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PD-1 versus PD-L1 inhibitors with consolidative thoracic radiotherapy in extensive-stage small cell lung cancer: a multicenter real-world cohort study

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Abstract

Background

Although the addition of immune checkpoint inhibitors (ICIs) to platinum-etoposide chemotherapy has improved outcomes in extensive-stage small cell lung cancer (ES-SCLC), whether PD-1 and PD-L1 inhibitors provide differential clinical benefit when combined with consolidative thoracic radiotherapy (TRT) remains unknown.

Methods

This multicenter retrospective cohort study included patients with ES-SCLC who received first-line platinum-etoposide chemotherapy plus PD-1 or PD-L1 inhibitors followed by consolidative TRT between February 2017 and January 2024 at four Chinese institutions. Survival outcomes were analyzed using the Kaplan–Meier method and Cox regression models.

Results

A total of 81 patients were enrolled (31 PD-1, 50 PD-L1). In the overall cohort, median progression-free survival (PFS) and overall survival (OS) were 11.0 months and 23.1 months, respectively. The PD-1 group showed numerically longer median PFS (13.2 vs. 9.2 months, P = 0.307) and OS (25.3 vs. 20.4 months, P = 0.073) compared with the PD-L1 group. Brain metastasis was independently associated with shorter PFS (HR = 0.531, 95%CI 0.327–0.864, P = 0.011), and bone metastasis independently predicted worse OS (HR = 0.522, 95%CI 0.291–0.938, P = 0.030). Patients receiving > 12 cycles of immunotherapy had significantly longer OS than those receiving fewer cycles (P = 0.027), and cisplatin-based chemotherapy was associated with longer PFS than carboplatin (12.2 vs. 8.6 months, P = 0.030). No significant differences in objective response rate, disease control rate, or treatment-related adverse events were observed between groups.

Conclusions

Chemoimmunotherapy plus consolidative TRT achieved encouraging survival in ES-SCLC, with a favorable trend for PD-1 over PD-L1 inhibitors when combined with TRT. These findings provide real-world evidence for integrating TRT into first-line chemoimmunotherapy and warrant further investigation in prospective studies.

Introduction

Small cell lung cancer (SCLC) is a highly aggressive malignancy that accounts for approximately 15% of all lung cancers, with a 5-year survival rate of less than 7% [1, 2]. Approximately 70% of patients present with extensive-stage disease (ES-SCLC) at diagnosis, characterized by rapid proliferation and early widespread metastasis [3]. Platinum-etoposide chemotherapy has remained the standard first-line treatment for decades, offering transient disease control but limited long-term survival, with median overall survival (OS) ranging from 10 to 12 months [4, 5].

The integration of immune checkpoint inhibitors (ICIs) into first-line regimens has modestly improved outcomes in ES-SCLC. The phase III IMpower133 and CASPIAN trials demonstrated that adding programmed death-ligand 1 (PD-L1) inhibitors (atezolizumab or durvalumab) to platinum-etoposide significantly prolonged OS compared with chemotherapy alone [6, 7]. More recently, programmed death-1 (PD-1) inhibitors including serplulimab, tislelizumab, and toripalimab have also shown survival benefits in this setting [8–10]. Despite these advances, the absolute survival benefit remains modest —with median OS improvements of only 2–3 months—and the majority of patients eventually progress within one year, underscoring the need for additional therapeutic strategies [6, 7].

Consolidative thoracic radiotherapy (TRT) has re-emerged as a critical component in ES-SCLC management. The phase III CREST trial established that TRT after chemotherapy reduced thoracic recurrence and improved 2-year OS[11]. In the immunotherapy era, radiotherapy may exert synergistic antitumor effects with ICIs by inducing immunogenic cell death, releasing tumor neoantigens, and promoting T-cell infiltration into the tumor microenvironment [12, 13]. Several real-world studies have reported promising outcomes with the addition of TRT to chemoimmunotherapy, with median OS ranging from 24.1 to 27.7 months [14, 15]. However, the optimal integration of radiotherapy with immunotherapy remains undefined, particularly regarding the comparative effectiveness of different ICI classes.

While both PD-1 and PD-L1 inhibitors are clinically approved for ES-SCLC, their differential efficacy and safety when combined with TRT have not been directly compared. Previous meta-analyses have suggested comparable efficacy between PD-1 and PD-L1 inhibitors in ES-SCLC, but these analyses were predominantly based on chemoimmunotherapy without radiotherapy [16]. Whether the addition of TRT modifies the relative efficacy of PD-1 versus PD-L1 inhibitors remains unknown, and this knowledge gap hinders evidence-based selection of ICIs in multimodal ES-SCLC therapy. In this multicenter retrospective study, we compared the efficacy and safety of consolidative TRT combined with PD-1 versus PD-L1 inhibitors in patients with ES-SCLC, aiming to provide real-world evidence for optimizing immunotherapeutic strategies in combination with radiotherapy.

Methods

Study Design and Patients

This multicenter retrospective cohort study enrolled patients with ES-SCLC who received first-line treatment at four Chinese institutions between February 2017 and January 2024: Weihai Municipal Hospital Affiliated to Shandong University, Dezhou Hospital of Shandong University, People's Hospital of Rongcheng, and Shanxian Hospital.

Eligible patients were aged ≥ 18 years with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–3, and had histologically or cytologically confirmed ES-SCLC according to the Veterans Administration Lung Study Group staging system. Patients were required to have completed at least two cycles of platinum-etoposide chemotherapy combined with either a PD-1 or PD-L1 inhibitor, followed by consolidative TRT to residual intrathoracic lesions, with a total dose ranging from 30 to 60 Gy administered in 10–30 fractions. Baseline imaging and at least one post-treatment radiologic evaluation using contrast-enhanced computed tomography (CT) or positron emission tomography/computed tomography (PET-CT) were required.

