Clinical Outcomes of Extensive Stage Small Cell Lung Cancer Patients Treated With Thoracic Radiotherapy at different timing and fractionation

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Research

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Abstract

Objective: The purpose of this study was to assess whether combined thoracic radiotherapy (TRT) on the basis of chemotherapy (CHT) showed promising anti-tumor activity in extensive-stage small cell lung cancer (ES-SCLC), then to explore practice patterns for radiation time and dose/ fractionation and to identify prognostic factors for patients who would benefit from CHT/TRT.

Methods: A total of 492 ES-SCLC patients were included from January 2010 to March 2019, of which 244 patients experienced CHT/TRT. Propensity score matching (PSM) was performed to minimize bias between the CHT/TRT and CHT-alone groups. Patients in CHT/TRT group were categorized into four groups based on the number of induction CHT cycles. For effective dose fractionation calculation, we introduced the time-adjusted biological effective dose(tBED). Categorical variables were analyzed with Chi-square tests and Fisher's exact tests. Kaplan-Meier curves were performed to estimate survival rates using R-project. Multivariate prognostic analysis was performed with Cox proportional hazard models.

Results: Patients who received CHT/TRT were associated with improved OS (18.2 vs 10.8 months), PFS (9.0 vs 6.0 months) and LRFS (12.0 vs 6.0 months) before matching, with similar results after matching. In the CHT/TRT group, the median LRFS times for groups based on radiation time were 12.7, 12.0, 12.7, and 9.0 months, respectively. Earlier TRT had a tendency to prolong PFS (median 10.6 vs 9.8 vs 9.1 vs 7.7 months, respectively, $p = 0.109$), as was not seen in OS (median 17.6 vs 19.5 vs 17.2 vs 19.1 months, respectively, $p = 0.722$). To note, patients performed TRT within 6 cycles CHT had better LRFS ($p<0.001$). For radiation dose, patients in the high-dose group (tBED>50Gy) had relatively shorter OS (median 25.9 vs 22.9, $p = 0.048$) and PFS (median 12.1 vs 11.2, $p=0.004$) in patients with complete response and partial response (CR and PR) to systemic therapy, but the above-mentioned results were not drawn after the exclusion of patients receiving hyperfractionated radiotherapy (all $p>0.05$).

Conclusion: CHT/TRT could improve survival for ES-SCLC patients. TRT performed within 6 cycles CHT and receiving hyperfractionated 45Gy in 30 fractions may be a feasible treatment scheme for ES-SCLC patients.

Introduction

Small cell lung cancer (SCLC) accounts for approximately 13-15% of primary lung cancers, which is characterized by its highly aggressive, early dissemination and highly response to treatment, with almost two-thirds of SCLC cases present with extensive stage (ES) at first clinical diagnosis [1,2]. 4-6 cycles of platinum-based chemotherapy (CHT) alone is the historic standard treatment for ES-SCLC, with thoracic radiation (TRT) and prophylactic cranial irradiation (PCI) could be considered for patients who achieved response despite controversy[3,4].Recently, the FDA has approved immunotherapy (IO) as a front-line treatment option in combination with CHT given the results of IMpower133 and CASPIAN trials [5,6]. Moreover, the use of PCI may further erode if IO could prove to reduce the incidence of brain metastasis in ES-SCLC[7].

Prior studies have demonstrated that TRT played a vital role in terms of regional control and an improved survival for ES-SCLC. A previous study published by Jeremic et al. was the first to point out the importance of TRT in ES-SCLC but with less attention[8].The CREST trial, despite the primary endpoint at 1-year did not meet, illustrated a 10% 2-year improvement for patients who responded to CHT with subsequent TRT [9]. Subgroup analysis of the CREST concluded that TRT should not be offered to those patients with complete intrathoracic response [10]. In other separate secondary analysis, survival was improved in patients with 2 or fewer metastases and the presence of liver and/or bone metastases was important factors in identifying beneficiaries [11,12]. Additionally, the RTOG 0937 study, which delayed progression but regrettably failed to improve 1-year OS, observed no difference among patients who undergone TRT early or late [13]. Several retrospective analyses also suggested that TRT in combination with CHT was associated with long-term survival [14-18].It has been advocated for certain ES-SCLC patients both in the 2020 NCCN guidelines [19]and in the ASTRO 2020 guidelines [20].Nevertheless, there is no clear consensus on the application of TRT in ES-SCLC to date. Especially in the absence of TRT, IO with atezolizumab or durvalumab incorporation with CHT has shown increased survival in first-line treatment, making the role of TRT even more unclear. Hence, we held on this retrospective real-world study. The aims of this study were as follows: first, to characterize whether TRT added to CHT (CHT/TRT) showed promising anti-tumor activity in ES-SCLC; second, to explore the appropriate TRT time and optimal radiation dose/fraction on survival, and third to identify prognostic factors influencing the clinical outcome for ES-SCLC patients in order to distinguish who would benefit from CHT/TRT

Materials And Methods

Patients and study design

We retrospectively registered ES-SCLC patients who were treated in Shandong Cancer Hospital between January 2010 and March 2019. Clinical information was collected from the electronic medical records, including demographic details, Eastern Cooperative Oncology Group (ECOG) PS score, metastatic sites, treatment information, hematological and nonhematological toxicities. Eligible patients had to satisfy the following criteria: (1) histologically or cytologically confirmed SCLC and in extensive stage via imaging at the time of initial diagnosis. (2) at least two cycles of CHT regardless of TRT receipt. (3) ECOG PS score was 0-2. Exclusion criteria were as follows: (1) patients with salvage radiotherapy due to recurrence; (2) a history of malignancy in other sites that affect survival; (3) incomplete clinical data or loss to follow-up. Our study was approved by the Ethics Review Committee of the Shandong Cancer Hospital.

