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Clinical outcomes and synergistic effect between radiotherapy and immunotherapy in patients with extensive-stage small cell lung cancer: a real-world study

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Abstract

Background Patients with extensive-stage small cell lung cancer (ES-SCLC) experience significant therapeutic challenges and limited survival rates. This study aimed to investigate the efficacy of combining immunotherapy (IT) with chemotherapy (CT) for treating ES-SCLC and to explore the synergistic effect between radiotherapy (RT) and IT.

Methods This retrospective analysis examined patients with ES-SCLC who received treatment at three centers. Furthermore, propensity score-matched (PSM) analysis was conducted. The Kaplan–Meier method and Cox proportional hazards regression were used to compare the survival outcomes.

Results A total of 257 eligible patients with ES-SCLC were included in the analysis. Among all patients, the median overall survival (mOS) was 18.0 m in the chemoimmunotherapy (CT + IT) group and 15.7 m in the CT group ($p = 0.208$). The median real-world progression-free survival (mrwPFS) was 7.7 m and 6.8 m ($p = 0.043$) in the CT + IT and CT group, respectively. Moreover, the mOS was 22.0 m in the chemoradiotherapy (CT + RT) group and 13.6 m in the CT group ($p < 0.001$). The mrwPFS was 7.4 m and 6.0 m ($p = 0.175$) in the CT + RT group and CT group, respectively. The multivariate analyses revealed that sex, liver metastasis and RT were independent prognostic factors for OS ($p < 0.05$), while liver metastasis and IT were found to be independent predictive factors of real-world progression-free survival (rwPFS) ($p < 0.05$). After PSM, the mOS was 23.2 m in the CT + IT group and 13.0 m in the CT group ($p = 0.008$). The mrwPFS was 7.3 m and 6.2 m ($p = 0.096$) in the CT + IT group and the CT group, respectively. Moreover, the mOS was 21.4 m in the CT + RT group and 12.5 m in the CT group ($p < 0.001$). The mrwPFS was 7.3 m and 5.2 m ($p = 0.220$) in the CT + RT group and the CT group, respectively. Additionally, our study revealed that in the PD-1 group, RT significantly improved patient survival (36.0 m vs. 15.8 m, $p = 0.041$).

Conclusion An increasing number of treatment options are being explored for ES-SCLC, and CT is the cornerstone of treatment for this disease. Combining CT with IT and RT has demonstrated remarkable efficacy and excellent safety profiles, and such treatments are worthy of further exploration.

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Keywords Extensive-stage small cell lung cancer, Chemotherapy, Immunotherapy, Radiotherapy, Propensity score matching

Background

Lung cancer is the malignant tumor with the highest morbidity and mortality rates in China and the world; specifically, small-cell lung cancer (SCLC) accounts for approximately 15% of lung cancer cases [1]. Clinically, SCLC is classified into extensive-stage SCLC (ES-SCLC) and limited-stage SCLC (LS-SCLC), and it is characterized by rapid proliferation and early development of widespread metastases. Patients with SCLC usually present with ES-SCLC at the time of diagnosis [2]. In the chemoradiotherapy era, the traditional treatment for SCLC is comprehensive chemotherapy (CT). The median survival time of patients receiving this treatment is reportedly 18–24 months for LS-SCLC patients and only 10–12 months for ES-SCLC patients, with a 5-year survival rate of only 7% [3].

Recent phase 3 trials of the programmed cell death ligand 1 (PD-L1) inhibitor atezolizumab or durvalumab combined with CT revealed significantly prolonged overall survival (OS) in patients with ES-SCLC [4–6]. In addition, the programmed cell death 1 (PD-1) inhibitor serplulimab plus CT significantly improved OS, and pembrolizumab plus CT prolonged progression-free survival (PFS) [7, 8]. In addition, the CREST trial showed that thoracic radiotherapy (TRT) after first-line CT could increase local control rates and improve OS [9]. Studies have shown that patients who underwent TRT after chemo-immunotherapy (CT + IT) had significantly longer OS and PFS in patients with ES-SCLC [10]. This study aimed to explore the clinical efficacy and safety of IT and radiotherapy (RT) in ES-SCLC patients in the real world.

Methods

Data collection

We retrospectively extracted data from the electronic health records of patients with ES-SCLC who received first-line CT with or without immunotherapy (IT) from April 2016 to August 2023 across three public tertiary hospitals (Weihai Municipal Hospital, Qilu Hospital of Shandong University Dezhou Hospital and Qilu Hospital Affiliated to Shandong University). The patients' basic information was collected. All data were obtained from clinical medical records and followed up from the date of diagnosis until the date of all-cause death or up to the latest available follow-up.

Patient selection

(1) The inclusion criteriawere as follows: aged 18 years or older; had an Eastern Cooperative Oncology Group performance status (ECOG PS) ranging from 0 to 3; had a pathological diagnosis of SCLC; and had undergone at least two cycles of chemotherapy. (2) The exclusion criteria were as follows: no clear pathological diagnosis information; patients with other tumors at the same time; ECOG PS > 3; less than 2 cycles of chemotherapy; no efficacy evaluation after treatment or loss to follow-up; and autoimmune diseases.

Efficacy assessment

The response to therapies was evaluated based on imaging examinations according to the Response Evaluation Criteria in Solid Tumors version 1.1. The primary endpoint was OS, which was defined as the time from the date of chemotherapy initiation to all-cause mortality or censored on the date of the last follow-up. PFS was defined as the time from chemotherapy initiation to tumor progression, death or the last follow-up. However, in the real world, some patients can determine the time of death, but because there is no regular review or follow-up in other hospitals, the specific progress time cannot be determined, which is likely to lead to errors in the assessment of PFS. Because ES-SCLC is characterized by rapid proliferation, in order to minimize the inaccuracy of PFS caused by this error, we did not include these patients in the analysis of PFS.In order to make fully use this data in the analysis of OS, we used the secondary endpoint was real-world progression-free survival (rwPFS), which was defined as the time from chemotherapy initiation to tumor progression, death from no progression or the last follow-up. Adverse effects were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The patients were followed up by consulting outpatient records, hospitalization medical records, and telephone inquiries. The latest follow-up date was January 31, 2024.

