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Addition of thoracic radiotherapy to a PD-L1 inhibitor plus chemotherapy regimen delays brain metastasis onset in extensive-stage small cell lung cancer patients without baseline brain metastasis

Baiyang Huang[1†], Senyuan Liu[2†], Kaiyue Wang[3,1], Jiarui Zhao[1], Min Li[1], Xingpeng Wang[3,1], Weiqing Wang[4,1], Xiaohan Wang[1], Jinming Yu[1], Xue Meng[1,5] and Guoxin Cai[1*]

Abstract

Background With the application of immune checkpoint inhibitors (ICIs) and the discovery of the synergistic effect of radiotherapy and immunotherapy, the intracranial benefit of thoracic radiotherapy (TRT) is receiving signiffcant clinical attention. The purpose of this study was to analyze the cranial benefits of ICIs and TRT in patients with extensive-stage small cell lung cancer (ES-SCLC) without baseline brain metastases (BMs).

Materials and methods From August 2019 to August 2022, data from patients diagnosed with ES-SCLC without baseline BMs were retroactively recorded. The Kaplan–Meier method was used to calculate overall survival (OS), progression-free survival (PFS), and brain metastasis-free survival (BMFS), and the differences between the treatment groups were compared with the log-rank test. Risk factors associated with OS were analyzed via the Cox regression model.

Results A total of 216 patients were included, with a median follow-up of 24.73 months. Among these patients, 137 (63.4%) received first-line ICIs combined with chemotherapy (ChT), including 32 patients treated with anti-programmed death 1 antibody (αPD-1) and 105 patients treated with anti-programmed death-ligand 1 antibody (αPD-L1), and 79 patients (36.6%) received first-line ChT alone. Compared with the ChT-alone group, the ICI + ChT group demonstrated significantly improved PFS (8.07 vs. 6.87 months; $p < 0.001$) and OS (19.83 vs. 13.80 months; $p = 0.001$). The addition of ICIs to the ChT regimen did not significantly delay the onset of BMs compared to that with ChT alone (16.93 vs. 12.67 months; $p = 0.379$). Notably, the addition of TRT to the αPD-L1 + ChT regimen significantly prolonged BMFS compared to that without TRT (20.27 vs. 8.80 months; $p = 0.045$).

†Baiyang Huang and Senyuan Liu contributed equally to this work.

*Correspondence:
Guoxin Cai
15562481150@163.com

Full list of author information is available at the end of the article

Conclusion In patients with ES-SCLC without baseline BMs, first-line chemoimmunotherapy significantly improves PFS and OS. However, it does not delay intracranial metastasis. The addition of TRT to αPD-L1 + ChT therapy significant delays the development of BMs.

Clinical trial number Not applicable.

Keywords Extensive-stage small cell lung cancer (ES-SCLC), Immune checkpoint inhibitors (ICIs), Brain metastases (BMs), Thoracic radiotherapy (TRT), Programmed death-ligand 1 (PD-L1) checkpoint inhibitors

Background

Lung cancer is one of the cancers with the highest morbidity and mortality rates worldwide [1], with small cell lung cancer (SCLC) accounting for approximately 13-18% of lung cancer cases [2]. Compared with non-small cell lung cancer (NSCLC), SCLC is characterized by faster and earlier growth and early metastasis [3]. More than half of all patients newly diagnosed with SCLC have extensive-stage small cell lung cancer (ES-SCLC) [2]. The central nervous system is the main site of distant metastasis in patients with SCLC, and studies have shown that the risk of brain metastases (BMs) in SCLC patients is significantly greater than that in patients with NSCLC [4]. The frequency of BMs in newly diagnosed SCLC patients is approximately 24%, and BMs occur during treatment in 40% of patients [5], which strongly affects the prognosis and quality of life of patients with SCLC. Therefore, effective treatments to reduce the negative impact of BMs on the disease prognosis are urgently needed.

Chemotherapy (ChT) is the main first-line treatment for ES-SCLC [6], but its clinical efficacy is poor, with a median overall survival (OS) of approximately 10 months [7–9]. Owing to the presence of the blood–brain barrier, ChT drugs have little effect on the prevention and treatment of BMs. Since 2018, studies on immune checkpoint inhibitors (ICIs) combined with ChT mode, represented by IMpower133 [10], CASPIAN [11], ASTRUM-005 [12], and CAPSTONE-1 [13], have greatly advanced such therapy, which in turn has prolonged the median OS of ES-SCLC patients to nearly 12–16 months. CASPIAN [14] and IMpower133 [15] trials have also shown that immunotherapy and ChT have been proven to delay intracranial progression. However, a recent study [16] showed that the addition of anti-programmed death-ligand 1 antibody (αPD-L1) did not reduce the risk of metastases in the brain. Therefore, the question of whether the addition of immunotherapy can effectively delay intracranial progression still lingers in debates. A randomized trial of prophylactic cranial irradiation (PCI) in patients with ES-SCLC who responded to ChT revealed that PCI reduced the incidence of symptomatic BMs and prolonged OS [17], but a more comprehensive trial from Japan refuted this view [18]. Therefore, PCI does not seem to provide a survival benefit for patients with ES-SCLC. Prospective studies [19–22] suggest that thoracic radiotherapy (TRT) administered to patients with a good systemic response improves local control and OS. In addition, many studies [23–27] have shown that radiotherapy can affect the regulation of the immune system and may augment systemic antitumoral responses to immunotherapy [28–31]. However, it is still unknown whether the addition of radiotherapy to ICIs combined with ChT can affect the timing of BMs in ES-SCLC patients without BMs at baseline.

Therefore, the purpose of this study was to evaluate the cranial benefits of first-line ICIs + ChT with or without TRT and to explore the clinical characteristics associated with survival benefits in ES-SCLC patients without BMs.