Treatment strategy

The CHT regimens were platinum combined with etoposide. All patients were administered with either 3D conformal radiotherapy (3D-CRT) or intensity-modulated radiation (IMRT). The gross tumor volume (GTV) encompassed the primary tumor and the positive lymph nodes. The clinical target volume (CTV) was defined as the GTV with a 5mm margin, and the planning target volume (PTV) was expanded from the CTV with a 5-8mm margin. If the tumor lesion was too large to carry out a tolerable radiotherapy plan, 5-

10mm margin could be directly expanded on the basis of GTV to form the planning gross target volume (PGTV). Considering different radiation fractionations and time efficiencies, we employed the time-adjusted biological effective dose (tBED) formula [21]: tBED = (nd) { 1 + [d/(α/β)]} – [0.693t/(αTpot)],where n is the number of fractions, d represents the dose per fraction, α/β = 10, α = 0.3Gy, t is the number of radiotherapy days, and Tpot is the potential doubling time (5.6 days) [22,23].

Assessment of Response and Toxicity

Imaging examinations were required almost every 2 cycles of CHT, before or after TRT, or as worsening clinical manifestations. Tumor response to first-line treatment was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Efficacy was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [24]. Toxic effects were assessed according to Common Terminology Criteria for Adverse Events (version 4.0) [25].

Statistical analysis

Statistical analysis was presented via SPSS version 24.0 software (IBM Corp). 1:1 propensity score matching (PSM) was performed to ensure the well-balanced characteristics between the CHT/TRT and CHT-alone groups. Propensity score was calculated by a multivariable logistic regression model, with TRT as the dependent variable and age, gender, ECOG PS, smoking index, metastasis organs, number of metastasis, brain metastasis, liver metastasis, bone metastasis, hydrothorax, weight loss, PCI were taken as the covariates. The Chi-square and Fisher's exact tests were employed to compare baseline characteristics for different groups. Survival information, including OS, PFS and LRFS (local recurrence-free survival), was collected until October 31, 2019. Kaplan-Meier curves including numbers at risk were plotted using R-project. Univariable and multivariate Cox regression analyses were used to identify the potential predictors of ES-SCLC patients. All statistical analyses were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Patient characteristics

After rigorous reviews, 492 patients met the eligibility criteria for final analysis, of which 244 patients experienced CHT/TRT and 248 undergone CHT-alone. The clinical characteristics of the study cohort between these two groups were comparable after PSM (Table S1).

Relative to the CHT/TRT group, the median follow-up duration was 36 months. There were 196 patients receiving conventional fractionationated radiotherapy with 40-66Gy at 1.8-2Gy/fraction daily, 40 patients receiving hyperfractionated radiotherapy with 45Gy at 1.5Gy/fraction twice per day and 8 patients receiving hypofractionationated radiotherapy group with 30-51Gy at 3Gy/fraction daily. PCI was given as 25Gy in ten fractions. A total of 98 patients had bone metastases, of whom 31 accepted bisphosphonates and 28 received palliative radiotherapy to relieve pain. 153 patients had brain

metastases, with nearly 80% (121 cases) undergone either whole brain irradiation (WBRT) or stereotactic radiotherapy (SRT).What was worth mentioning was that 33 patients received IO or targeted therapy after recurrence.

Patients were apportioned to four groups regarding the number of induction CHT cycles prior to TRT. Group A received TRT before or at the second cycle of CHT (≤2 cycles, n= 41);Group B received TRT at the third cycle to the fourth cycle of CHT (3-4cycles, n=78);Group C received TRT at the fifth cycle to the sixth cycle of CHT (5-6cycles, n= 92); and Group D received TRT after the sixth cycle of CHT (>6 cycles, n=33). There were no differences in the distribution of most variables other than bone metastasis among the four groups. In order to determine if escalated doses to TRT had any significant impact on the outcomes, patients were classified into low-dose (tBED≤50Gy,n=159) and high-dose (tBED>50Gy,n=85) according to two previous studies[26,27]. Patient characteristics were presented in Table 1 and Table 2.

Survival outcome

Patients who received CHT/TRT were associated with improved OS (18.2 vs 10.8 months), PFS (9.0 vs 6.0 months) and LRFS (12.0 vs 6.0 months) compared with CHT-alone group before matching (all $p < 0.001$, Figure 1).The survival benefit was also remained significant in OS (17.2 vs 11.5 months), PFS (9.0 vs 6.0 months) and LRFS (11.0 vs 6.0 months) after matching (all $p < 0.001$, Figure 2). On subgroup analysis of patients without brain metastasis, significantly increased was witnessed in patients who received PCI compared with non-PCI, the same as TRT+PCI vs non-(TRT+PCI) (all $p < 0.001$, Figure 3 and Figure 4).

We then attempted to explore appropriate TRT time and optimal dose/fraction in the population who had CHT/TRT. With regard to radiation time, the median LRFS times (mLRFS) based on radiation time were 12.7, 12.0, 12.7, and 9.0 months, respectively. The median PFS times (mPFS) were 10.6, 9.8, 9.1, and 7.7 months, respectively. And the median OS times (mOS) for groups were 17.6, 19.5, 17.2, and 19.1 months, respectively. The mLRFS, mPFS and mOS in terms of radiation time and radiation dose were presented in Table 3. Patients receiving TRT within 6 cycles CHT had better mLRFS than those ones who received TRT for more than 6 cycles CHT ($p < 0.001$). Kaplan-Meier survival curves concerning radiation time were shown in Figure 5. In view of radiation dose, patients in the high-dose group had better OS, PFS and LRFS, but the differences were non-statistically significant (all $p >0.05$). We further analyzed those patients with CR and PR to systemic therapy, with the ~~in~~ low-dose group had better OS (median 25.9 vs 22.9, $p = 0.048$) and PFS (median 12.1 vs 11.2, $p =0.004$) (Figure 6). Unfortunately, there were no longer any differences when patients receiving hyperfractionated radiotherapy were excluded (all $p>0.05$). Specifically, patients receiving 45Gy at 1.5Gy/fraction twice per day presented better OS (median 22.2 vs 18.2, $p = 0.037$) and PFS (median 11.3 vs 9.3, $p = 0.049$) than those undergoing 60Gy radiotherapy at 2Gy/fraction daily (Figure 7). Besides, patients in hypofractionationated radiotherapy group had similar outcomes compared with patients in conventional fractionationated radiotherapy (all $p>0.05$).

