BMC Cancer

RESEARCH

Open Access

Early radiotherapy improved survival of patients with extensive-stage small cell lung cancer treated with first-line chemo-immunotherapy

Yunfeng Wang[1†], Xi Su[1†], Jingyi Jia[1], Tongfang Zhou[1], Yifei Lu[1], Lei Zhao[1], Zhangru Yang[1], Xiaolong Fu[1], Ya Zeng[1*] and Xuwei Cai[1*]

Abstract

Background and purpose This real-world study aimed to investigate the efficacy of early radiotherapy (RT) in ES-SCLC patients treated with first-line chemo-immunotherapy.

Materials and methods ES-SCLC patients were enrolled from August 2018 to October 2023. Patients who received early radiotherapy before disease progression were defined as Early RT group, while the others, named Salvage and Non-RT (S&N RT) group. Propensity score matching (PSM) with a 1:1 ratio was performed to balance the baseline characteristics.

Results In this study, 375 patients with ES-SCLC treated with first-line chemo-immunotherapy were enrolled. The median PFS was 11.4 months of the Early RT group compared to 6.1 months of the S&N RT group (HR = 0.59, 95%CI 0.45–0.77; $p < 0.001$). The median OS was 23.8 months of the Early RT group versus 18.0 months of the S&N RT group (HR = 0.50, 95%CI 0.34–0.73; $p = 0.004$). The survival benefit persisted in the PSM cohort. Furthermore, survival was significantly improved in Early RT group compared to Salvage RT group ($p = 0.028$), while Salvage RT group had a similar survival with Non-RT group ($p = 0.868$). The risk of adverse events was tolerable. The multivariate analysis also demonstrated that early radiotherapy was an independently positive predictor for PFS and OS.

Conclusions Administering early radiotherapy significantly improved both PFS and OS in patients with ES-SCLC treated with first-line chemo-immunotherapy with tolerable adverse events, while salvage radiotherapy did not improve survival. This finding warrants further validation through prospective randomized studies.

Keywords Extensive-stage small cell lung cancer, Immunotherapy, Early radiotherapy, Survival

Introduction

Small cell lung cancer, characterized as a high-grade neuroendocrine neoplasm, accounts for approximately 15% of newly diagnosed cases of lung cancer [1, 2]. Due to its markedly aggressive growth, lack of early detection techniques and rapid proliferation, 80% of patients receive an initial diagnosis of extensive-stage small cell lung cancer (ES-SCLC), with a median survival of approximately 2 to 4 months in the absence of interventions [3, 4].

†Yunfeng Wang and Xi Su contributed equally to this work.

*Correspondence:
Ya Zeng
zengya1225@126.com
Xuwei Cai
birdhome2000@163.com
[1] Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China

Platinum-based chemotherapy has acted as the standard treatment of ES-SCLC for a long period. In consequence of barely changed composition of chemical agents, the median survival, ranging from 8–13 months, has shown limited improvement [5]. Immunotherapy emerged and significantly improved prognosis of various solid tumors [6, 7]. The IMpower133 and CASPIAN, randomized, multi-center, controlled phase III trials, proved that the standard doublet chemotherapy combined with immune checkpoint inhibitors (ICIs) significantly improved survival by 2 months compared to the control group in ES-SCLC patients. Platinum and etoposide plus atezolizumab or durvalumab has been recommended as the standard first-line regimen for ES-SCLC based on these results [8–10].

Radiotherapy played a paramount role in the comprehensive treatment of SCLC [11, 12]. In the CREST study, the untreated ES-SCLC patients who received platinum-based chemotherapy plus thoracic radiotherapy after systemic treatment obtained a 2-year overall survival (OS) benefit (13% vs. 3%, $p = 0.004$) and a 6-month progression-free survival (PFS) benefit (24% vs. 7%, $p = 0.001$) compared to the control group [13]. Consistent with the CREST study, the efficacy and safety of the combination of chemotherapy and radiotherapy have also been confirmed in some retrospective studies and clinical trials [14, 15].

In the preclinical and clinical studies, radiotherapy has been proven to reshape the tumor microenvironment by enhancing the cross-presentation of tumor specific antigen, increasing the expression of PD-L1, and promoting T cell-mediated immune responses [16–19]. These alterations facilitate the synergistic potential of combining immunotherapy with radiotherapy [19–27]. PEMBRO-RT trial and MDACC trial, focusing on the combination of radiotherapy and immunotherapy in NSCLC, have reported a significantly favorable propensity in combined modality group [28, 29]. A pooled analysis showed that immunotherapy combined with radiotherapy obtained more than double median OS and median PFS [30]. In the context of ES-SCLC, numerous studies have investigated the value of radiotherapy in the treatment of ES-SCLC in the era of immunotherapy [22–26, 31]. A single-arm, phase II clinical study showed that chemo-immunotherapy combined with thoracic radiotherapy achieved a notable median PFS of 8.6 months for ES-SCLC patients [32]. However, the small sample size limited the conclusions regarding the efficacy and safety of this regimen. Further investigation is warranted to determine the optimal combination of radiotherapy and immunotherapy in the treatment of ES-SCLC. So far, there is no recommendation to date for the combination of radiotherapy and immunotherapy. This real-world study was performed to investigate the efficacy of the combination of radiotherapy and immunotherapy and the value of early radiotherapy in ES-SCLC patients treated with first-line chemo-immunotherapy.