Methods and materials

Patient selection

In this study, we retrospectively analyzed patients with ES-SCLC who were treated at Shandong Cancer Hospital from August 2019 to August 2022. The main inclusion criteria were as follows: (1) age ≥ 18 years; (2) SCLC confirmed by histology or cytology; (3) ES-SCLC patients who were assessed by imaging according to the Veterans Administration Lung Study Group (VALG) staging system combined with the American Joint Committee on Cancer (AJCC) eighth edition Cancer Staging System; (4) patients without BMs on CT or MRI at baseline; and (5) patients who received at least 2 cycles of standard therapy. The main exclusion criteria were as follows: (1) progression of the primary tumor; (2) presence of other primary tumor; (3) a history of prior treatment; (4) treatment with ICIs other than anti-programmed death 1 antibody (αPD-1) or αPD-L1; and (5) comorbid autoimmune disease. Patients who had incomplete medical records at diagnosis or treatment were also excluded. The detailed screening process of the patients is illustrated in Fig. 1. The general characteristics of the patients, including age, sex, Karnofsky performance status (KPS) score, liver/bone/adrenal metastasis status, smoking history, drinking history, and number of systemic treatment cycles, were recorded. The study complied with the Declaration of Helsinki and International Good Clinical Practice Guidelines.

Treatment

The enrolled patients received a standard first-line etoposide plus cisplatin/carboplatin (EP/EC) regimen

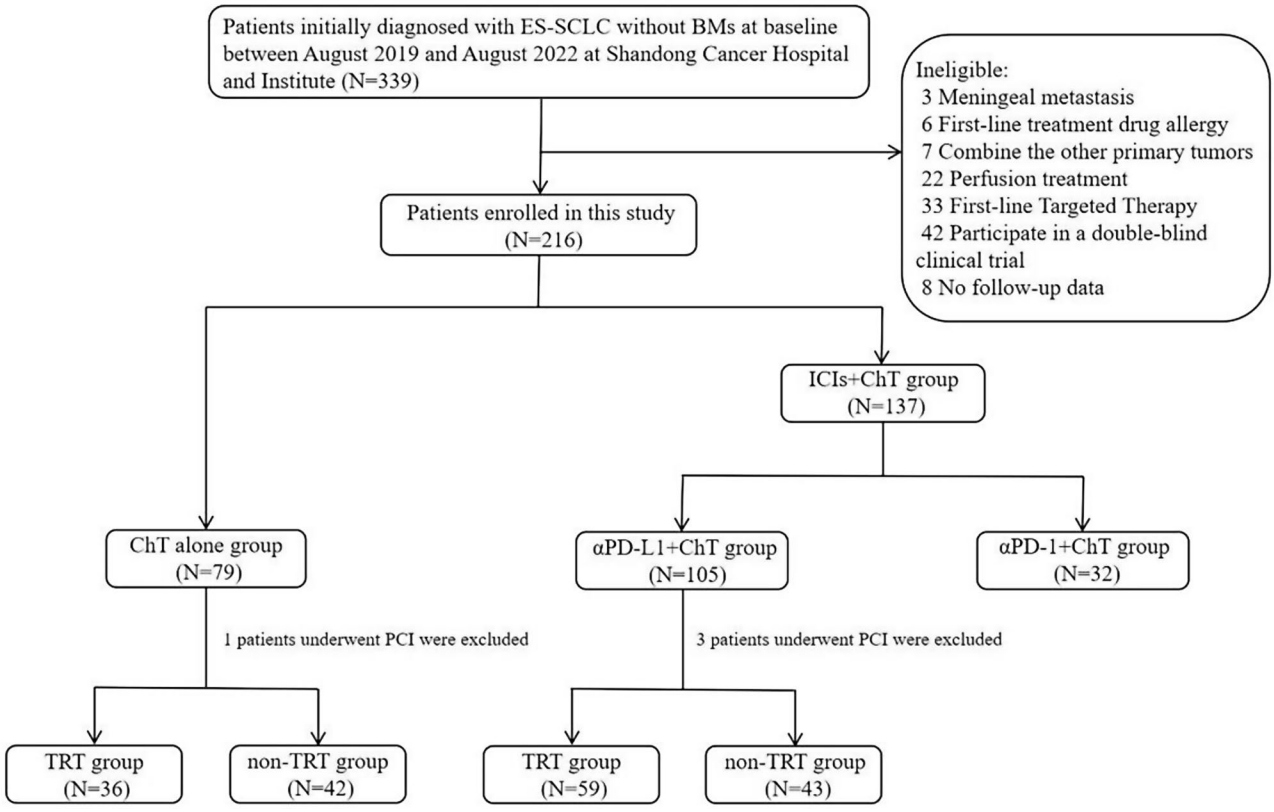

Fig. 1 Flowchart of the screening procedure. Abbreviations: ES-SCLC, extensive-stage small cell lung cancer; BMs, brain metastases; ICIs, immune checkpoint inhibitors; ChT, chemotherapy; αPD-L1, anti-programmed death-ligand 1 antibody; αPD-1, anti-programmed death 1 antibody; PCI, prophylactic cranial irradiation; TRT, thoracic radiotherapy

(etoposide 100 mg/m^2, cisplatin 75–80 mg/m^2, or carboplatin AUC = 5) every 21 days, with or without αPD-L1/PD-1 therapy. In the ICIs + ChT group, the majority of patients (65.7%) received atezolizumab or durvalumab. Following the completion of ChT or ICIs + ChT, clinical response assessment was performed according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). Patients with stable disease (SD), partial response (PR), and complete response (CR) selectively underwent TRT. Additionally, in the ICIs + ChT group, TRT was administered concurrently with subsequent maintenance ICIs therapy. The median time interval from the end of ChT or ICIs + ChT to the initiation of TRT is approximately 4 weeks (IQR, 3–5).The gross tumor volume (GTV) encompassed residual lung lesions and lymph nodes, with a 5–8 mm expansion to the clinical target volume (CTV) and a further 5 mm expansion from the CTV to the planning target volume (PTV). The median prescribed dose of TRT was 50 Gy (IQR, 45–50), with the majority of patients receiving 45 Gy/15 fractions(30/108, 27.8%) and 50 Gy/25 fractions (46/108, 42.3%), and only 9.3% ($n = 10$) of patients receiving a prescribed dose exceeding 50 Gy. Patients who developed BMs during follow-up received either whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or WBRT plus focal radiation boost (WBRT + boost). For the WBRT and WBRT + boost groups, the CTV included the whole brain, with a 3 mm expansion to the PTV. The prescribed dose for WBRT ranged from 30 to 45 Gy in 10–20 fractions. For focal boost, the GTV included BMs, with an additional dose of 10–12 Gy. SRS was administered via a CyberKnife or GammaKnife, with doses ranging from 20 to 30 Gy in 1–2 fractions.