Statistical analysis

Standard descriptive statistics or contingency tables were used for demographic and baseline characteristics. Proportions were compared between groups using the chi-squared test. Propensity score matching was conducted using a 1:1 matching design with a tolerance of 0.02. A logistic regression model was constructed to estimate the

propensity score, which included the following covariates: age, sex, smoking history, hypertension status, diabetes status, ECOG PS score, brain metastasis status, liver metastasis status, bone metastasis status, lung metastasis status, adrenal gland metastasis status, chemotherapy status and radiotherapy status. Kaplan–Meier analysis was performed to estimate the survival rate, and the log-rank test was performed to test the differences in survival distribution. To investigate predictors of OS and rwPFS, univariate and multivariate Cox regression models were used. All the statistical analyses were performed using SPSS version 27.0. $P < 0.05$ was considered to indicate statistical significance.

Ethical statement

This program was performed in accordance with the principles of good clinical practice and was approved by the institutional review board of Weihai Municipal Hospital of Shandong University. Because this study was retrospective, informed consent from the included patients was not required, and patient information was anonymized.

Results

Data collection

A total of 495 patients were initially screened, 183 patients with LS-SCLC were excluded, 19 patients were excluded because of less than 2 cycles of CT or less than 2 cycles of IT, 13 patients were excluded because they did not receive first-line IT, and 23 patients were excluded because both OS and rwPSF were uncertain. A total of 257 eligible patients were included in the analysis. A total of 105 patients had both OS and rwPSF data, 81 patients had only OS data, and 71 patients had only rwPFS data. Overall, OS data from 186 patients were analyzed, including 106 patients who received CT alone and 80 patients who received CT + IT. Additionally, rwPFS data from 176 patients were analyzed, including 97 patients who received CT alone and 79 patients who received CT + IT (Fig. 1).

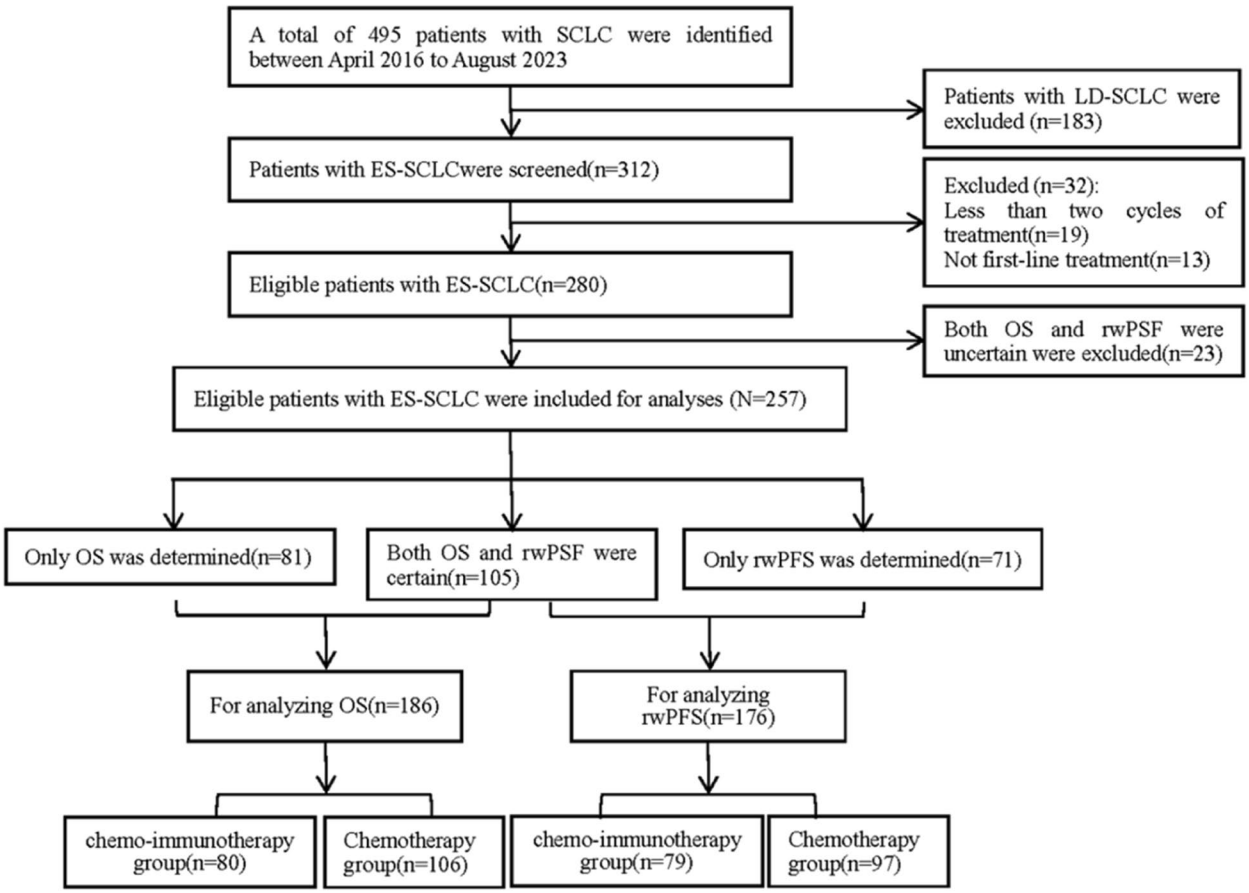

Fig. 1 Diagram of patient's selection process. Abbreviations: SCLC, small-cell lung cancer; LS-SCLC, limited-stage SCLC; ES-SCLC, extensive-stage SCLC; OS, overall survival; rwPFS, real-world progression-free survival

