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 chemotherapy 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. Survival rates were computed by the Kaplan-Meier method. 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 = 0.1095), as was not seen in OS (median 17.6 vs 19.5 vs 17.2 vs 19.1 months, respectively, p = 0.7224). To note, patients within 6 cycles had better LRFS (p = 0.0006). For radiation dose, patients in high-dose group (tBED>50Gy) had worse OS (median 25.9 vs 22.9, p = 0.0484) and PFS (median 12.1 vs 11.2, p=0.0042) in patients with complete response and partial response (CR and PR) to systemic therapy, but the above-mentioned results were not drawn when the population was confined to those receiving standard fractionation with CR and PR.

**Conclusion:** ChT/TRT could improve survival for ES-SCLC patients. We cautiously recommend that TRT should be performed within 6 cycles 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 annually, which is characterized by its highly aggressive, early dissemination and highly response to treatment, with almost two-thirds of SCLC cases present with distant metastasis at first clinical diagnosis [1, 2]. Four to six cycles of platinum-based first-line chemotherapy and prophylactic cranial irradiation (PCI) are identified as the standard treatment for extensive stage small cell lung cancer (ES-SCLC) despite discrepant, which contribute to a median survival time (MST) of 9–12 months and a 5-year survival rate of 1%-2% [3, 4]. Although it has always been considered a chemo-radiotherapy-sensitive disease, intrathoracic progression is still a major challenge for ES-SCLC patients, which leading to a disappointing prognosis.
Prior studies have demonstrated that thoracic radiation (TRT) played a vital role in terms of regional control and an improved survival for ES-SCLC. A survival advantage was reported in ES-SCLC patients when TRT was given after three cycles chemotherapy by the Jeremic trial [5]. The Chest Radiotherapy Extensive-Stage Small Cell Lung Cancer Trial (CREST) illustrated a 10% 2-year improvement, and the risk of intrathoracic recurrence could be reduced for patients who had chemotherapy with subsequent TRT [6]. Palma et al later systematically summarized these two trials and concluded that TRT increased overall survival (OS) and progression-free survival (PFS) in ES-SCLC patients [7]. Moreover, the RTOG 0937 study and NTR1527 trial emphasized that TRT should be performed for ES-SCLC patients who responded to chemotherapy [8]. Several retrospective analyses also suggested that TRT in combination with chemotherapy was associated with long-term survival [9–13]. Recently, the additional use of TRT has been strongly advocated for certain ES-SCLC patients after chemotherapy treatment in the 2020 NCCN guidelines [14] and in the ASTRO 2020 guidelines [15].

Nevertheless, there have been no clear consensus on the application of TRT in ES-SCLC to date even though the effectiveness of TRT among ES-SCLC patients was increasingly reported. Hence, we held on this retrospective real-world study. The aims of this study were as follows: first, to characterize whether TRT added to chemotherapy (ChT/TRT) showed promising anti-tumor activity in ES-SCLC; second, to explore the appropriate TRT time and optimal radiation dose/fraction protocol, 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 (defined as disease beyond the hemithorax, hilar, mediastinal, and supraclavicular nodes). (2) at least two cycles of chemotherapy 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 (previously or at the same time); (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

Platinum combined with etoposide, either EP (etoposide + cisplatin) or EC (etoposide + carboplatin) or EL (etoposide + lobaplatin). 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, while the planning target volume (PTV) was expanded from the CTV with a 5-8mm margin. Some patients with extensive tumor disease for a tolerable radiation plan were treated with TRT to a planning gross target volume (PGTV). PGTV was defined as GTV plus a 5–10mm margin. Considering different radiation fractionations and time efficiencies, we employed the time-adjusted biological effective dose (tBED) formula [16]: \[ tBED = (nd) \left\{ 1 + \left[ \frac{d}{(\alpha/\beta)} \right] - \left[ \frac{0.693t}{(\alpha \cdot Tpot)} \right] \right\} , \]

where \( n \) is the number of fractions, \( d \) represents the dose per fraction, \( \alpha/\beta = 10 \), \( \alpha = 0.3 \text{Gy} \), \( t \) is the time of radiotherapy, and \( Tpot \) is the potential doubling time (5.6 days) according to the previous reports [17,18].