Materials and methods

Patients

Patients diagnosed with small cell lung cancer and treated with immunotherapy were screened from August 2018 to October 2023 in Shanghai Chest Hospital. The inclusion criteria were as follows: (I) aged over 18 years; (II) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; (III) SCLC diagnosed by histology or cytology, with extensive stage confirmed based on the Veterans Administration Lung Study Group (VALG) staging system or recurrent disease after curative-intent treatment in certain limited-stage small cell lung cancer patients; (IV) receiving immunotherapy as first-line treatment at least one dose. Irradiated lesions were considered measurable only if there was confirmed disease progression at irradiated site. These lesions, along with non-irradiated lesions and newly emergent lesions were incorporated into assessment of treatment response. This study adhered to the principles of Declaration of Helsinki and received approval from Ethics Committee of Shanghai Chest Hospital (Ethics approval ID: IS24011). Informed consent for this real-world study was waived.

Treatment

Patients included received standard care of systemic treatment according to the guidance of the National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology. In general, patients with disease control after systemic treatment were recommended to receive early radiotherapy prior to disease progression and patients with symptomatic brain metastasis at diagnosis were recommended to receive brain radiotherapy. The appropriate radiation dose and fractionation schedule were selected based on the irradiation site and tumor burden of individuals, which determined whether conventional radiotherapy or stereotactic radiotherapy was administered. Patients were grouped as Early RT group, Salvage RT and Non-RT group according to the time of radiotherapy initiation. Patients who received radiotherapy prior to disease progression were assigned into Early RT group and patients who received radiotherapy after disease progression were assigned into Salvage RT group, while radiotherapy was not applied to patients in Non-RT group. Treatment-related adverse events were graded according to Common Terminology Criteria for Adverse Events v4.0.

Statistical analysis

Efficacy assessment was conducted according to the response evaluation criteria in solid tumors (RECIST) version 1.1. Examinations included enhanced contrast chest computed tomography (CT), ultrasound examination of supraclavicular and abdominal areas, magnetic resonance imaging (MRI) and whole-body bone scan. Positron emission tomography (PET)—CT is not mandatory. PFS was defined as the interval between the initiation of immunotherapy and occurrence of disease progression or death, or last follow-up date. OS was defined from the initial immunotherapy treatment to the death for any cause or last follow-up date.

Patients' characteristics were presented in descriptive data. Baseline characteristics were compared between different groups using Chi-square test or Fisher's exact test and PSM (1:1) with a caliper of 0.02 was performed to balance the potential bias. PFS and OS were illustrated with Kaplan–Meier curves and the difference between groups was assessed using Log-rank test. Multivariate Cox regression analysis was respectively performed for PFS and OS, including the variables with significant difference ($p < 0.1$) in the univariate regression analysis. Statistical analysis was performed by SPSS (version 22.0, IBM Corporation, USA), GraphPad Prism (version 9.0, GraphPad Software, USA) and R Studio (version 4.4.0, R Core Team, Austria). Statistical significance was defined as two-tailed p-value less than 0.05.

Results

Baseline characteristics

Among a total of 611 screened patients, 375 patients diagnosed with ES-SCLC who received chemo-immunotherapy as first-line treatment were eventually enrolled in this study. Seventy-six patients were assigned into Early RT group, while 54 patients were assigned into Salvage RT group. Additionally, 245 patients who received chemo-immunotherapy alone were assigned into Non-RT group. The Salvage RT group and the Non-RT group were combined as the S&N RT group in this analysis. In Early RT group, 53.9% (41/76) patients received thoracic radiotherapy, which was the most common irradiated site followed by brain (35.5%), bone (14.5%) and others. There were 13 patients who received thoracic radiotherapy with a prescription dose of 30 Gy in 10 fractions and 12 patients in a dose of 60 Gy in 30 fractions. The most common dose fraction was also 30 Gy/10 fractions in the irradiation of brain, covering 14 patients in a total of 27 patients receiving brain radiotherapy. More details of irradiation site and dose were listed in Table S1 in supplementary. Baseline characteristics between groups are outlined in Table 1. After PSM, 76 pairs of patients were enrolled in further analysis and the baseline characteristics were well balanced.

Efficacy

With a median follow-up time of 15.2 months for the survivors, the median PFS was 6.8 months and the median OS was 19.1 months for the whole cohort. The 12-month and 18-month PFS rates were 23.8% and 16.6%, respectively, and the 12-month and 18-month OS rates were 67.5% and 57.6%, respectively. The disease control rate of ES-SCLC patients was 88.0% after receiving first-line chemo-immunotherapy.

Before PSM, the median PFS of Early RT group and S&N RT group was 11.4 months and 6.1 months (HR 0.59, 95%CI 0.45–0.77, $p < 0.001$) (Fig. 1A). The Early RT group showed a median OS of 23.8 months compared to 18.0 months in the S&N RT group (HR 0.50, 95%CI 0.34–0.73, $p = 0.004$), respectively (Fig. 1B). In the PSM cohort, Early RT group still remained superior in survival compared to S&N RT group. The median PFS of Early RT group and S&N RT group was 11.4 months and 6.0 months (HR = 0.50, 95%CI 0.34–0.74; $p < 0.001$) (Fig. 1C). The median OS was 23.8 months and 18.2 months (HR = 0.51, 95%CI 0.30–0.86; $p = 0.015$), respectively (Fig. 1D).

Pairwise comparison was performed between Early RT group and Salvage RT group, Salvage RT group and Non-RT group to validate survival benefit brought by early radiotherapy. The baseline characteristics of groups before and after PSM were outlined in Supplementary Table S2, S3. Before PSM, patients in Early RT group had an obviously favorable trend in median OS (23.8 months vs. 18.0 months; HR 0.58, 95%CI 0.33–1.03; $p = 0.061$) compared with Salvage RT group (Fig. 2A). However, Salvage RT group had a similar mOS (18.0 months vs. 18.2 months; HR 0.85, 95%CI 0.57–1.23; $p = 0.441$) with Non-RT group (Fig. 2C). After PSM, survival benefit of OS brought by early radiotherapy obtained statistically significant in comparison of Early RT group and Salvage RT group (not reached vs. 18.0 months; HR 0.48, 95%CI 0.26–0.89; $p = 0.028$)(Fig. 2B). The results of comparison between Salvage RT group and Non-RT group were consistent with those before PSM. Salvage RT group had a non-differential mOS (18.0 months vs. 18.2 months; HR 1.05, 95%CI 0.60–1.82; $p = 0.868$) compared with Non-RT group (Fig. 2D).