Response to treatment and treatment failure

CHT/TRT did not improve the objective remission rate (ORR) compared with CHT-alone (66.0% vs 60.5%, p = 0.206). The ORRs according to radiation time and radiation dose were 75.6% vs 67.9% vs 64.1% vs 45.5% (p = 0.273), 82.4% vs 57.2% (p <0.001), respectively. For failure patterns, 29 (11.9%) patients had progression in the thoracic area, and 82 (33.6%) cases had progression at distant sites and 79 (32.4%) patients developed regional and distant recurrence in the CHT/TRT group, whereas, in the CHT-alone group, intrathoracic progression was observed in 42 (16.9%) patients, distant relapse was observed in 24 (9.7%) cases, and both occurred in 145 (58.5%) patients. The local relapse rate was significantly decreased with the receipt of TRT (44.3% vs 75.4%; p < 0.001); however, the distant control rate was disappointing (66.0% vs 68.2%, p=0.610).More detailed, the recurrence among these four groups were 68.3% ,71.8%,80.4%,97%, respectively (p < 0.001). No significant difference was found between the high-dose group and the low-dose group (76.7% vs 80.0%,p=0.544).

The prognostic factors influencing survival

The following factors were identified as significant prognostic factors for OS in univariate analysis: ECOG PS score (p = 0.013), Smoking index (p = 0.021), Number of metastasis (p = 0.048), Metastasis organs (p = 0.003), liver metastasis (p < 0.001), bone metastases (p = 0.012), Weight loss(p = 0.011), PCI (p = 0.010).Next, multivariate analysis revealed that excellent PS~~ good PS score~~ and PCI were independent, favorable prognostic factors for OS. Liver metastasis, weight loss and smoking index were adverse factors affecting prognosis in ES-SCLC patients (all p<0.05).Details were presented in **Table 4**.

Safety profile

Side effects of grade II and above (hematologic toxicity, gastrointestinal toxicity, acute radiation-induced pneumonitis, and esophagitis) were defined as toxic effects in the study. Leucopenia was more frequent than other toxicities and no treatment-related deaths occurred. No significant difference was observed among these four groups. Nausea/vomiting and TRT-induced esophagitis were more common in the high-dose group than in the low-dose group. Hematologic and nonhematologic toxicities were summarized in Table 5.

Discussion

In the present study, TRT added to CHT in ES-SCLC patients were associated with long-term survival both before and after matching. Our results reported that the mOS for patients treated with CHT/TRT was 18.2 months, and is similar to a retrospective study that demonstrated the comparable results regarding mOS was 17 months[14].-Until recently, two randomized phase III trials have confirmed survival advantages in ES-SCLC with IO incorporated into CHT. IMpower 133 was the first trial to show improved survival in patients treated with atezolizumab combined with CHT (mOS 12.3 months vs 10.3 months). CASPIAN study also showed an improvement in survival, which reported mOS 13.0 months in durvalumab combined with CHT group, and 10.3 months in the CHT-alone group. Based on the above two studies, atezolizumab or durvalumab combined with CHT become the prefer recommend protocol for ES-SCLC. It deserved to mention that patients could have PCI, but TRT was not allowed in these two studies. However,

survival data in both studies has not shown superior survival with CHT/IO compared to studies with CHT/TRT. Whether IO combined with TRT could improve survival remains to be further witnessed, and the role of TRT is more difficult to determine with the inclusion of IO, let alone the optimal time and radiation dose have not been uniformly characterized.

With respect to radiation time, a survival advantage was reported when TRT was given after three cycles CHT by the Jeremic trial [8], whereas, a retrospective study by Luo et al. did not show significant benefit between early and late TRT [28]. We evaluated the efficacy of introducing TRT at different points. An improvement but no statistically significant was found in PFS with earlier TRT compared to delayed TRT, suggesting that earlier TRT could prolong PFS and thus brought about an expectation of improved OS, although this benefit was not durable. Additionally, TRT within 6 cycles presented a significant difference in LRFS, which has been therefore administered to enhance locoregional control. Further evaluation is required to identify whether it could provide a clear survival benefit. Several reasons may account for this fact, firstly, ES-SCLC was a kind of systemic disease, earlier TRT may be more effective in improving local control than extrathoracic control; secondly, the unbalanced prognostic factor with bone metastasis may result in a statistical disconformity; lastly, the number of patients in each group was small and treatment regimens were inhomogeneity as second-line CHT after recurrence.

Whether a higher TRT dose could give rise to a favorable prognosis was still an unresolved question. Two recently published studies suggested that those in the high-dose group had longer OS than the low-dose group [26,27]. We found that patients treated with higher dose had better mOS, mPFS and mLRFS, but the differences were not statistically significant. We next analyzed those patients with CR and PR to systemic therapy but got discordant conclusion, that is, patients in the low-dose group had superiority over the high-dose group. Different radiation fractionations employed may lead to the opposite result. Unlike the above-mentioned studies, patients with hyperfractionated radiotherapy were included in our study. Moreover, receiving TRT at 45Gy/30 fractions twice per day translated into a survival benefit in contrast with receiving radiotherapy at 60Gy/30 fractions daily, which was concurs with the findings of Luan et al [29].Thus, TRT at 45Gy/30 fractions twice daily appears to be a feasible treatment scheme for ES-SCLC patients. An interesting finding was that patients in hypofractionationated radiotherapy group have similar prognosis and acceptable adverse effects compared with patients in conventional fractionationated radiotherapy group, which brought great convenience for those patients with weak physical condition. Fewer patients in hypofractionationated radiotherapy were enrolled that more homogeneous studies were needed to confirm the results.