OS

Baseline characteristics

The median age was 65 years (32–85). The majority of patients were males (75.8%). The ECOG PS0-1 group constituted 95.2% of the cohort. Brain metastasis was present in 20.4% of the cohort, liver metastasis was present in 21.0%, bone metastasis was present in 28.0%, lung metastasis was present in 19.9% and adrenal gland metastasis was present in 9.1%. Among them, CT combined with RT accounted for 46.8% of the treatment regimens, while CT combined with IT accounted for 43.0%. The CT regimen used for 174 patients was carboplatin ($n=67$) or cisplatin ($n=107$) combined with etoposide; 8 patients received nedaplatin combined with etoposide, and 4 patients received irinotecan combined with cisplatin (Table 1). Regarding IT, 35 patients received PD-1 (including 17 who received tislelizumab, 5 who received serplulimab, 5 who received camrelizumab, 3 who received sintilimab, 3 who received pembrolizumab, 1 who received toripalimab and 1 who received penpulimab), and 45 patients received PD-L1 (including 34 who received durvalumab, 7 who received atezolizumab and 4 who received adebrelimab).

The radiation dose was decided by a doctor based on the guidelines of the Chinese Society of Clinical Oncology guidelines or National Comprehensive Cancer Network, intensity-modulated radiotherapy (IMRT) was the chosen modality for treatment-related therapy (TRT). The delineation of target volumes and the identification of organs at risk (OARs) adhered to the protocols established by the Radiation Therapy and Oncology Group for lung cancer. The gross target volume encompassed any remaining primary tumor sites and any positive lymph nodes post-treatment, while the clinical target volume was determined by adding an 8 mm margin to the gross target volume, along with the nodal regions that were implicated prior to treatment initiation. The total radiation dose ranged from 30 to 60 Gy, with a median dose of 45 Gy, delivered at a rate of 2 Gy to 3 Gy per fraction on a daily basis, with a total of five fractions administered weekly. To guarantee the accuracy of the radiation therapy, the plans were meticulously reviewed to confirm that the minimum target volume (PTV) received at least 95% of the stipulated radiation dose. Constraints were applied to the radiation dosage received by the OARs, with the following parameters: the maximum dose to the spinal cord was capped at 45 Gy, the average lung dose was kept below 17 Gy, with V5 of the total lung volume at $\leq 60\%$, V20 at $\leq 30\%$, and V30 at $\leq 20\%$. For the heart, the mean radiation dose was limited to 20 Gy, with V30 at $\leq 40\%$ and V40 at $\leq 30\%$. Additionally, the mean radiation dose to the esophagus was restricted to ≤ 30 Gy, and V60 was kept below 17%.

rwPFS

The median age of this group was 65 years (41–85). Most of the patients were males (75.6%). The ECOG PS0-1 group accounted for 96.0% of the cohort. Brain metastasis was present in 28.7% of the cohort, liver metastasis was present in 22.7%, bone metastasis was present in 30.1%, lung metastasis was present in 28.7% and adrenal gland metastasis was present in 8.5%. Among them, the combination of CT with RT accounted for 52.8% of the treatment regimens, and CT plus IT accounted for 44.9%. The CT regimens used for 166 patients were carboplatin ($n=56$) or cisplatin ($n=110$) combined with etoposide; 4 patients received nedaplatin combined with etoposide; 2 patients received irinotecan combined with cisplatin; 2 patients received irinotecan combined with carboplatin; and 2 patients received the single agent etoposide. (Table 1) Regarding IT, 37 patients received PD-1 (including 3 who received sintilimab, 3 who received pembrolizumab, 18 who received tislelizumab, 6 who received camrelizumab, 3 who received serplulimab, 2 who received toripalimab and 2 who received penpulimab) and 42 received PD-L1 (including 28 who received durvalumab, 9 who received atezolizumab and 5 who received adebrelimab).

Survival analysis

OS

A total of 186 patients were included in the OS analysis. The median follow-up time was 21.5 months. The median OS (mOS) was 16.5 months (95% CI 16.0–23.7) for all patients. The 1-year and 5-year OS rates were 66.2% and 7.0%, respectively (Table 2).

Among these patients, 80 (43.0%) received CT + IT, and 106 (57.0%) were treated with CT alone. During the follow-up period, 138 (74.2%) patients reached the primary endpoint, including 48 (60.0%) in the CT + IT group and 90 (84.9%) in the CT-alone group. There were no significant differences in OS between patients who received CT + IT and those who received CT alone (18.0 m vs. 15.7 m, respectively; $p=0.208$). The 1-year OS rates in the CT + IT and CT alone group were 72.5% and 61.8%, respectively; the 2-year OS rates were 42.7% and 28.6%, respectively, and the 3-year OS rates were 22.9% and 14.4%, respectively. In addition, 87 (46.8%) patients received chemoradiotherapy (CT + RT), and 99 (53.2%) patients were treated with CT alone. During the follow-up period, 62 (71.7%) patients in the CT + RT group and 76 (76.8%) in the CT-alone group reached the primary endpoint. Patients who received RT had a better prognosis (22.0 m; 95% CI [16.1–27.9] vs. 13.6 m; 95% CI [10.8–16.4]; $p<0.001$). The 1-year OS rates in the CT + RT and CT alone group were 75.4% and

Table 1 Baseline characteristics of patients before and after PSM according to first-line therapy

