort included 72 patients in each group. There was an expected balance of covariates in the two groups (Table 1).

Survival

The median follow-up across the whole study population was 12.5 (range: 3–118) months. In the overall study cohort, the two and five-year OS rates were 34.7% and 12.3%, respectively, in the CHT + TRT group, which were significantly higher than in the CHT group (2-year: 11.1%, 5-year: 3.6%; log-rank $\chi 2 = 25.037$; $P < 0.001$) (Fig 1a). In the CHT + TRT group, two and five-year PFS rates were 11.8% and 3.2% respectively, which were significantly higher than in the CHT group (2-year: 7.4%, 5-year: 1.7%; log-rank $\chi 2 = 7.543$; $P = 0.006$) (Fig 1b).

Univariate survival analysis was performed to determine whether there was any correlation between OS and clinical features, including gender, age, presence of brain metastasis at diagnosis, Karnofsky performance status score, smoking status, superior vena cava syndrome, T stage, N stage, number of metastatic organs, liver metastasis, bone metastasis, number of CHT cycles, and response evaluation after CHT and TRT (Table 2). The results showed that response evaluation after CHT and TRT were significant prognostic factors of OS.

Using these characteristics as parameters, multivariate analysis revealed that N stage 0–1 ($P = 0.02$), > 6 cycles of CHT ($P = 0.042$), CR + PR after CHT ($P < 0.001$), and TRT ($P < 0.001$) were independent, favorable prognostic factors of OS (Table 3).

These findings were confirmed in the matched samples. In the CHT + TRT group, the two and five-year OS rates were 32.9% and 10.5%, respectively, which were significantly higher than in the CHT group (2-year: 6.4%, 5-year: 1.6%; log-rank $\chi 2 = 21.314$; $P < 0.001$) (Fig 2a). In the CHT + TRT group, the two and five-year PFS rates were 10.1% and 4.3%, respectively, which were also significantly higher than in the CHT group (2-year: 5.0%; 5-year: 0.0%; log-rank $\chi 2 = 5.189$; $P = 0.023$) (Fig 2b).

Recurrence

In the overall study cohort, 275 (94.2%) patients experienced disease progression during follow-up, including LRR in 159 cases (48.6%), distant metastasis in 101 cases (30.9%) and both at the same time in 15 cases (4.6%), which consisted of 22 (16.9%), 66 (50.8%), and 3 cases (2.3%) in the CHT + TRT group and 137 (69.5%), 35 (17.8%), and 12 cases (6.1%) in the CHT group, respectively. The local area recurrence rate was 19.2% in the CHT + TRT group and 75.6% in the CHT group. TRT greatly reduced LRR. The difference between the two groups was statistically significant ($\chi 2 = 100.080$; $P = 0.001$).

Toxicities

In the CHT + TRT group, 46 patients experienced ≥ 3 grade hematological toxicities and the incidence rate was 35.4% (46/130) compared to 31.9% (63/197) in the CHT group. The difference between the groups was not statistically significant ($\chi 2 = 0.409$; $P = 0.550$). The addition of

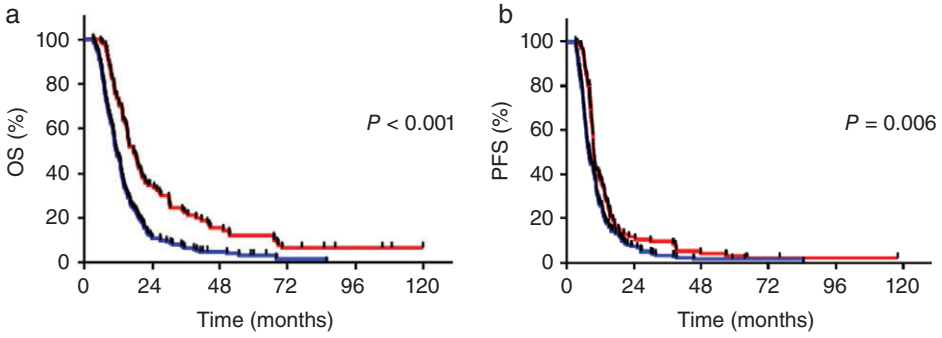

Figure 1 The (**a**) overall survival (OS). (——) Group C and (——) Group C+TRT and (**b**) progression-free survival (PFS) curves between the chemotherapy (CHT) + thoracic radiation therapy (TRT) and CHT groups (——) Group C and (——) Group c+TRT.