Meanwhile, we focused more on the independent predictors in ES-SCLC patients with TRT, including ECOG PS score, PCI, smoking index, liver metastasis and bone metastasis. In terms of ECOG PS score, it was traditionally used to predict the outcome of SCLC patients, with two previous studies investigated relatively shorter OS in patients with poor PS [30,31]. Our results were in conformity with their findings and proposed that TRT conferred a survival advantage in patients with good PS, indicating that the treatment tolerance in patients with excellent PS could be better than poor ones, thus it seemed reasonable to select ES-SCLC patients with excellent PS for systemic therapy with TRT. PCI was also

proved to be a prognostic factor for better survival. Further, OS was improved with TRT+PCI compared to non-(TRT+PCI). However, PCI was only administered to 16 patients, making statistical comparisons difficult. Taken together, the relationship between PCI and survival needed to be further verified.

According to distant metastasis, two previously studies by Nakazawa K et al. and Ren Y et al. revealed that single metastasis was associated with better OS compared with multiple ones[32,33].Contrastingly, metastasis sites (multiple vs single) and the number of metastasis in our analysis were significantly obvious in univariate analysis, but they did not affect the survival in multivariate analysis. One possible reason was the difference in sample size between the two groups. Cai et al and Qin et al ~~have~~ reported that patients diagnosed with liver metastasis had a significantly increased risk of death, while no benefit was found in patients without brain metastasis and bone metastasis [34,35]. Our study was consistent with these results and ~~also~~ confirmed that patients without liver metastasis had better OS than those with liver metastasis. A high proportion of patients with brain metastasis undergone either WBRT or SRT made the prognosis similar compared to those without brain metastasis. And owing to timely therapy with diphosphonates and palliative radiotherapy, there was no significant difference in OS between patients with or without bone metastasis. Further studies are needed to formulate the therapeutic schedule of ES-SCLC with liver metastasis.

Needless to say, smoking index was used as a negative predictor of OS [36, 37]. Weight loss was considered the diagnostic criterion for cancer cachexia according to a previous study by Fearon, K et al [38]. We speculated that weight loss in ES-SCLC patients may be connected with a heavy tumor burden, tumor progression or low food intake caused by chest pain and dyspnea, leading to lower quality of life and an increase in mortality. Furthermore, CHT/TRT was well tolerated in patients with ES-SCLC. The frequency of radiation esophagitis (23.7% vs 21.6%) and radiation pneumonitis (10.2% vs 8.4%) were slightly above than that reported previously [14], which may be due to the application of hyperfractionationated radiotherapy.

As previously reported, integrating IO and TRT may potentiate a synergistic effect and possibly augmenting anti-tumor immune response, resulting in locoregional control and enhance the IO effect of extrathoracic metastasis [39-41]. One prospective study by Welsh JW et al. corroborated that pembrolizumab added to TRT was safe and well-tolerated for ES-SCLC, with the risk of treatment-related complications manageable [42]. It is necessary to conduct large-scale prospective cohorts to put this treatment paradigm into practice in ES-SCLC.

Besides the retrospective nature of our research, several other limitations should be acknowledged. Firstly, the small number of patients in the subgroups limited the statistical analyses. Secondly, radiation dose/fraction, diversified therapeutic modality after disease progression and radiation target volume schemes may have contributed to study bias. Thirdly, no biomarker analysis was performed and patients who were lost to follow-up were not included in the study. Further studies are close warranted to clarify the findings of this study.

Conclusion

Considering the current and previous reports, there is no doubt that TRT could improve survival in ES-SCLC patients. TRT performed within 6 cycles CHT and delivered at hyperfractionated 45Gy in 30 fractions may be an appropriate treatment scheme. Consolidation TRT could be an option for patients who underwent PCI, no brain or liver metastasis, with satisfactory ECOG PS, no weight loss as well as smoking cessation. Nevertheless, whether TRT and PCI would bring superiority in the era of IO is unknown. Future prospective studies that established adjunct immune checkpoint inhibitors are required to document this hypothesis.

Abbreviations

SCLC: Small-cell lung cancer; ES-SCLC: Extensive-stage small-cell lung cancer; EP/EC/EL: Etoposide + cisplatin/etoposide +carboplatin/ etoposide + lobaplatin;

ECOG PS: Eastern Cooperative Oncology Group performance status; OS: Overall

survival; PFS: Progression-free survival; LRFS: Local recurrence-free survival; mOS:median survival time; mLRFS: median LRFS time; mPFS: median PFS time; PSM: Propensity score matching; RECIST : Response evaluation criteria in solid tumors; CHT: chemotherapy; TRT: Thoracic radiotherapy; CHT/TRT: TRT added to chemotherapy; PCI: Prophylactic cranial irradiation; tBED: time-adjusted biological effective dose; 3D-CRT: 3D conformal radiotherapy; IMRT: intensity-modulated radiation; WBRT: whole brain irradiation; SRT: stereotactic radiotherapy; GTV: gross tumor volume; CTV: clinical target volume; PTV: planning target volume; PGTV: planning gross target volume; CREST: The Chest Radiotherapy Extensive-Stage Small Cell Lung Cancer Trial; CR: complete response; PR: partial response, SD: stable disease; PD: progressive disease; immunotherapy: IO.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Board of Shandong Cancer Hospital, and informed consent was provided by all patients.

