Original Article

The efficacy of thoracic radiotherapy in extensive stage small cell lung cancer with baseline brain metastases: a multi-institutional retrospective cohort study

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Background: Thoracic radiotherapy (TRT) had been shown to improve overall survival (OS) in extensive-stage small cell lung cancer (ES-SCLC) patients. However, approximately one fourth of SCLC harbored baseline brain metastases (BMs) and were excluded from previous TRT trials. Thus, the role of TRT in this sub-cohort of ES-SCLC requires elucidation. In this study, we evaluated the efficacy of TRT in ES-SCLC patients with clinically controlled baseline BMs.

Methods: In this retrospective, multi-institutional cohort study, 49 patients fully staged as ES-SCLC with baseline BM, had their disease controlled at all sites with no BM symptoms for three months since treatment initiation were included. The patients were allocated to TRT or no-TRT groups according to whether they received consolidative TRT before progression. Their baseline characteristics were compared using the χ^2 test. OS was selected as the primary observational endpoint. Survival and the incidence of cumulative progression between the groups were compared using log-rank analysis, and the interaction between TRT and selected factors was assessed via Cox proportional hazard analysis. Subgroup analysis was performed in oligo-metastasis patients (defined as five or fewer metastatic lesions in two or fewer organs).

Results: Seventeen (34.7%) patients received TRT, with a median dose of 54 Gy. The failure pattern analysis revealed initial intrathoracic progression in 31.3% and 66.7% of patients in the TRT no-TRT groups, respectively. Also, the TRT group had a significantly longer OS than the no-TRT group [hazard ratio (HR) 0.426, P=0.011]. Clinical covariates including age, gender, performance status, smoking, metastatic state, response after chemotherapy, and TRT, were included in multivariate regression analysis. TRT remained significantly correlated with better OS (HR 0.430, P=0.029). Twenty-three (46.9%) patients had oligo-metastasis at baseline. Subgroup analyses showed that TRT was significantly correlated with better OS in oligo-metastatic patients but not in non-oligo metastatic patients.

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Conclusions: TRT improved the prognosis of select ES-SCLC patients with baseline BMs and should be considered in this sub-cohort, which has not been covered by previous randomized trials.

Keywords: Thoracic radiotherapy (TRT); extensive-stage small cell lung cancer (ES-SCLC); brain metastasis; consolidative radiotherapy

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Introduction

Small cell lung cancer (SCLC) accounts for approximately 15% of primary lung cancers and almost two-thirds of SCLC patients present in extensive stage (ES) at the first diagnosis. ES-SCLC is commonly defined by the Veterans Administration Lung Study Group staging system as disease that extends beyond the ipsilateral hemithorax and regional lymph nodes and cannot be safely encompassed in a radiotherapy field of definitive dose (1). Previous studies have demonstrated that thoracic radiotherapy (TRT) improved the overall survival (OS) of ES-SCLC patients (2,3). Jeremic *et al.* first reported the survival benefit of TRT in ES-SCLC patients, including systemic complete response or only thoracic residual disease (2). The phase III CREST trial established the role of TRT in ES-SCLC in patients who responded to initial chemotherapy and received prophylactic brain irradiation ([no baseline brain metastases (BMs)] (3).

SCLC is notorious for its high incidence of BM, with approximately 10% of patients presenting with BM symptoms at first diagnosis (4,5). Contrast-enhanced brain magnetic resonance imaging (MRI) can effectively detect asymptomatic BMs and increased the baseline BM detection rate from 10% to 24% (6,7). Thus, nearly a quarter of SCLC patients harbored baseline BMs, yet they were excluded from previous TRT trials due to concerns of uncontrolled BM might affect trial endpoints such as progression free survival. This leads to difficulties in making evidenced-based decisions for these ES-SCLC patients. Meanwhile, BMs could be controlled by initial local and systemic therapies and the efficacy of TRT in these ES-SCLC patients warrants investigation. In this study, we aimed to evaluate the efficacy of TRT in this expanding ES-SCLC sub-cohort that is inflicted with baseline BMs. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5853/rc).