OS	Before matching, n (%)				After matching, n (%)				After matching, n (%)			
Characteristics	All patients *N* = 186(%)	CT + IT *N* = 80(43.0)	CT *N* = 106(57.0)	*P*-Value	All patients *N* = 120(%)	CT + IT *N* = 60(%)	CT *N* = 60(%)	*P*-value	All patients *N* = 122 (%)	CT + RT *N* = 61(%)	CT *N* = 61(%)	*P*-Value
Median age	65(32–85)	65(32–85)	65(44–81)		65(32–85)	65(32–85)	64.5(44–81)					
Age, year				0.550				0.713				0.856
≤ 65 yrs	100(53.8)	41(51.3)	59(55.7)		68(56.7)	33(55.0)	35(58.3)		63(51.6)	32(52.5)	31(50.8)	
> 65 yrs	86(46.2)	39(48.7)	47(44.3)		52(43.3)	27(45.0)	25(41.7)		59(48.4)	29(47.5)	30(49.2)	
Gender				0.022				1.0				0.523
Female	45(24.2)	26(32.5)	19(17.9)		30(25.0)	15(25.0)	15(25.0)		29(23.8)	16((26.2)	13(21.3)	
Male	141(75.8)	54(67.5)	87(72.1)		90(75.0)	45(75.0)	45(75.0)		93(76.2)	45(73.8)	48(78.7)	
Smoking history				0.519				0.709				0.856
Never smoked	81(43.5)	37(46.3)	44(41.5)		48(40.0)	25(41.7)	23(38.3)		57(46.7)	29(47.5)	28(45.9)	
Former/current	105(56.5)	43(53.7)	62(58.5)		72(60.0)	35(58.3)	37(61.7)		65(53.3)	32(52.5)	33(54.1)	
Family tumor history				0.100				0.068				0.839
No	140(75.3)	65(81.2)	75(70.8)		86(71.7)	48(80.0)	38(63.3)		89(73.0)	44(72.1)	45(73.8)	
Yes	46(24.7)	15(18.8)	31(29.2)		34(28.3)	12(20.0)	22(36.7)		33(27.0)	17(27.9)	16(26.2)	
Hypertension				0.626				1.0				1.0
No	129(69.4)	57(71.3)	72(67.9)		86(71.7)	43(71.7)	43(71.7)		84(68.9)	42(68.9)	42(68.9)	
Yes	57(30.6)	23(28.7)	34(32.1)		34(28.3)	17(28.3)	17(28.3)		38(31.1)	19(31.1)	19(31.1)	
Diabetes				0.871				1.0				0.610
No	159(85.5)	68(85.0)	91(85.8)		104(86.7)	52(86.7)	52(86.7)		104(85.2)	53(86.9)	51(83.6)	
Yes	27(14.5)	12(15.0)	15(14.2)		16(13.3)	8(13.3)	8(13.3)		18(14.8)	8(13.1)	10(16.4)	
ECOG PS				0.584				0.648				1.0
0–1	177(95.2)	77(96.3)	100(94.3)		115(95.8)	58(96.7)	57(95.0)		120(98.4)	60(98.4)	60(98.4)	
2	9(4.8)	3(3.7)	6(5.7)		5(4.2)	2(3.3)	3(5.0)		2(1.6)	1(1.6)	1(1.6)	
Brain Metastasis				0.329				1.0				0.783
No	148(79.6)	61(76.3)	87(82.1)		94(78.3)	47(78.3)	47(78.3)		107(87.8)	53(86.9)	54(88.5)	
Yes	38(20.4)	19(23.)	19(17.9)		26(21.7)	13(21.7)	13(21.7)		15(12.2)	8(13.1)	7(11.5)	
Liver Metastasis				0.057				0.827				0.817
No	147(79.0)	58(72.5)	89(84.0)		93(77.5)	47(78.3)	46(76.7)		99(81.1)	50(82.0))	49(80.3)	
Yes	39(21.0)	22(27.5)	17(16.0)		27(22.5)	13(21.7)	14(23.3)		23(18.9)	11(18.0)	12(19.7)	
Bone Metastasis				0.385				0.559				0.832
No	134(72.0)	55(68.8)	79(74.5)		81(67.5)	42(70.0)	39(65.0)		93(76.2)	47(77.0)	46(75.4)	
Yes	52(28.0)	25(31.2)	27(25.5)		39(32.5)	18(30.0)	21(35.0)		29(23.8)	14(23.0)	15(24.6)	
Lung Metastasis				0.010				1.0				0.667
No	149(80.1)	71(88.8)	78(73.6)		102(85.0)	51(85.0)	51(85.0)		94(77.0)	48(78.7)	46(75.4)	
Yes	37(19.9)	9(11.2)	28(26.4)		18(15.0)	9(15.0)	9(15.0)		28(23.0)	13(21.3)	15(24.6)	

Table 1 (continued)