**Assessment of Response and Toxicity**

Physical and imaging examinations were required to assess the response every 2 cycles of chemotherapy or prior to TRT, every 3 months until 2 years, then annually. 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) [19]. Toxic effects were assessed according to Common Terminology Criteria for Adverse Events (version 4.0) [20].

**Statistical analysis**

Statistical analysis was presented via SPSS version 24.0 software (IBM Corp) and GraphPad Prism 7.0. The Chi-square and Fisher’s exact tests were employed to compare baseline characteristics for different groups. Propensity score matching (PSM) was performed in order to minimize bias between the ChT/TRT and ChT-alone groups. Survival information, including OS, PFS and LRFS (local recurrence-free survival), was collected until October 31, 2019. OS was calculated from the date of diagnosis to death, or the period up to the observation point. PFS was defined as the time of diagnosis until disease progression or death. LRFS was assessed from the date of diagnosis until the time of local recurrence or death. Kaplan-Meier curves were performed to estimate the cumulative probability of survival with log-rank statistics. 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 during the period from January 2010 to March 2019. The clinical characteristics of the study cohort between the ChT/TRT and ChT-alone groups were comparable after propensity score matching, as listed in Table S1.
Relative to the ChT/TRT group, the median follow-up duration was 36 months. There were 196 patients in conventional fractionation group, receiving 40-66Gy radiotherapy at 1.8-2Gy/fraction daily, 40 patients in hyperfraction radiotherapy group, receiving 45Gy radiotherapy at 1.5Gy/fraction twice per day and 8 patients in hypofractionation radiotherapy group, receiving 30-51Gy radiotherapy at 3Gy/fraction daily. Prophylactic cranial irradiation (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, while 150 patients had brain metastases, with more than 80% (121 cases) undergone either whole brain irradiation (WBRT) or stereotactic radiotherapy (SRT). At the time of disease progression, most patients received additional chemotherapy as second-line regimens, such as topotecan and/or palliative radiotherapy because of aggravated clinical symptoms. What was worth mentioning was that 33 patients received immunotherapy or targeted therapy after recurrence.

Patients were then apportioned to four groups with consideration of the number of induction chemotherapy cycles they received prior to TRT. Group A received TRT before or at the second cycle of chemotherapy (≤2 cycles, n= 41); Group B received TRT at the third cycle to the fourth cycle of chemotherapy (3-4cycles, n=78); Group C received TRT at the fifth cycle to the sixth cycle of chemotherapy (5-6cycles, n= 92); and Group D received TRT after the sixth cycle of chemotherapy (>6 cycles, n=33). Patient characteristics were presented in Table 1. 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[21,22]. The baseline characteristics between groups were comparable, as summarized in 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; Unadjusted Kaplan-Meier survival curves were shown in Figure S1 (all p < 0.001). 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, as listed in Fig. S2 (all p < 0.001).

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 survival times (MST) for groups were 17.6, 19.5, 17.2, and 19.1 months, respectively. The mLRFS, mPFS and MST in terms of radiation time and radiation dose were presented in Table 3. We observed that patients within 6 cycles had better mLRFS than those ones who received more than 6 cycles (p = 0.0006). The OS, PFS and LRFS rates among the four groups concerning radiation time were shown in Figure 1.

We further analyzed those patients with CR and PR to systemic therapy in low-dose group had better OS (median 25.9 vs 22.9, p = 0.0484) and PFS (median 12.1 vs 11.2, p = 0.0042) than patients in high-dose
group, as was displayed in Fig.2. On subgroup analysis, there were no longer any differences associated with radiation dose (all p>0.05) when the population was confined to those patients with CR and PR who received standard fractionation. Moreover, patients receiving 45Gy radiotherapy at 1.5Gy/fraction twice per day presented better OS (median 22.2 vs 18.2, p = 0.0374) and PFS (median 11.3 vs 9.3, p = 0.0402) than those undergoing 60Gy radiotherapy at 2Gy/fraction daily, as was presented in Fig.3. Besides, patients in hypofractionation radiotherapy group had similar outcomes compared with patients in conventional fractionation radiotherapy (all p>0.05).

**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). And female patients (p = 0.074) tended to have better OS, although it was not statistically significant. Next, multivariate analysis revealed that good PS score and PCI were independent, favorable prognostic factors for OS. Liver metastasis, weight loss as well as smoking index predicted unfavorable prognosis in ES-SCLC patients (all p<0.05). In addition, brain metastasis and bone metastasis were not relevant to prognostic factors for OS. Number of metastasis, metastasis organs as well as radiation dose were also not found to be associated with better survival. Details were presented in Table 4. Relationships between PFS\LRFS and baseline characteristics were statistically analyzed and listed in Table S2 and Table S3, respectively.