Highlight box

Key findings

- Thoracic radiotherapy (TRT) improved the prognosis of select extensive-stage small cell lung cancer (ES-SCLC) patients with baseline brain metastases (BMs).

What is known and what is new?

- TRT had been shown to improve prognosis in ES-SCLC patients without baseline BMs. Approximately a quarter of SCLC patients harbor baseline BMs who were not included in previous trials, and the role of TRT in these patients requires elucidation.
- In the present study, we have shown that in ES-SCLC patients with baseline BMs controlled by initial treatments, TRT improved overall survival, this effect is more prominent in oligo-metastatic patients.

What is the implication, and what should change now?

- In the brain magnetic resonance imaging era, the proportion of ES-SCLC patients diagnosed with baseline BMs is increasing. TRT should be considered in these patients and future clinical trials for TRT in ES-SCLC should include this sub-cohort.

Methods

Patient selection

In this multi-institutional retrospective cohort study, we inspected the medical records of ES-SCLC patients who were diagnosed and treated at Fudan University Shanghai Cancer Center and Tongji Hospital of Tongji Medical College from December 2012 to September 2020. All cases were re-staged according to the 8th edition of the American Joint Committee on Cancer lung cancer tumor node metastasis (TNM) staging system. The following inclusion criteria were employed in this study: (I) pathologically confirmed SCLC; (II) fully staged as ES-SCLC with baseline BM by MRI, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT)

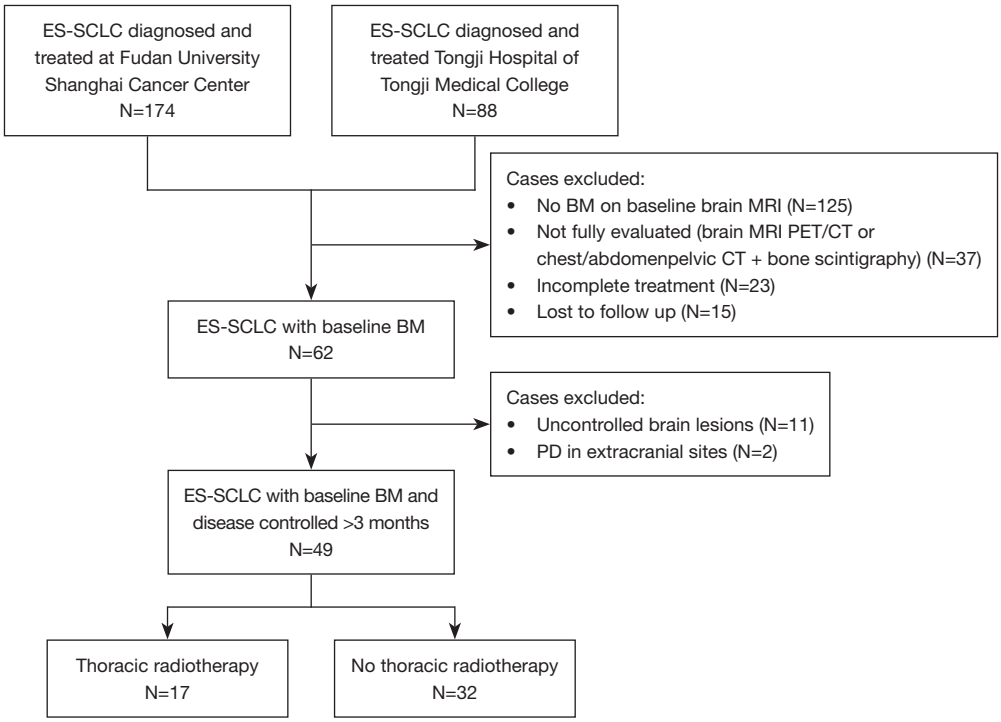

Figure 1 Patient selection flowchart. ES-SCLC, extensive-stage small cell lung cancer; BM, brain metastasis; MRI, magnetic resonance imaging; PET, positron emission tomography; CT, computed tomography; PD, progressive disease.