Consent for publication

All authors gave their consent for publication.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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Authors' contributions

JMH and CRF participated in the study design, collected the clinical data, performed the statistical analysis and drafted the manuscript. BSL conceived the study, participated in its design and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Clinical characteristics of ES-SCLC patients based on radiation time

Variables		≤2cycles	3-4cycles	5-6cycles	>6 cycles	*p*-value
Age, y	<60	21	42	46	18	
	≥60	20	36	46	15	0.950
Gender	Male	34	60	68	30	
	Female	7	18	24	3	0.189
ECOG PS score	0-1	38	71	85	32	
	2	3	7	7	1	0.487
Smoking index	≥400	21	31	54	18	
	<400	20	47	38	15	0.098
Metastasis organs	single	17	36	30	10	
	Multiple	24	42	62	23	0.141
Number of metastasis	≤2	11	16	15	4	
	>2	30	62	77	29	0.360
Brain metastasis	yes	25	49	58	21	
	no	16	29	34	12	0.995
Liver metastasis	yes	9	21	35	7	
	no	32	57	57	26	0.128
Bone metastasis	yes	18	22	38	20	
	no	23	56	54	13	0.014
Hydrothorax	yes	32	56	66	22	
	no	9	22	26	11	0.749
Weight loss	yes	37	70	78	28	
	no	4	8	14	5	0.695
PCI	yes	3	6	5	2	
	no	38	72	87	31	0.939
Radiation dose	≤50Gy	27	50	60	22	
	>50Gy	14	28	32	11	0.994

Abbreviations: ES-SCLC: Extensive-stage small-cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; PCI: Prophylactic cranial irradiation;

Table 2 Clinical characteristics of ES-SCLC patients based on radiation dose

Variables		Low -dose	High-dose	*p*-value
Age, y	<60	77	40	
	≥60	82	45	0.838
Gender	Male	128	64	
	Female	31	21	0.344
ECOG PS score	0-1	152	76	
	2	7	9	0.063
Smoking index	≥400	79	41	
	<400	80	44	0.829
Metastasis organs	single	59	32	
	Multiple	100	53	0.934
Number of metastasis	≤2	31	15	
	2	128	70	0.725
Brain metastasis	yes	100	53	
	no	59	32	0.934
Liver metastasis	yes	50	22	
	no	109	63	0.364
Bone metastasis	yes	68	30	
	no	91	55	0.257
Hydrothorax	yes	42	59	
	no	117	26	0.488
Weight loss	yes	24	7	
	no	135	78	0.125
PCI	yes	12	4	
	no	147	81	0.393

Abbreviations: ES-SCLC: Extensive-stage small-cell lung cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; PCI: Prophylactic cranial irradiation;

Table 3 MST, mPFS and mLRFS summarized respectively by time and dose of TRT

	OS		PFS		LRFS	
Variables	Median (mo)	p-value	Median (mo)	p-value	Median (mo)	p-value
Radiation time						
≤2 cycles	17.6	0.407	10.6	0.026	12.7	<0.001
3-4 cycles	19.5	0.564	9.8	0.051	12.0	0.001
5-6 cycles	17.2	0.973	9.1	0.096	12.7	<0.001
6 cycles	19.1	1.000	7.7	1.000	9.0	1.000
Radiation dose		0.800		0.810		0.942
≤50Gy	17.3		8.9		11.9	
>50Gy	20.8		10.1		12.8	

Abbreviations: OS: overall survival; PFS: progression-free survival; LRFS: local recurrence-free survival; TRT;thoracic radiotherapy;

Table 4 Univariate and multivariate survival analysis evaluating the prognostic factors for OS in patients receiving TRT.

Variables	Univariate	Multivariate	
	p-value	HR(95%CI)	p-value
Age, y (≥60 vs <60)	0.140	-	-
Gender (Male vs Female)	0.074	-	-
ECOG PS score (≤1 vs 1)	0.013	0.52 (0.31,0.87)	0.012
Smoking index (400 vs≥400)	0.021	1.51 (1.12,2.04)	0.007
Number of metastasis (≤2 vs 2)	0.021	1.11 (0.70,1.78)	0.658
Metastasis organs (Single vs Multiple)	0.003	1.18 (0.80,1.72)	0.408
Brain metastasis (yes vs no)	0.077	-	-
Liver metastasis (yes vs no)	<0.001	1.85 (1.32,2.59)	<0.001
Bone metastasis (yes vs no)	0.012	1.23 (0.90,1.68)	0.191
Hydrothorax (yes vs no)	0.242	-	-
Weight loss (yes vs no)	0.011	1.74 (1.14,2.66)	0.010
PCI (yes vs no)	0.010	0.41 (0.20,0.84)	0.015
Radiation time			
≤2 cycles vs 6 cycles	0.407	-	-
3-4 cycles vs 6 cycles	0.564	-	-
5-6 cycles vs 6 cycles	0.973	-	-
Radiation dose (≤50Gy vs 50Gy)	0.800	-	-

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; PCI: Prophylactic cranial irradiation; OS: overall survival; TRT: thoracic radiotherapy; HR: hazard ratio; CI: confidence interval

Table 5 Adverse events summarized respectively by time and dose of TRT

Toxic Effect/Grade	≤2 cycles	3-4 cycles	5-6 cycles	>6 cycles	*p*-value	Low-dose	High-dose	*p*-value
Hematologic toxicity grade ≥ 2								
Leucopenia	27	52	48	18	0.193	90	55	0.219
Anemia	9	10	7	6	0.111	20	12	0.734
Thrombocytopenia	7	12	14	5	0.994	24	14	0.778
Nausea/vomiting								
Grade 0-1	33	62	79	24		138	61	
>Grade 2	8	16	13	9	0.388	21	24	0.004
TRT-induced Esophagitis								
Grade 0-1	25	61	75	25		114	72	
>Grade 2	16	17	17	8	0.077	45	13	0.023
TRT-induced Pneumonitis								
Grade 0-1	36	68	85	30		144	75	
>Grade 2	5	10	7	3	0.688	15	10	0.567

Abbreviations: TRT: thoracic radiotherapy;

