Original Article

Efficacy and safety of consolidative thoracic radiotherapy after first-line chemoimmunotherapy in patients with extensive-stage small-cell lung cancer: a retrospective cohort study

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Background: Thoracic radiotherapy (TRT) has shown potential benefits in improving local control and overall survival (OS) in chemotherapy-responsive small-cell lung cancer (SCLC) cases. However, its role in the era of chemoimmunotherapy remains underexplored. In the current era of immunotherapy, this study evaluated the efficacy and safety of consolidative TRT (cTRT) in patients with extensive-stage SCLC (ES-SCLC) and assessed its impact on OS. Additionally, the optimal radiotherapy dose and fractionation schemes were also explored.

Methods: In this retrospective cohort study, 124 patients with ES-SCLC diagnosed at Taizhou Cancer Hospital between January 2019 and November 2023 were categorized into cTRT and non-cTRT groups. We compared the baseline characteristics, treatment processes, and survival outcomes between the two groups. Moreover, cTRT subgroups of different radiotherapy doses and fractionation schemes were formed and compared in terms of baseline characteristics, radiotherapy efficacy and safety, patterns of recurrence after radiotherapy, and survival outcomes. OS was selected as the primary endpoint for observation. Differences in OS between the groups were analyzed using log-rank tests. Univariable and multivariable Cox regression analyses were performed to identify factors correlated with OS in the overall patient cohort.

Results: The baseline characteristics between the two groups (cTRT and non-cTRT) were generally comparable, with the following significant differences: the cTRT group had a lower proportion of females (1.7% *vs.* 15.2%, P=0.02), lower levels of neuron-specific enolase (NSE, median: 15.87 *vs.* 32.00 ng/mL, P=0.009), and higher sodium concentrations (median: 140.50 *vs.* 138.25 mmol/L, P=0.01). Additionally, the cTRT group underwent more first-line treatment cycles (median: 4.00 *vs.* 3.00, P=0.001). Compared with the non-cTRT group, the cTRT group had a longer OS [median survival 15.5 *vs.* 10.5 months; hazard ratio (HR) =2.0497; 95% confidence interval (CI): 1.3548–3.1010; P<0.001]. There were no significant differences in survival outcomes associated with the different radiotherapy dosage or fractionation schedules. The most common adverse event was neutropenia, but no severe treatment-related deaths occurred. Multivariable

Cox analysis revealed that the sodium concentration (HR =0.8751; 95% CI: 0.7944–0.9642; P=0.007), initial treatment response (HR =0.7022; 95% CI: 0.4949–0.9964; P=0.048), total number of systemic treatment cycles (HR =0.5501; 95% CI: 0.3618–0.8364; P=0.005), and whether to receive cTRT (HR =1.7484; 95% CI: 1.1033–2.7708; P=0.02) were independent prognostic factors for OS.

Conclusions: cTRT improved the OS of patients with ES-SCLC and exhibited manageable associated toxicity. Further research is needed to confirm the effect of radiotherapy dose and fractionation scheme selection on treatment outcomes.

Keywords: Immunotherapy; small-cell lung cancer (SCLC); thoracic radiotherapy (TRT); overall survival (OS); safety

Submitted Dec 04, 2024. Accepted for publication Dec 17, 2024. Published online Dec 27, 2024.
doi: 10.21037/tlcr-2024-1182
View this article at: https://dx.doi.org/10.21037/tlcr-2024-1182

Introduction

Small-cell lung cancer (SCLC) accounts for 13–15% of lung cancers, and nearly two-thirds of patients with SCLC are diagnosed at an advanced stage (1,2). For more than three decades, the etoposide plus platinum doublet regimen has been the standard first-line treatment for extensive-stage SCLC (ES-SCLC) (3). Currently, immunotherapy has been widely used in patients with ES-SCLC (4,5). Prompted by the significant improvements in overall survival (OS) and progression-free survival (PFS) reported in recent studies such as the IMpower133 and CASPIAN trials (6,7), organizations such as the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) (8,9) have integrated immunotherapy into the first-line standard treatment for ES-SCLC in their guidelines. However, there remains a dearth of high-level phase III clinical studies that have assessed the efficacy of consolidative thoracic radiotherapy (cTRT) after immunotherapy combined with chemotherapy.

Despite standard first-line chemotherapy, residual intrathoracic lesions frequently persist, often causing disease recurrence within a year (7). Earlier studies have demonstrated that adding cTRT in chemotherapy-responsive patients can increase the local control rate (LCR) and OS (10,11). Chemoimmunotherapy has become the new standard first-line treatment for ES-SCLC, but only 2.5% of patients achieve a complete response (CR) (6). The residual lesions lead to disease progression and a poor prognosis. Given the high sensitivity of ES-SCLC to radiation, it is crucial to determine whether radiation therapy has a positive synergistic therapeutic effect as a local treatment modality in the era of chemotherapy and immunotherapy. Hoffmann *et al.* reported that cTRT significantly improved survival compared to systemic therapy alone (1-year survival rate: 78.6% *vs.* 39.7%) (12). Additionally, Li *et al.* reported that combining immunotherapy and cTRT was safe and significantly improved the survival of patients with ES-SCLC (13). Furthermore, Zheng *et al.* demonstrated that cTRT improved the prognosis for select ES-SCLC patients with baseline brain metastases (14). However, in another retrospective study, cTRT did not increase PFS and OS (15). Due to the fact that IMpower133 and CASPIAN used cTRT as an exclusion criterion in their study designs (6,7), controversies surround the efficacy and safety of cTRT in immunotherapy regimens. Additionally, there is no definitive conclusion regarding the ideal radiation dose and fractionation of cTRT in patients.

In the context of treating ES-SCLC with immunotherapy and chemotherapy, assessing the efficacy and safety of cTRT is crucial. We thus conducted a retrospective cohort study based on real-world data (RWD) from 124 patients with ES-SCLC to determine the following: the survival benefits and safety of cTRT, the optimal dose and fractionation of cTRT, and predictive factors of the clinical outcomes. RWD complements randomized controlled trial data by helping to evaluate treatment efficacy, safety, long-term applicability, and optimize personalized treatment strategies. These findings suggest that lower-dose cTRT (30 Gy/10 fraction) may offer effective results with fewer side effects. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1182/rc).

Methods

Study population and design

We conducted a retrospective cohort study by collecting histopathological or cytological data from patients with ES-SCLC diagnosed at Taizhou Cancer Hospital between January 2019 and November 2023. We included all patients who met the inclusion criteria during this period in the analysis, without performing sample size calculation. Clinical data, including pretreatment systemic evaluations [e.g., neck ultrasound, contrast-enhanced computed tomography (CT) of the chest and abdomen, contrast-enhanced magnetic resonance imaging (MRI) or CT of the brain, and nonroutine positron emission tomography (PET)-CT scans], imaging follow-up, hematological indices, specifics of treatment, and hematologic and nonhematologic toxicity details, were extracted from electronic medical records. This study was conducted in accordance with the Helsinki Declaration (as revised in 2013). The Ethics Committee of Taizhou Cancer Hospital approved our study (No. SL2024046). Due to its retrospective nature, the requirement for signed informed consent was waived for all patients.

