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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Metastatic location of extensive stage small-cell lung cancer: implications for thoracic radiation

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Abstract

Backgrounds This study was designed to evaluate the role of thoracic radiotherapy (TRT) in a selected patient population with oligometastatic extensive stage small-cell lung cancer (ES-SCLC) without brain or liver involved. The underlying hypothesis was that TRT will improve outcomes in this favorable patient population.

Methods 305 patients were included in an institutional review board (IRB)-approved study, of which 105 received TRT after chemotherapy (ChT) and 200 received ChT alone. The survival outcomes were compared between ChT+TRT group and ChT-alone group in patients with oligometastasis without brain or liver involved and patients with brain/liver/multimetastasis, respectively.

Results The 1-year, 2-year and 5-year overall survival (OS) for all patients were 60.3%, 23.9% and 1.6%, respectively. The addition of TRT significantly improved PFS in total patients than ChT alone (14.5 months vs. 10.1 months, $p=0.006$), but the OS benefit was not significant (17.8 months vs. 16.5 months, $p=0.061$). For patients with oligometastasis (n = 118), TRT offered significant progression free survival (PFS) (16.5 months vs. 9.1 months, $p=0.005$) and OS (19.2 months vs. 15.6 months, $p=0.039$) benefits. However, for patients with brain/liver/multimetastasis, the PFS and OS were not improved with TRT ($p=0.49$, $p=0.811$).

Conclusions TRT provided significant PFS and OS benefits in patients with oligometastatic ES-SCLC without brain or liver involved. The consolidative TRT is a reasonable treatment option for this favorable patient population.

Keywords Extensive stage small-cell lung cancer · Thoracic radiation · Metastatic location · Oligometastasis · Prognosis

Introduction

Small-cell lung cancer (SCLC) accounts for approximately 20% of all lung cancers (Siegel et al. 2017) with aggressive nature. The majority of patients with SCLC have metastatic disease when diagnosed. Extensive stage small-cell lung cancer (ES-SCLC) is defined as tumor beyond the confines of the hemithorax, mediastinum and ipsilateral or contralateral supraclavicular nodes that cannot be treated with a tolerable radiation plan (Stahel 1991; Micke et al. 2002), which accounts for approximately two-thirds of SCLC (Fruh et al. 2013). The primary therapy for ES-SCLC is 4–6 cycles of

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platinum-based chemotherapy followed by prophylactic cranial irradiation (PCI) in selected patients (NCCN guidelines version 2019). Despite high initial response rates to chemotherapy, the prognosis of ES-SCLC is still poor, with a median progression-free survival (PFS) and a median survival of 4–6 months and 8–12 months, respectively (Govindan et al. 2006; Hanna et al. 2006).

Locoregional control of ES-SCLC remains a challenge and approximately 90% of patients progress within chest within the first year of diagnosis (Slotman et al. 2015; Jeremic et al. 1999). The consolidative thoracic radiation (TRT) for ES-SCLC is still controversial, though several randomized trials have shown its benefits in survival and locoregional control (Slotman et al. 2015; Jeremic et al. 1999; Yao et al. 2008). Additional data assessing the potential benefit of TRT in selected patients with ES-SCLC are needed.

Patients with ES-SCLC with multiple metastatic disease represent a diverse population showing a wide range of anticipated outcomes (Cai et al. 2018).The metastatic location and burden are significantly associated with treatment effective and patient prognosis (Ou et al. 2009). Patients with brain or liver metastasis often progress early and show poorer prognosis than those with bone or adrenal metastasis. There should not be one treatment choice for all patients. Therefore, this study was designed to evaluate the role of TRT in a selected patient population with oligometastatic ES-SCLC without brain or liver involved. The underlying hypothesis was that TRT will improve time to progression and overall survival in this favorable patient population.