**Safety profile**

In the present study, side effects of grade II and above (hematologic toxicity, gastrointestinal toxicity, acute radiation-induced pneumonitis, and esophagitis) were defined as toxic effects. Leucopenia was more common 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 4.

**Discussion**

In the current 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 MST for patients treated with ChT/TRT was 18.2 months and the 2-year OS rate was about 35.4%. Similarly, a small-single previous article published by Zhu et al [9] demonstrated the consistent results that the MST in the TRT arm was 17 months and the 2-year survival rate was 35.3%. These two different studies have shown comparable survival benefits and indicated that TRT improved clinical outcome in ES-SCLC patients. However, the optimal time and radiation dose have not been characterized, and there was no clear evidence on who would benefit from TRT for ES-SCLC patients.
A retrospective study by Luo et al. indicated that early TRT did not show significant benefit over late TRT [23]. Based on the study, we evaluated the efficacy of introducing TRT at different points. To note, we found an improvement but no statistically significant in PFS with earlier TRT compared to delayed TRT. The results demonstrated that earlier TRT prolonged PFS which thus brought about an expectation of improved OS, however, this benefit was not durable. Further subgroup analysis showed that patients treated with TRT within 6 cycles presented a significant difference in LRFS. In addition, patients underwent TRT within 6 cycles could significantly lower the recurrence rate and the ORR within 6 cycles was also superior despite no statistically significance. TRT within 6 cycles has been therefore administered to enhance locoregional tumor control, whereas further evaluation is required to identify whether TRT within 6 cycles would provide a clear benefit to survival. There were several reasons for lack of a survival benefit in this study that may account for this fact, firstly, ES-SCLC was a kind of systemic disease, the tumor was not only limited to the lungs. Earlier TRT may be more effective in improving local control than systemic control; secondly, the unbalanced prognostic factor with bone metastasis may give rise to a statistical disconformity; Lastly, the number of patients started TRT after the sixth cycle of chemotherapy was small and treatment regimens were inhomogeneity as second-line chemotherapy after recurrence.

Concerning radiation dose, whether a higher TRT dose could achieve favorable prognosis. Two recently published studies suggested that high-dose TRT improved survival over low-dose group [21,22]. We analyzed those patients with CR and PR to systemic therapy but got discordant conclusion as the previous two studies mentioned above. Moreover, receiving TRT at 45Gy/30 fractions twice per day translated into a survival benefit in the OS and PFS in contrast with receiving radiotherapy at 60Gy/30 fractions daily, which was concurs with the findings of previous studies by Luan Z et al [24]. Different radiation fractionations employed may lead to the opposite result. Patients with hyperfractionation radiotherapy were included in our study, while the above-mentioned studies enrolled patients only with conventional fractionation radiotherapy or hypofractionation radiotherapy. Thus, TRT at 45Gy/30 fractions twice daily appears to be a feasible treatment scheme for ES-SCLC patients. An interesting finding of this study was that patients in hypofractionation radiotherapy group have similar prognosis and acceptable adverse effects compared with patients in conventional fractionation radiotherapy group, which brought great convenience for those patients with weak physical condition, however, there were fewer patients with hypofractionation radiotherapy that more homogeneous studies were needed to confirm the results.

Meanwhile, we paid more attention to the prognostic factors of ES-SCLC patients with TRT. In terms of ECOG PS score, it has traditionally been used to predict the outcome of SCLC patients, with two previous studies investigated OS was relatively short in patients with poor PS [25,26]. The findings of our study were consistent with the result and proposed that TRT conferred a survival advantage in patients with good PS score. The reason for this might be that the tolerance of treatment in patients with good PS score could be better than poor ones, thus it seemed reasonable to select ES-SCLC patients with good PS score for systemic therapy.
A phase III clinical trial, led by the European Organization Research and Treatment, elucidated a survival benefit and a reduction of symptomatic brain metastasis for ES-SCLC patients which may include asymptomatic brain metastasis patients who received PCI without brain magnetic resonance imaging routinely carried out before treatment [26], whereas, a Japanese study questioned the findings and confirmed that PCI failed to provide a similar survival advantage in the context of the mandated brain imaging before enrollment [27]. Similarly, several analyses also demonstrated the OS benefit of PCI in ES-SCLC, which were in line with our results [28-30]. However, PCI was only administered to 16 patients and no quality of life and limited neurocognition data were available. Thus, the association between PCI and survival needed to be further verified.