Key exclusion criteria included prior thoracic radiotherapy or immunotherapy, concurrent malignancies, active autoimmune diseases, lack of post-treatment efficacy assessment, or incomplete clinical records and loss to follow-up.

Treatment Regimens

Patients were categorized into two groups according to the type of ICI administered: the PD-1 group received PD-1 inhibitors plus platinum-etoposide chemotherapy followed by consolidative TRT, and the PD-L1 group received PD-L1 inhibitors plus platinum-etoposide chemotherapy followed by consolidative TRT. Chemotherapy regimens were platinum-based doublets (cisplatin or carboplatin plus etoposide).

All patients received intensity-modulated radiotherapy (IMRT) for TRT. The gross tumor volume included the residual primary tumor and involved lymph nodes after systemic treatment. The clinical target volume was generated by expanding the gross tumor volume by 8 mm and encompassing the lymph node regions involved before treatment initiation. The prescribed radiation dose ranged from 30 to 60 Gy (median, 45 Gy), delivered in daily fractions of 2–3 Gy,

five fractions per week. Dose constraints for organs at risk were applied according to Radiation Therapy Oncology Group guidelines.

Endpoints and Assessments

The primary endpoint was OS, defined as the interval from chemotherapy initiation to death from any cause or the last follow-up. Progression-free survival (PFS) was defined as the time from chemotherapy initiation to documented disease progression, death, or the last follow-up, whichever occurred first.

Tumor response was assessed by imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was calculated as (CR + PR) / total × 100%, and disease control rate (DCR) as (CR + PR + SD) / total × 100%.

Safety was evaluated at each follow-up visit through clinical and laboratory assessments. Immune-related adverse events (irAEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Grade 3–4 events were considered moderate-to-severe, and grade 5 events were classified as treatment-related deaths.

Follow-up data were obtained through outpatient records, inpatient medical records, and telephone interviews. The final follow-up was conducted on June 30, 2025.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics, with categorical variables presented as frequencies and percentages. Comparisons between groups were performed using the chi-square test. Survival outcomes were estimated using the Kaplan-Meier method and compared with the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to identify factors associated with OS and PFS. Variables with potential prognostic significance ($P < 0.10$) in univariable analysis were entered into multivariable models. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant. Analyses were performed using SPSS version 27.0 (IBM Corp, Armonk, NY, USA).

Results

Patient Disposition

A total of 397 patients were initially screened for eligibility. After excluding 128 patients with limited-stage SCLC, 30 who received fewer than two cycles of platinum-based chemotherapy or immunotherapy, 24 who did not receive first-line treatment, 59 who did not undergo thoracic radiotherapy, 42 who did not receive immunotherapy, and 33 with unavailable survival data, 81 patients were ultimately included in the final analysis. Of these, 31 patients (38.3%) received PD-1 inhibitors and 50 patients (61.7%) received PD-L1 inhibitors **(**Fig. 1**).**

Baseline Characteristics

Baseline patient characteristics are summarized in **Table 1**. The median age was 64 years (range, 33-79 years), and the majority of patients were male (64.2%). A history of smoking was present in 63.0% of patients, and 69.1% had a history of alcohol consumption. Most patients (91.4%) had an ECOG PS of 0-1. Brain metastases were present in 58.0% of patients, liver metastases in 29.6%, and bone metastases in 44.4%. Additionally, 46 patients (56.8%) received anti-angiogenic

therapy in combination with chemoimmunotherapy. Baseline characteristics were well balanced between the PD-1 and PD-L1 groups, except for alcohol consumption history.

Table 1 Baseline characteristics of patients according to first-line therapy.

Characteristics	All patients(n=81)	PD-1(n=31)	PD-L1(N=50)	*P*-Value
Median age	64(33-79)	64(48-79)	62.5(33-79)	
Age, year				0.908
≤65 yrs	32(39.5)	12(38.7)	20(40.0)	
65 yrs	49(60.5)	19(61.3)	30(60.0)	
Gender				0.167
Female	29(35.8)	14(45.2)	15(30.0)	
Male	52(64.2)	17(54.8)	35(70.0)	
Smoking history				0.233
Never smoked	30(37.0)	14(45.2)	16(32.0)	
Former/current	51(63.0)	17(54.8)	34(68.0)	
Drinking history				**0.028**
Never drinked	25(30.9)	14(45.20)	11(22.0)	
Former/current	56(69.1)	17(54.8)	39(78.0)	
Hypertension				0.099
No	51(63.0)	23(74.2)	28(56.0)	
Yes	30(37.0)	8(25.8)	22(44.0)	
Diabetes				0.776
No	64(79.0)	25(80.6)	39(78.0)	
Yes	17(21.0)	6(19.4)	11(22.0)	
CHD				0.415
No	71(87.7)	26(83.9)	45(90.0)	
Yes	10(12.3)	5(16.1)	5(10.0)	
ECOG PS				0.282
0-1	74(91.4)	27(87.1)	47(94.0)	
2	7(8.6)	4(12.9)	3(6.0)	
Brain Metastasis				0.166
No	34(42.0)	16(51.6)	18(36.0)	
Yes	47(58.0)	15(48.4	32(64.0)	
Liver Metastasis				0.274
No	57(70.4)	24(77.4)	33(66.0)	
Yes	24(29.6)	7(22.6)	17(34.0)	
Bone Metastasis				0.720
No	45(55.6)	18(58.1)	27(54.0)	

Yes	36(44.4)	13(41.9)	23(46.0)	
anti-angiogenic therapy				0.520
Yes	46(56.8)	19(61.3)	27(54.0)	
No	35(43.2)	12(38.7)	23(46.0)	

Abbreviations: CHD, Coronary Heart Disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Chemotherapy regimens consisted of cisplatin plus etoposide (n=55), carboplatin plus etoposide (n=24), and nedaplatin plus etoposide (n=2). PD-1 inhibitors included tislelizumab (n=11), serplulimab (n=8), toripalimab (n=7), camrelizumab (n=3), and sintilimab (n=2). PD-L1 inhibitors included durvalumab (n=38), atezolizumab (n=6), adebrelimab (n=4), and envafolimab (n=2).