or chest/abdomen/pelvic CT with bone scintigraphy; (III) patients aged ≥18 years; (IV) complete clinical, imaging, and follow-up data; (V) no previous anticancer therapies; (VI) Eastern Cooperative Oncology Group performance score 0–2; and (VII) disease controlled at all sites for at least 3 months since initial treatment and no BM symptoms. The exclusion criteria included mixed histology of non-SCLC components, a history of second malignancy, insufficient baseline staging, incomplete treatment records, lost to follow-up, uncontrolled brain lesions, and disease progression within 3 months of initial treatment. The patient selection flowchart is illustrated in *Figure 1*. Oligo-metastasis was defined as five or fewer metastatic lesions in two or fewer organs; patients with metastases beyond this limit were defined as non-oligo metastasis (8-11).

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics boards of Fudan University Shanghai Cancer Center and Tongji Hospital of Tongji Medical College (registration Nos. SCCIRB2019240-1 and TJ-IRB20190404). Individual consent for this retrospective analysis was waived.

Treatment

A total of 49 patients were included in the analyses, all of whom received chemotherapy that consisted of 4–6 cycles of cisplatin plus etoposide. For BM control, 37 patients received chemotherapy and first-line brain radiotherapy, and 12 patients received chemotherapy alone. The patients were allocated to either the no-TRT (65.3%) group or the TRT (34.7%) group according to whether they received TRT before disease progression. The administered TRT dose ranged from 50 to 60 gray (Gy), and the median dose was 54 Gy. TRT was administered with a 6 MV linear accelerator (Elekta, Sweden or Varian, United States) using the intensity-modulated radiation therapy (IMRT) technique. Concurrent and sequential TRT was delivered to seven and 10 patients, respectively.

Follow-up

The median follow-up was 12 months (range, 5–54 months). Patients were typically evaluated every two cycles of treatment during chemotherapy, then within 1 month after

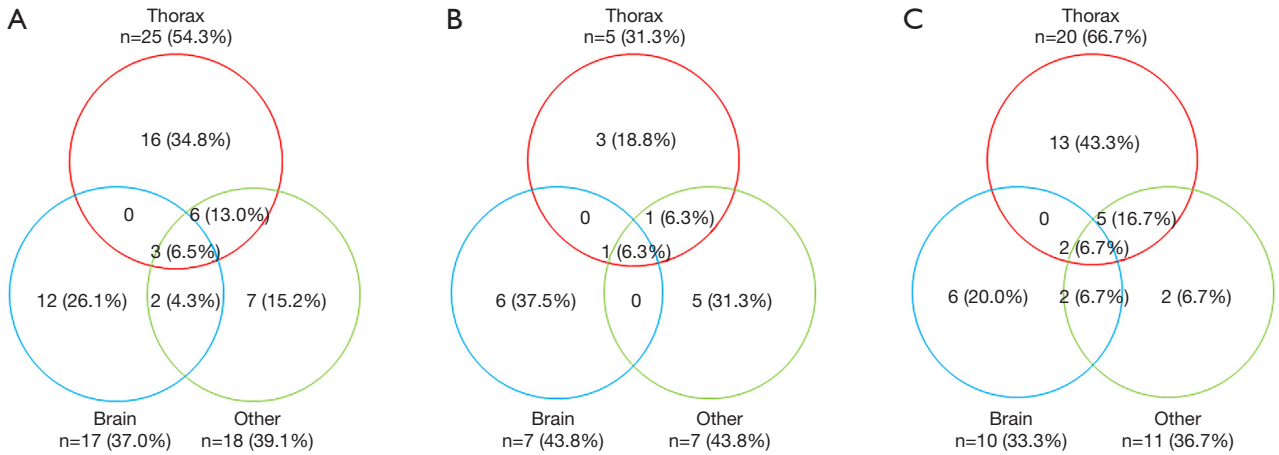

Figure 2 Pattern of treatment failure analyses: (A) the entire cohort; (B) TRT group; (C) no-TRT group. TRT, thoracic radiotherapy.