Materials and methods

Patients and evaluation

Between Jan 2005 and Jan 2016, 305 consecutive ES-SCLC patients without any prior treatment were systemically reviewed in an institutional review board (IRB)-approved study (see Fig. 1). All patients were diagnosed based on clinical features and histopathological results (Yao et al. 2008). Initial staging assessment was based on physical examination, and imaging with thoracic and abdominal computed tomography (CT), brain magnetic resonance imaging (MRI), and bone radionuclide imaging (ECT) or positron emission tomography (PET)/CT for all patients. The ES-SCLC was defined upon the criteria included in AJCC (7th Edition) stage IV (T any, N any, M1a/b) or T3-4 with multiple lung nodules that were too extensive or have tumor volume that was too large to be encompassed in a tolerable radiation plan (Kalemkerian 2015).

Based on previous literatures (Ashworth et al. 2013; Li-Ming et al. 2017), the concept of oligometastases was defined as: (1) only one organ metastasis or distant metastatic lymph nodes could be covered by a safe radiotherapy portal; (2) continuous vertebral bone metastases could be included in a tolerable radiotherapy field. Since patients with brain or liver metastases often progressed early and had poor prognosis, any brain or liver metastasis was excluded from this favorable group in our study.

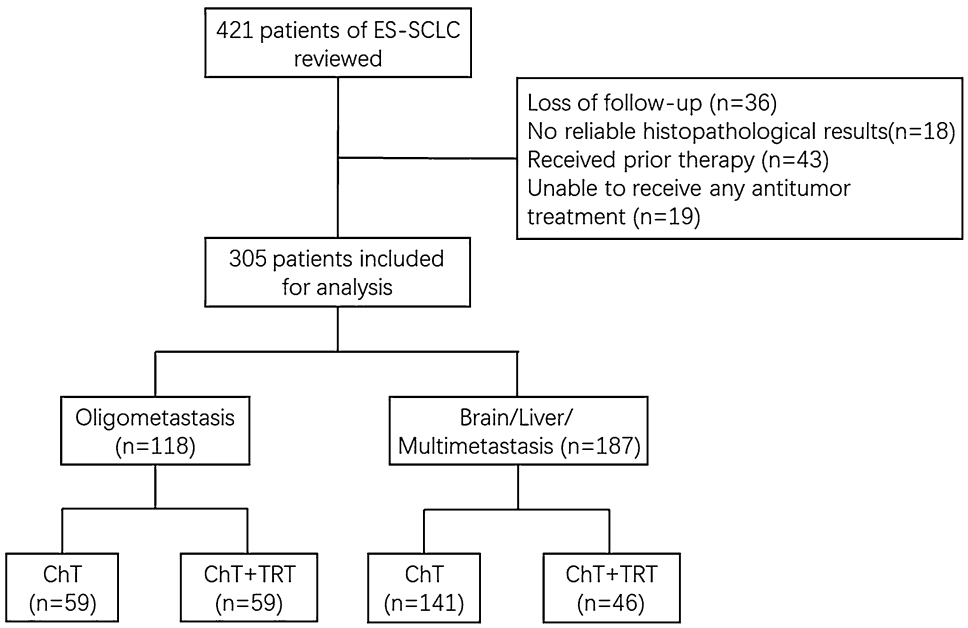


Fig. 1 The flowchart of patient selection

Treatment strategy

All ES-SCLC patients received chemotherapy (ChT) with or without TRT. All patients received either EP (cisplatin, 30 mg/m^2 from days 1 to 3; etoposide, 100 mg from days 1 to 5), CE (carboplatin, 400 mg or 500 mg for day 1; etoposide, 100 mg from days 1 to 5) or platinum-based chemotherapy as the first-line treatment. A median of six cycles of ChT was given to all patients.