Follow-up and study endpoints

The patient follow-up was scheduled to continue from the start of treatment until the final follow-up deadline (October 31, 2023) or death. Clinical response assessment was performed according to the RECIST 1.1. CT assessments were performed every 2 cycles during systemic therapy, and the median interval for MRI assessments is approximately every 3.2 months (IQR, 3.1–4.1). The date of BMs, progression and death in patients after first-line therapy were recorded according to information obtained from the follow-up and evaluation of treatment efficacy. The endpoints of the study were OS, progression-free survival (PFS), and brain metastasis-free survival (BMFS). OS was defined as the time from the start

of treatment to the date of death from any cause or the last known follow-up. PFS was defined as the time from the date of treatment to any form of disease progression, death due to any cause or the last known follow-up. BMFS was defined as the time from the date of treatment to the onset of BMs, death due to any cause or the last known follow-up.

Statistical analysis

Descriptive characteristics were compared via the χ^2 test, Fisher's exact test and the Mann–Whitney U test. The Kaplan–Meier method was used to calculate OS, PFS and BMFS, and the differences between groups were compared with the log-rank test. The Cox proportional hazards model was used for univariate survival analysis. Because of the small sample size of this study, variables with $p < 0.1$ in the univariate analysis were applied to the multivariate model. All the statistical analyses were performed via SPSS software, version 27.0 (IBM Corporation), and the survival curves were plotted via Prism software, version 10.1.2 (GraphPad). In all analyses, $P < 0.05$ (two-sided) was considered to indicate statistical significance.

Results

Patient characteristics

Between August 2019 and August 2022, 339 patients were diagnosed with ES-SCLC without BMs at Shandong Cancer Hospital, and 216 patients were ultimately included in our retrospective study (Fig. 1). The cohort was predominantly male (77.3%), with the majority of patients having a KPS score of ≥ 80 (95.4%). Most patients (87.5%) received 4–6 cycles of standard first-line therapy. Patients were stratified into two groups on the basis of whether their first-line ChT was combined with ICIs. The ICI + ChT group comprised 137 patients (63.4%), whereas the ChT-alone group included 79 patients (36.6%). Within the ICI + ChT group, 105 patients (76.6%) received αPD-L1 therapy combined with ChT, and 32 patients (23.4%) received αPD-1 therapy combined with ChT. Detailed baseline characteristics and clinical data are presented in Table 1, with no significant differences observed between the two groups.

Survival outcomes and BMFS in all patients

The median follow-up was 24.73 months (range: 19.29–30.17 months). The median OS was 17.43 months (range: 14.61–20.25 months), and the median PFS was 7.47 months (range: 6.87–8.07 months) (Fig. 2A). Significant differences in OS and PFS were observed between the ICI + ChT group and the ChT-alone group. The addition of ICIs significantly prolonged patient survival (median OS: 19.83 vs. 13.80 months, $p = 0.001$; median PFS: 8.07 vs. 6.87 months, $p < 0.001$) (Fig. 2B and C). However, the incorporation of ICIs did not delay the onset of BMs. Analysis revealed no statistically significant difference in BMFS between the two treatment groups (median BMFS, ICI + ChT vs. ChT alone: 16.93 vs. 12.67 months, $p = 0.379$) (Fig. 2D).

Survival outcomes and BMFS in patients treated with αPD-L1 + ChT

In the ICI + ChT cohort, 32 patients received PD-1 inhibitors. Given the diverse types of PD-1 inhibitors available and the limited sample size of only 10 patients treated with serplulimab which has demonstrated clinical benefit [12], we excluded these 32 patients from subsequent analyses. The baseline characteristics and clinical parameters did not significantly differ between the αPD-L1 + ChT group and the ChT-alone group, as detailed in Supplementary Table 1. Our findings demonstrated that compared with ChT alone, the addition of PD-L1 inhibitors significantly extended patient survival (median OS: 18.43 vs. 13.80 months, $p = 0.018$; median PFS: 7.53 vs. 6.87 months, $p = 0.003$) (Supplementary Fig.s 1 A and B). However, no significant difference in BMFS was observed between the two groups. Therefore, the addition of PD-L1 inhibitors to ChT did not delay the development of BMs (median BMFS, αPD-L1 + ChT vs. ChT alone: 14.03 vs. 12.67 months, $p = 0.825$) (Supplementary Fig. 1C).

Subgroup analysis was used to further explore prognosis in the TRT group and non-TRT group. In the subgroup that underwent sequential TRT, incorporating immunotherapy notably enhanced long-term survival (median OS: 20.97 vs. 14.00 months, $p = 0.040$; median PFS: 8.83 vs. 6.90 months, $p = 0.010$) (Supplementary Fig. 2A and B). Similar outcomes were seen in the group without sequential TRT (median OS: 15.67 vs. 11.60 months, $p = 0.046$; median PFS: 6.67 vs. 5.53 months, $p = 0.023$) (Supplementary Fig. 2C and D). In conclusion, regardless of TRT status, the addition of immunotherapy significantly prolongs patient survival and enhances prognosis.

Effect of TRT combined with a PD-L1 inhibitor on the BMFS

We excluded 4 patients who underwent PCI from among the patients receiving αPD-L1 + ChT or ChT alone ($n = 184$). To analyze the BMFS, patients were stratified on the basis of whether they received TRT. During or after systemic treatment, 85 patients did not receive TRT, and 95 patients underwent TRT. None of these patients developed BMs prior to TRT. The detailed baseline characteristics and clinical data are presented in Table 2, with no significant differences observed between the two groups. The median BMFS was 14.57 months (range: 8.59–20.56 months) in the TRT group and 12.27 months

