Efficacy and safety of thoracic radiotherapy for extensive stage small cell lung cancer after immunotherapy in real world

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Research Article

Keywords: ES-SCLC, Chemoimmunotherapy, Thoracic Radiotherapy, Toxicity

Posted Date: May 9th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2891756/v1

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Abstract

Purpose

The immunotherapy combined chemotherapy has been the standard treatment strategy for extensive-stage small lung cancer (ES-SCLC). The CREST trial reported consolidative thoracic radiotherapy (cTRT) improved overall survival (OS) for ES-SCLC with intrathoracic residual after chemotherapy. This study was aimed to evaluate the efficacy and safety of TRT for ES-SCLC after first line chemoimmunotherapy.

Methods

ES-SCLC patients who received immunotherapy in Zhejiang Cancer Hospital has been retrospectively analyzed between January 2020 and November 2021. Patients were assigned to receive either TRT or no TRT. Oligo-metastatic disease was defined as 3 or less discrete distant metastases with no more than 2 organs. Propensity score matching (PSM) was performed in two groups. The main outcome measures were progression-free survival (PFS), local recurrence-free survival (LRFS) and OS.

Results

111 patients with ES-SCLC were enrolled in this study, the median OS was 14 months. 39 patients received TRT after chemoimmunotherapy (TRT group) and 72 patients did not receive TRT (no TRT group). TRT group improved OS (HR 0.58, 95% CI 0.34–0.99, p = 0.0445), PFS (HR 0.59, 95% CI 0.38–0.90, p = 0.0149) and LRFS (HR 0.3, 95% CI 0.16–0.56, p = 0.0001). Further sub-cohort analysis, TRT significantly improved LRFS in patients with oligo-metastasis and without liver metastasis. This trend persisted after PSM. However, OS in oligo-metastasis and non-liver metastasis subgroup was without significant difference.

Conclusion

TRT improved LRFS, PFS and OS for ES-SCLC with thoracic residual after chemoimmunotherapy with well tolerated toxicity.

1. Introduction

Lung cancer is the main cause of cancer incidence and mortality in the world [1]. Nearly 15% of lung cancer patients diagnosed with small cell lung cancer (SCLC), and with two of thirds were extensive stage with poor prognosis [2]. In the past 40 years, platinum-doublet chemotherapy regimen was the standard treatment for ES-SCLC, with median overall survival (OS) only 10 months and 2-year survival rate of less than 5% [3].

Thoracic radiotherapy (TRT) plays an important role in the comprehensive treatment for ES-SCLC in the era of chemotherapy. Jeremic et al [4] demonstrated that TRT could significantly improve local control and survival compared with chemotherapy alone. The phase III randomized controlled trial of CREST
study confirmed the consolidative TRT significantly improved the survival and 2-year OS increased from 3–13%. TRT decreased approximately 50% intrathoracic progression (TRT vs no TRT, 43.6% vs 79.8%, p<0.0001) [5]. In addition, post-hoc analysis showed that patients with less than 2 metastases benefited more from TRT, and patients with bone or liver metastasis were related with worse OS [6].

Immunotherapy has changed the standard treatment strategy of ES-SCLC, which has remained unchanged for nearly 40 years. IMpower 133 [7] and CASPIAN [8] studies showed the combination of immunotherapy and chemotherapy improved OS of ES-SCLC by 2 months. Keynote 604 study also showed that compared with standard chemotherapy, PD-1 inhibitor plus chemotherapy significantly prolonged PFS [9]. ICIs have shown certain clinical benefit for ES-SCLC patient, however, still more than half of the patients progressed within 6 months, and the efficacy of ICIs is still unsatisfactory.

Radiotherapy could improve the efficacy of ICIs by inducing immunogenic cell death and regulating the microenvironment [10], both PACIFIC [11] and GEMSTOM 301 [12] study confirmed the combination of TRT and ICIs greatly improved the survival of NSCLC. Therefore, this retrospective study was aimed to evaluate the efficacy and safety of TRT for ES-SCLC after first line treatment of chemoimmunotherapy.

2. Methods

2.1 Patients eligibility

The patients diagnosed with ES-SCLC who received immunotherapy were retrospectively reviewed from January 2020 to November 2021 at xxx Hospital (n = 293). A total of 111 patients were screened from 293 patients and included in this study. The main inclusion criteria were: 1) patients were pathologically or cytologically diagnosed with ES-SCLC; 2) received at least 2 doses of chemoimmunotherapy as first line treatment therapy. The exclusion criteria were: 1) pathologically confirmed as mixed small cell carcinoma; 2) received any other anti-tumor therapy before immunotherapy. The immunotherapy regimen was durvalumab or atezolizumab. And the chemotherapy regimen was platinum etoposide. Oligometastatic disease was defined as 3 or less discrete distant metastases with no more than 2 organs. The study was approved by the Ethics Committee of xxx Hospital.