Overall, 105 patients received TRT following ChT and 200 patients received ChT alone without TRT. Thirty patients (28.6%) received TRT performed with a conventional [anteroposterior/posteroanterior (AP–PA) fields] technique, and 75 patients (71.4%) received TRT with 3-dimensional conformal radiotherapy (3D-CRT) technique. For conventional RT, the target volume included all gross lesions, ipsilateral hilum, and entire mediastinum with a 2 cm margin. Supraclavicular fossa was not included if no supraclavicular nodes were involved. Forty grays (Gy) were delivered using AP–PA fields and then oblique fields were used to spare the spinal cord. For 3D-CRT, the gross target volume (GTV) included the primary tumor and positive regional nodes. The clinical target volume (CTV) was expanded from GTV with a 0.5–0.8 cm margin and included all the positive regional nodal regions at diagnosis. The planning target volume (PTV) was expanded from CTV with a 0.5–1 cm margin. Radiation was delivered with 6 MV photons by linear accelerators. The radiation was given individualized with conventional RT with 40–60 Gy in 20–30 daily fractions (83 patients) or hypofractionated RT with 30–45 Gy in 10–15 fractions (22 patients). The median radiation dose was 60 Gy. There were 65 patients with brain metastasis received whole brain radiation therapy (WBRT) with a median dose of 30 Gy. Thirty-four patients received PCI with a median dose of 25 Gy.

Statistical analysis

Tumor response to treatment was assessed based on RECIST 1.0 criteria. Imaging examinations were performed every other cycle during ChT and every 4–8 weeks post-treatment until tumor progression. Adverse events were evaluated using the NCI CTCAE v4.0.

OS and PFS were calculated from the first date of treatment to the date of event or the date of last follow-up, if no event. The event was death due to any cause for OS and as first occurrence of recurrence of pre-existing lesions or develop of new lesions for PFS. The log-rank test was used to compare survival curves between groups. The Chi square method was used to compare the categorical data. Univariate survival analysis was estimated by Kaplan–Meier method to determine associations between survival and clinical features, including age, gender, smoking index, weight loss, Karnofsky performance status (KPS) score, metastatic location and number, cycles of ChT, and received TRT or not. All these above factors were included in a multivariate model and a Cox proportional hazards algorithm with a backward-forward, stepwise method was used to determine the significant variables. All statistical analysis was conducted using SPSS® version 24.0 (IBM, Chicago, IL, USA). A two-tailed p value less than 0.05 was assumed as statistical significance.