The inclusion criteria were as follows: (I) aged ≥18 years; (II) histologically or cytologically confirmed ES-SCLC based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging criteria (T any, N any, M1a-c), excessively extensive multiple lung nodules (T3–4), or lymph nodes or tumor too large to be included in a tolerable radiation plan; (III) at least one measurable lesion assessable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 before first-line treatment; and (IV) no history of prior thoracic radiotherapy (TRT). Meanwhile, the exclusion criteria were as follows: (I) other concurrent malignancies; (II) pregnancy or lactation; and (III) severe immune system disorder or concurrent use of immunosuppressive agents.

Highlight box

Key findings

- Consolidative thoracic radiotherapy (cTRT) following first-line chemoimmunotherapy improves overall survival (OS) in patients with extensive-stage small-cell lung cancer (ES-SCLC), with a median OS of 15.5 *vs.* 10.5 months for those not receiving cTRT.
- No significant survival differences were found between the different radiation doses or fractionation schemes.
- Sodium concentration, initial treatment response, total systemic treatment cycles, and cTRT were independent prognostic factors for OS.
- The toxicity was manageable, with neutropenia being the most common side effect, with no treatment-related deaths.

What is known and what is new?

- Previous studies suggest that thoracic radiotherapy may improve local control and survival in patients with ES-SCLC, but its role after chemoimmunotherapy is not well understood.
- This retrospective cohort study found that cTRT improved the OS in patients receiving chemoimmunotherapy and demonstrated manageable toxicity. These findings suggest that lower-dose cTRT (30 Gy/10 fraction) may offer effective results with fewer side effects.

What is the implication, and what should change now?

- cTRT should be considered as a standard treatment option for patients with ES-SCLC who respond well to first-line chemoimmunotherapy.
- Further trials are needed to confirm the optimal dose and fractionation of cTRT. Clinical practice should incorporate cTRT and focus on monitoring key prognostic factors in order to obtain better patient outcomes.

Treatment methods

The first-line chemotherapy regimen consisted of cisplatin (75 mg/m^2) or carboplatin [area under the curve (AUC) =5] combined with etoposide (100 mg/m^2) administered intravenously every 3 weeks for 4–6 cycles or until disease progression or intolerable adverse effects. Second-line treatment included irinotecan or albumin-bound paclitaxel. Some patients with a performance status (PS) >2 received 50–75 mg of etoposide capsules orally once daily on days 1–21 every 4 weeks or 12 mg of anlotinib capsules orally once daily on days 1–14 every 3 weeks. Third-line treatment consisted of administration of 12 mg of oral anlotinib capsules once daily on days 1–14 every 3 weeks. Immunotherapy commenced on the first day of each treatment cycle and was combined with chemotherapy in first-line treatment and used as monotherapy in later lines, administered every 21 days until disease progression or intolerable toxicity. Immunotherapy was paused during radiotherapy, with a 21-day interval before and after radiotherapy during which immunotherapy was not administered. The immunotherapy drugs were tislelizumab (200 mg) administered every 3 weeks, serplulimab (4.5 mg/kg) every 3 weeks, durvalumab (1,500 mg) every 3 weeks, and adebrelimab (20 mg/kg) every 3 weeks. The total number of systemic treatment cycles included the sum of the cycles from the first line, second line, third line, and subsequent lines of therapy.

Local radiotherapy

For local radiotherapy, radiation therapists positioned the patients using vacuum immobilization pads. Patients lay supine on the pad, with their arms raised and crossed above their heads, holding opposite handles. Once a comfortable and reproducible position was achieved, air was evacuated from the pads to create a mold for fixation. Surface markings were then made based on the positioning lasers and followed by simulation positioning scans under CT. Depending on the clinical requirements, either plain or enhanced scans were performed, and four-dimensional (4D) CT scans were obtained if needed. The scan covered the neck, chest, and upper abdomen, and the thickness was set to 3 or 5 mm. The target area was delineated as follows: lung lesions were outlined under lung window settings, including lesion spicule edges in the gross tumor volume (GTV). Mediastinal lymph nodes were delineated under mediastinal window settings, with the clinical target volume (CTV) expanded by 8 mm outside the GTV, not exceeding the anatomical boundaries. The planning target volume (PTV) was determined by expanding the CTV by 5 mm. If the tumor was too large for a tolerable radiotherapy plan, it was expanded by 5–10 mm based on the GTV to determine the planning GTV (PGTV). The visible lung lesions and lymph nodes delineated when the GTV was outlined were only those visible after first-line treatment. The intensity-modulated radiation therapy (IMRT) technique was employed using 6-MV X-rays.

To assess whether increasing the cTRT dose influenced survival outcomes, patients were classified based on the biologically effective dose (BED), with 60 Gy as the threshold. Patients with a BED ≤60 Gy composed the low-dose group, and those with a BED >60 Gy composed the high-dose group. Three fractionation schemes were used: conventional fractionation radiotherapy (30–60 Gy, once daily; 1.5–2.5 Gy/fraction), hyperfractionation radiotherapy (45 Gy, twice daily; 1.5 Gy/fraction), or hypofractionation radiotherapy (30 Gy, once daily; 3 Gy/fraction). The delineation of organs at risk included the spinal cord, lungs, esophagus, and heart. The dose constraints for normal tissue irradiation were primarily based on two articles published in the *International Journal of Radiation Oncology Biology Physics* (16,17).

Efficacy and toxicity assessment

Imaging examinations were conducted every two cycles of systemic therapy before and after cTRT or upon clinical deterioration. Tumor response was assessed using the RECIST version 1.1 and categorized as a CR, partial response (PR), stable disease (SD), or progressive disease (PD) (18). To determine the local control time after cTRT, we monitored the PFS in the cTRT subgroup. PFS was defined as the time from cTRT initiation to recurrence, metastasis, or cancer-related death. OS was defined as the time from pathological diagnosis to death from any cause. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (version 5.0) (19).

Assessment of recurrence pattern

Patients with ES-SCLC who received radiotherapy were categorized into chest recurrence and distant recurrence groups based on the site of first progression after tumor radiotherapy. Chest recurrence was further divided into in-field recurrence and out-of-field recurrence. Chest recurrence CT images were imported into the Pinnacle 9.8 Radiotherapy Planning System [Philips Medical System (Cleveland), Inc., Cleveland, Inc., Fitchburg, WI, USA] and fused with the initial planning CT images collected from a Philips BigBore16 CT scanner [Philips Medical System (Cleveland), Inc., Cleveland, Inc.]. Subsequently, we delineated the volume of the recurrent tumors without knowledge of the original treatment target area to minimize potential measurement bias. We then described the spatial relationship between the volume of the recurrent tumors and the isodose lines (IDLs) of the treatment target area. Based on this spatial relationship, we classified recurrences as follows: in-field recurrence referred to ≥80% of the recurrent volume overlapping within the IDL of the treatment target area, while out-of-field recurrence referred to <80% of the recurrent volume overlapping within the IDL of the treatment target area. In-field recurrence was further subdivided into primary lesion recurrence and lymph node recurrence.