Table 2 Univariate analysis of OS of ES-SCLC patients who reached CR/PR/SD after CHT

Characteristic	Patients (*n*)	MST (month)	Five-year OS (%)	χ^2 value	*P*
Gender					
Men	235 (80.5)	13.0	4.9	1.512	0.219
Women	57 (19.5)	13.9	12.9		
Age					
< 65	202 (69.2)	13.1	6.6	0.42	0.517
≥ 65	90 (30.8)	12.8	6.0		
Brain metastasis at diagnosis					
No	246 (84.2)	13.1	6.3	0.048	0.826
Yes	46 (15.8)	14.2	7.3		
KPS score					
< 80	42 (14.4)	12.7	4.9	0.726	0.394
≥ 80	250 (85.6)	13.1	6.8		
Smoking status					
No	68 (23.3)	13.0	9.4	0.012	0.915
Yes	224 (76.7)	13.3	5.7		
SVC syndrome					
No	269 (92.1)	13.0	7.1	0.045	0.831
Yes	23 (7.9)	15.0	0.0		
T Stage					
1	14 (4.8)	12.7	7.1	2.489	0.477
2	100 (34.2)	13.0	3.4		
3	85 (29.1)	13.7	7.4		
4	93 (31.8)	13.3	9.2		
N Stage					
0	6 (2.1)	70.3	53.3	4.796	0.187
1	14 (4.8)	15.6	14.3		
2	118 (40.4)	12.7	7.0		
3	154 (52.7)	13.0	5.0		
Number of metastatic organs					
1	141 (48.3)	14.2	8.8	5.378	0.068
2	77 (26.4)	12.6	3.8		
≥3	74 (25.3)	11.7	4.9		
Liver metastasis					
No	212 (72.6)	13.3	8.6	2.784	0.095
Yes	80 (27.4)	12.9	0.0		
Bone metastasis					
No	218 (74.7)	13.3	7.5	1.284	0.257
Yes	74 (25.3)	12.7	2.4		
Number of CHT cycles					
≤6	273 (93.5)	12.8	5.8	3.498	0.061
>6	19 (6.5)	21.9	15.8		
Response evaluation after CHT					
CR + PR	226 (77.4)	13.7	8.4	17.291	< 0.001
SD	66 (22.6)	10.3	0.0		
TRT					
Yes	96(32.9)	17.2	12.3	25.037	< 0.001
No	196(67.1)	11.4	3.6		

CHT, chemotherapy; CR, complete response; ES-SCLC, extensive-stage small cell lung cancer; KPS, Karnofsky performance status; MST, median survival time; OS, overall survival; PR, partial response; SD, stable disease; SVC, superior vena cava syndrome; TRT, thoracic radiation therapy.

TRT did not significantly increase the incidence of hematological toxicity after CHT. Radiation-related toxicities were mainly characterized by pneumonitis and esophagitis. The rates of ≥ 2 grade pneumonitis and esophagitis were 28.5% (37/130) and 12.3% (16/130) in the CHT + TRT group, respectively.