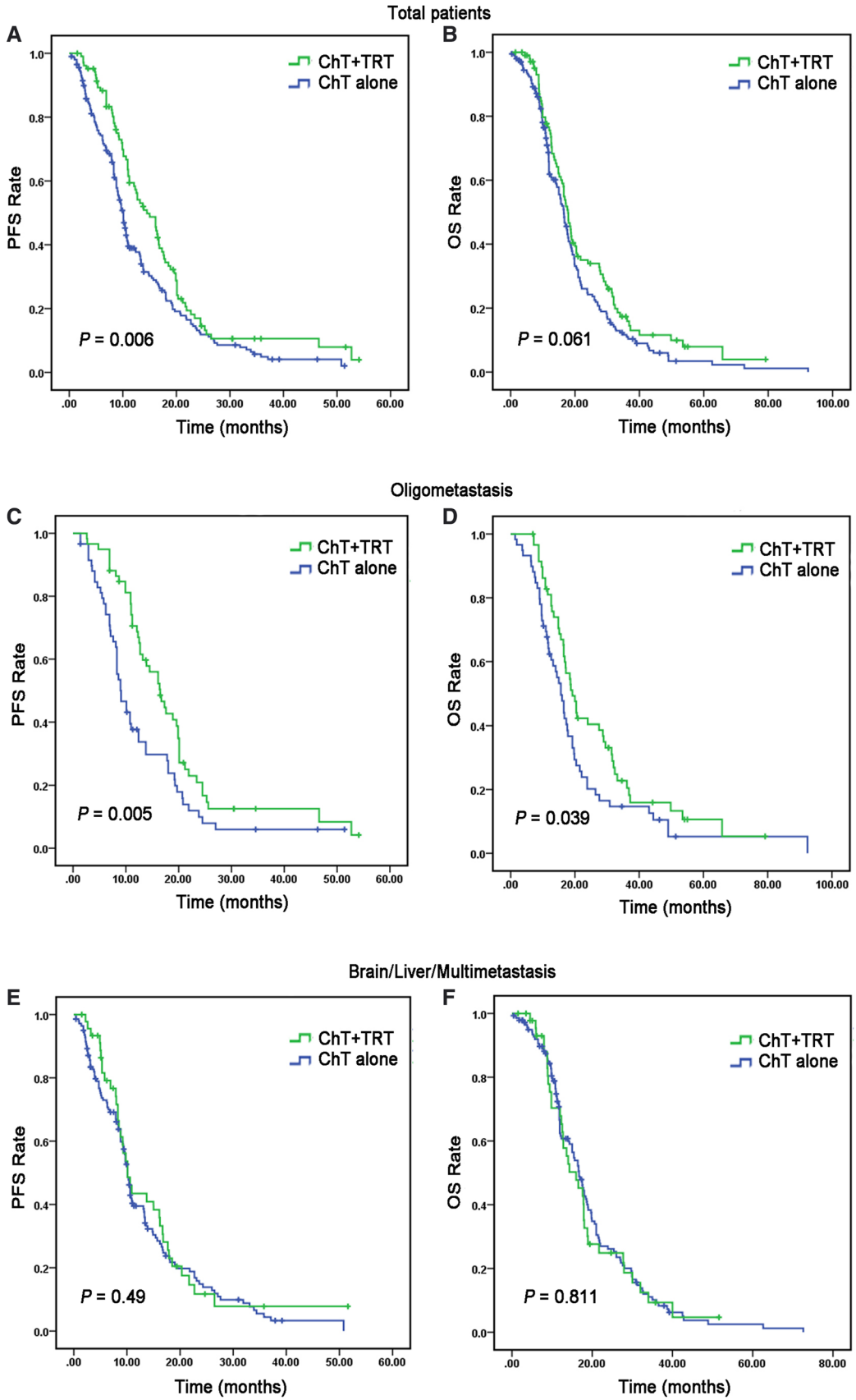
Results

Patient characteristics

The baseline characteristics of total 305 patients are shown in Table 1. In summary, 105 patients received ChT combined with TRT and 200 received ChT alone. The median age was 67 years with 59% of patients above 70 years. 78.3% of the patients were male and most patients had a

Table 1 Characteristics in patients with ChT + TRT vs. ChT alone

Characteristics	ChT + TRT ($n = 105$)	ChT ($n = 200$)	p value
Age, ≥ 70 years	61	119	0.813
Gender, male	82	157	0.935
KPS score, ≥ 80	80	140	0.252
Smoking index, ≥ 500	59	98	0.233
Weight loss, ≥ 5 kg	14	46	0.044
Location of metastatic organs			0.036
Brain	13	58	
Liver	25	68	
Bone	34	70	
Distant LN	17	19	
Pleural effusion	10	31	
Adrenal	8	20	
Others	9	39	
No. of metastatic organs			0.008
0–1	71	98	
2	26	76	
≥ 3	8	26	
No. of ChT cycles			0.155
1–3	23	59	
≥ 4	82	141	
Response to ChT			0.001
CR	8	2	
PR	94	179	
SD/PD	3	19	
PCI			0.001
Yes	20	14	
No	85	186	


Total patients
A
PFS Rate
ChT+TRT
ChT alone
P = 0.006
Time (months)
B
OS Rate
ChT+TRT
ChT alone
P = 0.061
Time (months)
Oligometastasis
C
PFS Rate
ChT+TRT
ChT alone
P = 0.005
Time (months)
D
OS Rate
ChT+TRT
ChT alone
P = 0.039
Time (months)
Brain/Liver/Multimetastasis
E
PFS Rate
ChT+TRT
ChT alone
P = 0.49
Time (months)
F
OS Rate
ChT+TRT
ChT alone
P = 0.811
Time (months)