Statistical methods

Categorical variables are represented as percentages. Continuous variables with a normal distribution are expressed as the mean ± standard deviation, while nonnormally distributed continuous variables are expressed as the median and interquartile range (IQR). Group differences were evaluated using the Chi-square test for categorical variables and either the *t*-test or Mann-Whitney

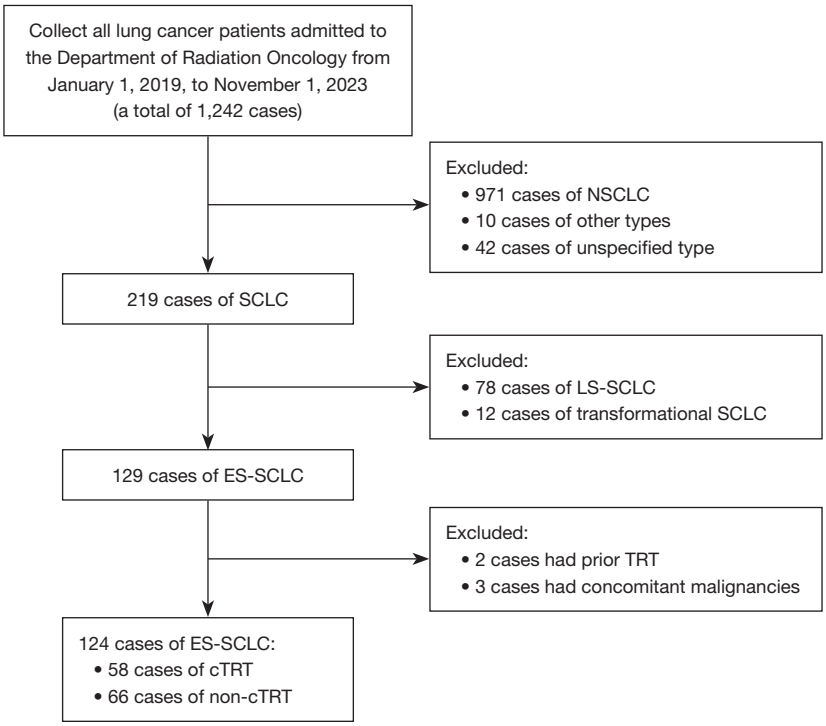

Figure 1 Flowchart of patient screening. NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; LS-SCLC, limited-stage small-cell lung cancer; ES-SCLC, extensive-stage small-cell lung cancer; TRT, thoracic radiotherapy; cTRT, consolidated thoracic radiotherapy.

test for continuous variables. Some continuous variables were dichotomized using the median cutoff or based on clinical significance. Survival data are presented as the Kaplan-Meier curves and were compared using the log-rank test. Univariable Cox regression was used for variable selection, and variables with a P value <0.05 were included in the multivariable Cox regression. If variables with a P value <0.05 in multivariable Cox regression were considered statistically significant and independently associated with prognosis. Statistical analysis was conducted using SPSS 25 (IBM Corp., Armonk, NY, USA) and R version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.Rproject.org).

Results

Patient characteristics and treatment

Out of 124 patients, 58 received cTRT and 66 did not. The patient selection process is detailed in *Figure 1*. There was a greater proportion of females in the non-cTRT group than in the cTRT group (P=0.02). Additionally, compared with the cTRT group, the non-cTRT group had a higher neuron-specific enolase (NSE) level (P=0.009) and lower blood sodium concentration (P=0.01). However, there were no significant differences between the two groups in terms of gender, age, PS, Nutritional Risk Screening (NRS) 2002 score, smoking status, underlying disease status, progastrin-releasing peptide (proGRP), or clinical stage. The baseline characteristics of the 124 patients are shown in *Table 1*.

In the cTRT group, patients received a median of four cycles of first-line chemotherapy, while in the non-cTRT group, the median was three cycles. Immunotherapy, primarily tislelizumab (27.27%) and serplulimab (21.21%), was administered to 33 patients. The median number of cycles for first-line immunotherapy was six across both groups. In the overall cohort, first-line treatment resulted in CR in 3.3%, PR in 51.7%, and SD in 30.8% of patients. Prophylactic cranial irradiation (PCI) was administered in nine patients: six in the cTRT group and three in the non-cTRT group. Among the 68 patients with brain metastases (54.8%), 60 received cranial irradiation, with bevacizumab injections added as needed to treat brain edema. Second-line treatment was administered to 77 (62.1%) patients,

Table 1 Baseline characteristics of patients with ES-SCLC

Characteristic	Overall (n=124)	Radiation targeting the thorax		P value
		cTRT (n=58)	Non-cTRT (n=66)	
Gender				0.02*
Female	11 (8.9)	1 (1.7)	10 (15.2)	
Male	113 (91.1)	57 (98.3)	56 (84.8)	
Age (years)	65.25 (9.64)	65.17 (8.36)	65.32 (10.70)	0.93
ECOG PS (points)				0.19
<2	95 (76.6)	48 (82.8)	47 (71.2)	
≥2	29 (23.4)	10 (17.2)	19 (28.8)	
NRS 2002 (points)				0.29
<3	85 (68.5)	43 (74.1)	42 (63.6)	
≥3	39 (31.5)	15 (25.9)	24 (36.4)	
Smoking				0.07
No	32 (25.8)	10 (17.2)	22 (33.3)	
Yes	92 (74.2)	48 (82.8)	44 (66.7)	
Underlying disease				0.34
No	66 (53.2)	34 (58.6)	32 (48.5)	
Yes	58 (46.8)	24 (41.4)	34 (51.5)	
ProGRP (pg/mL)	357.60 [52.18, 1,799.22]	204.36 [45.95, 860.34]	479.74 [69.36, 2,663.85]	0.15
NSE (ng/mL)	21.17 [8.56, 69.89]	15.87 [5.08, 42.84]	32.00 [12.57, 113.06]	0.009*
Sodium concentration (mmol/L)	139.85 [136.07, 141.80]	140.50 [138.57, 141.98]	138.25 [133.67, 141.48]	0.01*
T stage	n=117		n=59	0.81
1	17 (14.5)	10 (17.2)	7 (11.9)	
2	27 (23.1)	14 (24.1)	13 (22.0)	
3	10 (8.5)	5 (8.6)	5 (8.5)	
4	63 (53.8)	29 (50.0)	34 (57.6)	
N stage				0.30
0	3 (2.4)	3 (5.2)	0 (0.0)	
1	3 (2.4)	1 (1.7)	2 (3.0)	
2	58 (46.8)	27 (46.6)	31 (47.0)	
3	60 (48.4)	27 (46.6)	33 (50.0)	
M stage				0.81
1a	16 (12.9)	8 (13.8)	8 (12.1)	
1b	9 (7.3)	5 (8.6)	4 (6.1)	
1c	99 (79.8)	45 (77.6)	54 (81.8)	
Clinical stage				0.72
IVA	25 (20.2)	13 (22.4)	12 (18.2)	
IVB	99 (79.8)	45 (77.6)	54 (81.8)	