Subgroup analysis (Fig. 3) demonstrated that early radiotherapy improved PFS in most subgroups except female, PD-L1 expression 1%−49%, usage of ICI binding to PD-1 and the presence of baseline lung or liver metastasis. Subgroup analysis of OS showed that subgroups including male, current or previous smokers, PD-L1 expression status of less than 1%, usage of immune checkpoint

Table 1 Baseline characteristics of ES-SCLC patients before and after PSM

Characteristic	Before PSM			After PSM		
	Early RT Group ($n = 76$)	S&N RT Group ($n = 299$)	*p* value	Early RT Group ($n = 76$)	S&N RT Group ($n = 76$)	*p* value
Age group-no.(%)			0.904			0.626
< 65 yr	41(53.9)	159(53.2)		41(53.9)	38(50.0)	
≥ 65 yr	35(46.1)	140(46.8)		35(46.1)	38(50.0)	
Gender-no.(%)			0.843			0.616
male	68(89.5)	264(88.3)		68(89.5)	66(86.8)	
female	8(10.5)	35(11.7)		8(10.5)	10(13.2)	
ECOG PS-no.(%)			0.444			0.384
0	5(6.6)	28(9.4)		5(6.6)	8(10.5)	
1	71(93.4)	271(90.6)		71(93.4)	68(89.5)	
Smoking-no.(%)	47(61.8)	176(58.9)	0.695	47(61.8)	38(50.0)	0.141
Alcohol-no.(%)	8(10.5)	38(12.7)	0.698	8(10.5)	12(15.8)	0.337
Baseline metastasis-no.(%)						
brain	17(22.4)	28(9.4)	0.003	17(22.4)	17(22.4)	> 0.999
lung	8(10.5)	48(16.1)	0.281	8(10.5)	15(19.7)	0.113
bone	22(28.9)	91(30.4)	0.889	22(28.9)	22(28.9)	> 0.999
liver	8(10.5)	63(21.1)	0.048	8(10.5)	8(10.5)	> 0.999
PD-L1 status-no.(%)			0.808			0.601
no test	36(47.4)	139(46.5)		36(47.4)	39(51.3)	
< 1%	33(43.4)	139(46.5)		33(43.4)	34(44.7)	
1%–49%	5(6.6)	15(5.0)		5(6.6)	3(3.9)	
≥ 50%	2(2.6)	6(2.0)		2(2.6)	0	
Combined chemotherapy-no.(%)	74(97.4)	291(97.3)	0.706	74(97.4)	76(100.0)	0.497
Type of ICI-no.(%)			0.503			0.821
PD-1	11(14.5)	54(18.1)		11(14.5)	12(15.8)	
PD-L1	65(85.5)	245(81.9)		65(85.5)	64(84.2)	
Recurrent disease-no.(%)	8(10.5)	24(8.0)	0.486	8(10.5)	5(6.6)	0.384

Abbreviation: *PSM* Propensity score matching, *RT* Radiotherapy, *ECOG PS* Eastern Cooperative Oncology Group performance status, *PD-L1* Programmed cell death 1-ligand 1, *PD-1* Programmed cell death protein-1, *ICI* Immune checkpoint inhibitor

inhibitors binding to PD-L1, without baseline brain or lung or liver metastasis and presence of baseline bone metastasis could benefit from early radiotherapy.

Univariate and multivariate analysis were performed to identify predictors of PFS and OS. The variables were firstly calculated using univariate analysis and further incorporated in multivariate analysis (Table 2). Early radiotherapy was validated as an independently favorable predictor for PFS (HR 0.49, 95%CI 0.34–0.73; $p < 0.001$) and OS (HR 0.50, 95%CI 0.29–0.87; $p = 0.014$) in multivariate analysis. Besides, presence of baseline liver metastasis (HR 2.00, 95%CI 1.01–3.98; $p = 0.048$) was a poor predictor for OS.

Safety

No increase of adverse events was observed in the Early RT group. The incidence of adverse events of any grade and grade 3–5 (Table 3) showed no significant increase between the Early RT group and the S&N RT group. The most prevalent adverse events were hematologic toxicity, observed in 27.6% (21/76) of the Early RT group and 43.4% (33/76) of the S&N RT group. There were 3 patients in Early RT group developed grades 3 or higher radiation pneumonitis, while none in S&N RT group. The risk of early radiotherapy combined with immunotherapy was tolerable.

Discussion

This study showed that prescribing early radiotherapy significantly improved PFS and OS in patients with ES-SCLC receiving first-line chemo-immunotherapy. Pairwise comparison of Early RT group, Salvage RT group and Non-RT group further confirmed that early radiotherapy could improve survival, emphasizing that it is the sole method of improving prognosis for extensive-stage small cell lung cancer patients. Meanwhile, no increased