The median radiation dose was 45 Gy (range, 30-60 Gy). Among the 47 patients with brain metastases, 35 received cranial radiotherapy; among the 36 patients with bone metastases, 11 received palliative radiotherapy to bone lesions. Prophylactic cranial irradiation (PCI) was administered to 3 patients without brain metastases.

Survival Outcomes

The median follow-up duration was 29.5 months. In the overall cohort, the median PFS was 11.0 months (95% CI, 9.4-12.6 months), and the median OS was 23.1 months (95% CI, 18.6-27.6 months). The 6-month and 24-month PFS rates were 84.0% and 10.2%, respectively. The 1-year and 5-year OS rates were 86.4% and 11.2%, respectively **(Table 2).**

Table 2 The survival rate of OS and PFS.

	OS					PFS			
Time	1-year	2-year	3-year	4-year	5-year	6-month	12-month	18-month	24-month
All patients	86.4%	47.6%	24.1%	19.7%	11.2%	84.0%	41.9%	20.7%	10.2%
PD-1	90.2%	54.5%	34.0%	34.0%	12.7%	93.5%	54.6%	22.2%	9.3%
PD-L1	82.0%	43.1%	18.6%	11.6%	11.6%	78.0%	34.0%	19.6%	10.5%

Abbreviations: OS, Overall Survival; PFS, Progression-free Survival.

When comparing the two treatment groups, the PD-1 group showed a numerically longer median PFS than the PD-L1 group (13.2 vs. 9.2 months, P=0.307; **Fig. 2A, 2C**), and a numerically longer median OS (25.3 vs. 20.4 months, P=0.073; **Fig. 2B, 2D**). The corresponding 6-month PFS rates were 93.5% and 78.0%, 12-month PFS rates 54.6% and 34.0%, and 24-month PFS rates 9.3% and 10.5%, respectively. The 1-year OS rates were 90.2% and 82.0%, 2-year OS rates 54.5% and 43.1%, and 5-year OS rates 12.7% and 11.6%, respectively **(Table 2).**

Tumor response was evaluated after two treatment cycles. Overall, 1 patient achieved a CR, 43 achieved a PR, and 26 had SD, yielding an ORR of 54.3% (44/81) and a DCR of 86.4% (70/81). The ORR was 54.8% (17/31) in the PD-1 group and 54.0% (27/50) in the PD-L1 group, while the DCR was 87.1% (27/31) and 86.0% (43/50), respectively **(Table 3).**

Table 3 The short-term efficacy.

First-line（n=81）	n	CR	PR	SD	PD	ORR（%）	DCR（%）
All patients	81	1	43	26	11	54.3	86.4
PD-1	31	1	16	10	4	54.8	87.1
PD-L1	50	0	27	16	7	54.0	86.0

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, Objective response rate; DCR, disease control rate.

Prognostic Factors

Univariable and multivariable Cox regression analyses were performed to identify factors associated with survival outcomes **(Table 4).** In univariable analysis, smoking history (P=0.033), alcohol consumption (P=0.046), and brain metastasis (P=0.008) were significantly associated with PFS. Multivariable analysis identified brain metastasis as an independent prognostic factor for PFS (HR, 0.531; 95% CI, 0.327-0.864; P=0.011). For OS, univariable analysis showed bone metastasis as a significant factor (P=0.004), which was confirmed in multivariable analysis (HR, 0.522; 95% CI, 0.291-0.938; P=0.030).

Table 4 Analysis of potential risk factors for OS and PFS using univariate and multivariate Cox proportional hazard models.

Characteristics	OS				PFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Valu	HR (95% CI)	*P*-Value
Age, year(≤65 yrs vs. >65 yrs)	1.256(0.751-2.099)	0.386			1.231(0.770-1.968)	0.386		
Gender(Female vs. Male)	0.574(0.328-1.007)	0.053	0.850(0.197-3.665)	0.827	0.687(0.422-1.120)	0.132		
Smoking history(Never vs. Former/current)	0.589(0.336-1.031)	0.064	0.950(0.190-4.762)	0.950	0.588(0.360-0.959)	**0.033**	0.688(0.289-1.635)	0.397
Drinking history(No vs. Yes)	0.578(0.324-1.032)	0.064	0.860(0.357-2.070)	0.736	0.594(0.356-0.991)	**0.046**	0.883(0.369-2.114)	0.781
Hypertension(No vs. Yes)	0.649(0.385-1.096)	0.106			0.856(0.530-1.383)	0.526		
Diabetes(No vs. Yes)	0.651(0.359-1.180)	0.157			0.944(0.534-1.668)	0.842		
CHD	1.204(0.545-2.659)	0.646			1.150(0.571-2.319)	0.695		
ECOG PS(0-1 vs. ≥2)	0.742(0.317-1.734)	0.491			0.690(0.314-1.513)	0.354		
Brain Metastatic(No vs. Yes)	0.640(0.375-1.093)	0.102			0.524(0.325-0.846)	**0.008**	0.531(0.327-0.864)	**0.011**
Liver Metastatic(No vs. Yes)	0.662(0.379-1.158)	0.148			0.713(0.436-1.166)	0.178		
Bone Metastatic(No vs. Yes)	0.457(0.270-0.776)	0.004	0.522(0.291-0.938)	**0.030**	0.653(0.411-1.038)	0.072	0.869(0.512-1.475)	0.602
anti-angiogenic therapy (Yes vs. No)	0.981(0.577-1.669)	0.945			0.796(0.494-1.282)	0.348		

Abbreviations: OS, Overall Survival; PFS, Progression-free Survival; CI, Confidence Interval; HR, Hazard Ratio; CHD, Coronary Heart Disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Subgroup Analyses

Brain Metastasis

Patients were stratified by brain metastasis status: 34 without and 47 with brain metastasis at baseline. Median PFS was significantly longer in patients without brain metastasis (12.0 vs. 9.3 months, P=0.017), while median OS showed a numerical but non-significant difference (25.0 vs. 21.1 months, P=0.061).