Data are presented as n (%), mean (standard deviation), or median [IQR]. *, P<0.05. ES-SCLC, extensive-stage small-cell lung cancer; cTRT, consolidative thoracic radiotherapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NRS, Nutritional Risk Screening; proGRP, progastrin-releasing peptide; NSE, neuron-specific enolase; IQR, interquartile range.

resulting in PR in 14.3% and SD in 40.3% of patients. Chemotherapy alone was the most common second-line therapy (71.43%), followed by oral targeted therapy with anlotinib (20.78%). In 7.79% of patients, immunotherapy was continued as a second-line treatment due to the charitable provision of additional medications by the China Red Cross Society Tumor Aid Project or based on clinical judgement by the attending physician. Additionally, 37 (29.84%) patients received third-line treatment, primarily oral targeted therapy with anlotinib (72.97%), followed by single-agent chemotherapy (27.03%). Third-line treatment led to PR in 21.6% of patients and SD in 13.5% of patients. In total, 11.29% of patients received treatment beyond the third line. Details of the systemic and local treatments for the entire cohort are presented in *Table 2*.

Of the 58 patients who received cTRT, 27 were in the low-dose group (BED ≤60 Gy), and 31 were in the high-dose group (BED >60 Gy). The fractionation schemes varied: 41 patients underwent conventional fractionated radiotherapy (30–60 Gy, once daily; 1.5–2.5 Gy/fraction), nine patients received hyperfractionation radiotherapy (45 Gy, twice daily; 1.5 Gy/fraction), seven patients underwent hypofractionation radiotherapy (30 Gy, once daily; 3 Gy/fraction), and one patient received stereotactic body radiotherapy (SBRT) (50 Gy, once daily; 10 Gy/fraction). Four patients deviated from the prescribed radiotherapy plan. The baseline characteristics of these patients are outlined in Tables S1,S2.

Treatment response and survival outcomes

As of November 27, 2023, the median follow-up time for the entire cohort was 11.13 months (IQR, 6.36–17.58 months), with a median survival time of 12.67 months [95% confidence interval (CI): 10.59–14.75]. Of the 124 patients, 97 (78.23%) died, including 44 (75.86%) patients in the cTRT group and 53 (80.30%) patients in the non-cTRT group; 24 patients were alive, and three were lost to follow-up. Patients who received cTRT demonstrated superior OS compared to those who did not [median OS: 15.5 *vs.* 10.5 months; hazard ratio (HR) =2.0497; 95% CI: 1.3548–3.1010; P<0.001], as depicted in *Figure 2*.

Among the 58 patients who received cTRT, the objective response rate (ORR) was 56.8%. Patients were divided into high-dose and low-dose groups based on the BED. In the low-dose group, PD accounted for 14.8%, SD for 25.9%, PR for 55.6%, and CR for 3.7%. In the high-dose group, PD accounted for 16.1%, SD for 29.0%, PR for 51.6%, and CR for 3.2%. There was no significant difference between the two groups (P=0.99). The ORRs for conventional fractionated, hyperfractionated, and hypofractionated radiotherapy were 53.6%, 77.8%, and 50.0%, respectively, but this did not represent a significant difference between the three groups (P=0.72). The detailed data are provided in Tables S3,S4. The median PFS for the 58 patients who received radiotherapy was 4.37 months (95% CI: 2.19–6.55). There was no significant difference between the high-dose and low-dose BED groups in terms of PFS (median: 4.63 *vs.* 3.63 months, P=0.94) or OS (median: 17.33 *vs.* 13.70 months, P=0.46) (*Figure 3A,3B*). Similarly, there was no significant difference between the conventional fractionated, hyperfractionated, and hypofractionated groups in terms of PFS (median: 4.63 *vs.* 5.03 *vs.* 2.60 months, P=0.39) or OS (median: 13.70 *vs.* 15.50 *vs.* 21.23 months, P=0.68) (*Figure 3C,3D*).

Recurrence patterns after cTRT

Until the last follow-up, three of the 58 patients remained recurrence-free, while six did not seek timely medical attention and died at home due to deteriorating conditions. This left 49 patients whose recurrence patterns were observed. Among them, 12 patients (24.5%) experienced thoracic recurrence, 28 patients (57.1%) experienced distant recurrence, and 9 patients (18.4%) experienced both thoracic and distant recurrence. Among the 21 patients who experienced thoracic recurrence, 16 (32.65%) experienced recurrence within the radiation field, and 5 (10.20%) experienced lymph node recurrence. There were no significant differences in recurrence patterns between the high-dose and low-dose groups (P=0.16) or between the different fractionation schemes (P=0.85). The detailed data are provided in Tables S5,S6.

Prognostic factors

According to univariate analysis, factors significantly correlated with OS in the entire patient cohort included Eastern Cooperative Oncology Group (ECOG) PS score (P=0.03), NRS 2002 score (P=0.03), proGRP level (P<0.001), sodium concentration (P<0.001), multiple symptoms (P<0.001), PCI (P=0.02), number of first-line treatment cycles (P<0.001), RECIST-assessed initial treatment response (P<0.001), immunotherapy (P=0.01), number of immunotherapy cycles (P=0.009), total systemic treatment cycles (P<0.001), and cTRT/non-cTRT