Adrenal gland Metastasis				0.058				0.697				0.464
No	169(90.9)	69(86.3)	100(94.3)		113(94.2)	56(93.3)	57(95.0)		114(93.4)	58(95.1)	56(91.8)	
Yes	17(9.1)	11(13.7)	6(5.7)		7(5.8)	4(6.7)	3(5.0)		8(6.6)	3(4.9)	5(8.2)	
Radiotherapy				0.310				1.0				
Yes	87(46.8)	34(42.5)	53(50.0)		56(46.7)	28(46.7)	28(46.7)					
No	99(53.2)	46(57.5)	53(50.0)		64(53.3)	32(53.3)	32(53.3)					
Immunotherapy												0.127
Yes	80(43.0%)				60(50.0%)				42(34.4)	25(41.0)	17(27.9)	
No	106(57.0%)				60(50.0%)				80(65.6)	36(59.0)	44(72.1)	
Chemotherapy				0.836				0.618				0.069
EC	67(36)	27(33.8)	40(37.7)		41(34.2)	18(30.0)	23(38.3)		42(34.4)	18(29.5)	24(39.3)	
EP	107(57.5)	48(60.0)	59(55.7)		71(59.1)	38(63.3)	33(55.0)		71(58.2)	41(67.2)	30(49.2)	
Other	12(6.5)	5(6.2)	7(6.6)		8(6.7)	4(6.7)	4(6.7)		9(7.4)	2(3.3)	7(11.5)	
rwPFS	Before matching, n (%)				After matching, n (%)				After matching, n (%)			
Characteristics	All patients *N* = 176(%)	CT + IT *N* = 79(%)	CT *N* = 97(%)	*P*-Value	All patients *N* = 116(%)	CT + IT *N* = 58(%)	CT *N* = 58(%)	P-value	All patients *N* = 114 (%)	CT + RT *N* = 57(%)	CT *N* = 57(%)	*P*-Value
Median age	65(41–85)	64(45–85)	65(41–81)		65(41–85)	65(32–85)	64.5(44–81)					
Age, year				0.888				0.264				0.183
≤ 65 yrs	97(55.1)	44(55.7)	53(54.6)		62(53.5)	34(58.6)	28(48.3)		67(58.8)	37(64.9)	30(52.6)	
> 65 yrs	79(44.9)	35(44.3)	44(45.4)		54(46.5)	24(41.4)	30(51.7)		47(41.2)	20(35.1)	27(47.4)	
Gender				0.044				1.0				0.372
Female	43(24.4)	25(31.6)	18(18.6)		30(25.9)	15(25.9)	15(25.9)		26(22.8)	15(26.3)	11(19.3)	
Male	133(75.6)	54(68.4)	79(71.4)		86(74.1)	43(74.1)	43(74.1)		88(77.2)	42(73.7)	46(80.7)	
Smoking history				0.733				0.849				0.704
Never smoked	76(43.2)	33(41.8)	43(44.3)		45(38.8)	22(37.9)	23(39.7)		48(42.1)	25(43.9)	23(40.4)	
Former/current	100(56.8)	46(58.2)	54(55.7)		71(61.2)	36(62.1)	35(60.3)		66(57.9)	32(56.1)	34(59.6)	
Family tumor history				0.361				0.150				0.663
No	130(73.9)	61(77.2)	69(71.1)		83(71.6)	45(77.6)	38(65.5)		86(75.4)	42(73.7)	44(77.2)	
Yes	46(26.1)	18(22.8)	28(28.9)		33(28.4)	13(22.4)	20(34.5)		28(24.6)	15(26.3)	13(22.8)	
Hypertension				0.626				1.0				0.317
No	117(66.5)	51(64.6)	66(68.0)		72(62.1)	36(62.1)	36(62.1)		77(67.5)	36(63.2)	41(71.9)	
Yes	59(33.5)	28(35.4)	31(32.0)		44(37.9)	22(37.9)	22(37.9)		37(32.5)	21(36.8)	16(28.1)	
Diabetes				0.711				0.623				0.802
No	149(84.7)	66(83.5)	83(85.6)		96(82.8)	49(84.5)	47(81.0)		95(83.3)	47(82.5)	48(84.2)	
Yes	27(15.3)	13(16.5)	14(14.4)		20(17.2)	9(15.5)	11(19.0)		19(16.7)	10(17.5)	9(15.8)	
ECOG PS				0.506				0.309				0.079

Table 1 (continued)

0–1	169(96.0)	75(94.9)	94(96.9)		112(96.6)	57(98.3)	55(94.8)		111(97.4)	57(100)	54(94.7)	
2	7(4.0)	4(5.1)	3(3.1)		4(3.4)	1(1.7)	3(5.2)		3(2.6)	0(0)	3(5.3)	
Brain Metastasis				0.044				0.623				0.646
No	143(81.3)	59(74.7)	84(86.6)		96(82.8)	49(84.5)	47(81.0)		90(78.9)	44(77.2)	46(80.7)	
Yes	33(28.7)	20(25.3)	13(13.4)		20(17.2)	9(15.5)	11(19.0)		24(21.1)	13(22.8)	11(19.3)	
Liver Metastasis				0.143				0.816				0.395
No	136(77.3)	57(72.2)	79(81.4)		93(80.2)	46(79.3)	47(81.0)		84(73.7)	40(70.2)	44(77.2)	
Yes	40(22.7)	22(27.8)	18(18.6)		23(19.8)	12(20.7)	11(19.0)		30(26.3)	17(29.8)	13(22.8)	
Bone Metastasis				0.689				0.844				0.558
No	123(69.9)	54(68.4)	69(71.1)		77(66.4)	39(67.2)	38(65.5)		73(64.0)	35(61.4)	38(66.7)	
Yes	53(30.1)	25(31.6)	28(28.9)		39(33.6)	19(32.8)	20(34.5)		41(36.0)	22(38.6)	19(33.3)	
Lung Metastasis				0.275				1.0				0.590
No	143(81.3)	67(84.4)	76(78.4)		94(81.0)	47(81.0)	47(81.0)		98(86.0)	48(84.2)	50(87.7)	
Yes	33(28.7)	12(15.6)	21(21.6)		22(19.0)	11(19.0)	11(19.0)		16(14.0)	9(15.8)	7(12.3)	
Adrenal gland Metastasis				0.076				1.0				0.728
No	161(91.5)	69(87.3)	92(94.8)		108(93.1)	54(93.1)	54(93.1)		105(92.1)	52(91.2)	53(93.0)	
Yes	15(8.5)	10(12.7)	5(5.2)		8(6.9)	4(6.9)	4(6.9)		9(7.9)	5(8.8)	4(7.0)	
Radiotherapy				0.256				1.0				
Yes	93(52.8)	38(48.1)	55(56.7)		54(46.6)	27(46.6)	27(46.6)		57(50.0)			
No	83(47.2)	41(51.9)	42(43.3)		62(53.4)	31(53.4)	31(53.4)		57(50.0)			
Immunotherapy												0.450
Yes	79(44.9)				58(50.0)				50(43.9)	27(47.4)	23(40.4)	
No	97(55.1)				58(50.0)				64(56.1)	30(52.6)	34(59.6)	
chemotherapy				0.812				0.893				0.925
EC	56(31.8)	27(34.2)	29(29.9)		35(30.2)	18(31.0)	17(29.3)		30(26.3)	15(26.3)	15(26.3)	
EP	110(62.5)	48(60.8)	62(63.9)		74(63.8)	36(62.1)	38(65.5)		77(67.5)	39(68.4)	38(66.7)	
Other	10(5.7)	4(5.0)	6(6.2)		7(6.0)	4(6.9)	3(5.2)		7(6.2)	3(5.3)	4(7.0)	