◂**Fig. 2** Kaplan–Meier analysis of progression-free survival (PFS) and overall survival (OS) between ChT + TRT and ChT alone in total patients (**a** and **b**), patients with oligometastasis (**c** and **d**) and patients with brain/liver/multimetastasis (**e** and **f**)

good performance status with KPS score ≥ 80. A majority of patients had a heavy smoking history with smoking index ≥ 500. Fourteen (13.3%) patients had a weight loss more than 5 kg in ChT+TRT group, which was less than that (43.8%) in ChT group. Brain, liver, bone, distant LN, pleural effusion, and adrenal metastases were present in 23.2%, 30.5%, 34.1%, 11.8%, and 13.4% of patients, respectively. Patients with metastasis were limited to less than one organ in 55.4% of cases and 11.1% of patients had more than two organs involved with metastasis. 73.1% of patients received more than four cycles of ChT. Following the initial ChT, the CR, PR and SD/PD rates were 3.2%, 89.5% and 7.2%, respectively. For patients without brain metastasis, 34 patients received PCI.

Survival

In total cohort, at the median follow-up of 37.5 months, the median PFS and OS were 10.5 months and 16.7 months. The Kaplan–Meier survival for all patients was 60.3%, 23.9% and 1.6% for 1-year, 2-year and 5-year OS, respectively. The addition of TRT significantly improved PFS in total patients than ChT alone (14.5 months vs. 10.1 months, $p = 0.006$). Also, patients that received ChT+TRT showed a trend toward of better OS than those of ChT alone, but the statistical analysis was not significant (17.8 months vs. 16.5 months, $p = 0.061$).

To analyze the role of TRT in patients with oligometastasis without brain and liver involved, patients were divided into oligometastasis ($n = 118$) and brain/liver/multimetastasis group ($n = 187$) (Fig. 1). To reduce bias, the survival between patients with oligometastasis and patients with brain/liver/multimetastasis was analyzed first. Patients with oligometastasis showed significantly better OS than patients with brain/liver/multimetastasis (17.2 ms vs. 16.6 months, $p = 0.042$). Patients with oligometastasis also showed a trend toward better PFS than those of brain/liver/multimetastasis, but the statistical analysis was not significant (12.5 months vs. 10.1 months, $p = 0.067$).

For patients with oligometastasis, the median PFS was 16.5 months in ChT+TRT group ($n = 59$) and 9.1 months in ChT group ($n = 59$), the median OS was 19.2 months and 15.6 months, respectively. The addition of TRT significantly improved PFS and OS than ChT alone ($p = 0.005$, $p = 0.039$). However, for patients with brain/liver/multimetastasis, 46 patients received TRT. The PFS (10.1 months vs. 10.1 months, $p = 0.49$) and OS (16.0 months vs. 16.7 months, $p = 0.811$) were not improved with TRT (Fig. 2). It indicated that the survival benefit brought by TRT in the whole population cohort was mainly contributed by the selected patient population with oligometastasis without brain and liver involved.

Based on our univariate analysis, weight loss ≥ 5 kg, brain/liver/multimetastasis, ChT cycles < 4 and no PCI were adverse prognostic factors for OS (Table 2). In multivariate analysis, only No. of ChT cycles was found as an independent prognostic factor. KPS score ≥ 80 and receiving PCI showed a trend toward improved OS, but the statistical analysis was not significant.

In addition, RT to the oligometastatic site is also important. We assessed the prognostic effect of tumor sites received RT in patients with oligometastasis. Twenty-eight patients did not receive any RT, 48 patients received RT to single tumor site and 42 patients received RT to more than two tumor sites. We found that increased tumor sites received RT was significantly associated with a PFS benefit (HR 0.74, 95% CI 0.56–0.96, $p = 0.02$). However, it was not associated with OS (HR 0.82, 95% CI 0.64–1.05, $p = 0.12$). It indicated that for patients with oligometastatic disease, increased RT sites may improve PFS, but not OS.