Table 2 Characteristics of systemic and local therapy treatment of ES-SCLC

Variables	Overall (n=124)	Radiation targeting the thorax		P value
		cTRT (n=58)	Non-cTRT (n=66)	
Local symptoms				0.17
No	73 (58.9)	39 (67.2)	34 (51.5)	
Bone metastases	44 (35.5)	17 (29.3)	27 (40.9)	
Spinal cord compression	3 (2.4)	0 (0.0)	3 (4.5)	
Superior vena cava syndrome	1 (0.8)	1 (1.7)	0 (0.0)	
Multiple symptoms	3 (2.4)	1 (1.7)	2 (3.0)	
Local radiotherapy	n=51	n=19	n=32	0.53
No	28 (54.9)	12 (63.2)	16 (50.0)	
Yes	23 (45.1)	7 (36.8)	16 (50.0)	
Brain metastasis				0.09
No	56 (45.2)	21 (36.2)	35 (53.0)	
Yes	68 (54.8)	37 (63.8)	31 (47.0)	
Brain radiotherapy	n=68	n=37	n=31	0.54
No	8 (11.8)	3 (8.1)	5 (16.1)	
WBRT	33 (48.5)	19 (51.4)	14 (45.2)	
SRT	15 (22.1)	7 (18.9)	8 (25.8)	
WBRT + SRT	12 (17.6)	8 (21.6)	4 (12.9)	
PCI				0.37
No	115 (92.7)	52 (89.7)	63 (95.5)	
Yes	9 (7.3)	6 (10.3)	3 (4.5)	
First-line chemotherapy regimens				0.26
No	3 (2.4)	0 (0.0)	3 (4.5)	
EP	89 (71.8)	46 (79.3)	43 (65.2)	
EC	29 (23.4)	11 (19.0)	18 (27.3)	
IP	2 (1.6)	1 (1.7)	1 (1.5)	
IC	1 (0.8)	0 (0.0)	1 (1.5)	
Cycles of first-line treatment	4.00 [2.00, 6.00]	4.00 [4.00, 6.00]	3.00 [2.00, 5.00]	0.001*
Immunotherapy				0.67
No	91 (73.4)	41 (70.7)	50 (75.8)	
Yes	33 (26.6)	17 (29.3)	16 (24.2)	
Initial treatment response	n=120		n=62	0.07
PD	17 (14.2)	5 (8.6)	12 (19.4)	
SD	37 (30.8)	17 (29.3)	20 (32.3)	
PR	62 (51.7)	32 (55.2)	30 (48.4)	
CR	4 (3.3)	4 (6.9)	0 (0.0)	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Overall (n=124)	Radiation targeting the thorax		P value
		cTRT (n=58)	Non-cTRT (n=66)	
Cycles of second-line treatment	1.00 [0.00, 3.00]	1.50 [0.00, 2.00]	1.00 [0.00, 3.00]	0.75
Second-line treatment response	n=77	n=37	n=40	0.60
PD	35 (45.5)	19 (51.4)	16 (40.0)	
SD	31 (40.3)	13 (35.1)	18 (45.0)	
PR	11 (14.3)	5 (13.5)	6 (15.0)	
Cycles of third-line treatment	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.78
Third-line treatment response	n=37	n=16	n=21	0.10
PD	24 (64.9)	9 (56.3)	15 (71.4)	
SD	5 (13.5)	1 (6.3)	4 (19.0)	
PR	8 (21.6)	6 (37.5)	2 (9.5)	
Cycles of fourth-line treatment	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	>0.99
Fourth-line treatment response	n=11	n=5	n=6	0.27
PD	6 (54.5)	2 (40.0)	4 (66.7)	
SD	4 (36.4)	3 (60.0)	1 (16.7)	
PR	1 (9.1)	0 (0.0)	1 (16.7)	
Cycles of fifth-line treatment	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.48
Fifth-line treatment response	n=3	n=2	n=1	0.67
PD	1 (33.3)	0 (0.0)	1 (100.0)	
SD	2 (66.7)	2 (100.0)	0 (0.0)	
Total cycles	6.00 [4.00, 11.00]	7.00 [5.00, 11.75]	5.00 [3.25, 11.00]	0.044*

Data are presented as n (%) or median [IQR]. *, P<0.05. ES-SCLC, extensive-stage small-cell lung cancer; cTRT, consolidative thoracic radiotherapy; WBRT, whole-brain radiotherapy; SRT, stereotactic radiotherapy; PCI, prophylactic cranial irradiation; EP, etoposide plus cisplatin; EC, etoposide plus carboplatin; IP, irinotecan plus cisplatin; IC, irinotecan and carboplatin; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; IQR, interquartile range.

(P<0.001). Multivariable Cox regression analysis revealed that the sodium concentration (P=0.007), initial treatment response as per RECIST (P=0.048), total number of systemic treatment cycles (P=0.005), and cTRT/non-cTRT (P=0.02) were independently correlated with OS. The detailed information is provided in *Table 3*.

Toxicity

In the comparison of the radiation doses in normal tissues between the high-dose and low-dose groups, the low-dose group exhibited a lower average lung dose than did the high-dose group (P=0.045). The lung V_{20} did not significantly differ between the groups, whereas the lung V_{30} was lower in the low-dose group (P=0.02). Additionally, the low-dose group had a lower spinal cord dose (P=0.004) and heart V_{40} (P=0.02). The details are provided in *Table 4*. As it relates to the fractionation schemes, doses to normal tissues were lowest in the hypofractionation radiotherapy group (all P values <0.05), as indicated in *Table 5*.

In terms of hematologic toxicity, grade ≥3 neutropenia was the most common adverse event, occurring in approximately 31% of patients. One patient experienced grade 4 thrombocytopenia, but there were no treatment-related deaths. Concerning nonhematologic toxicity, 5.2% of patients developed grade 2 radiation-induced esophagitis (RIE), with no instances of grade 3 or higher RIE. Additionally, 17.2% of patients experienced grade

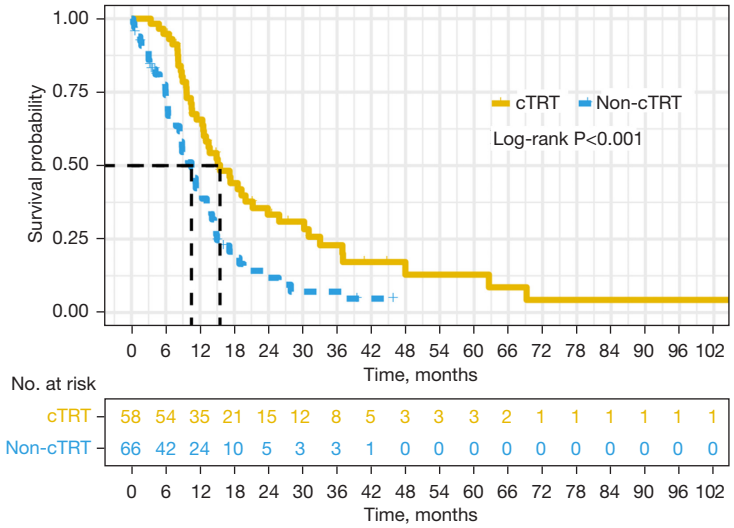

Figure 2 K-M survival curves of patients with ES-SCLC treated with cTRT or non-cTRT. cTRT, consolidative thoracic radiotherapy; K-M, Kaplan-Meier; ES-SCLC, extensive-stage small-cell lung cancer.

2 radiation-induced pneumonia (RIP), without any occurrences of RIP of grade 3 or higher. Adverse reactions were similar across the high-dose and low-dose groups, and patients treated with different fractionation schemes experienced comparable adverse reactions. Detailed summaries of the hematologic and nonhematologic toxicities can be found in *Tables 4*,*5*, respectively.

Discussion

We conducted a retrospective cohort study to investigate the efficacy and safety of cTRT in patients with ES-SCLC in the context of immunotherapy. Our study revealed that patients receiving cTRT exhibited improved OS, which is consistent with previous findings (12,13). This single-center, retrospective cohort study examined the importance of ongoing cTRT in ES-SCLC treatment within the context of immunotherapy. Our results support the continued clinical significance of cTRT for patients with ES-SCLC. Despite advancements in immunotherapy, radiotherapy can exert synergistic effects and contribute to survival benefit. However, in contrast to the findings of Li *et al.* (15), they did not find that cTRT improved PFS or OS, and thus the safety and outcomes of this regimen may remain unclear until the randomized phase III NRG-LU007 and TRIPLEX trials mature. However, we did find that the toxicity of cTRT was manageable, which is consistent with prior research (13,20-22). Neutropenia was the most common hematologic side effect, while nonhematologic side effects such as RIE and pneumonia were grade 2 or lower, indicating the safety and feasibility of cTRT in patients with ES-SCLC receiving immunotherapy. This suggests that myeloprotection should be enhanced after chemotherapy in patients with ES-SCLC (23,24).