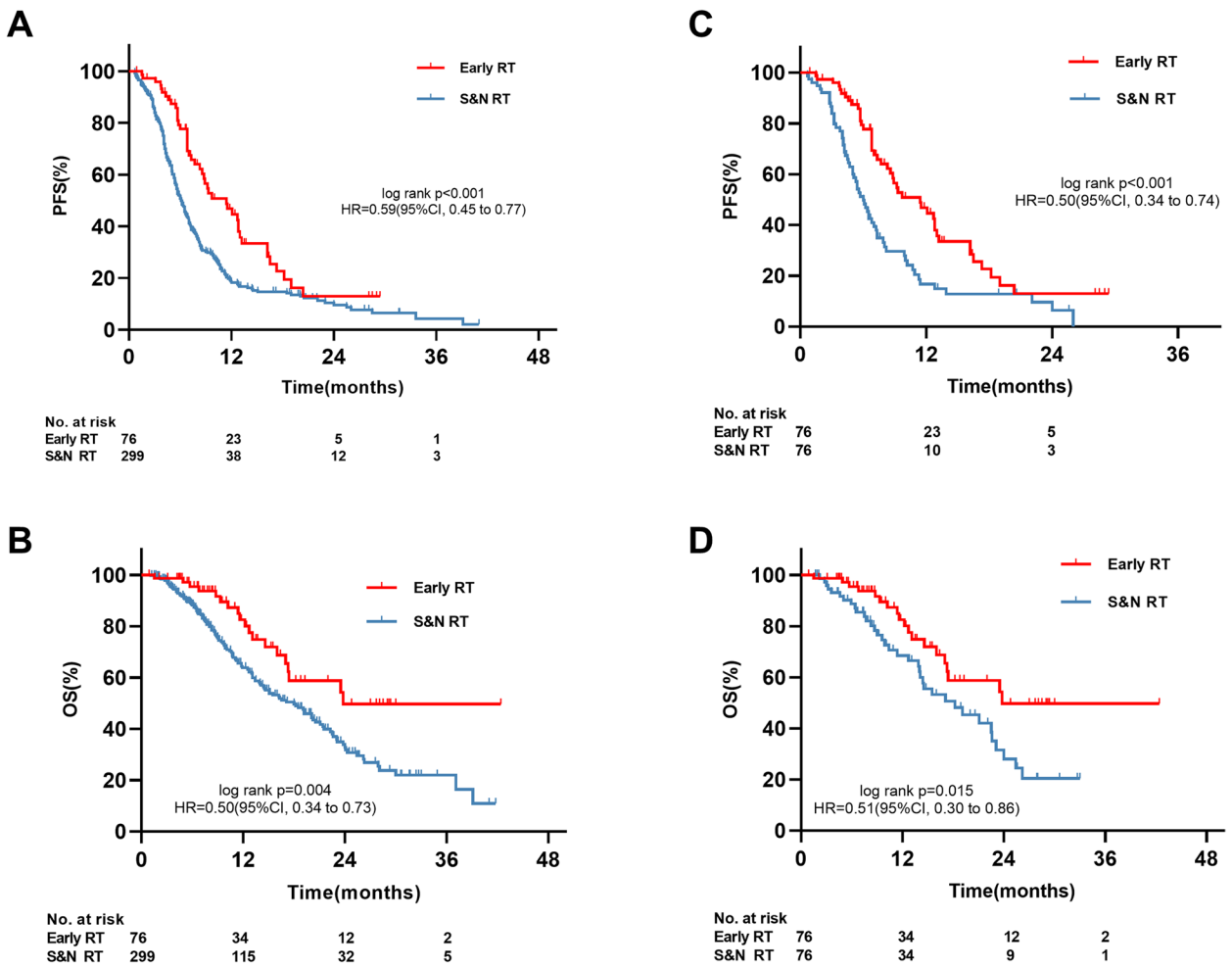

Fig. 1 Kaplan–Meier curves of PFS and OS of Early RT group and S&N RT group before and after PSM (**A**) Kaplan–Meier curves of PFS before PSM. **B** Kaplan–Meier curves of OS before PSM. **C** Kaplan–Meier curves of PFS after PSM. **D** Kaplan–Meier curves of OS after PSM PSM, propensity score matching; PFS, progression-free survival; OS, overall survival; S&N RT, Salvage and Non-radiotherapy; HR, hazard ratio; CI, confidence interval

incidence of adverse events was observed in Early RT group. Our findings emphasized the advantage of combining early radiotherapy with current standard treatment and might help clinical oncologists make medical decisions.

In fact, the management of ES-SCLC is still a challenging issue in clinical practice for its exceedingly poor prognosis. Early overlong overlaps and unsatisfactory tailing performance of survival curves were observed in IMpower133 and CASPIAN, indicating that patients might suffer from disease progression in priming stage and acquire resistance to ICI within a year [33]. The most common failure patterns were oligo-progression and progressive disease at existing sites [34].

In the pre-ICI era, radiotherapy demonstrated unique privilege in local control [13]. A meta-analysis of five studies including CREST study showed that the combination of chemotherapy and TRT significantly improved the survival of patients with ES-SCLC compared to chemotherapy alone [35].

Stepping into immunotherapy era, efficacy of radiotherapy combined with immunotherapy was validated in various tumors, especially the landmark achievement of PACIFIC trial in non-small cell lung cancer [36]. It encouraged some exploratory attempts in ES-SCLC while the results were heterogeneous [22–24, 26, 31, 37–39]. Considering the efficacy of radiotherapy in chemotherapy era and the synergistic effect of radiotherapy and immunotherapy validated in pre-clinical and clinical studies, patients with ES-SCLC might have survival benefit from the combined regimen. Thus, patients with disease control after systemic treatment were recommended to receive early radiotherapy in clinical practice. Our findings indicated that irradiation before disease progression could significantly improve