TRT, and subsequently at 3-month intervals for the first 2 years, and at 6-month intervals thereafter. The follow-up routine included symptoms and physical evaluations, chest CT examination, brain MRI, and neck, supraclavicular, and abdominal ultrasonography. Bone scintigraphy or PET/CT was only performed when necessary.

Outcomes

OS was selected as the primary observational endpoint and was defined as the time from treatment initiation to the time of death or last follow-up (February 28, 2022); deaths from all causes were defined as events. The other endpoints of interest included intrathoracic progression (ITP), progression-free survival (PFS), and failure pattern. ITP was defined as the appearance of a new intrathoracic lesion or progression of the existing baseline thoracic lesions. PFS was defined as the time from the beginning of treatment to the time of disease progression or new metastasis or the date of the last follow-up. At the first disease progression, all progressed disease sites were recorded and grouped into three categories: (I) brain progression; (II) thoracic progression; and (III) progression of other sites. The Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria were utilized to assess the responses to chemotherapy.

Statistical analysis

SPSS 24.0 software (IBM Corp, United States) was used for statistical analysis. Data comparison between the groups was performed by chi-square or Fisher's exact tests. Kaplan-Meier curves were employed to illustrate the OS and PFS. The log-rank test was used to compare the survival and cumulative ITP incidence between the groups. Univariable and multivariate Cox proportional hazard regression analyses were carried out to evaluate the interaction between TRT and selected factors. A two-sided P value of less than 0.05 was considered statistically significant.

Results

Pattern of failure

A total of 46 disease progression events were recorded. Progressions occurring at different sites within 30 days were considered simultaneous progressions. Failure pattern analysis revealed initial progression in the thorax (54.3%), brain (37.0%), and other sites (39.1%). The isolated ITP rate was 34.8% (*Figure 2A*). The initial ITP rates were 31.3% and 66.7% in the TRT and no-TRT groups, respectively; isolated ITP was rarer in the TRT group (n=3, 18.8%) than in the control group (n=13, 43.3%). (*Figure 2B,2C*). The cumulative ITP incidence was significantly lower in the TRT group than in the no-TRT group (P=0.05) (*Figure 3A*), as was the initial ITP incidence (P=0.02) (*Figure 3B*).

Survival and confounding factors

The patients' baseline clinical characteristics including patient age at diagnosis, gender, smoking status, performance score, metastatic state, response to chemotherapy after two cycles of chemotherapy were displayed in *Table 1*.