Our study also accounted for various potential confounding factors in multivariable analysis, such as first-line treatment response and total systemic treatment cycles, providing a more comprehensive evaluation of cTRT's impact on the survival of patients with ES-SCLC. These findings suggest that cTRT can be an effective treatment strategy for improving the survival outcomes of patients with ES-SCLC receiving immunotherapy combined with chemotherapy.

Several retrospective studies have indicated that administering cTRT after first-line immunotherapy combined with chemotherapy can confer survival benefits (12,13,20). Our study's conclusions align with these findings, but we provided a more comprehensive comparison of the impact of different radiotherapy doses and fractionation schemes on patient survival, offering more specific clinical guidance. We found no significant differences in PFS or OS among patients treated with various radiotherapy doses and fractionation schemes. Considering the reduction in the radiation dose to normal tissues and the conservation of medical resources, we believe a prescription dose of 30 Gy/10 fraction seems appropriate. Although no significant differences in survival outcomes were observed between the different doses and fractionation

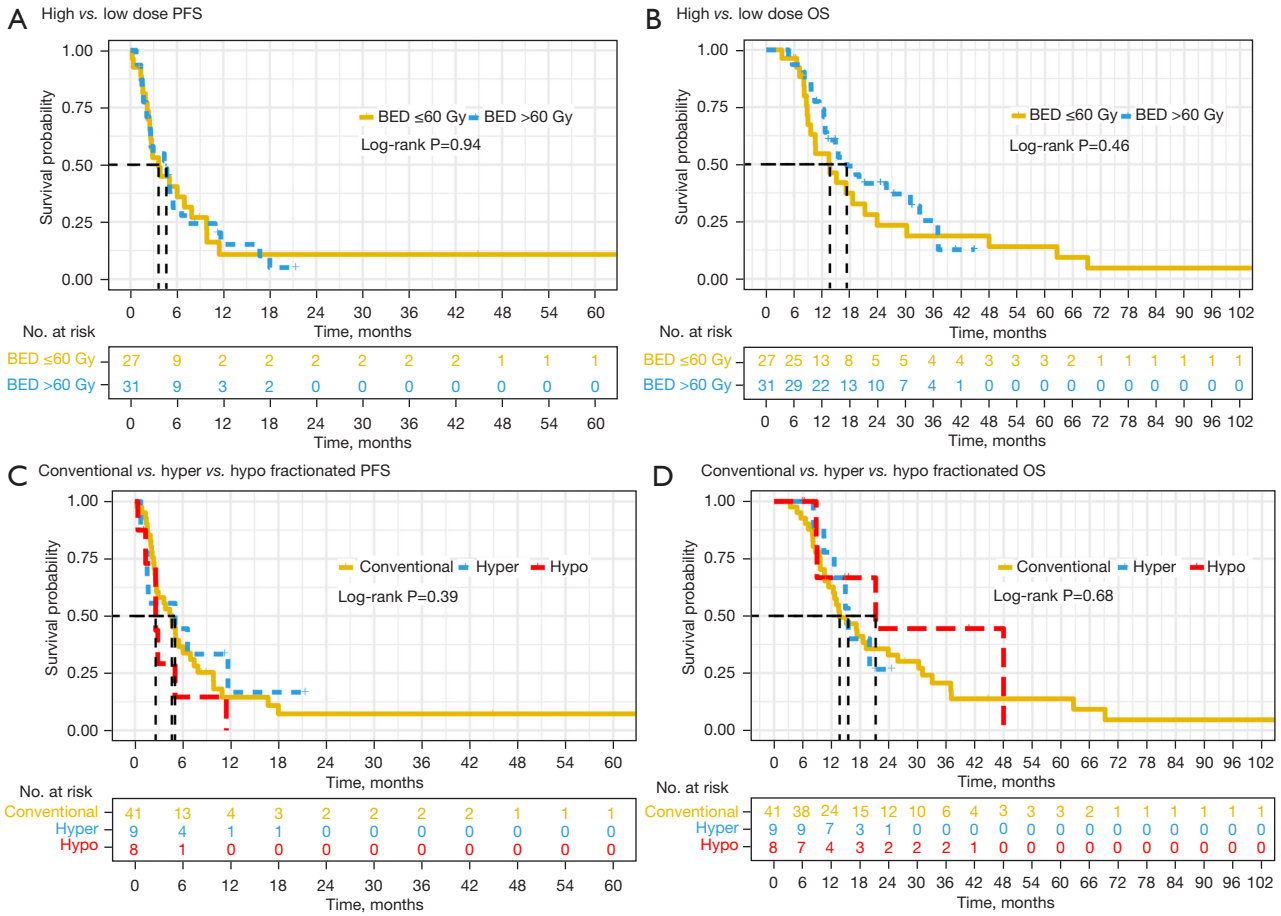

Figure 3 K-M survival curves of patients with ES-SCLC who received different doses of fractionated radiotherapy. (A) PFS curves of patients who received different radiotherapy doses. (B) OS curves of patients who received different radiotherapy doses. (C) PFS curves of patients who received different radiotherapy fractions. (D) OS curves of patients who received different radiotherapy fractions. PFS, progression-free survival; BED, biologically effective dose; OS, overall survival; hyper, hyperfractionated; hypo, hypofractionated; K-M, Kaplan-Meier; ES-SCLC, extensive-stage small-cell lung cancer.

schemes, the small sample sizes in certain subgroups might have influenced this conclusion. There may be differences in the synergistic therapeutic response between different radiotherapy doses, fractionation schemes, and immunotherapeutic agents (25,26), and it is important to balance the dose of radiotherapy with side effects such as radiation pneumonitis (27). Therefore, it may not be that radiotherapy dose and fractionation are insignificant. More research on the personalized treatment decisions based on patient factors and clinical conditions is required. In the era of immunotherapy, reevaluating cTRT dosing and fractionation is essential. Our study offers valuable insights and urges further investigation to optimize the synergy between radiotherapy and immunotherapy.