Further stratification by brain metastasis status and receipt of cranial radiotherapy yielded four subgroups: brain metastasis without cranial radiotherapy (n=12), brain metastasis with cranial radiotherapy (n=35), no brain metastasis

without PCI (n=31), and no brain metastasis with PCI (n=3). Median PFS across the four groups was 8.6, 9.8, 11.8, and 12.7 months, respectively (P=0.119). Median OS was 18.6, 23.1, 24.0, and 31.0 months, respectively (P=0.087). Pairwise comparisons demonstrated that patients in both no-brain-metastasis groups had significantly longer OS than those with brain metastasis who did not receive cranial radiotherapy (P=0.015 and P=0.035, respectively; **Fig. 3A, 3B**).

Bone Metastasis

Patients were stratified by bone metastasis status: 45 without and 36 with bone metastasis. Median PFS was comparable between the two groups (11.8 vs. 8.1 months, P=0.068), whereas median OS was significantly longer in patients without bone metastasis (31.0 vs. 18.6 months, P=0.003).

Further stratification into three subgroups—bone metastasis without radiotherapy (n=23), bone metastasis with radiotherapy (n=11), and no bone metastasis (n=47)—revealed median PFS of 7.8, 9.2, and 12.0 months, respectively (P=0.109), and median OS of 17.8, 18.8, and 28.0 months, respectively (P=0.012). Pairwise comparisons showed that patients without bone metastasis had significantly longer PFS than those with bone metastasis who did not receive radiotherapy (P=0.043). For OS, patients without bone metastasis had significantly longer survival than patients with bone metastasis regardless of radiotherapy administration (vs. no radiotherapy, P=0.010; vs. radiotherapy, P=0.020; **Fig. 3C, 3D)**.

Number of Immunotherapy Cycles

Patients were stratified by number of immunotherapy cycles: <4 cycles (n=31), 4-12 cycles (n=31), and >12 cycles (n=19). Median PFS was 9.0, 12.0, and 11.8 months, respectively (P=0.259). Median OS was 19.5, 24.0, and 31.7 months, respectively, with a significant difference across the three groups (P=0.027). Pairwise comparisons confirmed that patients receiving >12 cycles had significantly longer OS than those receiving <4 cycles (P=0.009) or 4-12 cycles (P=0.018), whereas no significant difference was observed between the <4-cycle and 4-12-cycle groups (P=0.352; **Fig. 3E, 3F**).

Platinum Agent

Among patients receiving cisplatin (n=55) or carboplatin (n=24), those treated with cisplatin achieved significantly longer median PFS (12.2 vs. 8.6 months, P=0.030). Although median OS was numerically longer in the cisplatin group (25.3 vs. 18.5 months), the difference did not reach statistical significance (P=0.103; **Fig. 3G, 3H**).

Safety

Treatment-related adverse events (trAEs) are summarized in **Table 5**. Across the entire cohort, 13 patients (16.0%) experienced no adverse events, 54 patients (66.7%) developed grade 1-2 trAEs, and 14 patients (17.3%) developed grade 3-4 trAEs. No treatment-related deaths occurred. The distribution of trAE severity was comparable between the PD-1 and PD-L1 groups (P=0.812).

Table 5 Treatment-related adverse event.

	Total(81)	PD-1(31)	PD-L1(50)	*P*-Value
No	13(16.0%)	6(19.4%)	7(14.0%)	0.812
Grade 1-2	54(66.7%)	20(64.5%)	34(68.0%)	
Grade 3-4	14(17.3%)	5(16.1%)	9(18.0%)	
IrAEs	32(39.5%)	13(41.9%)	19(38.0%)	0.725
thyroid dysfunction	16(19.8%)	7(22.6%)	9(18.0%)	
rash	8(9.9%)	4(12.9%)	4(8.0%)	
pneumonitis	5(6.2%)	2(6.5%)	3(6.0%)	
hepatic dysfunction	2(2.5%)	1(3.2%)	1(2.0%)	
colitis	1(1.2%)	0	1(2.0%)	
RrAEs	23(28.4%)	9(29.0%)	14(28.0%)	0.920
esophagitis	12(14.8%)	5(16.1%)	7(14.0%)	
pneumonitis	8(9.9%)	3(9.7%)	5(10.0%)	
dermatitis	3(3.7%)	1(3.2%)	2(4.0%)	

Abbreviations: IrAEs, immune-related adverse events; RrAEs, radiation-related adverse events

Any-grade immune-related adverse events (irAEs) occurred in 32 patients (39.5%), with the most common being thyroid dysfunction (16 patients, 19.8%), rash (8 patients, 9.9%), immune-related pneumonitis (5 patients, 6.2%), hepatic dysfunction (2 patients, 2.5%), and colitis (1 patient, 1.2%). IrAEs were observed in 13 patients (41.9%) in the PD-1 group and 19 patients (38.0%) in the PD-L1 group, with no significant intergroup difference (P=0.725). Grade ≥3 irAEs occurred in 4 patients (4.9%), including immune-related pneumonitis (n=2), rash (n=1), and hyperthyroidism (n=1). No patients discontinued treatment or died due to irAEs.