Toxicities

Forty-seven patients (44.8%) in ChT+TRT group and 79 (39.5%) patients in ChT group developed grade ≥ 3 hematologic toxicities (Table 3). Leucopenia was most common hematologic toxicity as 38.1% in ChT+TRT group and 29% in ChT group. The addition of TRT did not increase hematologic or non-hematologic toxicity compared to ChT alone. For patients received ChT+TRT, 29 (27.6%) patients developed pneumonitis and 15 (14.3%) developed esophagitis. Among those patients, two experienced grade four pneumonitis and one experienced grade four esophagitis. No grade five radiation-related toxicity was found. It indicated that addition of TRT to ChT was well tolerated in patients with ES-SCLC.

Discussion

In this study, we confirmed that TRT provided significant PFS and OS benefits in patients with oligometastatic ES-SCLC without brain or liver involved. However, TRT failed to improve outcomes of the patients with brain/liver/multimetastasis. The survival benefit brought by TRT in the whole population cohort was mainly contributed by the selected patient population with oligometastasis without brain and liver involved. The consolidative TRT is a reasonable treatment option for this favorable patient population. To our knowledge, this is the first study to show the metastatic locations as implications for TRT in ES-SCLC.

Table 2 Univariate and multivariate analysis of prognosis for overall survival

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.005	0.783–1.292	0.966	1.009	0.781–1.303	0.948
Gender	0.793	0.586–1.074	0.134	0.760	0.547–1.057	0.103
KPS score	0.789	0.600–1.037	0.090	0.762	0.578–1.007	0.056
Smoking index	1.018	0.796–1.303	0.884	1.024	0.789–1.330	0.857
Weight loss	1.386	1.002–1.879	0.036	1.309	0.954–1.795	0.095
Metastasis	1.299	1.007–1.675	0.044	1.224	0.929–1.667	0.143
Brain/liver/multimetastasis						
Oligometastasis						
TRT	0.780	0.601–1.013	0.063	1.012	0.753–1.359	0.938
No. of ChT cycles	0.451	0.341–0.596	< 0.001	0.429	0.320–0.547	0.001
Response to ChT	0.904	0.624–1.310	0.594	1.155	0.779–1.713	0.473
PCI	0.575	0.382–0.864	0.008	0.654	0.420–1.018	0.060

Table 3 Incidence of toxic effects in ChT + TRT vs. ChT alone group

Toxicities	No. of patients (%)		*p* value
	ChT + TRT ($n = 105$)	ChT ($n = 200$)	
Hematologic toxicity grade ≥ 3	47 (44.8)	79 (39.5)	0.375
Leucopenia	40 (38.1)	58 (29.0)	0.106
Anemia	6 (5.7)	8 (4.0)	0.497
Thrombocytopenia	8 (7.6)	14 (7.0)	0.843
Non-hematologic toxicity	7 (6.7)	13 (6.5)	0.955
Radiation-related toxicity			
Pneumonitis	29 (27.6)		
Esophagitis	15 (14.3)		

The metastatic locations are strongly associated with treatment effective and patient prognosis since brain and liver metastasis often progress early than bone and adrenal. There should not be one treatment choice for all patients. Based on our results, the metastatic location and number of ES-SCLC should be considered as implications for TRT.