Table 1 Baseline characteristics of all patients

Patient characteristic, *n* (%)	All patients (*n* = 216)	ICIs + ChT (*n* = 137)	ChT-alone (*n* = 79)	*p* value
Age, years				
< 65	129 (59.7)	86 (62.8)	43 (54.4)	0.229
≥ 65	87 (40.3)	51 (37.2)	36 (45.6)	
Gender				
Male	167 (77.3)	105 (76.6)	62 (78.5)	0.756
Female	49 (22.7)	32 (23.4)	17 (21.5)	
KPS sore				
≥ 80	206 (95.4)	132 (96.4)	74 (93.7)	0.571
< 80	10 (4.6)	5 (3.6)	5 (6.3)	
Smoking status				
Yes	132 (61.1)	81 (59.1)	51 (64.6)	0.430
No	84 (38.9)	56 (40.9)	28 (35.4)	
Drinking status				
Yes	90 (41.7)	59 (43.1)	31 (39.2)	0.583
No	126 (58.3)	78 (56.9)	48 (60.8)	
Baseline liver metastases				
Yes	75 (34.7)	53 (38.7)	22 (27.8)	0.107
No	141 (65.3)	84 (61.3)	57 (72.2)	
Baseline bone metastases				
Yes	81 (37.5)	53 (38.7)	28 (35.4)	0.635
No	135 (62.5)	84 (61.3)	51 (64.6)	
Baseline Adrenal metastases				
Yes	28 (13.0)	16 (11.7)	12 (15.2)	0.459
No	188 (87.0)	121 (88.3)	67 (84.8)	
No. of first-line therapy cycles				
< 4	16 (7.4)	14 (10.2)	2 (2.5)	0.084
4–6	189 (87.5)	115 (84.0)	74 (93.7)	
> 6	11 (5.1)	8 (5.8)	3 (3.8)	
PCI therapy				
Yes	6 (2.8)	5 (3.6)	1 (1.3)	0.551
No	210 (97.2)	132 (96.4)	78 (98.7)	
MRI frequency, months				
Median	3.2	3.2	3.2	0.578
IQR	3.1–4.1	3.0-4.2	3.1–4.1	
TRT				
Yes	108 (50.0)	72 (52.6)	36 (45.6)	0.323
No	108 (50.0)	65 (47.4)	43 (54.4)	
Immunotherapy drug				
PD-1 inhibitors	32 (23.4)	32 (23.4)	-	-
PD-L1 inhibitors	105 (76.6)	105 (76.6)	-	

Abbreviations: ChT, chemotherapy; ICIs, immune checkpoint inhibitors; KPS, Karnofsky performance status; PCI, prophylactic cranial irradiation; MRI, Magnetic Resonance Imaging; IQR, Interquartile range; TRT, thoracic radiotherapy; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

(range: 6.18–18.36 months) in the non-TRT group ($p = 0.202$) (Fig. 3A).

Subgroup analysis was used to further explore the development of BMs in the ChT-alone group and the αPD-L1 + ChT group. In the ChT-alone subgroup ($n = 78$), the addition of TRT did not significantly delay the onset of BMs, with median BMFS values of 14.33 and 12.33 months for non-TRT and TRT patients ($p = 0.704$), respectively (Fig. 3B). Conversely, in the αPD-L1 + ChT subgroup, the incorporation of TRT significantly prolonged the BMFS, with median times of 20.27 months for TRT patients and 8.80 months for non-TRT patients ($p = 0.045$) (Fig. 3C). Further survival analysis of the αPD-L1 + ChT group revealed that the addition of TRT significantly prolonged patient survival (median OS: 20.97 vs. 15.67 months, $p = 0.025$; median PFS: 8.83 vs. 6.67 months, $p = 0.006$) (Fig. 3D and E).

At the final follow-up, the TRT group exhibited intrathoracic progression in 21 patients (22.1%), whereas the non-TRT group had 59 patients (69.4%) with

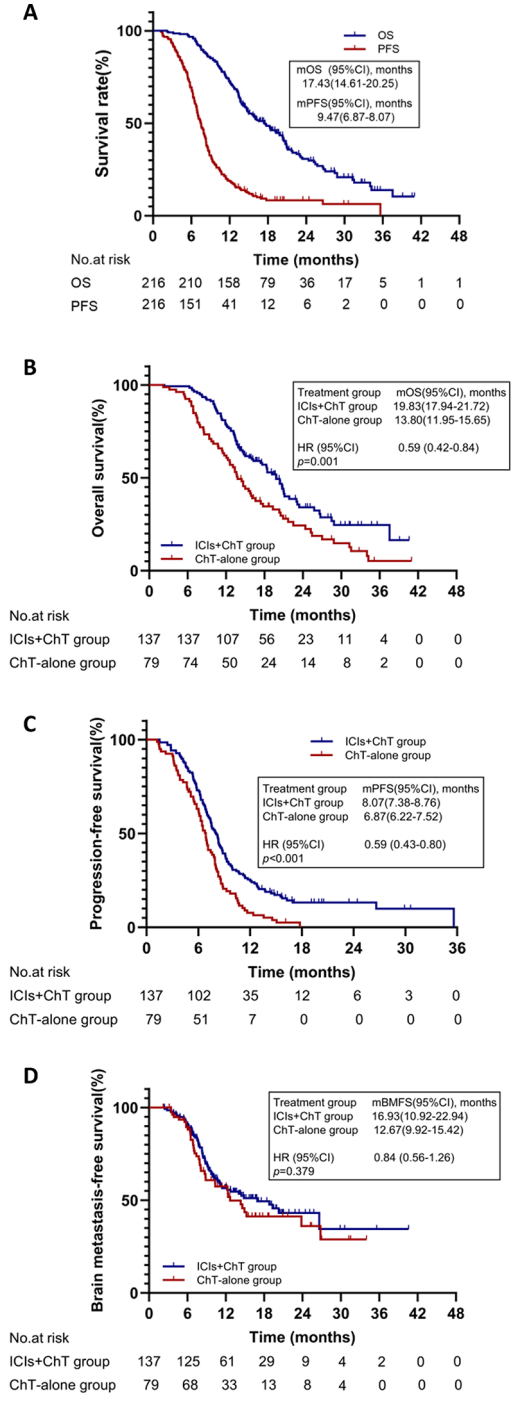

Fig. 2 (**A**) OS and PFS of the overall population. (**B**) OS and (**C**) PFS for ICIs + ChT vs. ChT-alone. (**D**) BMFS for ICIs + ChT vs. ChT-alone. Abbreviations: ICIs, immune checkpoint inhibitors; ChT, chemotherapy; mOS, median overall survival; mPFS, median progression-free survival; mBMFS, median brain metastasis-free survival; CI, confidence interval; HR, hazard ratio

intrathoracic progression ($p < 0.001$). Within the TRT group, 60 patients (63.2%) developed extracranial new metastases or progression, compared to 62 cases (72.9%) in the non-TRT group ($p = 0.161$). Similar outcomes were noted in the analysis of patients in the αPD-L1 + ChT group. The addition of TRT significantly controlled the rate of intrathoracic progression (16.9% vs. 58.1%, $p < 0.001$), but did not affect the incidence of new extracranial metastases (50.8% vs. 62.8%, $p = 0.230$). The progression patterns of patients are illustrated in Supplementary Fig. 3A and B.