Discussion

The use of TRT in ES-SCLC is a focus of research attention. TRT has routinely been used for limited-stage SCLC. Combined with CHT, RT could improve local control rates and overall survival. However, few studies of RT for ES-

Table 3 Multivariate analysis of the prognostic factors of survival in patients with ES-SCLC

Characteristic	Chi-square Statistic	*P*	HR	95% CI
Gender	1.694	0.193	0.746	0.479~1.16
Age	0.077	0.781	1.04	0.787~1.375
Brain metastasis at diagnosis	0.503	0.478	1.144	0.789~1.658
KPS score	0.166	0.684	0.93	0.654~1.321
Smoking status	2.497	0.114	0.723	0.483~1.081
SVC syndrome	0.054	0.817	0.948	0.602~1.493
T Stage	0.518	0.472	0.948	0.82~1.096
N Stage	5.448	0.02	1.261	1.038~1.532
Number of metastatic organs	2.623	0.105	0.754	0.536~1.061
Liver metastasis	0.658	0.417	1.134	0.837~1.538
Bone metastasis	0.252	0.616	1.08	0.8~1.458
Number of CHT cycles	4.124	0.042	0.604	0.371~0.983
Response evaluation after CHT	18.742	< 0.001	1.95	1.441~2.639
TRT	19.297	< 0.001	0.514	0.382~0.692

CHT, chemotherapy; CI, confidence interval; CR, complete response; ES-SCLC, extensive-stage small cell lung cancer; KPS, Karnofsky performance status; PR, partial response; SD, stable disease; SVC, superior vena cava syndrome; TRT, thoracic radiation therapy.

SCLC have been conducted and their conclusions have been controversial. Currently, ES-SCLC is mainly treated with CHT, which can relieve symptoms and prolong survival in most patients but few survive for a long duration.[18,19] Although the objective response rate of CHT can reach 60–80%, median survival is only approximately nine months.[20] Previous literature has reported that more than half of the patients with ES-SCLC experience intrathoracic failure after effective CHT.[21] SCLC is the most sensitive pathological type to RT among all types of lung cancer, and drug-resistant SCLC is not completely resistant to RT, which can maximally eliminate the residual cancer cells resistant to CHT in the primary tumor. Therefore, TRT can theoretically improve lung cancer and thus provide OS benefits.[22] In addition, several studies have reported that TRT is an independent prognostic factor for improving survival in ES-SCLC,[23,24] proving that TRT can reduce the recurrence of thoracic lesions and improve OS. If a patient experiences local or distant recurrence after first-line CHT, TRT is no longer effective.[25] The CREST study, a phase III study with "consolidative" RT (30 Gy/10 fx) after completion of CHT and PCI, showed improved two-year survival, with two-year OS of 13% in the consolidative group.[26] However, this result conflicts with those of other studies. In the RTOG 0937 study, patients were administered either PCI alone or PCI + TRT (45 Gy/15 fx) after achieving CR or PR from initial CHT. The one-year OS was similar between the PCI and PCI + TRT groups (60.1% vs. 50.8%, respectively; $P = 0.21$).[11]

This study retrospectively analyzed the efficacy of TRT in ES-SCLC patients who did not progress after CHT. Among the patients who received RT for primary thoracic lesions, most received RT after PR and CR, while a few received focal RT to strengthen local control after SD. Long-term follow-up results showed that the two and five-year OS rates in the CHT + TRT group were 37.7% and 12.3%, respectively, significantly higher than 11.1% and 3.6%, respectively, in the CHT group in the same period. The survival benefits observed in the TRT group were related to the significant improvement in local control gained by TRT treatment. Zhu *et al.* reported that the incidence of intrathoracic recurrence was 29.6% (21/89) in the chemoradiotherapy group and 64.1% (42/65) in the CHT group, and the difference between the groups was statistically significant ($P < 0.001$).[13] In our study, the LRR rate in the CHT + TRT group significantly reduced to 19.2%, while that in the CHT group was as high as 75.6% ($P = 0.001$). The median survival rates in our sample were higher than the 10 months reported in previous studies. The two-year OS in the CHT + TRT group was significantly better than 26.1% and 13% reported by Zhu *et al.* and the CREST study, respectively.[13,26] The five-year OS in our CHT + TRT group (10.5%) was similar to that reported by Jeremic *et al.* (9.1%) in their phase III randomized study, showing improvement in survival when concurrent CHT and TRT (54 Gy/1.5 Gy BID) are employed