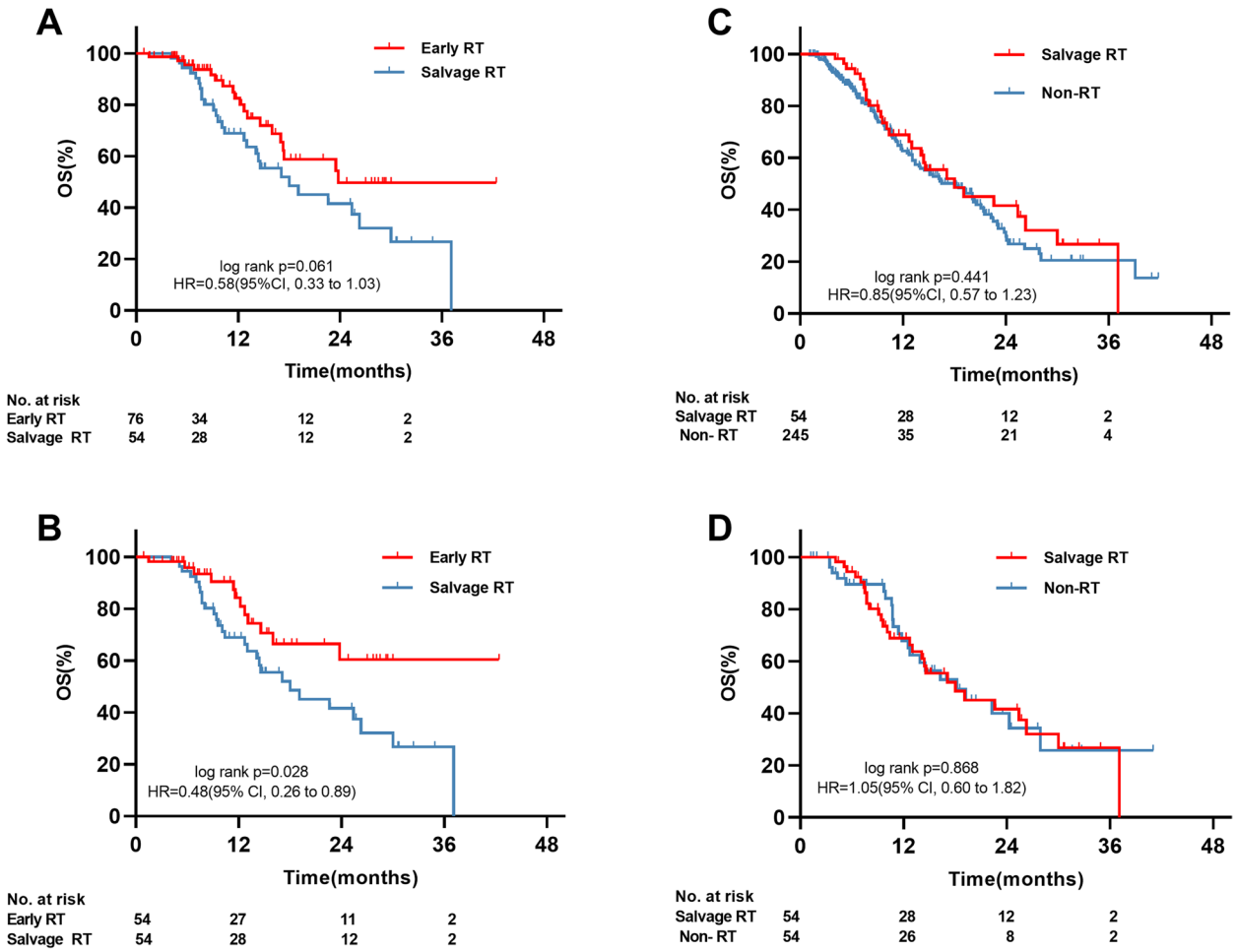

Fig. 2 Kaplan–Meier curves of OS of Early RT group. Salvage RT group and Non-RT group before and after PSM (**A**) Kaplan–Meier curves of OS between Early RT group and Salvage RT group before PSM. **B** Kaplan–Meier curves of OS between Early RT group and Salvage RT group after PSM. **C** Kaplan–Meier curves of OS between Salvage RT group and Non-RT group before PSM. **D** Kaplan–Meier curves of OS between Salvage RT group and Non-RT group after PSM. PSM, propensity score matching; PFS, progression-free survival; OS, overall survival; S&N RT, Salvage and Non-radiotherapy; HR, hazard ratio; CI, confidence interval

survival and was an independently positive predictor of prognosis in ES-SCLC patients.

By contrast, our study showed a mPFS of 11.4 months and mOS of 23.8 months in combined regimen group, which were comparable to recently published retrospective studies [31, 37]. Particularly, we compared the survival of patients who received salvage radiotherapy and those who received systemic therapy alone. Compared with Non-RT group, Salvage RT group showed no statistical significance in OS, emphasizing that the timing of radiotherapy should be prior to disease progression. The univariate and multivariate analysis validated efficacy of early radiotherapy once again. Of particular note, the radiotherapy in our study was delivered with palliative intent, with a substantial amount of patients receiving 30 Gy in 10 fractions. This aligns with prior evidence demonstrating the efficacy of combining relatively low-dose radiotherapy and immunotherapy in ES-SCLC. The MATCH trial conducted by Lu demonstrated a low-dose radiotherapy (15 Gy in 5 fractions) concurrently with chemo-immunotherapy had an excellent 12-month PFS and OS with tolerable risk of adverse events in ES-SCLC [40]. A prospective, single-arm study conducted by Chen explored the efficacy of consolidative thoracic radiotherapy combined with standard regimen in the treatment of ES-SCLC and analyzed the survival benefits between different biological effective dose (BED) groups (divided by 60 Gy). The median PFS ($p = 0.81$) and median OS ($p = 0.90$) had no significant differences or those patients received BED-high ($N = 24$) and BED-low ($N = 21$) [41]. Some retrospective studies also showed that low-dose radiotherapy was not inferior to high-dose radiotherapy in terms of the survival benefits in ES-SCLC [23, 38]. The validation of this conclusion warranted further research.