Survival outcomes of patients with BMs treated with different brain radiotherapy strategies

We conducted a statistical analysis of the BMs burden among patients who developed cerebral metastases. Patients were categorized into oligometastatic and extensive metastatic groups on the basis of the number and location of brain lesions. The oligometastatic group was defined as patients with ≤ 3 BMs, whereas the extensive metastatic group included those with > 3 lesions or leptomeningeal involvement. At the final follow-up, 103 patients had developed BMs: 66 in the ICI + ChT group, 39 in the ChT-alone group, and 50 in the αPD-L1 + ChT group (Supplementary Fig. 4). The addition of immunotherapy had no impact on the number of metastatic lesions. No significant difference was observed in the incidence of oligometastatic or extensive metastatic disease between the ChT-alone group and either the ICI + ChT group ($p = 0.531$) or the αPD-L1 + ChT group ($p = 0.411$).

All patients with BMs underwent cranial radiotherapy. We collected survival data following cranial irradiation and found that WBRT + boost may prolong survival in SCLC patients with BMs compared with SRS ($p < 0.001$) or conventional WBRT ($p = 0.003$) alone (Supplementary Fig. 5).

Univariate and multivariate analyses of OS and BMFS

We utilized univariate and multivariate Cox proportional hazards models to assess the impact of various factors on OS. In the univariate analysis, age, KPS score, liver metastases, bone metastases, immunotherapy, and TRT emerged as significant prognostic factors associated with OS ($p < 0.1$). These variables were subsequently incorporated into the multivariate analysis, which revealed that immunotherapy (HR, 0.560; 95% CI, 0.401–0.783; $p < 0.001$), TRT (HR, 0.628; 95% CI, 0.449–0.878; $p = 0.007$), and baseline bone metastases (HR, 1.589; 95% CI, 1.135–2.225; $p = 0.007$) were significantly associated with OS. Interestingly, BMs did not demonstrate a significant association with OS in this analysis. The detailed results are presented in Table 3. Subsequently, we conducted univariate Cox regression analysis of BMFS in patients treated with αPD-L1 + ChT, revealing that only TRT was significantly associated with BMFS (HR, 0.549; 95% CI, 0.306–0.986; $p = 0.045$). The detailed results are presented in Supplementary Table 2.

Table 2 Baseline characteristics of patients in the TRT and non-TRT groups

Patient characteristic, *n* (%)	All patients (*n* = 180)	TRT group (*n* = 95)	non-TRT group (*n* = 85)	*p* value
Age, years				
< 65	105 (58.3)	61 (64.2)	44 (51.8)	0.091
≥ 65	75 (41.7)	34 (35.8)	41 (48.2)	
Gender				
Male	145 (80.6)	73 (76.8)	72 (84.7)	0.183
Female	35 (19.4)	22 (23.2)	13 (15.3)	
KPS sore				
≥ 80	172 (95.6)	92 (96.8)	80 (94.1)	0.601
< 80	8 (4.4)	3 (3.2)	5 (5.9)	
Smoking status				
Yes	115 (63.9)	59 (62.1)	56 (65.9)	0.598
No	65 (36.1)	36 (37.9)	29 (34.1)	
Drinking status				
Yes	75 (41.7)	40 (42.1)	35 (41.2)	0.900
No	105 (58.3)	55 (57.9)	50 (58.8)	
Baseline liver metastases				
Yes	60 (33.3)	26 (27.4)	34(40.0)	0.073
No	120 (66.7)	69 (72.6)	51 (60.0)	
Baseline bone metastases				
Yes	66 (36.7)	29 (30.5)	37 (43.5)	0.071
No	114 (63.3)	66 (69.5)	48 (56.5)	
Baseline Adrenal metastases				
Yes	24 (13.3)	10 (10.5)	14 (16.5)	0.242
No	156 (86.7)	85 (89.5)	71 (83.5)	
First-line therapy				
αPD-L1 + ChT	102 (56.7)	59 (62.1)	43 (50.6)	0.120
ChT-alone	78 (43.3)	36 (37.9)	42 (49.4)	
No. of first-line therapy cycles				
< 4	13 (7.2)	4 (4.2)	9 (10.6)	0.154
4–6	159 (88.3)	88 (92.6)	71 (83.5)	
> 6	8 (4.5)	3 (3.2)	5 (5.9)	
The response to first-line therapy				
CR/PR	110 (61.1)	60 (63.2)	50 (58.8)	0.552
SD	70 (38.9)	35 (36.8)	35 (41.2)	
Tumor status				
≤ T2	95 (52.8)	49 (51.6)	46 (54.1)	0.733
≥ T3	85 (47.2)	46 (48.4)	39 (45.9)	
Lymph node status				
≤ N1	11 (6.1)	7 (7.4)	4 (4.7)	0.457
≥ N2	169 (93.9)	88 (92.6)	81 (95.3)	
Total metastasis sites				
< 2	135 (75.0)	74 (77.9)	61 (71.8)	0.343
≥ 2	45 (25.0)	21 (22.1)	24 (28.2)	
LDH levels, U/L				0.425
≤ 245	96 (53.3)	48 (50.5)	48 (56.5)	
> 245	84 (46.7)	47 (49.5)	37 (43.5)	

Abbreviations: KPS, Karnofsky performance status; ChT, chemotherapy; αPD-L1, anti-programmed death-ligand 1 antibody; TRT, thoracic radiotherapy; CR, complete response; PR, partial response; SD, stable disease; LDH, Lactate dehydrogenase

Safety

Among a cohort of 137 patients undergoing ICIs, safety evaluations were conducted for pneumonia, esophagitis, and hematological toxicities using imaging, symptoms, and laboratory tests. In the group receiving ICIs + ChT along with TRT, 34 patients (47.2%) encountered grade 3 or higher treatment-related adverse events. In contrast, 27 patients (41.5%) in the non-TRT group faced similar challenges. The most prevalent hematologic toxicities observed were neutropenia (73.0%) and leukopenia