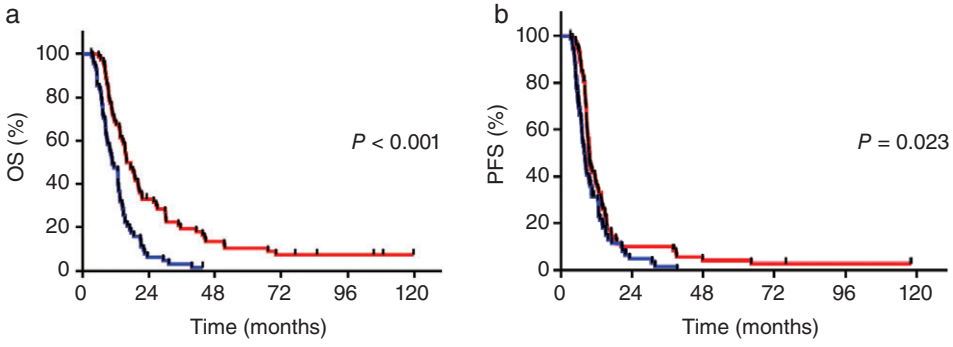

Figure 2 The (**a**) overall survival (OS). (——) Group C and (——) Group c+TRT and (**b**) progression-free survival (PFS) curves between the chemotherapy (CHT) + thoracic radiation therapy (TRT) and CHT groups in propensity score matched samples. (——) Group C and (——) Group C+TRT

after three cycles of induction CHT, and superior to the 7.1% reported by Zhu *et al.*[12,13] In addition, PFS in our CHT + TRT group was obviously improved. We consider that the following factors were responsible: only CR + PR + SD patients after CHT were included in this study and patients with progressive disease were not included; and the average dose of RT in this study was 56 Gy (1.8~2.3 Gy/fraction), higher than the 30~45 Gy/10~15 or 50 Gy/25 fractions administered in previous reports.[10,12,13] Consistent with some previous studies, our results show that TRT can reduce the incidence of local failure of ES-SCLC and prolong OS and PFS.

The adverse reactions of RT were tolerable, and no RT-related death occurred. Although TRT led to increased incidence of adverse reactions, including radiation pneumonia and radiation esophagitis, grade 3 or higher adverse reactions were not significantly increased with the addition of RT. The incidence of radiation esophagitis and radiation pneumonia was also low.

Our results provide further data to develop a promising strategy for this patient population. First, all patients enrolled in this study were administered IMRT, whereas previous CREST studies and most randomized studies included a subset of patients treated using two-dimensional techniques. As a result, our conclusions are based entirely on modern RT techniques. Second, we recruited patients without PCI. Because the impact of PCI on survival of ES-SCLC is controversial, we excluded PCI in this study, showing that patients without PCI who received TRT could also obtain long-term survival benefits. Finally, and perhaps most importantly, the RT dose used in this study was significantly higher than that in the CREST study. However, there are several limitations associated with this study. First, this is a retrospective analysis, which may optimize the use of RT in ES-SCLC: low-burden disease, responding disease, site-specific disease, optimal patient performance, and clinical factors. However, we mimicked randomization through PS-matching, which eliminated potential bias by creating two comparable groups. Second, this was a uni-institutional study. However, this guaranteed the homogeneity of treatment, and the large ES-SCLC sample enhances the reliability of our results.

In conclusion, TRT using IMRT is strongly associated with improved OS and PFS in ES-SCLC patients reaching CR, PR or SD after CHT. A multicenter, randomized phase III clinical trial is warranted to confirm our findings.

Acknowledgment

This study was supported by the National Key Projects of Research and Development of China (2016YFC0904600).