Abbreviations: PSM propensity score-matched, *OS* overall survival;CT, chemotherapy, *IT* immunotherapy, *RT* radiotherapy, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EP* etoposide combined with platinum(cisplatin), *EC* etoposide combined with carboplatin, *rwPFS* real-world progression-free survival

Table 2 The survival rate of OS and rwPFS

	OS ($n=186$)					rwPFS ($n=176$)		
Time	**1-year**	**2-year**	**3-year**	**4-year**	**5-year**	**6-month**	**12-month**	**18-month**
All patients	66.2%	33.7%	17.2%	11.1%	7.0%	59.0%	13.9%	6.8%
CT + IT	72.5%	42.7%	22.9%	11.4%	0	63.2%	19.8%	12.1%
CT	61.8%	28.6%	14.4%	10.2%	7.3%	55.7%	9.3%	3.1%
CT + RT	75.4%	43.8%	28.5%	19.8%	12.3%	68.8%	14.3%	6.2%
CT	58.0%	23.7%	4.7%	0	0	48.1%	13.6%	7.7%

Abbreviations: OS overall survival, *rwPFS* real-world progression-free survival, *CT* chemotherapy, *IT* immunotherapy, *RT* radiotherapy

58.0%, respectively; the 2-year OS rates were 43.8% and 23.7%, respectively; and the 3-year OS rates were 28.5% and 4.7%, respectively (Fig. 2, Table 2).

Univariate survival analysis was used to determine the associations between OS and clinical features. Sex ($p=0.002$), liver metastasis ($p=0.015$), and radiotherapy ($p<0.001$) were found to be significant prognostic factors for OS. Multivariate analysis revealed that sex (HR, 0.571; 95% CI [0.370–0.882]; $p=0.011$), liver metastasis (HR, 0.661; 95% CI [0.444–0.984]; $p=0.041$), and radiotherapy (HR, 0.524; 95% CI [0.367–0.748]; $p<0.001$) were independent prognostic factors for OS (Table 3).

rwPFS

A total of 176 patients were included in the rwPFS analysis. The median follow-up time was 7.5 months. The median rwPFS (mrwPFS) was 7.0 months (95% CI 6.5–7.5) for all patients. The 6-month, 12-month and 18-month PFS rates were 59.0%, 13.9% and 6.8%, respectively (Table 2).

Among these patients, 79 (44.9%) received CT + IT, and 97 (55.1%) were treated with CT alone. During the follow-up period, 166 (94.3%) patients reached the endpoint: 69 (87.3%) in the CT + IT group and 97 (100%) in the CT-alone group. The mrwPFS was 7.7 months (95% CI [6.8–8.6]) in the CT + IT cohort and 6.8 months (95% CI [6.1–7.5]) in the CT-alone cohort

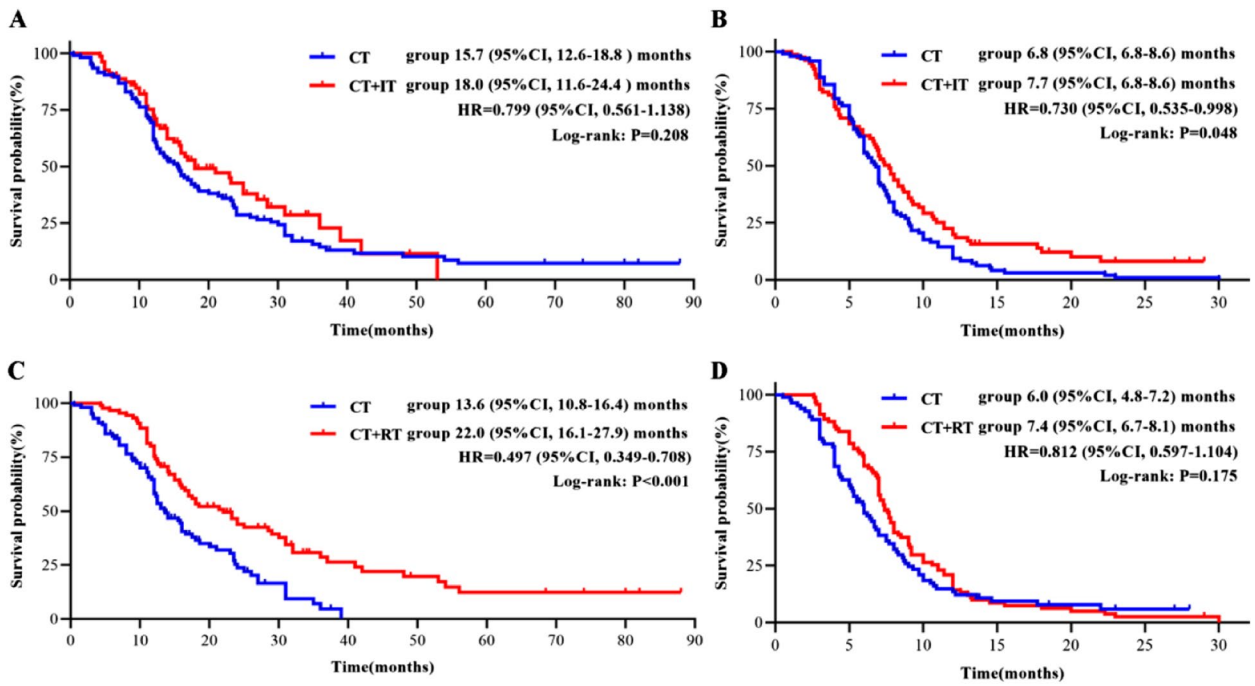

Fig. 2 **A** Kaplan-Mier curves showing OS based on immunotherapy. **B** Kaplan-Mier curves showing rwPFS based on immunotherapy. **C** Kaplan-Mier curves showing OS based on radiotherapy. **D** Kaplan-Mier curves showing rwPFS based on radiotherapy. Abbreviations: OS, overall survival; rwPFS, real-world progression-free survival; CT, chemotherapy; IT, immunotherapy; RT, radiotherapy