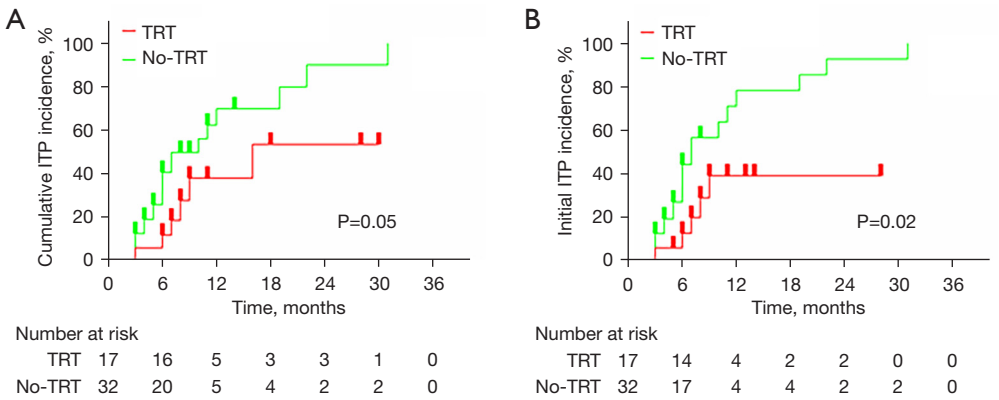

Figure 3 The incidence of intrathoracic progression. (A) The cumulative incidence of all intrathoracic progression events; (B) the cumulative incidence of intrathoracic progression as the initial site of failure. ITP, intrathoracic progression; TRT, thoracic radiotherapy.

Table 1 Characteristics of ES-SCLC patients with baseline brain metastasis

Characteristics	Total patients (n=49)	TRT (n=17)	No-TRT (n=32)	P
Age (years), median [range]	64 [45–75]	66 [45–75]	61.5 [48–74]	0.392
Gender				1.000
Male	44	15	29	
Female	5	2	3	
Smoking				0.556
Yes/ever	41	13	28	
Never	8	4	4	
ECOG PS score				0.847
0–1	34	11	23	
2–3	15	6	9	
Metastatic state				0.034*
Oligo	23	12	11	
Non-oligo	26	5	21	
Response				0.395
PR + CR	38	12	26	
SD + PD	11	5	6	

*, statistically significant P values. ES-SCLC, extensive-stage small cell lung cancer; TRT, thoracic radiotherapy; no-TRT, without thoracic radiotherapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; oligo, oligo-metastatic patients; non-oligo, non-oligo metastatic patients; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

The baseline characteristics between the TRT and no-TRT groups were comparable, except for metastatic state (P=0.034).

For the entire cohort, the median and 2-year survival rates were 13 months and 26.1%, respectively. In the TRT group, the median and 2-year survival rates were 23 months and 47.1%, which corresponded to 11 months and 14.0% in the no-TRT group, respectively. The TRT group had significantly longer OS than the no-TRT group (P=0.010, *Figure 4A*). PFS was not significantly different between the

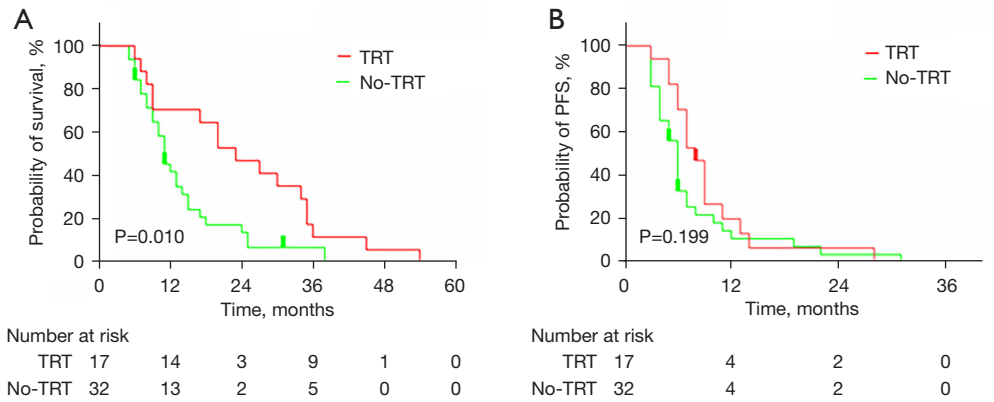

Figure 4 Prognostic analysis of thoracic radiotherapy in extensive-stage small cell lung cancer patients with baseline brain metastasis. (A) Overall survival; (B) progression-free survival. TRT, thoracic radiotherapy.