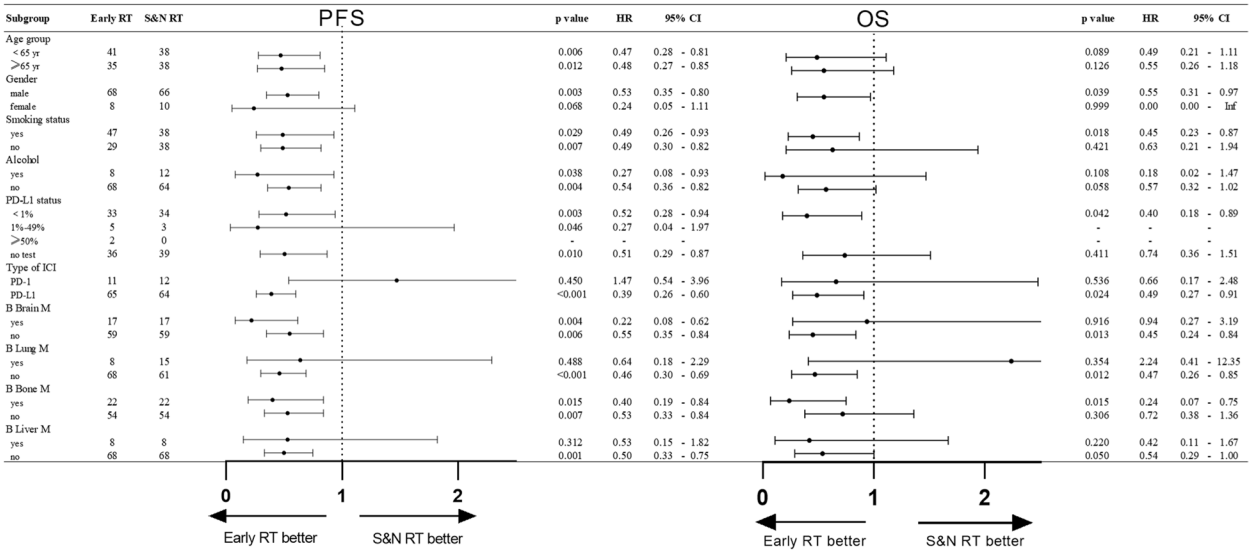

Fig. 3 Subgroup analysis for PFS and OS in ES-SCLC patients after PSM Subgroup analysis for PFS and OS. Patients in S&N group served as the reference. The value of HR less than 1 indicated that patients in Early RT group had survival benefits. PFS, progression-free survival; OS, overall survival; RT, radiotherapy; S&N RT, salvage and non-radiotherapy; HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; PD-L1, programmed cell death 1- ligand 1; PD-1, programmed cell death protein 1; B Brain M, baseline brain metastasis; B Lung M, baseline lung metastasis; B Bone M, baseline bone metastasis; B Liver M, baseline liver metastasis

Table 2 Univariate and multivariate Cox analysis of PFS and OS

Variable	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	*p* value	HR(95%CI)	*p* value	HR(95%CI)	*p* value	HR(95%CI)	*p* value
RT(Early vs. Late)	0.49(0.34–0.73)	< 0.001	0.49(0.34–0.73)	< 0.001	0.51(0.29–0.89)	0.02	0.50(0.29–0.87)	0.014
Age(< 65 yr vs. ≥ 65 yr)	0.98(0.67–1.44)	0.94	-	-	0.60(0.35–1.03)	0.06	-	-
Gender(female vs. male)	1.37(0.75–2.52)	0.30	-	-	0.97(0.41–2.26)	0.94	-	-
ECOG PS(0 vs. 1)	0.80(0.43–1.51)	0.50	-	-	0.34(0.08–1.41)	0.14	-	-
Smoking(yes vs. no)	0.87(0.59–1.28)	0.49	-	-	1.10(0.63–1.93)	0.74	-	-
Alcohol(yes vs. no)	0.65(0.36–1.18)	0.16	-	-	0.68(0.31–1.51)	0.35	-	-
Baseline brain metastasis(yes vs. no)	1.36(0.84–2.20)	0.22	-	-	1.06(0.56–2.01)	0.86	-	-
Baseline lung metastasis(yes vs. no)	1.01(0.57–1.77)	0.98	-	-	1.52(0.71–3.26)	0.28	-	-
Baseline bone metastasis(yes vs. no)	1.07(0.71–1.64)	0.74	-	-	1.07(0.59–1.94)	0.84	-	-
Baseline liver metastasis(yes vs. no)	1.15(0.63–2.10)	0.65	-	-	1.93(0.97–3.83)	0.06	2.00(1.01–3.98)	0.048
Type of ICIs(PD-1 vs. PD-L1)	0.83(0.49–1.42)	0.51	-	-	1.01(0.50–2.07)	0.97	-	-

Abbreviation: *PFS* Progression-free survival, *OS* Overall survival, *RT* Radiotherapy, *S&N RT* Salvage and non-radiotherapy, *HR* Hazard ratio, *CI* Confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ICI* Immune checkpoint inhibitor, *PD-L1* Programmed cell death 1- ligand 1, *PD-1* Programmed cell death protein 1

Concerning of independent predictors of survival, baseline liver metastasis merited our attention. In a secondary analysis of CREST trial, patients with liver metastasis showed a negative association with survival, even though it failed to be a significant predictor in multivariate analysis [42]. Recently, some retrospective studies also revealed the negative association between baseline liver metastasis and survival in ES-SCLC patients treated with first-line chemo-immunotherapy [26, 31, 37]. In our study, baseline liver metastasis was also proved to be an independently negative predictor for OS in patients with ES-SCLC, indicating poor prognosis of patients with baseline liver metastasis. Even worse was that patients with liver metastasis could not benefit from the combination of early radiotherapy and systemic treatment in subgroup analysis, which further limits the treatment