2.2 TRT procedure

The patients who underwent TRT were immobilized in supine position on vacuum cushions or thermoplastic masks and underwent CT scan with a maximal slice thickness of 5mm. The planning target volume included the post-treatment volume including primary tumor and lymph nodes. Treatment was delivered by linear accelerator (6 MV) with prescribed doses ranged from 24Gy to 60Gy.

2.3 Follow up

Patients were followed up every 3 months for first 2 years, then every 6 months thereafter. A routine chest and abdomen CT scan were necessary for each follow-up. And additional examination including FDG-PET CT scan, brain CT or magnetic resonance imaging (MRI) for metastatic lesions surveillance or
confirm suspected disease relapse were optional. Progression-free survival was defined as the time interval between the date of diagnosis and the date of radiologic progression or death. Local recurrence-free survival was defined as the time interval between the date of diagnosis and the date of radiologic thoracic progression or death. Overall survival was defined as the time interval between the date of diagnosis and death. The treatment-related toxicity was evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCICTCAE, version 5.0).

### 2.4 Statistical analysis

Median follow-up time was calculated by the reverse Kaplan-Meier method. OS and PFS were calculated by the Kaplan-Meier method and compared with the log-rank test between RT and no RT group, and TPFS was compared with the log-rank test between consolidative TRT and no RT group. Hazard ratios (HRs) and 95% CIs estimated by a Cox proportional hazards model after testing the proportional hazards assumption. Statistical analyses were performed in all enrolled patients and also in patients by using PSM. To perform PSM, a logistic regression model was fit to the data using the following variables: oligometastasis and liver metastasis. The propensity score calculated for each observation was saved to a data set and used to match similar records from the RT and no RT groups. The macro OneToManyMTCH was used to perform a 1:1 match [13]. All analyses were performed in SAS software 9.4 (SAS Inc., Cary, N.C., USA). A two-sided P value 0.05 was considered statistically significant.

### 3. Results

#### 3.1 Patients and treatment characteristics

Between January 2020 to November 2021, a total of 111 patients identified from 293 patients with ES-SCLC who received at least 2 doses of chemoimmunotherapy were enrolled in this study. Chemotherapy consisted of a platinum etoposide combination for 110 patients, with 1 patient received irinotecan plus cis-platinum regimen. 39 patients received TRT (TRT group), and 72 patients did not receive TRT (no TRT group). TRT was delivered as 45Gy in 30 fractions for most patients (21/39), twice daily, 30Gy in 10 fractions for 2 patients and 50-60Gy in 25–30 fractions for 13 patients. 3 patients were delivered with stereotactic body radiation therapy for the primary sites with 40-50Gy in 5 fractions. The basic characteristics of the 111 patients were shown in Table 1.
Table 1. The clinical characteristics of 111 patients with ES-SCLC.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TRT (N = 39)</th>
<th>No TRT (N = 72)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>62 (58–68)</td>
<td>64 (61–70)</td>
<td>0.0686</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.8844</td>
</tr>
<tr>
<td>Male</td>
<td>36 (92.31%)</td>
<td>68 (93.06%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3 (7.69%)</td>
<td>5 (6.94%)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td>0.0448</td>
</tr>
<tr>
<td>Yes</td>
<td>26 (66.67%)</td>
<td>60 (83.33%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (33.33%)</td>
<td>12 (16.67%)</td>
<td></td>
</tr>
<tr>
<td>Oligo-metastasis</td>
<td></td>
<td></td>
<td>0.0030</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (43.59%)</td>
<td>52 (72.22%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (56.41%)</td>
<td>20 (27.78%)</td>
<td></td>
</tr>
<tr>
<td>Bone metastasis</td>
<td></td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>No</td>
<td>31 (79.49%)</td>
<td>43 (59.72%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (20.51%)</td>
<td>29 (40.28%)</td>
<td></td>
</tr>
<tr>
<td>Liver metastasis</td>
<td></td>
<td></td>
<td>0.0012</td>
</tr>
<tr>
<td>No</td>
<td>34 (87.18%)</td>
<td>41 (56.94%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (12.82%)</td>
<td>31 (43.06%)</td>
<td></td>
</tr>
<tr>
<td>Immunotherapy maintenance</td>
<td></td>
<td></td>
<td>0.5788</td>
</tr>
<tr>
<td>No</td>
<td>11 (28.21%)</td>
<td>24 (32.33%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (71.79%)</td>
<td>48 (66.67%)</td>
<td></td>
</tr>
<tr>
<td>Response after chemoimmunotherapy</td>
<td></td>
<td></td>
<td>0.5154</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (2.56%)</td>
<td>1 (1.39%)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (92.32%)</td>
<td>61 (84.72%)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>1 (2.56%)</td>
<td>7 (9.72%)</td>
<td></td>
</tr>
<tr>
<td>Progression disease</td>
<td>1 (2.56%)</td>
<td>3 (4.17%)</td>
<td></td>
</tr>
</tbody>
</table>