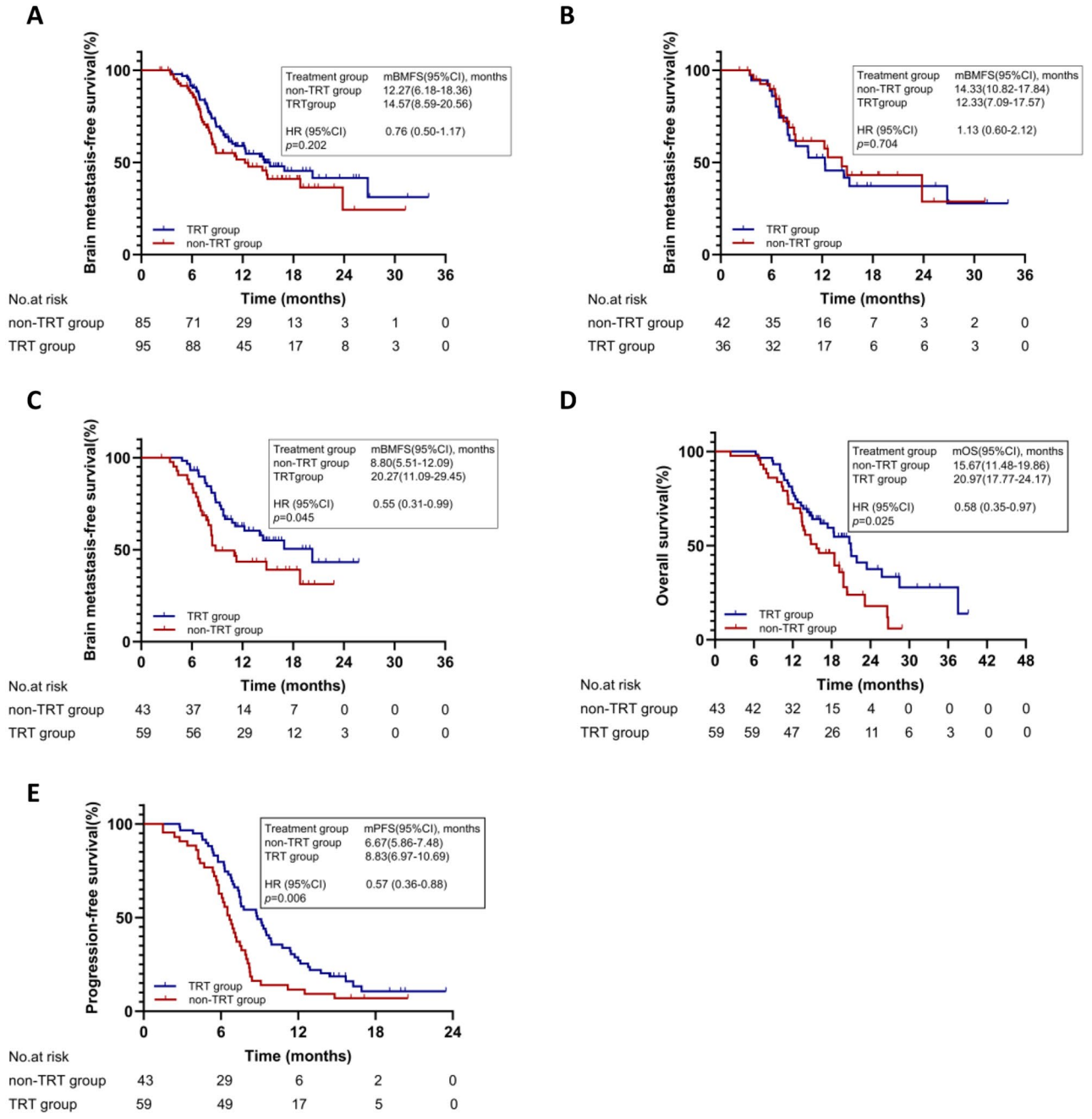

Fig. 3 (**A**) BMFS for TRT vs. non-TRT. (**B**) BMFS for TRT vs. non-TRT in ChT-alone subgroup. (**C**) BMFS for TRT vs. non-TRT in αPD-L1 + ChT subgroup. (**D**) OS and (**E**) PFS for TRT vs. non-TRT in αPD-L1 + ChT subgroup. Abbreviations: TRT, thoracic radiotherapy; αPD-L1, anti-programmed death-ligand 1 antibody; ChT, chemotherapy; mOS, median overall survival; mPFS, median progression-free survival; mBMFS, median brain metastasis-free survival; CI, confidence interval; HR, hazard ratio

(66.4%). Severe leukopenia and neutropenia were often the primary reasons for treatment cessation. Furthermore, 21 patients (29.2%) and 2 patients (3.1%) in their respective groups experienced treatment-related pneumonia. Notably, 4 patients (5.6%) and 1 patient (1.5%) progressed to serious pneumonia. The detailed results are presented in Supplementary Table 3.

Discussion

SCLC is a malignant tumor that originates in the lungs. In recent years, significant progress has been made in understanding the molecular biological characteristics of SCLC and in developing immunotherapies. As a result, ICIs [32] have emerged as a treatment option for SCLC. Our study aimed to retrospectively analyze the impact of adding ICIs and TRT on the prognosis and intracranial

Table 3 Univariate and multivariate analyses of factors influencing OS of all patients

Factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Age, years <65 ≥65	1.379 (0.980–1.940)	0.051*	1.242 (0.882–1.747)	0.214
Gender Male Female	1.116 (0.763–1.632)	0.581		
KPS sore ≥80 <80	0.491 (0.183–1.319)	0.045*	0.567 (0.272–1.185)	0.131
Smoking status Yes No	1.157 (0.830–1.612)	0.397		
Drinking status Yes No	1.001 (0.722–1.388)	0.997		
Baseline liver metastases Yes No	1.336 (0.938–1.903)	0.087*	1.399 (0.986–1.986)	0.060
Baseline bone metastases Yes No	1.660 (1.169–2.359)	0.002*	1.589 (1.135–2.225)	**0.007**
Baseline Adrenal metastases Yes No	1.326 (0.810–2.171)	0.211		
No. of first-line therapy cycles <4 ≥4	1.044 (0.556–1.960)	0.896		
Secondary brain metastases Yes No	0.878 (0.634–1.215)	0.425		
ICIs Yes No	0.592 (0.419–0.836)	0.001*	0.560 (0.401–0.783)	**<0.001**
TRT Yes No	0.580 (0.418–0.805)	0.001*	0.628 (0.449–0.878)	**0.007**

Abbreviations: KPS, Karnofsky performance status; ICIs, immune checkpoint inhibitors; TRT, thoracic radiotherapy

*p value < 0.1

benefits in patients with ES-SCLC without baseline BMs. Additionally, we conducted a prognostic analysis of the clinical and pathological factors that influence the outcomes of ES-SCLC patients, providing valuable insights to guide clinical treatment decisions.