Table 2 Univariate and multivariate analysis of the prognostic factors for OS in the entire cohort

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.985 (0.948–1.023)	0.427	0.995 (0.953–1.038)	0.814
Gender				
Male *vs.* female	1.614 (0.574–4.537)	0.364	2.359 (0.433–12.842)	0.321
Smoking				
Yes or ever *vs.* never	1.176 (0.520–2.657)	0.697	0.700 (0.172–2.846)	0.619
ECOG PS score				
2–3 *vs.* 0–1	1.038 (0.550–1.958)	0.909	1.139 (0.542–2.393)	0.730
Metastatic state				
Non-oligo *vs.* oligo	1.497 (0.822–2.725)	0.187	1.051 (0.522–2.114)	0.889
Response				
PR + CR *vs.* SD + PD	0.600 (0.293–1.227)	0.162	0.693 (0.305–1.574)	0.381
Thoracic radiotherapy				
With *vs.* without	0.426 (0.220–0.824)	0.011*	0.430 (0.201–0.918)	0.029*

*, statistically significant P values. OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; oligo, oligo-metastases; non-oligo, non-oligo metastases; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

two groups (P=0.199, *Figure 4B*). The potential risk factors for OS, including age, gender, performance status, smoking, metastatic state, response after two cycles of chemotherapy, and TRT, were analyzed. TRT was significantly correlated with better OS in both the univariate [hazard ratio (HR) 0.426, 95% confidence interval (CI): 0.22–0.82, P=0.011] and multivariate (HR 0.430, 95% CI: 0.201–0.918, P=0.029) regression analyses (*Table 2*).

Subgroup analysis

Considering that metastatic state was unbalanced between the TRT and no-TRT groups, we subsequently evaluated TRT's efficacy in both the oligo and non-oligo metastasis subgroups. All baseline characteristics were balanced between the TRT and no-TRT groups in the oligo metastasis subcohort (*Table 3*). TRT markedly improved the OS of patients

Table 3 Baseline characteristics of ES-SCLC patients with oligo-metastatic disease

Characteristics	Total patients (n=23)	TRT (n=12)	No-TRT (n=11)	P
Age (years), median [range]	64 [45–75]	65.5 [45–75]	61 [48–72]	0.956
Gender				1.000
Male	21	11	10	
Female	2	1	1	
Smoking				0.590
Yes/ever	19	9	10	
Never	4	3	1	
ECOG PS score				1.000
0–1	16	8	8	
2–3	7	4	3	
Response				0.317
PR + CR	18	8	10	
SD + PD	5	4	1	

ES-SCLC, extensive-stage small cell lung cancer; TRT, thoracic radiotherapy; no-TRT, without thoracic radiotherapy; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

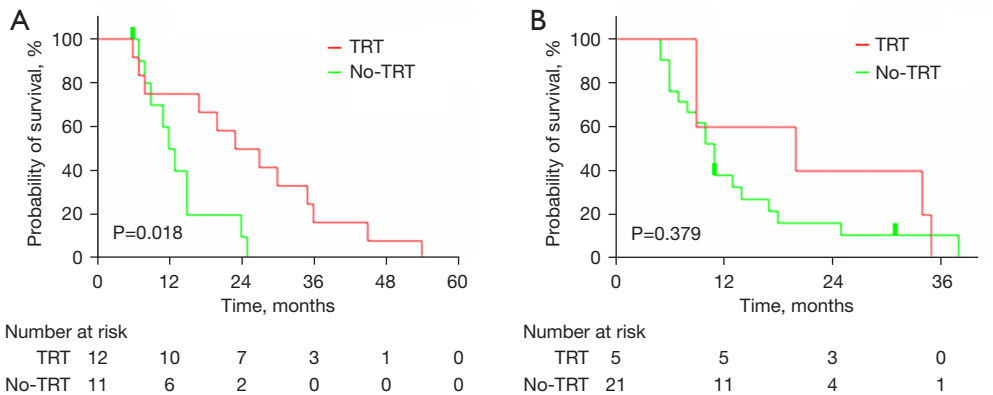

Figure 5 Prognostic analysis of thoracic radiotherapy in subgroups with different metastatic status. (A) Oligo-metastatic patients; (B) non-oligo-metastatic patients. TRT, thoracic radiotherapy.

with oligo-metastasis (P=0.018, *Figure 5A*) and remained independently correlated with OS in both the univariate and multivariate regression analyses (*Table 4*). On the other hand, TRT did not notably improve the OS of non-oligo metastasis patients (*Figure 5B*).