All patients received consolidative TRT. Radiation-related adverse events (rrAEs) occurred in 23 patients (28.4%), most commonly radiation esophagitis (12 patients, 14.8%), radiation pneumonitis (8 patients, 9.9%), and radiation dermatitis (3 patients, 3.7%). Only one patient (1.2%) experienced grade 3 radiation pneumonitis, which resolved with corticosteroid therapy. The rrAE rates were 29.0% (9/31) in the PD-1 group and 28.0% (14/50) in the PD-L1 group, with no significant intergroup difference (P=0.920).

Discussion

The addition of ICIs to platinum-etoposide chemotherapy has modestly improved outcomes in ES-SCLC, yet most patients eventually progress and die from their disease. It has been reported that approximately 75%-90% of deaths in ES-SCLC are attributed to persistent intrathoracic disease [17]**.** Radiotherapy, as an effective local treatment modality, therefore plays an important role in the management of ES-SCLC. Consolidative TRT after chemotherapy has been shown to significantly reduce intrathoracic relapse and improve survival outcomes, with a reported increase in 5-year OS from 3.6% to 12.3% (P < 0.001) [18, 19]**.** In this multicenter retrospective study, we found that consolidative TRT combined with chemoimmunotherapy achieved a median OS of 23.1 months and a median PFS of 11.0 months, with a 1-year OS rate of 86.4% and 5-year OS rate of 11.2%. Similarly, Zhang et al. recently reported that ES-SCLC patients receiving cTRT after first-line chemoimmunotherapy had a median OS of 26 months and a median PFS of 10 months, with a 1-year OS rate of 84.4% [20]. These figures are highly concordant with our findings. Our survival figures also compare favorably with historical data from the pivotal chemoimmunotherapy trials, where median OS ranged from 12.3 to 15.4 months and

median PFS ranged from 4.5 to 5.8 months [7, 8, 21]. Our findings align with the growing body of evidence supporting the addition of TRT to chemoimmunotherapy in ES-SCLC [14, 15].

The primary objective of this study was to compare the efficacy of PD-1 and PD-L1 inhibitors when combined with TRT. While no statistically significant differences in PFS or OS were observed between the two groups, patients receiving PD-1 inhibitors showed a numerical improvement in median OS (25.3 vs. 20.4 months, P=0.073). This trend is consistent with previous meta-analyses suggesting a possible survival advantage for PD-1 over PD-L1 inhibitors in ES-SCLC, though these analyses were based on chemoimmunotherapy without radiotherapy [22, 23]. In our previous real-world study, we observed that PD-1 inhibitors combined with radiotherapy significantly prolonged OS compared with radiotherapy-naive patients (36.0 vs. 15.8 months), whereas no such benefit was seen with PD-L1 inhibitors [24]. The present study extends these findings by focusing specifically on patients receiving consolidative TRT, providing additional real-world evidence that PD-1 inhibitors may confer greater clinical benefit than PD-L1 inhibitors in the context of radiotherapy. However, given the retrospective design and limited sample size, these results should be interpreted as hypothesis-generating rather than definitive, and warrant prospective validation.

Brain metastasis is a common and poor-prognosis manifestation of ES-SCLC [25]. Brain radiotherapy has long been considered a cornerstone of intracranial disease management in SCLC, providing effective local control for both established brain metastases and prophylactic cranial irradiation (PCI) [26]. In addition to achieving durable local control, emerging evidence indicates that radiotherapy may enhance antitumor immunity by promoting tumor antigen release, increasing immune cell infiltration, and facilitating systemic immune activation[27]. In our cohort, patients with brain metastases had significantly shorter PFS than those without (9.3 vs. 12.0 months, P=0.017), and brain metastasis remained an independent prognostic factor in multivariable analysis (HR=0.531, P=0.011). Although the OS difference did not reach statistical significance, likely due to the limited sample size, patients with brain metastases who did not receive cranial radiotherapy had significantly worse OS than those without brain metastases, regardless of PCI administration. These findings underscore the importance of effective intracranial disease control in patients receiving chemoimmunotherapy and provide additional rationale for integrating cranial radiotherapy into the multidisciplinary management of ES-SCLC.

Bone is one of the most common sites of distant metastasis in patients with ES-SCLC and is generally associated with an unfavorable prognosis owing to a higher tumor burden and an increased risk of skeletal-related events [28]. Radiotherapy remains the standard local treatment for bone metastases, providing effective pain relief, improving functional status, and reducing skeletal complications [29]. In our cohort, bone metastasis was also identified as an independent negative prognostic factor for OS (HR=0.522, P=0.030). Patients with bone metastases had significantly shorter OS than those without (18.6 vs. 31.0 months, P=0.003). Notably, among patients with bone metastases, receipt of bone radiotherapy was not associated with a significant survival benefit, suggesting that the adverse prognostic impact of bone metastasis may outweigh the potential benefit of local palliative radiotherapy in this population. This finding does not diminish the established role of bone radiotherapy for symptom palliation, but suggests that its impact on overall survival in the context of chemoimmunotherapy may be limited.

The optimal duration of immunotherapy in ES-SCLC remains undefined. Current guidelines recommend continuation until disease progression or unacceptable toxicity, but evidence supporting specific treatment durations is limited, particularly in patients receiving consolidative TRT [26, 30]. In our study, patients receiving more than 12 cycles of immunotherapy had significantly longer OS than those receiving 4-12 cycles or fewer than 4 cycles (31.7 vs. 24.0 vs. 19.5 months, P=0.027). While this association should be interpreted with caution due to potential survival bias—patients who survive longer are inherently more likely to receive more treatment cycles—it nonetheless supports the hypothesis that patients deriving durable clinical benefit from chemoimmunotherapy may continue to benefit from prolonged maintenance therapy. Accordingly, patients who remain progression-free after consolidative TRT and tolerate treatment well may be reasonable candidates for continued maintenance immunotherapy, although the optimal treatment duration remains to be defined.