Figures

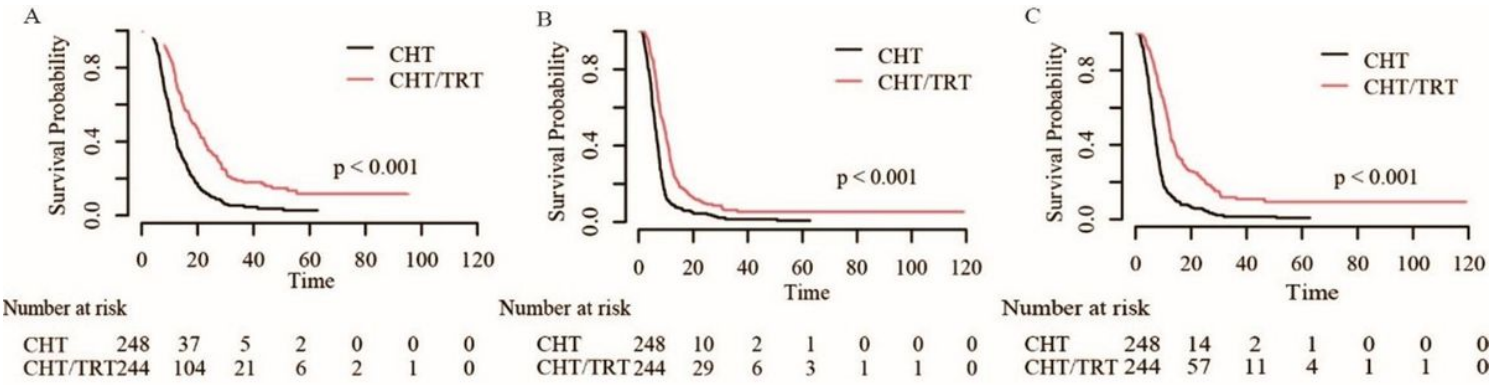

Figure 1

Kaplan-Meier survival curves of all patients between CHT/TRT and CHT-alone before matching: (A) overall survival, (B) progression-free survival, and (C) local recurrence-free survival

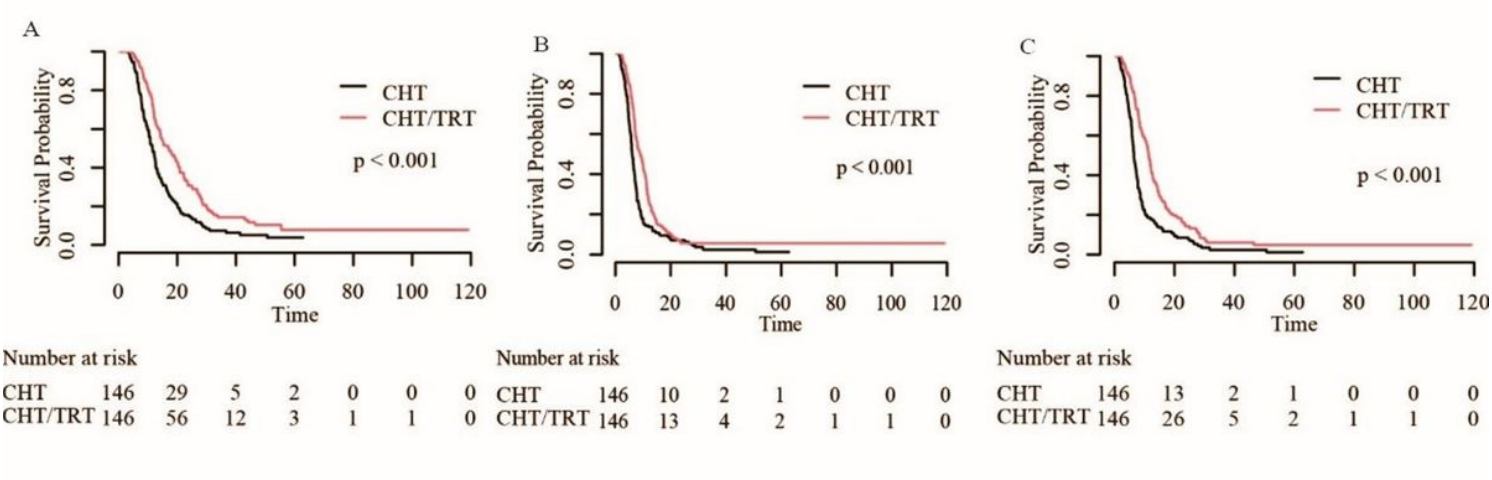

Figure 2

Kaplan-Meier survival curves of all patients between CHT/TRT and CHT-alone after matching: (A) overall survival, (B) progression-free survival, and (C) local recurrence-free survival.