Table 3 Analysis of potential risk factors for OS and rwPFS using univariate and multivariate Cox proportional hazard models

Characteristics	OS				rwPFS			
	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)					0.846(0.622–1.152)	0.289		
Gender(Female vs. Male)	0.509(0.331–0.782)	0.002	0.571(0.370–0.882)	0.011	0.722(0.501–1.040)	0.080		
Smoking history(Never vs. Former/current)	0.719(0.514–1.007)	0.055			0.863(0.633–1.176)	0.351		
Family tumor history(No vs. Yes)	1.189(0.795–1.778)	0.398			1.093(0.769–1.552)	0.620		
Hypertension(No vs. Yes)	0.994(0.658–1.354)	0.755			1.146(0.827–1.589)	0.413		
Diabetes(No vs. Yes)	0.737(0.463–1.175)	0.200			0.714(0.469–1.088)	0.117		
ECOG PS(0–1 vs. ≥ 2)	0.704(0.344–1.441)	0.337			0.881(0.412–1.883)	0.744		
Brain Metastatic(No vs. Yes)	1.056(0.688–1.620)	0.802			0.897(0.609–1.320)	0.580		
Liver Metastatic(No vs. Yes)	0.612(0.412–0.908)	0.015	0.661(0.444–0.984)	0.041	0.621(0.434–0.889)	0.009	0.609(0.425–0.872)	0.007
Bone Metastatic(No vs. Yes)	0.855(0.590–1.239)	0.408			1.145(0.819–1.600)	0.429		
Lung Metastatic(No vs. Yes)	0.972(0.645–1.465)	0.892			0.939(0.631–1.397)	0.756		
Adrenal gland Metastasis(No vs. Yes)	1.184(0.622–2.256)	0.607			0.969(0.549–1.170)	0.914		
Radiotherapy(Yes vs. No)	0.497(0.349–0.708)	< 0.001	0.524(0.367–0.748)	< 0.001	0.812(0.597–1.104)	0.184		
Immunotherapy(Yes vs. No)	0.799(0.561–1.138)	0.214			0.730(0.535–0.998)	0.048	0.716(0.524–0.979)	0.037
Chemotherapy(EC vs. EP)	1.360(0.950–1.947)	0.093			1.132(0.811–1.579)	0.468		

Abbreviations: OS overall survival, *rwPFS* real-world progression-free survival, *HR* hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EP* etoposide combined with platinum(cisplatin), *EC* etoposide combined with carboplatin

($p = 0.043$). The 6-month rwPFS rates in the CT + IT and CT alone group were 63.2% and 55.7%, respectively; the 12-month rwPFS rates were 19.8% and 9.3%, respectively; and the 18-month rwPFS rates were 12.1% and 3.1%, respectively. In addition, 93 (52.8%) patients received CT + RT, and 83 (47.2%) were treated with CT alone. During the follow-up period, 90 (96.8%) patients in the CT + RT group and 76 (91.6%) in the CT-alone group reached the endpoint. There were no significant differences in rwPFS between the two groups (7.4 m vs. 6.0 m, $p = 0.175$). The 6-month rwPFS rates in the CT + RT and CT alone group were 68.8% and 48.1%, respectively; the 12-month rwPFS rates were 14.3% and 13.6%, respectively; and the 18-month rwPFS rates were 6.2% and 7.7%, respectively (Fig. 2, Table 2).

Univariate analysis revealed that liver metastasis ($p = 0.009$) and immunotherapy ($p = 0.048$) were significant prognostic factors for rwPFS. Multivariate analysis revealed that liver metastasis (HR, 0.609; 95% CI [0.425–0.872]; $p = 0.007$) and immunotherapy (HR, 0.716; 95% CI [0.524–0.979]; $p = 0.037$) were independent prognostic factors for rwPFS (Table 3).

Survival outcomes after PSM

OS

To reduce the interference of confounding factors and potential biases, PSM was carried out. PSM was used to match the CT + IT group and the CT group. A total of 60 pairs completed PSM, with comparable baseline characteristics. The mOS was 23.2 m (95% CI [15.1–31.3]) in the CT + IT cohort and 13.0 m (95% CI [10.3–15.7]) in the CT cohort ($p = 0.008$). Similarly, PSM was also used to match the CT + RT group and the control group. Among the 61 pairs completed, the mOS was 21.4 m (95% CI [13.4–29.4]) in the CT + RT group and 12.5 m (95% CI [11.2–13.8]) in the control cohort ($p < 0.001$). (Fig. 3, Table 1).

rwPFS

PSM was used to match the CT + IT group and the control group. Among the 58 pairs that were subjected to PSM, there was no significant difference in the mrwPFS (7.3 m; 95% CI [6.5–8.1] vs. 6.2 m; 95% CI [5.5–6.9]; $p = 0.096$), but we found that IT tended to improve PFS**.** Similarly, PSM was also used to match the CT + RT