Table 3 Comparison of adverse events of any grade and grade 3–5 between two groups

Adverse events	Early RT group ($N = 76$)		S&N RT group ($N = 76$)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
Hematologic toxicity	21(27.6)	13(17.1)	33(43.4)	21(27.6)
Pneumonitis				
Radiation pneumonitis	3(3.9)	3(3.9)	1(1.3)	0
Immune-related pneumonitis	2(2.6)	1(1.3)	3(3.9)	1(1.3)
Cough	1(1.3)	0	0	0
Abnormal liver function	2(2.6)	0	4(5.3)	0
Pain	0	0	3(3.9)	0
Dizziness	0	0	1(1.3)	0
Headache	0	0	2(2.6)	0
Ulceration	0	0	1(1.3)	0
Rash	1(1.3)	0	6(7.9)	0
Fatigue	2(2.6)	0	5(6.6)	0
Hypothyroidism	1(1.3)	0	3(3.9)	0
Hyperthyroidism	1(1.3)	0	0	0
Diarrhea	1(1.3)	0	0	0
Constipation	1(1.3)	0	2(2.6)	0
Nausea and vomiting	4(5.2)	0	6(7.9)	0

Abbreviation: *S&N RT* Salvage and non-radiotherapy

options for this cohort. For patients with brain metastasis, subgroup analysis demonstrated that early RT significantly improved PFS but not OS, indicating the advantage of early RT in locoregional control in brain metastasis.

No significant increase of adverse events in Early RT group was observed and combined regimen did not lead to grade 4–5 adverse events in our study. The risk of adverse events in combined regimen was tolerable. Of note, while early RT group seemed to have a numerically higher incidence of pneumonitis (≥ grade 3) compared with S&N RT group (5.2% vs 1.3%), this difference did not reach statistical significance. The incidence of pneumonitis (≥ grade 3) in early RT group was similar to that of 6% in the prospective, single-arm study conducted by Chen, which explored the efficacy and safety of sequential thoracic radiotherapy combined with systemic treatment in ES-SCLC [41]. In terms of radiation pneumonitis, the incidence in our study was 3.9%, which was comparable to that of 3.0% in a meta-analysis conducted by Na [27]. In accordance with our study, the combination of radiotherapy and immunotherapy was verified to be safe in many small size retrospective studies and prospective studies [22, 24–26, 31]. A phase I, prospective study showed that combined radiotherapy and pembrolizumab in patients with ES-SCLC did not induce grade 4 or 5 adverse events and only 2 patients among 33 patients experienced grade 3 adverse events [25]. Furthermore, combined radiotherapy and double ICIs was also proved to be free from additional adverse events [24]. What was mentioned above firmly indicated the safety of combined regimen in ES-SCLC.

Overall, our study offers several advantages over similar studies: Firstly, our study enrolled a relatively large cohort. Secondly, the radiotherapy regimens administered in our study are more reflective of real-world clinical practice. Most importantly, our findings emphasize the critical role of early integration of radiotherapy prior to disease progression in patients with ES-SCLC. This could provide valuable guidance for oncologists in clinical decision-making.

This study inherently possesses limitations that must be acknowledged. First, this study is a single-center study, which may lead to selection bias of patients. Second, mainly limited by sample size, some details, such as irradiation site and dose, remain unanswered and we will keep attention on these questions in future research. Especially, we have noticed that the value of thoracic radiotherapy combined with immunotherapy in ES-SCLC patients and conclusion remains to be seen in the near future. Our findings need to be verified by further large-scale, randomized, prospective phase III study.

Conclusions

Receiving early radiotherapy before disease progression significantly prolonged PFS and OS with acceptable adverse events risk in ES-SCLC patients treated with first-line chemo-immunotherapy, while salvage

radiotherapy after disease progression could not improve survival. Our findings indicated that incorporating early radiotherapy into standard treatment modality of ES-SCLC may improve prognosis of patients. This finding should be further verified by prospective randomized studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14417-0.

Supplementary Material 1.

Acknowledgements
This work was supported by the National Natural Science Foundation of China (grant number 82273575).

Authors' contributions
Data collection, formal analysis and the writing of original manuscript were performed by Yunfeng Wang and Xi Su. Visualization of results was performed by Tongfang Zhou, Jingyi Jia and Yifei Lu. Data validation was performed by Zhangru Yang and Lei Zhao. The methodology of analysis was performed by Xiaolong Fu. Review of the manuscript was performed by Xuwei Cai and Ya Zeng, and Xuwei Cai initiated the project. All authors read and approved the final manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (grant number 82273575).

Data availability
All research data are presented in the article and original data are available on request from the corresponding authors.

Declarations

Ethics approval consent to participate
This study adhered to the principles of Declaration of Helsinki and received approval from Ethics Committee of Shanghai Chest Hospital (Ethics approval number: IS24011).
Informed consent for this real-world study was waived.