The choice of platinum agent in ES-SCLC remains a topic of clinical debate. Both cisplatin and carboplatin are considered acceptable options, with comparable efficacy in meta-analyses [31, 32]. However, this paradigm has recently been challenged by a large cohort study from the Cleveland Clinic (n=602), in which Batah et al. demonstrated that cisplatin-based regimens were associated with higher response rates than carboplatin-based regimens, though no significant OS or PFS differences were observed after propensity score weighting [33]. In our cohort, cisplatin was associated with significantly longer PFS than carboplatin (12.2 vs. 8.6 months, P=0.030), though the OS difference did not reach statistical significance (25.3 vs. 18.5 months, P=0.103). Our findings align with Batah et al. in suggesting a potential advantage for cisplatin, particularly in the context of TRT. However, this observation should be interpreted with caution, as treatment allocation was not randomized and the selection of platinum agents in routine practice is often influenced by patient age, performance status, comorbidities, and anticipated treatment-related toxicities [34, 35]. Nonetheless, our findings suggest that cisplatin-based chemoimmunotherapy combined with TRT may be associated with improved disease control in appropriately selected patients with good performance status, and warrant further investigation in prospective studies.

The safety profile of chemoimmunotherapy plus TRT was acceptable and consistent with previous reports. The incidence of grade ≥3 adverse events were 17.3%, with no treatment-related deaths. Immune-related adverse events (irAEs) occurred in 39.5% of patients, predominantly thyroid dysfunction, rash, and pneumonitis, consistent with the spectrum reported in the IMpower133 trial[7]. Notably, the rate of grade ≥3 irAEs (4.9%) was lower than that reported in IMpower133 (8.1%) and CASPIAN (5%) [6, 7]. Radiation-related adverse events occurred in 28.4% of patients, primarily esophagitis, pneumonitis, and dermatitis, with only one grade 3 event, consistent with previous reports of consolidative TRT [36, 37]. No unexpected safety signals were identified, and the toxicity profiles were similar between the PD-1 and PD-L1 groups, further supporting the feasibility of this multimodal approach in real-world practice.

This study has several limitations. First, its retrospective design introduces the potential for selection bias and residual confounding, despite balanced baseline characteristics between groups. Second, the relatively small sample size (n=81) limited statistical power to detect survival differences, particularly in subgroup analyses. Third, the heterogeneous use of different PD-1 and PD-L1 inhibitors, variations in radiotherapy timing and dose, and subsequent lines of therapy may have influenced outcomes. Fourth, the high proportion of patients with brain metastases (58.0%) in our cohort may limit generalizability to other populations, though this likely reflects real-world practice. Finally, all participating centers were located within the same region of China, which may affect the external validity of our findings. Larger prospective multicenter studies are warranted to validate our observations.

Conclusion

Chemoimmunotherapy plus consolidative TRT achieved encouraging survival outcomes in patients with ES-SCLC. While no statistically significant difference was observed between PD-1 and PD-L1 inhibitors, PD-1-based regimens showed a favorable trend toward improved OS when combined with TRT. Brain metastasis remained an important negative prognostic factor, whereas prolonged immunotherapy duration and cisplatin-based chemotherapy were associated with more favorable outcomes in selected patients. These findings provide real-world evidence supporting the integration of TRT into first-line chemoimmunotherapy and generate clinically relevant hypotheses regarding the optimal selection of ICIs in combination with radiotherapy. Prospective randomized studies are needed to further define the optimal immunotherapeutic strategy in this setting.

Abbreviations

ICIs checkpoint inhibitors

TRT thoracic radiotherapy

ES-SCLC Extensive-stage small cell lung cancer

PD-L1 programmed death-ligand 1

PD-1 programmed death-1

ECOG PS Eastern Cooperative Oncology Group performance status

CT computed tomography

PET-CT positron emission tomography/computed tomography

IMRT intensity-modulated radiotherapy

ORR Objective response rate

DCR Disease control rate

PFS Progression-free survival

OS Overall survival

CR complete response

PR partial response

SD stable disease

PD progressive disease

RECIST Response Evaluation Criteria in Solid Tumors

AEs Adverse events

CHD Coronary Heart Disease

irAEs Immune-related adverse events

trAEs Treatment-related adverse events

rrAEs Radiation-related adverse events

Declarations

Author contributions

Concept and design: Huaijun Ji and Yongbing Chen. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Huaijun Ji and Jingyi Li. Critical revision of the manuscript for important intellectual content: Jingyi Li, Ge Yu and Kexin Zhang. Statistical analysis: Huaijun Ji, Jie Sui and Yuanyuan Duan. Obtained funding: Yongbing Chen. Supervision: Ge Yu and Yongbing Chen.

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Data availability

Data supporting the findings of this study are available upon request from the corresponding authors. The data are not publicly available because of privacy and ethical restrictions. These data are also related to unpublished studies. However, these data involve privacy issues for some patients and are not publicly shared.

Ethical Statement

This study was conducted in accordance with the World Medical Association Declaration of Helsinki (as revised in 2024) and was approved by the Institutional Review Board of Weihai Municipal Hospital, Shandong University (Approval No. 20240110). Informed consent was waived due to the retrospective nature of the study, and all data were anonymized prior to analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