This study focused primarily on evaluating the impact of ICIs, specifically the inclusion of αPD-L1 therapy, on the survival of patients exhibiting ES-SCLC without baseline BMs. Additionally, we investigated whether the addition of TRT would prolong the median BMFS in these patients. ICIs have shown promising results in extending the OS of ES-SCLC patients without BMs (median OS: 19.83 vs. 13.80 months, $p = 0.001$). Notably, patients receiving αPD-L1 therapy also displayed similar survival benefits (median OS: 18.43 vs. 13.80 months, $p = 0.018$). Successful trials such as IMpower-133 [10] and CASPIAN [11] have instilled hope for ES-SCLC patients treated with PD-L1 inhibitors in combination with the EP regimen. The noteworthy outcome of the ASTRUM-005 trial [12] also highlighted PD-1 inhibitors. The addition of ICIs significantly extends the survival of ES-SCLC patients. However, our findings indicated that the addition of ICIs did not significantly reduce the risk of BMs in patients initially free of cerebral involvement (HR, 0.84; 95% CI, 0.56–1.26; $p = 0.379$), consistent with the retrospective study by Lu et al. [16]. These results suggest that immunotherapy may primarily impact extracranial lesions, thus extending OS in this patient cohort. However, further investigations into the CASPIAN [14] and IMpower133 [15] study have revealed that the addition of ICIs can actually delay intracranial progression. One possible reason could be the diverse variety of PD-L1

inhibitors used in retrospective studies compared to the specified immunotherapeutic agents used in clinical trials. Another factor could be the difference in patient race, as both our study and Lu's study focused on Chinese populations.

Notably, the combination of TRT and αPD-L1 therapy yielded promising results (median BMFS, TRT vs. non-TRT: 20.27 vs. 8.80 months; HR, 0.55; 95% CI, 0.31–0.99; $p = 0.045$). Although TRT following αPD-L1 + ChT treatment can delay the occurrence of BMs, statistical analysis of progression patterns revealed that the addition of TRT did not completely prevent the development of BMs (TRT vs. non-TRT: 44.1% vs. 55.8%, $p = 0.241$). Our study also demonstrated that within the αPD-L1 + ChT subgroup, the addition of TRT significantly prolonged patient survival outcomes. A study [33] utilizing the National Cancer Database examined the impact of TRT on survival outcomes in patients presenting ES-SCLC without BMs. The results demonstrated that patients who received TRT had significantly longer survival than patients who did not receive TRT (median OS: 11 vs. 9 months, $p < 0.001$). Another retrospective study [34] yielded similar results, demonstrating that TRT administered following first-line chemoimmunotherapy in patients with ES-SCLC was associated with prolonged PFS and OS without significantly increasing treatment-related toxicity. Professors Zhuo and Zhao's team investigated the survival of ES-SCLC patients with BMs via the IMpower133 model [35]. The median OS was 26.2 months in the atezolizumab group, whereas it was only 14.8 months in the EP group. This represents a considerable extension compared with the 12.3 months for the chemo-immunotherapy group and 10.4 months for the ChT-alone group observed in the IMpower133 trial. Therefore, this extended survival may be partially attributed to the synergistic effect of immunotherapy and radiotherapy, as 21.3% of patients in that study underwent TRT. In our study, 53% (72/137) of patients underwent TRT following treatment with ICIs + ChT. Compared to the survival outcomes reported in IMpower133 [10] and CAPSTONE-1 [13] trials, the median OS in our study extended to 19.83 months. This difference may be attributed to the fact that patients in those trials were not permitted to receive TRT, indicating that TRT could potentially enhance long-term prognosis.

In this study, the median prescribed dose of 50 Gy is significantly higher than the consensus for consolidative TRT. This may be because, in China, many radiation oncologists consider the risk of recurrence of residual thoracic tumors after first-line chemoimmunotherapy for ES-SCLC to be relatively high. In a recently published clinical trial [36] conducted in China involving consolidative TRT for ES-SCLC patients, the median prescribed dose was also 50 Gy (IQR: 45–50). Subsequent analysis of this clinical trial evaluated the impact of TRT dose on survival and found no significant differences between different dose groups or between the low biological effective dose (BED-low) and high biological effective dose (BED-high) groups. Therefore, we believe that the prescribed dose of consolidative TRT in this study is acceptable.

Radiotherapy has the potential to reprogram the tumor-inhibiting microenvironment into an immune-stimulating phenotype [37]. Ionizing radiation can induce immune changes within the tumor microenvironment, such as enhancing the release of tumor antigens, increasing infiltration of effector T cells, and boosting the expression of MHC-I molecules on tumor cells. Research indicates that radiation-induced DNA double-strand breaks elevate PD-L1 expression on tumor cells via the ATM/ATR/Chk1 kinase pathway [38]. Therefore, aside from directly damaging tumor cells and reducing the risk of local recurrence, radiotherapy can also facilitate the exposure of tumor-specific antigens, enhance the immunogenicity of tumor cells, modulate signal transduction, alter the inflammatory tumor microenvironment, and induce systemic, immune-mediated anti-tumor effects within and beyond the irradiated area, known as the "abscopal effect," thereby improving tumor control. Moreover, with the integration of immunotherapy, this response can be further enhanced. Additionally, some ES-SCLC patients may develop resistance to immunotherapy during treatment, which can be reversed through the combination of radiotherapy and immunotherapy. A review of 23 cases treated with radiation [39] effectively summarized the potential abstract effects of radiotherapy. These findings provide a theoretical basis for the delayed onset of BMs observed with the combination of TRT and αPD-L1 treatment. Additionally, TRT may indirectly impact the integrity of the blood-brain barrier by altering circulating cytokine levels. For instance, research indicates that overexpression of vascular endothelial growth factor (VEGF) increases the permeability of the blood-brain barrier by disrupting tight junctions, promoting neovascularization, and activating inflammatory responses [40, 41], thereby creating favorable conditions for tumor cells to migrate across the barrier. Previous studies have reported that radiotherapy can significantly reduce VEGF levels in peripheral blood [42]. This could also explain why TRT helps delay the onset of BMs.