Administering cTRT after first-line chemotherapy combined with immunotherapy has been shown to improve LCR (12,13). However, most published clinical trials did not categorize recurrence into specific types, such as hilar or mediastinal lymph node recurrence, primary site recurrence, and distant recurrence. Our study revealed an ORR of 56.8% among 58 patients who received radiotherapy, with a median PFS of 4.37 months (95% CI: 2.19–6.55). Pure chest progression occurred in 24.5% of patients, while 18.4% experienced both chest and distant recurrence, indicating that 57.1% achieved local control. We believe that maintaining local control to minimize or delay symptom onset is a crucial clinical goal in managing incurable malignant tumors. If the goal is to control local symptoms, the fact that only 10.20% (5/49) of patients experienced intrathoracic recurrence in the radiation field

Table 3 Univariable and multivariable Cox regression analysis in 124 patients with ES-SCLC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender	0.9499 (0.4719–1.9121)	0.89		
Age (years)	1.2605 (0.9148–1.7370)	0.16		
ECOG PS (points)	4.5973 (1.1758–17.975)	0.03	1.3204 (0.2349–7.4211)	0.75
NRS 2002 (points)	1.6063 (1.0498–2.4578)	0.03	1.3545 (0.8379–2.1896)	0.22
Smoking	0.9999 (0.6330–1.5798)	>0.99		
Underlying disease	1.2450 (0.8335–1.8596)	0.28		
ProGRP (pg/mL)	1.0808 (1.0337–1.1301)	<0.001	1.0207 (0.9576–1.0880)	0.53
NSE (ng/mL)	1.0034 (0.9979–1.0090)	0.22		
Sodium concentration (mmol/L)	0.8653 (0.8022–0.9334)	<0.001	0.8751 (0.7944–0.9642)	0.007*
T stage	1.1690 (0.8260–1.6545)	0.38		
N stage	1.1752 (0.8987–1.5368)	0.24		
M stage	0.9330 (0.5376–1.6193)	0.81		
Clinical stage	0.9979 (0.6147–1.6200)	0.99		
Local symptoms	1.3062 (0.8658–1.9705)	0.20		
Bone metastases	1.2540 (0.8231–1.9107)	0.29		
Spinal cord compression	1.0402 (0.2548–4.2468)	0.96		
Superior vena cava syndrome	0.0065 (0.0000–244620)	0.62		
Multiple symptoms	7.7051 (2.3334–25.443)	<0.001	2.6295 (0.2151–32.141)	0.45
Local radiotherapy	1.0286 (0.5432–1.9477)	0.93		
Brain metastasis	0.8650 (0.5767–1.2975)	0.48		
Brain radiotherapy	2.0461 (0.9146–4.5778)	0.08		
WBRT	1.3195 (0.7732–2.2518)	0.31		
SRT	0.8707 (0.4679–1.6202)	0.66		
WBRT + SRT	0.4873 (0.2194–1.0824)	0.08		
PCI	0.3482 (0.1403–0.8638)	0.02	0.4722 (0.1781–1.2520)	0.13
First-line chemotherapy regimens[†]	0.8959 (0.5205–1.5420)	0.69		
Cycles of first-line treatment	0.1530 (0.0851–0.2751)	<0.001	0.4684 (0.2134–1.0282)	0.059
RECIST-assessed initial treatment response	0.4846 (0.3681–0.6379)	<0.001	0.7022 (0.4949–0.9964)	0.048*
Immunotherapy	0.5160 (0.3085–0.8632)	0.01	0.9696 (0.4054–2.3188)	0.94
Cycles of immunotherapy	0.9243 (0.8712–0.9806)	0.009	1.0359 (0.9146–1.1733)	0.58
Total systemic treatment cycles	0.5377 (0.3985–0.7255)	<0.001	0.5501 (0.3618–0.8364)	0.005*
cTRT or non-cTRT	2.0497 (1.3548–3.1010)	<0.001	1.7484 (1.1033–2.7708)	0.02*

[†], the first-line chemotherapy regimen was categorized into two groups: cisplatin or carboplatin. *, P<0.05. ES-SCLC, extensive-stage small-cell lung cancer; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NRS, Nutritional Risk Screening; proGRP, progastrin-releasing peptide; NSE, neuron-specific enolase; WBRT, whole-brain radiotherapy; SRT, stereotactic radiotherapy; PCI, prophylactic cranial irradiation; RECIST, Response Evaluation Criteria in Solid Tumors; cTRT, consolidative thoracic radiotherapy.

Table 4 Radiation doses to normal tissues and RTOG acute and chronic radiation injury grading were evaluated in 58 patients with ES-SCLC treated with regimens of different doses

Variables	Overall (n=58)	Radiation dose		P value
		BED ≤60 Gy (n=27)	BED >60 Gy (n=31)	
Lung mean (cGy)	1,139.70 [860.22, 1,293.17]	1,074.20 [768.90, 1,220.10]	1,221.90 [977.50, 1,356.20]	0.045*
Lung V_5 (%)	42.42 [34.00, 48.12]	43.02 [33.80, 47.21]	41.34 [34.89, 48.87]	0.98
Lung V_{20} (%)	22.02 [16.66, 26.20]	19.15 [15.19, 26.17]	22.82 [19.89, 26.21]	0.26
Lung V_{30} (%)	13.95 [9.32, 17.65]	10.84 [5.12, 17.16]	16.53 [12.90, 18.42]	0.02*
Spinal cord Dmax (cGy)	4,335.50 [3,744.90, 4,481.92]	4,060.10 [3,339.20, 4,419.80]	4,449.90 [4,154.30, 4,588.10]	0.004*
Heart mean (cGy)	1,482.34 (588.46)	1,457.17 (668.56)	1,506.50 (512.81)	0.77
Heart V_{30} (%)	20.30 (10.35)	19.04 (11.97)	21.52 (8.60)	0.41
Heart V_{40} (%)	12.51 [5.62, 19.03]	7.73 [0.14, 15.12]	15.77 [11.10, 21.15]	0.02*
WBC suppression grade				0.29
Normal	26 (44.8)	14 (51.9)	12 (38.7)	
I/II	14 (24.1)	4 (14.8)	10 (32.3)	
III/IV	18 (31.0)	9 (33.3)	9 (29.0)	
Neutrophil suppression grade				0.65
Normal	19 (32.8)	8 (29.6)	11 (35.5)	
I/II	21 (36.2)	9 (33.3)	12 (38.7)	
III/IV	18 (31.0)	10 (37.0)	8 (25.8)	
Hemoglobin suppression grade				0.71
Normal	19 (32.8)	10 (37.0)	9 (29.0)	
I/II	39 (67.2)	17 (63.0)	22 (71.0)	
Platelet suppression grade				0.51
Normal	54 (93.1)	25 (92.6)	29 (93.5)	
I/II	3 (5.2)	2 (7.4)	1 (3.2)	
III/IV	1 (1.7)	0 (0.0)	1 (3.2)	
Radiation esophagitis grade				0.25
Normal	38 (65.5)	19 (70.4)	19 (61.3)	
I	17 (29.3)	8 (29.6)	9 (29.0)	
II	3 (5.2)	0 (0.0)	3 (9.7)	
Radiation pneumonitis grade				0.14
Normal	45 (77.6)	24 (88.9)	21 (67.7)	
I	3 (5.2)	1 (3.7)	2 (6.5)	
II	10 (17.2)	2 (7.4)	8 (25.8)	

Data are presented as median [IQR], mean (standard deviation), or n (%). *, P<0.05. RTOG, Radiation Therapy Oncology Group; ES-SCLC, extensive-stage small-cell lung cancer; BED, biologically effective dose; Dmax, maximum dose; WBC, white blood cell; IQR, interquartile range.