Previous studies have discussed the benefit of the addition of consolidative TRT in the management of ES-SCLC, but the results were controversial (Slotman et al. 2015; Jeremic et al. 1999; Rathod et al. 2019; Gore et al. 2017). Jeremic et al. (1999) conducted the first randomized clinical trial (RCT) in 1999 addressing the role of TRT in ES-SCLC. They showed significant PFS and OS advantages in patients with ES-SCLC with TRT. Patients included were all having good PS and good response to initial ChT (a CR/PR at local levels and CR at distant level). Approximately 90% of patients had 1–2 metastasis. As a guide for future studies, the metastatic number was independently associated with prognosis. It showed that patients with more than two metastases had significantly worse outcomes than those with only one metastasis. The CREST is the second and largest RCT assessing the role of TRT in ES-SCLC (Slotman et al. 2015) with total 495 patients included. The 1-year survival as the primary end point was not significantly improved with TRT (33% vs. 28%, $p = 0.066$). The 2-year OS (13% vs. 3%, $p = 0.004$) and 6-month PFS (24% vs. 7%) were improved with TRT. The authors concluded that TRT should be considered for patients with good response to ChT. To be noted, no survival benefit for TRT was observed in patients without residual intrathoracic disease after ChT in CREST study, suggesting that the presence of residual intrathoracic disease was a factor that needed be considered in patient selection. A third phase II RCT, RTOG 0937 (Gore et al. 2017), included 97 ES-SCLC patients randomized to TRT + PCI vs. PCI alone after 4-6 cycles of ChT. This study was closed prematurely as the study crossed the futility boundary for OS at planned interim analysis. This study failed to show any significant difference in 1-year OS. The time to progression favored TRT + PCI ($p = 0.01$). In a recent meta-analysis (Rathod et al. 2019), pooled analysis showed that TRT offered significant improvement in PFS ($p < 0.0001$) and reduction in thoracic failures, but not in OS ($p = 0.36$). However, none of those above studies taken the location of metastasis into account. Since patients with brain or liver metastasis often progress early and show worse prognosis

than those with bone, adrenal or distant lymph nodes metastasis. Patients with oligometastasis without brain or liver involved, this favorable population group, are most likely to benefit from TRT. Our results showed that in total patients the benefit for PFS was significant but the benefit for OS was not. In subgroup analysis, TRT significantly improved the PFS and OS in patients with oligometastasis without brain or liver involved. However, no benefit was seen in patients with brain/liver/multimetastasis. It indicated that the survival benefit from TRT in the whole population cohort was mainly contributed by the patients with oligometastasis without brain and liver involved. TRT is strongly suggested for this favorable patient population.

Based on previous studies, there was a correlation between radiation dose and the treatment efficacy in limited stage (LS-SCLC) (Turrisi et al. 1999). Considering the aggressive nature of SCLC and the potential toxicity of TRT, the optimal dose and fractionation of TRT for ES-SCLC is still unknown (Palma et al. 2016). Accelerated hyperfractionated RT (54 Gy/36f, 1.5 Gy bid) and concurrent low-dose daily ChT followed by PCI were performed in the trail conducted by Jeremic et al. (1999). The acute esophageal toxicity was increased with TRT, as 27% of patients having grade three or four esophagitis and 5% having bronchopulmonary toxicity. In the CREST, 30 Gy in 10 fractions was used for TRT. The toxicity was lower as grade three esophagitis observed in only 1.6% of patients with TRT and no grade four or greater toxicity observed. In our study, 20.9% of patients received hypofraction TRT with a median dose of 30 Gy in ten fraction and 79.1% of patients received conventional RT with a median dose of 60 Gy. The toxicity was acceptable as 1.9% for grade four pneumonitis and 0.9% for grade four esophagitis. No greater radiation related toxicity was seen.

Considering the short tumor potential doubling time of SCLC and the modest survival and tumor control benefit, continuing researches are still working on the optimal TRT dose and fractionation for SCLC. A recent randomized phase III trial (CONVERT) (Faivre-Finn et al. 2017), compared hyperfracionated TRT with 45 Gy/30F/19D to conventional TRT with 66 Gy/33F/45D in LS-SCLC. No statistical difference was found in survival between two arms. Also, there was no difference in grade 3/4 acute oesophagitis and pneumonitis. Conventional RT did not result in a superior survival or worse toxicity than hyperfractionated RT. This study supported the use of either regimen for standard of care treatment of LS-SCLC. Another similar ongoing RTOG 0538 trial (Clinical Trials 2016), is comparing 45 Gy/1.5 Gy Bid to 70 Gy/2 Gy in LS-SCLC. They tried to figure out whether dose escalated RT in single daily fractions to 70 Gy offer superior clinical efficacy over 45 Gy bid. The previous RCTs all assessed dose for LS-SCLC, but not for ES-SCLC, the optimal dose and fractionation of TRT for ES-SCLC remains unclear. Well assigned RCTs are needed in the future.