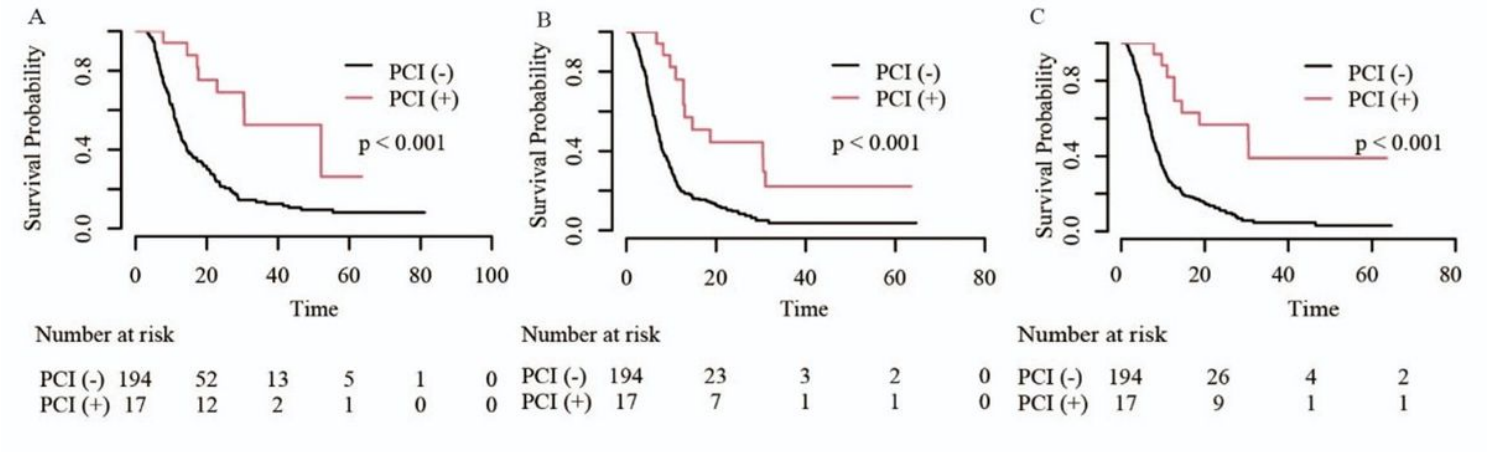

Figure 3

Kaplan-Meier survival curves of patients without brain metastasis between PCI (+) and PCI (-) : (A) overall survival, (B) progression-free survival, and (C) local recurrence-free survival

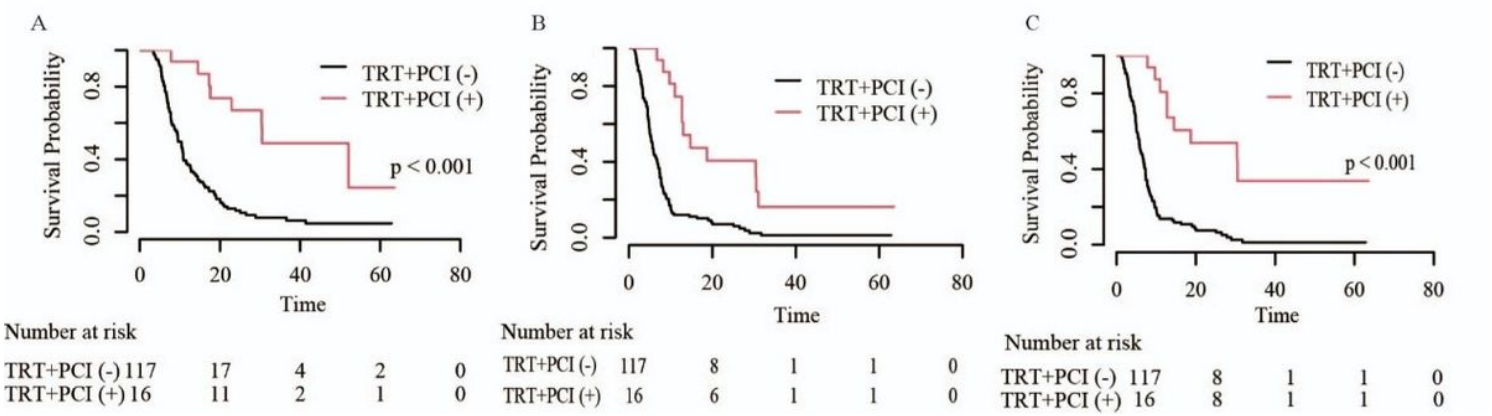

Figure 4

Kaplan-Meier survival curves of patients without brain metastasis between TRT+PCI(+) and TRT+PCI(-) : (A) overall survival, (B) progression-free survival, and (C) local recurrence-free survival

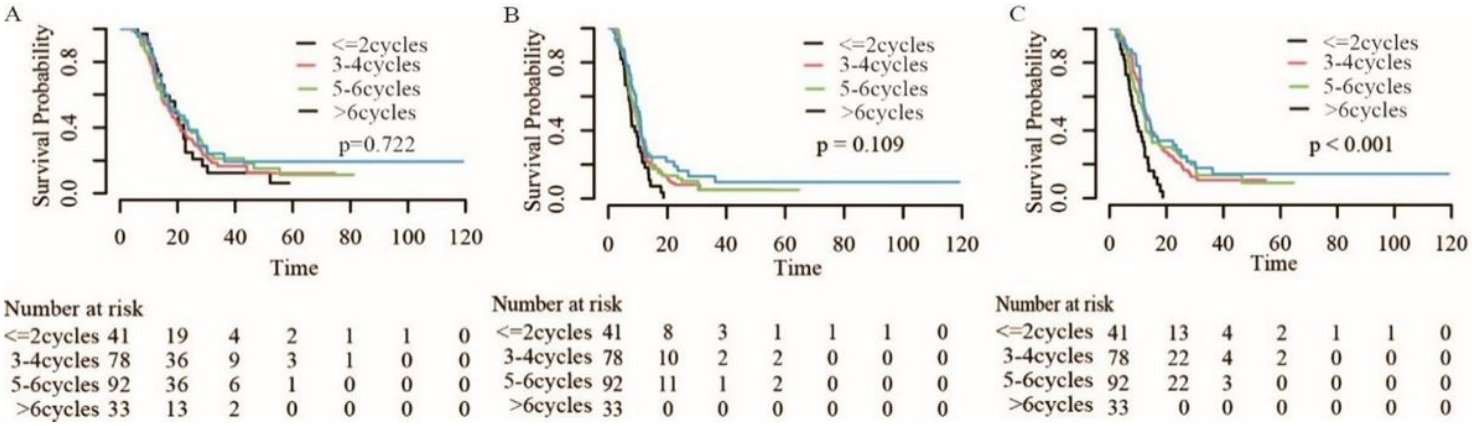

Figure 5

Kaplan-Meier survival curves of ES-SCLC patients based on radiation time : (A) overall survival, (B) progression-free survival, and (C) local recurrence-free survival.