Discussion

SCLC is a malignancy that is notorious for its high incidence of BM, with approximately 10% of patients presenting with BM symptoms in the pre-MRI era (4,5). The introduction of brain MRI as part of the standard work-up further increased the BM detection rate to 24% at initial diagnosis (6). The benefits of consolidative TRT in ES-SCLC were previously established in several randomized trials (2,3,12). However, ES-SCLC patients with baseline BMs were excluded from these studies, and the value of TRT in this expanding ES-SCLC sub-cohort

Table 4 Univariate and multivariate analysis of the prognostic factors for OS in the oligo-metastatic subgroup

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.994 (0.945–1.046)	0.812	1.009 (0.935–1.090)	0.811
Smoking				
Yes or ever *vs.* never	0.740 (0.244–2.240)	0.594	2.740 (0.149–50.372)	0.497
ECOG PS score				
2–3 *vs.* 0–1	0.711 (0.273–1.847)	0.483	0.594 (0.122–2.902)	0.520
Response				
PR + CR *vs.* SD + PD	0.540 (0.172–1.693)	0.290	0.107 (0.010–1.133)	0.063
Thoracic radiotherapy				
With *vs.* without	0.296 (0.103–0.851)	0.024*	0.253 (0.074–0.868)	0.029*

*, statistically significant P values. OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

remains largely undefined.

The randomized phase III CREST study enrolled ES-SCLC patients without BM symptoms, and only a fraction of patients underwent baseline brain imaging, so the actual BMs status was unknown in a substantial proportion of enrolled patients. In this study, consolidative TRT (30 Gy in 10 fractions) decreased the rate of initial ITP (41.7% *vs.* 77.8%) and isolated ITP (19.8% *vs.* 46.0%). Although the primary endpoint of 1-year OS rate failed to reach statistical significance, a post-hoc analysis revealed that the 2-year OS rate was significantly increased in the TRT group (13% *vs.* 3%, P=0.004) (3). An earlier study reported by Jeremic *et al.* demonstrated that in carefully selected ES-SCLC patients (complete response in all extrathoracic sites after three cycles of chemotherapy), TRT (54 Gy in 36 fractions) significantly improved the median OS (17 *vs.* 11 months) and 5-year OS rate (9.1% *vs.* 3.7%, P=0.041). It is also worth noting that this accomplishment was achieved using two-dimensional radiation techniques (2). Since both of these studies either excluded patients with baseline BMs or included patients with unknown BMs status, the conclusions drawn from these trials cannot be directly applied to ES-SCLC patients with known baseline BMs.

In the present study, we analyzed the role of TRT in ES-SCLC with baseline BMs and disease controlled for at least 3 months; adding TRT significantly reduced the ITP and prolonged OS compared to patients who did not receive TRT. The 2-year survival rates were 47.1% and 14.0% in the TRT and no-TRT groups. In addition, the benefits for the initial ITP rate (31.3% *vs.* 66.7%) and isolated ITP rate (18.8% *vs.* 43.3%) were comparable to the results reported in the CREST trial. Despite that all analyzed patients harbored BMs at baseline and most did not receive immunotherapy, they achieved numerically longer OS and lower ITP rates than those reported in previous studies including only non-BM patients. Possible explanations for these results are as follows. Firstly, TRT was only considered in patients with BM controlled for at least 3 months, thus minimizing the interference from rapid intracranial progression. Secondly, the TRT dose delivered in our study was higher than that in the CREST study (median 54 *vs.* 30 Gy), which might have led to better intrathoracic disease control and subsequently better OS; this result was consistent with a previous national cancer database analysis (13). Thirdly, TRT was delivered using the IMRT technique in all patients, and this advanced radiotherapy technique could also have contributed to better survival data.