According to distant metastasis, Cai et al and Qin et al have reported that patients who diagnosed with liver metastasis had a significantly increased risk of death, while no benefit from TRT was found in patients with brain metastasis and bone metastasis [31,32]. Our study also confirmed that patients without liver metastasis had better OS than those with liver metastasis did. Most patients with brain metastasis undergone either WBRT or SRT which made the prognosis was similar compared to those without brain metastasis. And among patients without bone metastasis, there was no significant difference in OS compared to bone metastasis owing to timely therapy with diphosphonates and palliative radiotherapy. More in-depth research should be made to work out to further explain therapeutic schedule about liver metastasis of ES-SCLC. 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[33,34].Contrastingly, metastasis site (multiple vs single) as well as number of metastasis were significantly obvious in univariate analysis ,while they did not affect the survival time in multivariate analysis, which was consistent with a published study by Luo J et al[23]. One possible reason was the difference in sample size between the two groups.

With respect to smoking index, it could be used as a negative predictor of OS. A 2014 report by the US Surgeon General reached a conclusion that smoking may be related to higher cancer-specific mortality [35]. An investigation by OuSH et al confirmed that smoking is an adverse factor affecting prognosis (p=0.0125) [36]. Our study concluded similar results (p<0.0001). Previous studies have also demonstrated that smoking was responsible for nicotine-promoted cell migration, invasion, and tumor angiogenesis in lung cancer cells [37]. Smoking may increase the likelihood of genetic mutation and a high risk of pulmonary complications which thus attributed to poor prognosis [38]. Given all the evidence above, clinicians should strongly provide necessary support to help patients to quit smoking.

Weight loss could be considered the diagnostic criterion for cancer cachexia according to a previous study by Fearon, K et al [39]. 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, resulting in lower quality of life and an increase in mortality. Age and gender were not observed as independent factors affecting prognosis in this study, which might be due to the limitation of sample size or the inclusion of only ES-SCLC patients were enrolled, which was also similar to the results of Cai H et al [31].
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 [9]. The possible reason was the application of hyperfractionation radiotherapy.

This study had its own limitations. Firstly, it was a retrospective study from a single institution, the possibility of bias is unavoidable. Secondly, the 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. It is necessary to conduct large-scale prospective cohorts to further clarify the findings of this study.

**Conclusion**

Considering the current and previous reports, it was a key issue to select suitable patients for ChT/TRT. The study showed that patients treated with PCI without brain metastasis, without liver metastasis, in good ECOG PS score, no weight loss as well as smoking cessation may be good indications for TRT. We cautiously recommend that TRT should be completed within 6 cycles and TRT delivered at hyperfractionated 45Gy in 30 fractions may be an appropriate treatment scheme. Additional data is 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; MST :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;

**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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Not applicable.

**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  |
|-------------------------------|----------|-----------|-----------|-----------|----|
| **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                           | 16       | 32        | 37        | 9         |    |
| No                            | 25       | 46        | 55        | 24        | 0.555 |
| **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                       | 97       | 53        |         |
| no                        | 62       | 32        | 0.837   |
| 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 thoracic radiotherapy

| Variables      | OS Median (mo) | OS p-value | PFS Median (mo) | PFS p-value | LRFS Median (mo) | LRFS p-value |
|----------------|----------------|------------|-----------------|-------------|------------------|--------------|
| Radiation time |                |            |                 |             |                  |              |
| ≤ 2 cycles     | 17.6           | 0.407      | 10.6            | 0.026       | 12.7             | 0.000        |
| 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             | 0.000        |
| ≥ 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           |            | 10.1            |             | 11.9             |              |
| >50Gy          | 20.8           | 8.9        |                 |             | 12.8             |              |

**Abbreviations:** OS: overall survival; PFS: progression-free survival; LRFS: local recurrence-free survival;

**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)           | 0.345      | -            | -       |
| 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 thoracic radiotherapy
| 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         |

**Figures**

**Figure 1**

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 2

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

Figure 3

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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