3.2 Survival analyses
Up to 30 September 2022, the median follow-up was 18 months. In the entire cohort, the median OS was 14 months (95% CI 12–20), 95 patients have progressed after chemoimmunotherapy. 20 patients in TRT group died compared with 46 in no TRT group, with 32 versus 63 progression-free survival events. The intrathoracic progression has significantly decreased after TRT (Table S1).

**Supplementary Table S1. Progression patterns of 95 patients.**

Median overall survival was 21 months (95% CI 14–25) in TRT group versus 12 months (95% CI 10–15) in no TRT group. Overall survival at 12- and 18-month were 71.21% and 57.86% respectively, in TRT group versus 61.52% and 45.52% in no TRT group (HR 0.58 95% CI 0.34–0.99, p = 0.0445, Fig. 1).

**Figure 1. Kaplan-Meier curve for overall survival.**

Median PFS was 7 months in TRT group (95% CI 6–9) and 5 months in no TRT group (95% CI 4–6). The 6- and 12- month PFS were 64.10% and 12.52%, respectively, in TRT group, versus 31.65% and 10.33% in no TRT group (HR 0.59, 95% CI 0.38–0.90, p = 0.0149, Fig. 2.) In addition, the PFS was significantly different between patients who were with oligo-metastasis (p = 0.01).

**Figure 2. Kaplan-Meier curve for progression-free survival.**

Among the 39 patients in TRT group, 27 patients received consolidative TRT (cTRT) after chemoimmunotherapy, and another 12 patients received TRT after local thoracic progression. Thus, 27 patients were included in analysis of local recurrence-free survival (LRFS). Thoracic progression was less likely in cTRT group than in no cTRT group (HR = 0.30, 95% CI 0.16–0.56, p = 0.0001, Fig. 3.) In the subgroup analysis, the LRFS was significantly different between patients who were with oligo-metastasis (p = 0.0029) and non-liver metastasis (p = 0.0006) (Fig. 4).

**Figure 3. Kaplan-Meier curve for local recurrence-free survival.**

**Figure 4. Local recurrence-free survival in subgroups.**

### 3.3 Survival analyses after PSM

Further, PSM was performed as 1:1 match in oligo-metastasis, liver metastasis and bone metastasis subgroup. TRT significantly improved LRFS and PFS in patients with oligo-metastasis and non-liver metastasis after PSM. However, there was no significant difference of OS in these subgroups (Table 2).
Table 2. Statistical analyses result after PSM.

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>OS</th>
<th>PFS</th>
<th>LRFS</th>
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<tr>
<td></td>
<td></td>
<td>TRT</td>
<td>No TRT</td>
<td>P</td>
</tr>
<tr>
<td>Overall</td>
<td>66</td>
<td>21 (12–25)</td>
<td>13 (14-NR)</td>
<td>0.5893</td>
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<tr>
<td>Oligo-metastasis</td>
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<tr>
<td>Yes</td>
<td>32</td>
<td>17 (9–25)</td>
<td>14 (10–16)</td>
<td>0.9225</td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>25 (11–25)</td>
<td>NR</td>
<td>0.4154</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>17 (8–NR)</td>
<td>12 (5–NR)</td>
<td>0.2595</td>
</tr>
<tr>
<td>No</td>
<td>56</td>
<td>21 (12–25)</td>
<td>15 (11–NR)</td>
<td>0.6901</td>
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<td>Bone metastasis</td>
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<tr>
<td>Yes</td>
<td>20</td>
<td>25 (5–25)</td>
<td>16 (6–NR)</td>
<td>0.9790</td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>21 (12–25)</td>
<td>12 (10–NR)</td>
<td>0.6588</td>
</tr>
</tbody>
</table>

3.4 Toxicity

Hematologic toxicity was mild to moderate in both groups. There was no grade V adverse event. Severe hematologic toxicity was infrequent. 11 patients developed grade III-IV myelosuppression in TRT group and 15 patients in no TRT group. 1 patient in TRT group underwent grade III esophagitis. In no TRT group, 1 patient have grade III pneumonitis.

4. Discussion
The combination of chemotherapy and immunotherapy has been new treatment standard for ES-SCLC after decades without a change based on the etoposide with platinum chemotherapy [14]. The OS has been approximately prolonged 2 months with the combination of PD-L1 inhibitors and chemotherapy [7, 15]. However, in these studies, consolidative TRT was not designed. The number of patients who received palliative TRT was very low and no unexpected adverse events were observed. Thus, in the era of immunotherapy, the role of TRT in ES-SCLC is still unclear.