Disclosure

No authors report any conflict of interest.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016; **66**: 7–30.
2 Chen W, Zheng R, Baade PD *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.
3 Karve SJ, Price GL, Davis KL *et al.* Comparison of demographics, treatment patterns, health care utilization, and costs among elderly patients with extensive-stage small cell and metastatic non-small cell lung cancers. *BMC Health Serv Res* 2014; **14**: 555.
4 Ihde DC, Mulshine JL, Kramer BS *et al.* Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small cell lung cancer. *J Clin Oncol* 1994; **12**: 2022–34.
5 Bunn PA Jr, Cohen MH, Ihde DC, Fossieck BE Jr, Matthews MJ, Minna JD. Advances in small cell bronchogenic carcinoma: A commentary. *Cancer Treat Rep* 1977; **61**: 333–42.
6 Beck LK, Kane MA, Bunn PA Jr. Innovative and future approaches to small cell lung cancer treatment. *Semin Oncol* 1988; **15**: 300–14.
7 Fiegl M, Pircher A, Waldthaler C *et al.* Small steps of improvement in small-cell lung cancer (SCLC) within two decades: A comprehensive analysis of 484 patients. *Lung Cancer* 2014; **84**: 168–74.
8 Kalemkerian GP. Running in place: The 20th anniversary of the NCCN small cell lung cancer guidelines panel. *J Natl Compr Canc Netw* 2015; **13**: 704–6.
9 Eckert F, Müllailer AC. SCLC extensive disease-treatment guidance by extent or/and biology of response? *Radiat Oncol* 2008; **3**: 33.
10 Giuliani ME, Atallah S, Sun A *et al.* Clinical outcomes of extensive stage small cell lung carcinoma patients treated with consolidative thoracic radiotherapy. *Clin Lung Cancer* 2011; **12**: 375–9.
11 Gore EM, Hu C, Sun AY *et al.* Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ED SCLC): NRG oncology RTOG 0937. *J Thorac Oncol* 2017; **12**: 1561–70.
12 Jeremic B, Shibamoto Y, Nikolic N *et al.* Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *J Clin Oncol* 1999; **17**: 2092–9.
13 Zhu H, Zhou Z, Wang Y *et al.* Thoracic radiation therapy improves the overall survival of patients with extensive-stage small cell lung cancer with distant metastasis. *Cancer* 2011; **117**: 5423–31.

14 Schick U, Huguet F, Pointreau Y, Pradier O. Radiotherapy for head and neck squamous cell carcinoma: State of the art and future directions. *Cancer Radiother* 2017; **21**: 498–504.
15 Zhang W, Liu X, Xiao Z *et al*. Efficacy of intensity-modulated radiotherapy for resected thoracic esophageal squamous cell carcinoma. *Thorac Cancer* 2015; **6**: 597–604.
16 Simon M, Shochat T, Peled N *et al*. Intensity-modulated radiotherapy is a safe and effective treatment for localized malignant pleural mesothelioma. *Thorac Cancer* 2018; **9**: 1470–5.
17 Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; **31**: 1341–6.
18 Johnson BE, Janne PA. Basic treatment considerations using chemotherapy for patients with small cell lung cancer. *Hematol Oncol Clin North Am* 2004; **18**: 309–22.
19 Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of extensive stage small cell lung carcinoma: Current status and future prospects. *Eur Respir J* 2010; **35**: 202–15.
20 Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: Perceptible progress. *J Clin Oncol* 1999; **17**: 1794–801.
21 Allen J, Jahanzeb M. Extensive-stage small-cell lung cancer: Evolution of systemic therapy and future directions. *Clin Lung Cancer* 2008; **9**: 262–70.
22 Yee D, Butts C, Reiman A. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer. *Radiother Oncol* 2012; **102**: 234–8.
23 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**:2088–92.
24 Puglisi M, Dolly S, Faria A, Myerson JS, Popat S, O'Brien MER. Treatment options for small cell lung cancer - do we have more choice? *Br J Cancer* 2010; **102**: 629–38.
25 Slotman BJ, van Tinteren H. Which patients with extensive stage small-cell lung cancer should and should not receive thoracic radiotherapy? *Transl Lung Cancer Res* 2015; **4**: 292–4.
26 Slotman BJ, van Tinteren H, Praag JO *et al*. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: A phase 3 randomised controlled trial. *Lancet* 2015; **385**: 36–42.