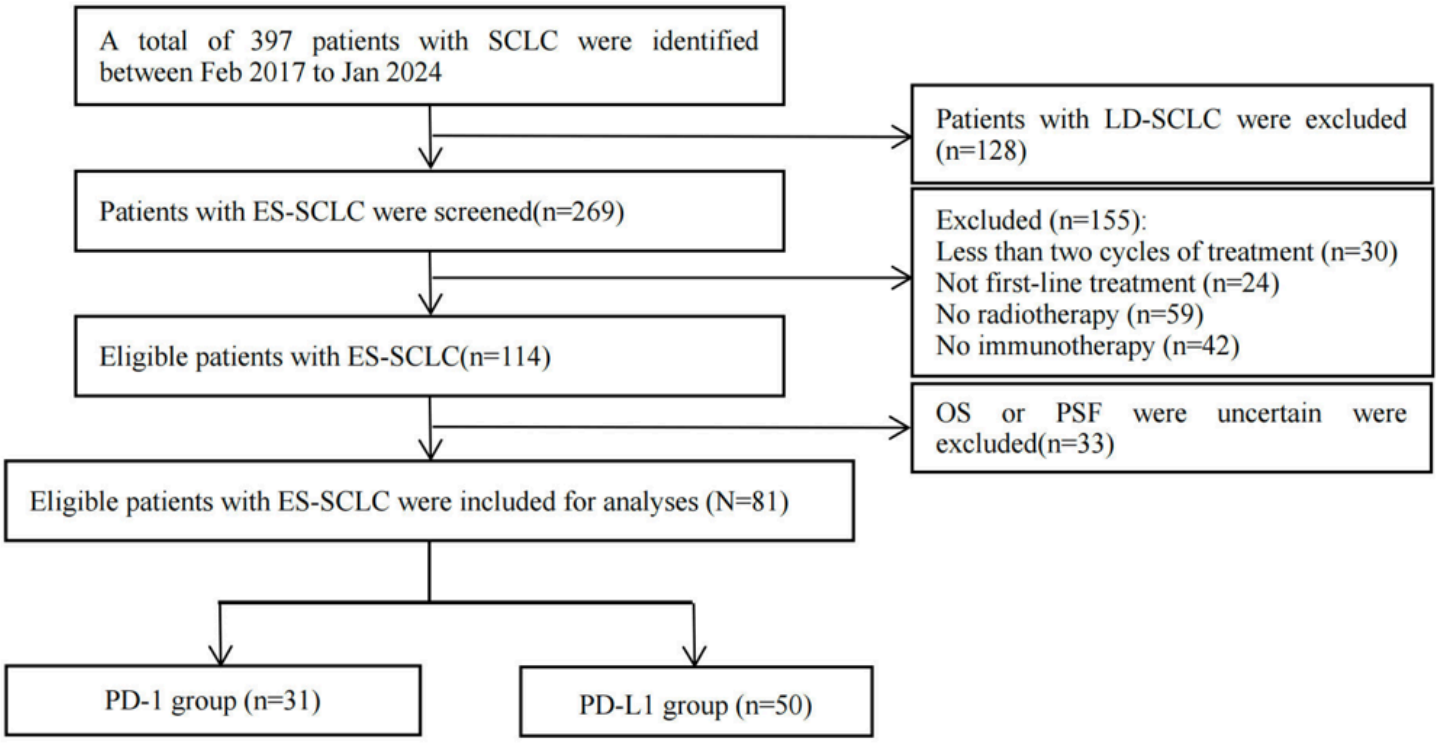


Figure 1

Diagram of patient's selection process. ES-SCLC, extensive-stage small-cell lung cancer; LD-SCLC, limited-disease small-cell lung cancer; SCLC, small-cell lung cancer; OS, overall survival; PFS,progression-free survival.