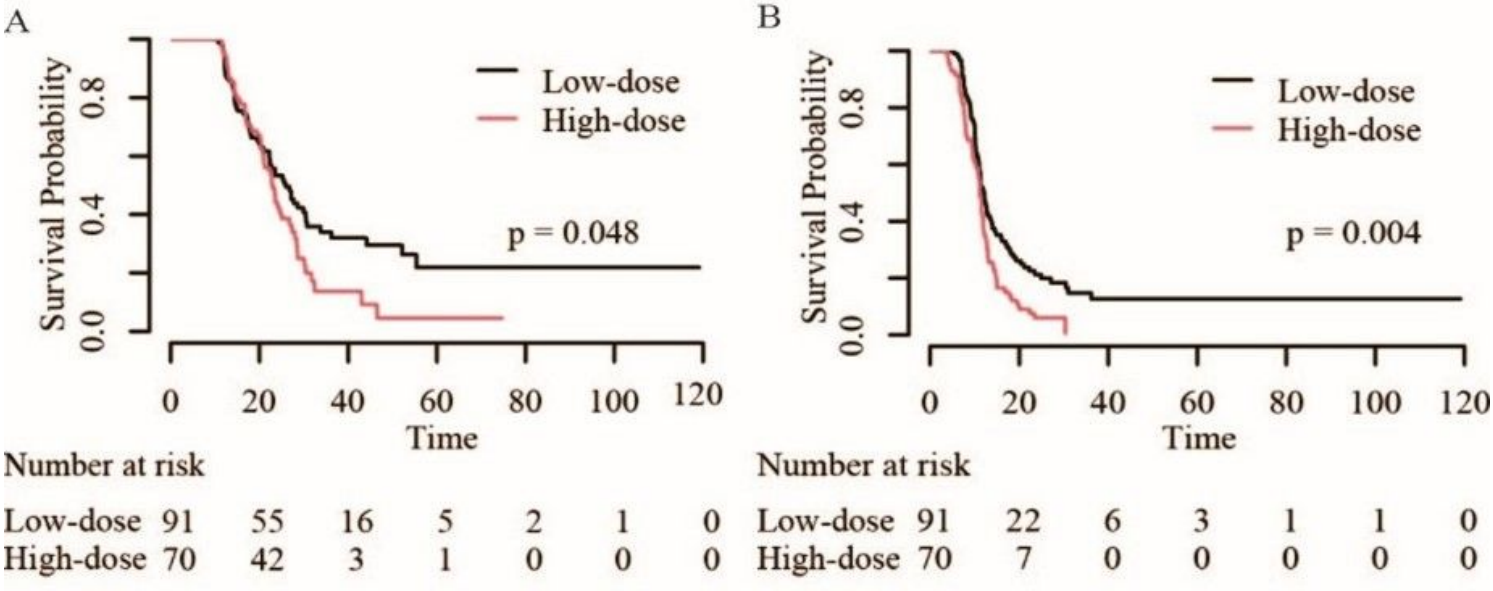

Figure 6

Kaplan-Meier survival curves of ES-SCLC patients with CR and PR based on radiation dose: (A) overall survival, (B) progression-free survival.

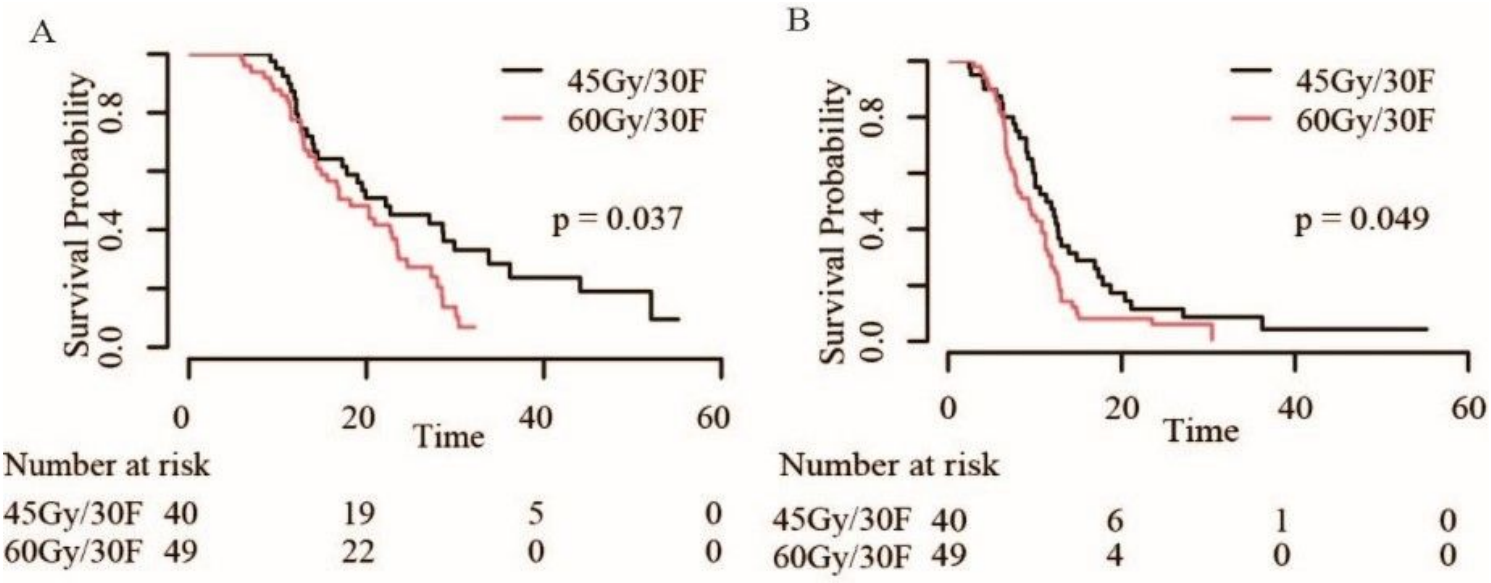

Figure 7

Kaplan-Meier survival curves of ES-SCLC patients between 45Gy/30F and 60Gy/30F: (A) overall survival, (B) progression-free survival.

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