Approximately 75% of ES-SCLC patients have intrathoracic residual after chemotherapy [5, 16]. The CREST trial reported consolidative TRT could improve the outcome for ES-SCLC with intrathoracic residual after first line chemotherapy. Furthermore, it is also reported an almost 50% reduction in intrathoracic recurrence [5]. In IMpower 133 trial, approximately 80% of patients had lung or thoracic lymph node involvement. As only 2.5% of patients experienced a complete response after atezolizumab plus chemotherapy. Thus, the locoregional treatment may further improve outcomes in this population.

In our study, TRT group significantly prolonged OS, PFS and LRFS. Compared with no TRT, the OS at 1 year in TRT group improved 10% (71.2% vs 61.5%). And the 1-year OS in no TRT group was consistent with the data of recent ASTRUM 005 trial reported [17]. In addition, the PFS at 6 months increased from 31.6–64.1% after TRT. And the PFS at 6 months in no TRT group was consistent with the data reported in IMpower 133 trial [18], suggesting that our findings are representative and applicable to patients with ES-SCLC. In the further analysis of CREST trial, the results showed that patients with non-liver metastasis or less distant metastases could benefit more from consolidative TRT [6]. Several studies have demonstrated oligo-metastatic ES-SCLC without brain and liver metastasis could benefit more from TRT [19, 20]. In our study, TRT significantly improved LRFS and PFS for ES-SCLC with oligo-metastasis and without liver metastasis subgroup. This trend persisted after PSM. However, there was no significant difference of OS in oligo-metastasis and non-liver metastasis subgroup, which need large scale population to confirm the OS benefit from TRT.

TRT was well tolerated and no severe toxic effects were recorded in our study. There were no randomized data reporting the safety of TRT in ES-SCLC after immunotherapy. Welsh et al. reported the good safety of concurrent pembrolizumab and TRT, with no grade 4–5 toxic events [21]. Another retrospective study also demonstrated the relative safety for consolidation TRT after atezolizumab [22]. Notably, RAPTOR/NRG LU-007 is an ongoing randomized trial to study the efficacy and safety of RT for ES-SCLC patients after atezolizumab plus chemotherapy (NCT 04402778). In our study, the radiation dose was delivered heterogeneously according to the intrathoracic residual. The radiation dose for the ES-SCLC is also debatable, which need more studies to illustrate.

In addition, the safety and efficacy of prophylactic cranial irradiation (PCI) for ES-SCLC after immunotherapy has not yet been defined and need further studies. In our study, only 3 patients underwent PCI without cranial progression and central nervous system-related events during follow up. But there were 19 of 95 progression patients have developed cranial metastasis after immunotherapy plus
chemotherapy. In IMpower 133 trial, central nervous system-related events has been evaluated in 22 patients who received PCI, appeared to be more common in the atezolizumab group.

There were several limitations in our study. This was a retrospective study with limited number of patients and the patient population and thoracic radiation dose was not consistent. Although, the PSM analysis was used to decrease the baseline characteristics difference in both groups, prospective randomized trials are in great urgency to confirm the role of TRT for ES-SCLC in the era of immunotherapy.

**Declarations**

**Acknowledgments**

This work was supported by National Natural Science Foundation (grant number 81703018) and Zhejiang Medical and Health Science and Technology Project (grant numbers 2022RC110 and 2023KY614).

**References**


Figures
Figure 1

Kaplan-Meier curve for overall survival.

Median PFS was 7 months in TRT group (95% CI 6-9) and 5 months in no TRT group (95% CI 4-6). The 6- and 12- month PFS were 64.10% and 12.52%, respectively, in TRT group, versus 31.65% and 10.33% in no TRT group (HR 0.59, 95% CI 0.38-0.90, p=0.0149, Figure 2.) In addition, the PFS was significantly different between patients who were with oligo-metastasis (p=0.01).
Figure 2

Kaplan-Meier curve for progression-free survival.

Among the 39 patients in TRT group, 27 patients received consolidative TRT (cTRT) after chemoimmunotherapy, and another 12 patients received TRT after local thoracic progression. Thus, 27 patients were included in analysis of local recurrence-free survival (LRFS). Thoracic progression was less likely in cTRT group than in no cTRT group (HR=0.30, 95% CI 0.16-0.56, p=0.0001, Figure 3.) In the subgroup analysis, the LRFS was significantly different between patients who were with oligo-metastasis (p=0.0029) and non-liver metastasis (p=0.0006) (Figure 4).
Figure 3

Kaplan-Meier curve for local recurrence-free survival.
Figure 4

Local recurrence-free survival in subgroups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1.docx