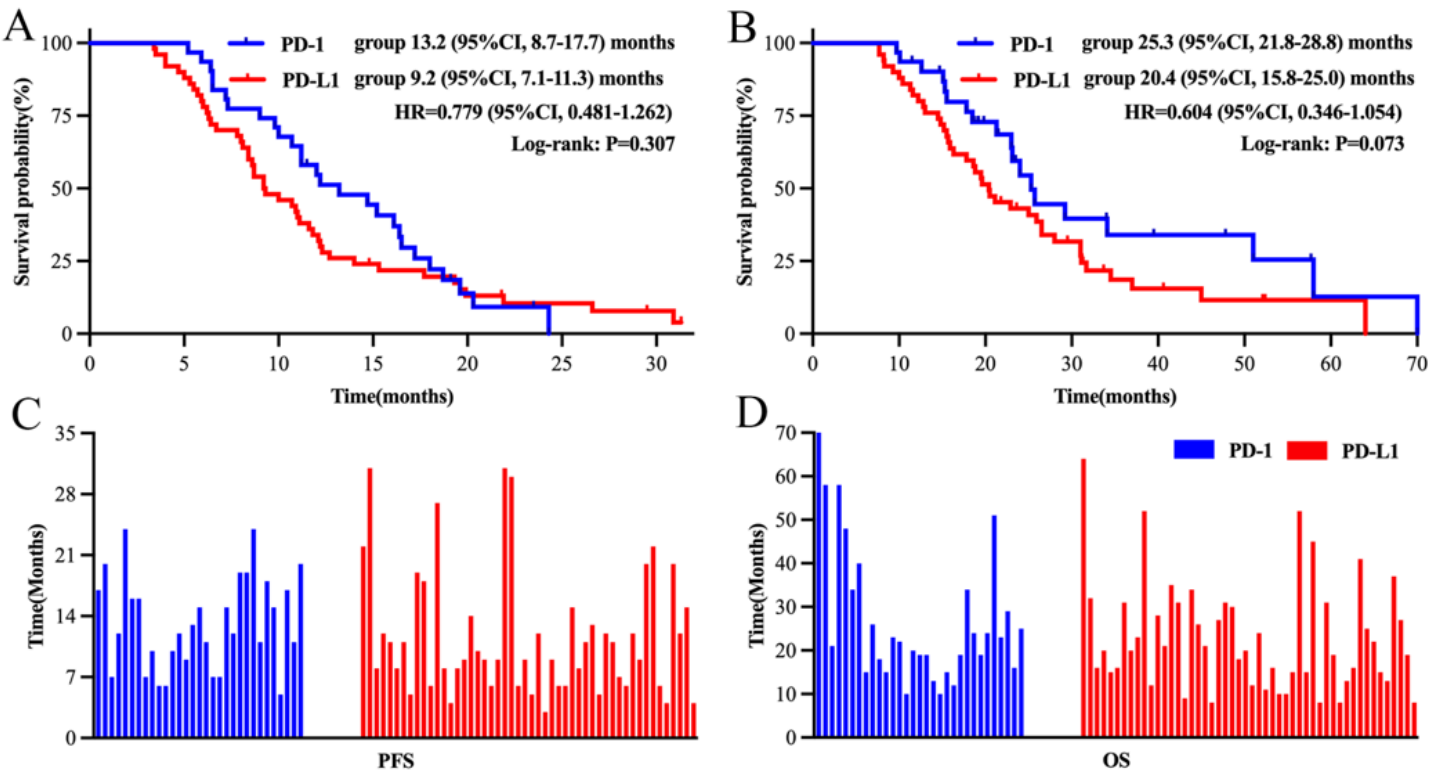


Figure 2

PFS and OS in patients with ES-SCLC receiving PD-1 versus PD-L1 inhibitors combined with consolidative TRT. Kaplan-Meier curves of PFS (A) and OS (B) for the PD-1 group and PD-L1 group. Swimmer plot showing PFS (C) and OS (D) duration for each individual patient in the PD-1 and PD-L1 groups. HR, hazard ratio; CI, confidence interval; TRT, thoracic radiotherapy; ES-SCLC, extensive-stage small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

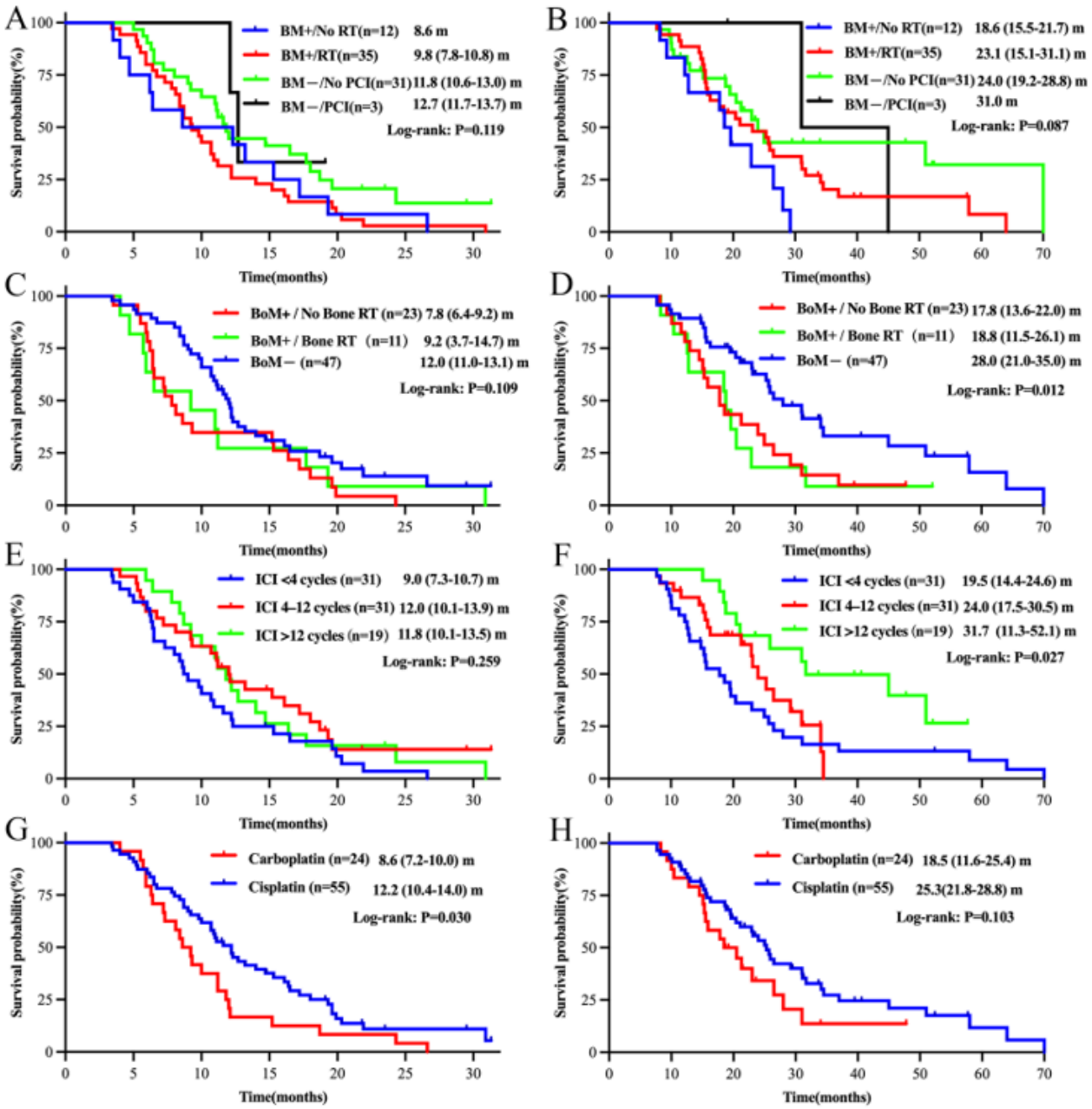


Figure 3

Subgroup analyses of PFS and OS. (A) PFS and (B) OS stratified by brain metastasis status and cranial radiotherapy. (C) PFS and (D) OS stratified by bone metastasis status and bone radiotherapy. (E) PFS and (F) OS stratified by number of immunotherapy cycles (<4, 4-12, >12 cycles). (G) PFS and (H) OS stratified by platinum agent (cisplatin vs. carboplatin). BM, brain metastasis; RT, radiotherapy; BoM, bone metastasis; ICI, immune checkpoint inhibitors.