Consent for publications
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 11 March 2025 Accepted: 30 May 2025
Published online: 06 June 2025

References

1. Thai AA, et al. Lung cancer. Lancet. 2021;398(10299):535–54.
2. Nicholson AG, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. J Thorac Oncol. 2022;17(3):362–87.
3. Kahnert K, Kauffmann-Guerrero D, Huber RM. SCLC-State of the art and what does the future have in store? Clin Lung Cancer. 2016;17(5):325–33.
4. Kato Y, et al. Oat cell carcinoma of the lung. A review of 138 cases. Cancer. 1969;23(3):517–24.
5. Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J. 2010;35(1):202–15.
6. Reck M, Remon J, Hellmann MD. First-Line immunotherapy for non-small-cell lung cancer. J Clin Oncol. 2022;40(6):586–97.
7. Tang Q, et al. The role of PD-1/PD-L1 and application of immune-checkpoint inhibitors in human cancers. Front Immunol. 2022;13:964442.
8. Horn L, et al. First-Line Atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9.
9. Paz-Ares L, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929–39.
10. NCCN. Small Cell Lung Cancer, Version 3.2024. 2024; Available from: https://www.nccn.org/guidelines/nccn-guidelines/guidelines-detail?category=1&id=1462. Cited 24 6.
11. Bogart JA, Waqar SN, Mix MD. Radiation and systemic therapy for limited-stage small-cell lung cancer. J Clin Oncol. 2022;40(6):661–70.
12. Zugazagoitia J, Paz-Ares L. Extensive-stage small-cell lung cancer: first-line and second-line treatment options. J Clin Oncol. 2022;40(6):671–80.
13. Slotman BJ, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015;385(9962):36–42.
14. Giuliani ME, et al. Clinical outcomes of extensive stage small cell lung carcinoma patients treated with consolidative thoracic radiotherapy. Clin Lung Cancer. 2011;12(6):375–9.
15. Jeremic B, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. J Clin Oncol. 1999;17(7):2092–9.
16. Sharabi AB, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer Immunol Res. 2015;3(4):345–55.
17. Dovedi SJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res. 2014;74(19):5458–68.
18. Herrera FG, et al. Low-dose radiotherapy reverses tumor immune desertification and resistance to immunotherapy. Cancer Discov. 2022;12(1):108–33.
19. Gupta A, et al. Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation. J Immunol. 2012;189(2):558–66.
20. Sharabi AB, et al. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. Lancet Oncol. 2015;16(13):e498-509.
21. Galluzzi L, et al. Emerging evidence for adapting radiotherapy to immunotherapy. Nat Rev Clin Oncol. 2023;20(8):543–57.
22. Xie Z, et al. Real-World Efficacy and Safety of Thoracic Radiotherapy after First-Line Chemo-Immunotherapy in Extensive-Stage Small-Cell Lung Cancer. J Clin Med, 2023;12(11).
23. Li L, et al. First-line atezolizumab/durvalumab plus platinum-etoposide combined with radiotherapy in extensive-stage small-cell lung cancer. BMC Cancer. 2023;23(1):318.
24. Perez BA, et al. Prospective Single-Arm Phase 1 and 2 Study: ipilimumab and nivolumab with thoracic radiation therapy after platinum chemotherapy in extensive-stage small cell lung cancer. Int J Radiat Oncol Biol Phys. 2021;109(2):425–35.
25. Welsh JW, et al. Phase I trial of pembrolizumab and radiation therapy after induction chemotherapy for extensive-stage small cell lung cancer. J Thorac Oncol. 2020;15(2):266–73.
26. Cai Z, et al. Safety and efficacy of thoracic radiotherapy combined with chemo-immunotherapy in patients with extensive-stage small cell lung cancer: a multicenter retrospective analysis. Transl Lung Cancer Res. 2023;12(10):1987–2000.
27. Feng B, et al. Chemoimmunotherapy combined with consolidative thoracic radiotherapy for extensive-stage small cell lung cancer: A systematic review and meta-analysis. Radiother Oncol. 2023;190:110014.
28. Theelen W, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT Phase 2 randomized clinical trial. JAMA Oncol. 2019;5(9):1276–82.
29. Welsh, J., et al., Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. J Immunother Cancer, 2020;8(2).

30. Theelen W, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respir Med. 2021;9(5):467–75.
31. Yao Y, et al. Efficacy and safety of thoracic radiotherapy in extensive-stage small-cell lung cancer patients receiving first-line immunotherapy plus chemotherapy: a propensity score matched multicentre retrospective analysis. Radiat Oncol. 2024;19(1):25.
32. Liu C, et al. Hypofractionated radiotherapy with immunochemotherapy for extensive-stage small-cell lung cancer. Front Immunol. 2023;14:1175960.
33. Kang K, et al. Tackling the current dilemma of immunotherapy in extensive-stage small cell lung cancer: A promising strategy of combining with radiotherapy. Cancer Lett. 2023;565:216239.
34. Liu L, et al. Patterns of treatment failure for PD-(L)1 refractory extensive-stage small cell lung cancer in continued PD-(L)1 treatment. Transl Oncol. 2023;33:101687.
35. Zhang X, et al. Consolidative thoracic radiotherapy for extensive stage small cell lung cancer. Oncotarget. 2017;8(13):22251–61.
36. Antonia SJ, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377(20):1919–29.
37. Peng J, et al. Real-world outcomes of PD-L1 inhibitors combined with thoracic radiotherapy in the first-line treatment of extensive stage small cell lung cancer. Radiat Oncol. 2023;18(1):111.
38. Longo V, et al. Consolidative thoracic radiation therapy for extensive-stage small cell lung cancer in the era of first-line chemoimmunotherapy: preclinical data and a retrospective study in Southern Italy. Front Immunol. 2023;14:1289434.
39. Cozzi S, et al., Thoracic Radiotherapy in Extensive Disease Small Cell Lung Cancer: Multicenter Prospective Observational TRENDS Study. Cancers (Basel), 2023;15(2).
40. Wang H, et al. Preclinical study and phase II trial of adapting low-dose radiotherapy to immunotherapy in small cell lung cancer. Med. 2024;5(10):1237-1254.e9.
41. Chen D, et al. Adebrelimab plus chemotherapy and sequential thoracic radiotherapy as first-line therapy for extensive-stage small-cell lung cancer (ES-SCLC): a phase II trial. EClinicalMedicine. 2024;75:102795.
42. Slotman BJ, et al. Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: A secondary analysis of the Phase III CREST trial. Lung Cancer. 2017;108:150–3.

Publisher's Note