The median PFS and OS were 10.5 months and 16.7 months. The Kaplan–Meier survival for all patients were 60.3%, 23.9% and 1.6% for 1-year, 2-year and 5-year OS, respectively. Our results were better than those of two pivotal clinical trials. In the study conducted by Jeremic et al. the MST of patients was 9 months. The yearly survival rates at 1, 2, 3, 4, and 5 years were 38%, 19%, 9.7%, 4.9%, and 3.4%, respectively. In CREST study, the MST was 8 months. One-year and 2-year OS were 33% in TRT+ChT group and 28% in ChT alone group, 13% in TRT + ChT group and 3% in ChT alone group, respectively. However, to be noted, the patients were collected between January 1988 and June 1993 in Jeremic study. Radiotherapy treatment planning was conducted using 2D imaging, with treatment volumes including the gross chest disease and ipsilateral hilum with a 2 cm margin, the entire mediastinum and the bilateral supraclavicular fossae. Radiation toxicity was increased and potentially affected prognosis. Similar situations were seen in patients in CREST study, which enrolled patients from 2009 to 2012. In our study, though 305 patients across 11 years collected, 80% of patients were collected from recent 5 years. 71.4% of patients received TRT with 3-dimensional conformal radiotherapy (3D-CRT) technique and 73.1% of patients received more than four cycles of standard chemotherapy. It has been reported that 3D-CRT technique and ≥ 4 cycles of chemotherapy were associated with improved prognosis. Besides, the latest IMpower 133, a global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated efficacy and safety of adding atezolizumab or placebo to 1L carboplatin and etoposide in ES-SCLC. Median OS was 12.3 months in the atezolizumab group and 10.3 months in the placebo group. The survival outcomes were also worse than those in our study. To be noted, in the study of IMpower 133, no patients received thoracic RT and PCI. It has been reported that radiotherapy could offer benefit in PFS and OS. In our study, 34% of patients received TRT and 32% of patients received WBRT or PCI. It may contributed to our favorable survival. As reported in two recent studies, the 2-year and 5-year OS were 18.8–34.7% and 12.3%, respectively, which were similar and even higher than our results. Both of these 2 studies enrolled Asian patients. The impact of race on prognosis needs further studied.

There are still some limitations in our study. First, as a retrospective study, inhomogeneity of treatment options was unavoidable. It is possible that the number of ChT cycles and receiving PCI or not influenced the outcomes of patients with TRT or not. Second, the dose and regimen of TRT was diverse in our study, the effect of radiation dose to outcomes was not analyzed. Third, though relatively large patient population was included in our retrospective study compared to previous studies of ES-SCLC, additional patients were still

needed to better assess the role of TRT in selected patients with oligometastasis without brain or liver involved.

In conclusion, we confirmed that TRT provided significant PFS and OS benefits in patients with oligometastatic ES-SCLC without brain or liver involved. TRT improved survival outcomes in this favorable patient population. However, TRT failed to improve outcomes of the patients with brain/liver/multimetastasis. Large, prospective studies are needed to validate our findings. Besides, other factors should be considered when discussing TRT with patients, such as the schemes and volumes or RT and the toxicities. The consolidative TRT is a reasonable treatment option for ES-SCLC, though future studies are still needed.

Author contribution FFT and JMY designed the study; HQZ, LD, XW, DYW collected and analyzed data; HQZ and FFT drafted the article.

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Compliance with ethical standards

Conflict of interest The authors have no disclosures.

Ethical approval The study has been reviewed and approved by the Ethics Committee of Shandong Cancer Hospital and Institute, China. Either a signed informed consent or authorisation from the National Supervisory for Welfare and Health was obtained for all patients. This study has been conducted according to the Declaration of Helsinki.

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