The prognostic analysis in our study demonstrated that immunotherapy and TRT are favorable prognostic factors associated with improved OS, whereas the presence of baseline bone metastases is an adverse prognostic factor. Interestingly, the development of BMs posttreatment did not significantly impact patients' OS. These findings align with those of the study by Riihimaki et al. [43], which reported that patients with extracranial metastases (such as bone metastases) presented relatively lower survival rates than did those with central nervous system

metastases. In our study, the median OS for patients was 17.43 months, whereas the median BMFS was 14.57 months. There was no statistically significant difference between these two endpoints (HR = 0.89; 95% CI: 0.69–1.15; $p = 0.373$). We believe that in most patients, BMs occurs shortly before death, which may explain why BMs did not significantly impact the prognosis.

Our study has several limitations that warrant consideration. First, as a single-center investigation, the results may be influenced by an insufficient sample size, potentially limiting the statistical power and generalizability of the findings. Second, owing to the retrospective nature of the study, researchers were unable to randomize participant allocation, which may have introduced potential confounding biases. For example, in patients with non-TRT, the higher BMFS in the ChT-alone group compared to the αPD-L1 + ChT group might be attributed to the small number of patients or patient selection bias. We reanalyzed the BMFS of the αPD-L1 + ChT and ChT-alone groups in the non-TRT subgroup. The results indicated that although the median BMFS of αPD-L1 + ChT was numerically lower than that of ChT-alone, there was no statistical difference between the two groups (HR, 0.75; 95% CI, 0.412–1.381; $p = 0.357$). Finally, the impact of the timing of TRT initiation and the selection of radiation dose on outcomes remains undetermined. These limitations underscore the need for validation of our findings in future large-scale, multicenter prospective studies.

Conclusion

For patients with ES-SCLC without baseline BMs, first-line ICIs in combination with ChT significantly prolong PFS and OS compared to those with ChT alone, and first-line αPD-L1 therapy combined with ChT also significantly improves PFS and OS. However, ICIs do not significantly prolong the median BMFS or reduce the risk of intracranial metastasis. Notably, our findings highlight that the combination of αPD-L1 therapy with TRT significantly delays the onset of intracranial metastasis, providing valuable insights to guide clinical treatment strategies for ES-SCLC patients without baseline BMs.

Abbreviations

ICIs	Immune checkpoint inhibitors
TRT	Thoracic radiotherapy
SCLC	Small cell lung cancer
ES-SCLC	Extensive-stage small cell lung cancer
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
BMFS	Brain metastasis-free survival
ChT	Chemotherapy
αPD-1	Anti-programmed death 1 antibody
αPD-L1	Anti-programmed death-ligand 1 antibody
BMs	Brain metastases
VALG	Veterans Administration Lung Study Group
AJCC	American Joint Committee on Cancer
KPS	Karnofsky performance status
EP/EC	Eoposide plus cisplatin/carboplatin
SD	Stable disease
PR	Partial response
CR	Complete response
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume
WBRT	Whole brain radiotherapy
SRS	Stereotactic radiosurgery
WBRT + boost	Whole brain radiotherapy plus focal radiation boost

Supplementary Information

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Supplementary Material 1: Supplementary Table 1 Baseline characteristics of patients treated with ChT alone or αPD-L1+ChT.

Supplementary Material 2: Supplementary Fig. 1. (A) OS and (B) PFS for αPD-L1+ChT vs ChT-alone. (C) BMFS for αPD-L1+ChT vs ChT-alone. Abbreviations: αPD-L1, anti-programmed death ligand 1 antibody; ChT, chemotherapy; mOS, median overall survival; mPFS, median progression-free survival; mBMFS, median brain metastasis-free survival; CI, confidence interval; HR, hazard ratio.

Supplementary Material 3: Supplementary Fig. 2. (A) OS and (B) PFS for αPD-L1+ChT vs ChT-alone in TRT subgroup. (C) OS and (D) PFS for αPD-L1+ChT vs ChT-alone in non-TRT subgroup. Abbreviations: αPD-L1, anti-programmed death ligand 1 antibody; ChT, chemotherapy; mOS, median overall survival; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

Supplementary Material 4: Supplementary Fig. 3. (A) The progression patterns of patients in the TRT and non-TRT groups. (B) The progression patterns of patients treated with αPD-L1+ChT in the TRT and non-TRT groups. Abbreviations: TRT, thoracic radiotherapy.

Supplementary Material 5: Supplementary Fig. 4. Number of patients of cranial oligometastases and extensive brain metastases. ICIs, immune checkpoint inhibitors; αPD-L1, anti-programmed death ligand 1 antibody; ChT, chemotherapy.

Supplementary Material 6: Supplementary Fig. 5. OS analyses according to treatment group in all patients with brain metastases. The median OS was 15.7 months for patients receiving WBRT+boost, 7.4 months for patients receiving WBRT, and 6.4 months for patients receiving SRS. WBRT+boost, whole-brain radiation therapy plus focal radiation boost; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery.

Supplementary Material 7: Supplementary Table 2 Univariate analyses of factors influencing BMFS of patients treated with αPD-L1+ChT.

Supplementary Material 8: Supplementary Table 3 Adverse events in patients treated with ICIs+ChT±TRT.

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Not applicable.

Author contributions

MX, YJM and CGX supervised the study. CGX and MX guided the study concept and design. HBY and LSY wrote the main manuscript. CGX revised the manuscript. LM and WXP collected data. HBY, LSY, WKY, ZJR, WWQ and WXH analyzed data. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute owing to its retrospective nature with minimal risk, and informed consent was obtained from all included individuals.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, No. 440, Jiyan Road, Jinan, Shandong 250117, China
[2]The Affiliated Taian City Central Hospital of Qingdao University, Taian, Shandong, China
[3]School of Clinical Medicine, Shandong Second Medical University, Weifang, China
[4]The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China
[5]School of Public Health, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, China

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