Table 5 Radiation doses to normal tissues and RTOG acute and chronic radiation injury grading were evaluated in 58 patients with ES-SCLC receiving different fractionation regimens

Variables	Different fractionated radiotherapy			P value
	Conventional fractionated (n=41)	Hyperfractionated (n=9)	Hypofractionated (n=8)	
Lung mean (cGy)	1,221.00 [1,033.38, 1,333.62]	918.35 [854.87, 1,022.62]	618.40 [531.05, 706.13]	<0.001*
Lung V_5 (%)	44.26 [39.75, 49.42]	39.11 [35.68, 41.11]	31.98 [27.37, 40.28]	0.02*
Lung V_{20} (%)	25.16 [20.01, 26.71]	19.16 [17.55, 22.14]	10.33 [6.67, 12.92]	<0.001*
Lung V_{30} (%)	17.01 [11.75, 18.29]	10.27 [9.32, 13.40]	1.30 [0.96, 1.64]	<0.001*
Spinal cord Dmax (cGy)	4,382.05 [4,122.12, 4,484.98]	4,436.80 [4,005.95, 4,507.73]	2,351.20 [2,254.05, 2,686.20]	0.003*
Heart mean (cGy)	1,659.18 (502.63)	1,268.95 (464.51)	755.77 (517.41)	<0.001*
Heart V_{30} (%)	23.56 (8.46)	17.99 (8.92)	5.53 (7.04)	<0.001*
Heart V_{40} (%)	14.90 [8.50, 21.20]	10.77 [6.68, 15.77]	0.00 [0.00, 0.00]	<0.001*
WBC suppression grade				0.38
Normal	20 (48.8)	2 (22.2)	4 (50.0)	
I/II	11 (26.8)	2 (22.2)	1 (12.5)	
III/IV	10 (24.4)	5 (55.6)	3 (37.5)	
Neutrophil suppression grade				0.34
Normal	14 (34.1)	3 (33.3)	2 (25.0)	
I/II	17 (41.5)	1 (11.1)	3 (37.5)	
III/IV	10 (24.4)	5 (55.6)	3 (37.5)	
Hemoglobin suppression grade				0.07
Normal	16 (39.0)	0 (0.0)	3 (37.5)	
I/II	25 (61.0)	9 (100.0)	5 (62.5)	
Platelet suppression grade				0.78
Normal	37 (90.2)	9 (100.0)	8 (100.0)	
I/II	3 (7.3)	0 (0.0)	0 (0.0)	
III/IV	1 (2.4)	0 (0.0)	0 (0.0)	
Radiation esophagitis grade				0.20
Normal	24 (58.5)	6 (66.7)	8 (100.0)	
I	15 (36.6)	2 (22.2)	0 (0.0)	
II	2 (4.9)	1 (11.1)	0 (0.0)	
Radiation pneumonitis grade				0.55
Normal	31 (75.6)	7 (77.8)	7 (87.5)	
I	2 (4.9)	0 (0.0)	1 (12.5)	
II	8 (19.5)	2 (22.2)	0 (0.0)	

Data are presented as median [IQR], mean (standard deviation), or n (%). *, P<0.05. RTOG, Radiation Therapy Oncology Group; ES-SCLC, extensive-stage small-cell lung cancer; Dmax, maximum dose; WBC, white blood cell; IQR, interquartile range.

of the hilum or mediastinal lymph nodes raises the question as to whether these areas should be included as target regions. This presents a dilemma for radiation oncologists. However, including these lymph nodes in the target area may increase the irradiation of normal tissues, raising the risk of adverse reactions, which could counter the goal of symptom control, while excluding these lymph nodes from the target area may reduce LCR. Therefore, future research should investigate the optimal radiation target range and explore the potential of involved-field irradiation.

First-line favorable treatment response, longer total systemic treatment cycles, and receiving cTRT were identified as independent factors correlated with a longer OS. These findings highlight the importance of treatment response, especially in patients receiving cTRT after first-line treatment, which may lead to improved survival outcomes. Additionally, consistent with previous studies (28,29), hyponatremia was identified as an adverse prognostic factor in patients with ES-SCLC. This underscores the importance of considering hematologic parameters when assessing patient survival and highlights the need for nutritional support and metabolic management in the treatment of ES-SCLC (30,31).

This retrospective cohort study reflects actual clinical practice but has several limitations. First, as a single-center retrospective study, selection and information biases could be a factor. Second, the relatively small sample size may reduce the stability and reliability of the results. Additionally, due to the study design, some clinical data were missing, which might have impacted the analysis. Given these limitations, future research should involve multicenter, prospective, randomized controlled trials to further validate the efficacy and safety of cTRT in treating patients with ES-SCLC on immunotherapy. Furthermore, in-depth molecular biology studies could clarify the effect of different doses and fractionations on tumor characteristics. Additionally, comparisons should be made between concurrent cTRT with immunotherapy and sequential immunotherapy after cTRT to identify more effective treatment strategies.

Conclusions

cTRT treatment improved the OS of patients with ES-SCLC, and the associated treatment-related toxicity was tolerable and manageable. However, further research is needed to assess the impact of administering different radiotherapy doses and fractionation schemes on patients OS. Multicenter, prospective, randomized controlled trials are needed in the future to further validate the efficacy and safety of cTRT in the treatment of ES-SCLC in the immunotherapy context.

Acknowledgments

Funding: This research was supported by the National Natural Science Foundation of China (No. 82003231), the Zhejiang Basic Public Welfare Research Fund (No. ZCLTGY24H1606), the Zhejiang Medical Health Science and Technology Program (Nos. 2024KY553 and 2025KY1897), the Taizhou Cancer Hospital Science and Technology Incubation Project (Nos. 2024TZZD02, 2024TZZD03, and 2024TZYB04), and the Wenling Science and Technology Program (Nos. 2020S0040001, 2021S00002, 2021S00080, 2021S00081, 2021S00088, 2024S00137, and 2024S00138).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1182/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1182/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1182/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1182/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the institutional ethics committee of the Taizhou Cancer Hospital (No. SL2024046) and was conducted in accordance with the Helsinki Declaration (as revised in 2013). The requirement of informed consent was waived due to the retrospective nature of the study.

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Cite this article as: Zheng L, Yang Y, Bu F, Ye R, Zhang F, Ji Z, Zhu X, Chen H, Shao R, Liu L, Ying X, Zhu L, Wang E, Feng J, Shi Z, Fang J, Wang Y, Zhou Z, You G. Efficacy and safety of consolidative thoracic radiotherapy after first-line chemoimmunotherapy in patients with extensive-stage small-cell lung cancer: a retrospective cohort study. Transl Lung Cancer Res 2024;13(12):3675-3691. doi: 10.21037/tlcr-2024-1182