In a secondary analysis of the CREST trial data, Slotman *et al.* reported that in patients with less than three distant metastases, TRT significantly improved the PFS (HR 2.02, P=0.003) and also showed a trend of improving OS (HR 1.55, P=0.09). Meanwhile, they found that TRT provided no significant PFS and OS improvements in ES-SCLC patients burdened with three or more metastases. The authors also suggested investigating more intensive TRT in ES-SCLC patients with a limited metastatic burden (14). Consistent with the aforementioned report, we also observed similar

results in terms of different TRT efficacies in patients with different metastatic burdens. In the present study, TRT improved OS in oligo-metastatic patients but exerted no significant impact on OS in non-oligo metastatic patients. Although the probability of a less prominent effect of TRT in the later sub-group still exists, the small cohort might not have enough power to reveal this effect. Therefore, a larger sample analysis of TRT in non-oligo metastatic patients is warranted.

In another study reported by Xu *et al.*, TRT improved the 2-year OS in both oligo-metastatic (25.3% *vs.* 14.4%, P=0.001) and non-oligo metastatic (13.2% *vs.* 6.1%, P<0.001) ES-SCLC patients (10). The inconsistency between non-oligo-metastatic patients might be attributed to the more stringent criteria applied for defining oligo-metastatic as well as the larger non-oligo metastatic cohort size.

In addition to TRT, it had also been suggested that consolidative radiotherapy to extra-thoracic sites should be investigated (14). The RTOG0937 study provided evidence to this end, which delivered prophylactic brain irradiation and consolidative radiotherapy (45 Gy in 15 fractions) to all metastatic tumors that had not reached complete response. No significant difference in OS was observed in the RTOG0937 study, but the risk of intrathoracic recurrence was reduced from 62.5% to 25.8%, and the recurrence rates in treated metastases decreased from 78.1% to 41.9%. It is worth mentioning that the control arm (no consolidative radiotherapy) exhibited an unexpectedly good prognosis (median OS 15.8 months, 1-year OS 60.1%) (15). Experience from the RTOG0937 and other aforementioned studies suggests that candidates for consolidative radiotherapy should be carefully selected (14,15), and earlier and more intensive consolidative radiotherapy for ES-SCLC patients with a limited tumor burden might be the future direction.

The standard first-line treatment for ES-SCLC had shifted to chemo-immunotherapy since the publication of the IMpower133 and CASPIAN trials (16,17), and the role of TRT in the era of immunotherapy requires further exploration. In a pattern of progression post-hoc analysis of the IMpower133 study, the progression at initial sites remained the dominant pattern of failure in the atezolizumab arm (56.2%) versus the control arm (59.4%), suggesting that consolidative radiotherapy might remain beneficial in the chemo-immunotherapy era (18). Several ongoing trials are also investigating the role of TRT in ES-SCLC patients receiving chemo-immunotherapy (NCT04462276; NCT04402788) and their results are eagerly awaited.

The limitations of the present study included the relatively small cohort size and the retrospective design, which might introduce selection bias. Thus, larger prospective studies with a more balanced design are warranted to confirm the findings of this study.

Conclusions

In conclusion, the present study demonstrated that TRT reduced ITP and improved survival in selected ES-SCLC patients with baseline BMs. Oncologists should consider offering TRT to brain metastatic ES-SCLC patients if their disease and BM symptoms are controlled and their metastatic burden is limited.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5853/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5853/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5853/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 conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics boards of Fudan University Shanghai Cancer Center and Tongji Hospital of Tongji Medical College (registration Nos. SCCIRB2019240-1 and TJ-IRB20190404). Individual consent for this retrospective analysis was waived.

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