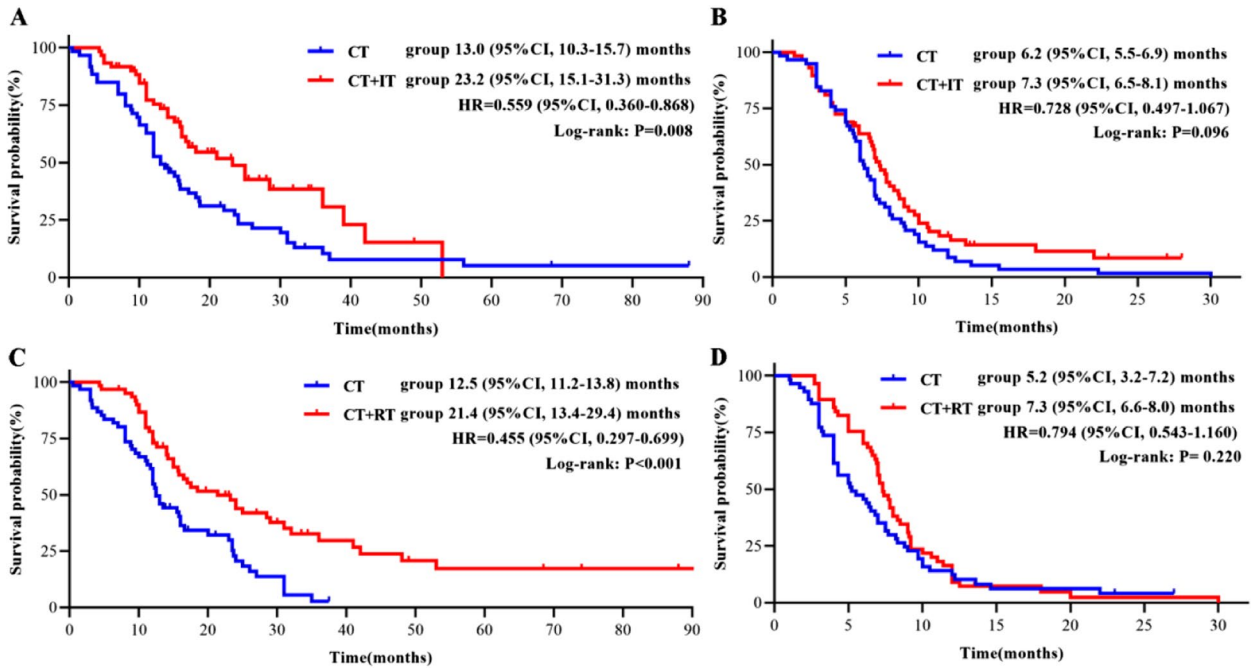

Fig. 3 **A** Kaplan-Mier curves showing OS based on immunotherapy after PSM. **B** Kaplan-Mier curves showing rwPFS based on immunotherapy after PSM. (**C**) Kaplan-Mier curves showing OS based on radiotherapy after PSM. (**D**) Kaplan-Mier curves showing rwPFS based on radiotherapy after PSM. Abbreviations: OS, overall survival; rwPFS, real-world progression-free survival; PSM, propensity score-matched; CT, chemotherapy; IT, immunotherapy; RT, radiotherapy

group and the control group. Among the 57 pairs that were subjected to PSM, the mrwPFS was not significantly different (7.3 m vs. 5.2 m, $p=0.220$). (Fig. 3, Table 1).

Survival Outcomes in Selected Patient Subgroups

Division into four groups according to RT and IT

We divided all patients into four groups: 34 patients in the RT + IT group, 53 in the RT group, 46 in the IT group, and 53 in the CT-alone group. The mOS for these groups was 25.0 m, 21.4 m, 16.6 m, and 12.0 m, respectively. The three groups showed significant improvements in OS compared with the CT-alone group ($p<0.001$, $p<0.001$, $p=0.021$), but there was no significant difference among the 3 groups. In terms of rwPFS, there were 38 patients in the RT + IT group, 55 in the RT group, 41 in the IT group, and 42 in the CT group. The mrwPFS for these groups was 7.8 m, 7.1 m, 6.8 m, and 5.3 m, respectively. Similarly, the 3 groups showed significant improvements in PFS compared with the CT-alone group ($p=0.005$, $p=0.005$, $p=0.015$), and there was no significant difference among the 3 groups (Fig. 4, Table 4).

Comparison of PD-1 inhibitors, PD-L1 inhibitors and radiotherapy

For OS, 80 patients received IT, including 35 patients in the PD-1 group and 45 patients in the PD-L1 group, and the mOS was 23.2 m versus 18.0 m ($p=0.380$). In the PD-1 group, RT significantly improved patient survival (36.0 m vs. 15.8 m, $p=0.041$). The same results were not observed in the PD-L1 group (15.0 m vs. 21.0, $p=0.926$). In addition, 34 patients received RT, among them 13(38.2%) patients were treated with IT following RT, while 21(61.8%) patients underwent RT after IT, 46 did not receive RT, and the mOS was 25.0 m versus 16.6 m ($p=0.149$). In the RT group, PD-1 inhibitors tended to improve OS compared with PD-L1 inhibitors (36.0 m vs. 15.0 m, $p=0.086$) (Figs. 4 and 5, Table 5).

For rwPFS, 79 patients received IT, including 37 patients in the PD-1 group and 42 patients in the PD-L1 group, and thirty-eight patients received RT, among them 15(39.5%) patients were treated with IT following RT, while 23(60.5%) patients underwent RT after IT. We found that treatment with PD-1 inhibitors combined with RT (9.2 m vs. 5.9 m) prolonged the mrwPFS more than treatment with PD-L1 inhibitors (7.3 m vs. 6.8 m), but there were no significant differences ($p>0.05$). Additionally, patients who underwent RT had longer mrwPFS when treated with PD-L1 inhibitors were combined with RT, whereas those who did not receive RT had longer mrwPFS in the PD-L1 group. This finding is similar to the results obtained in the OS analysis ($p>0.05$).(Table 5).

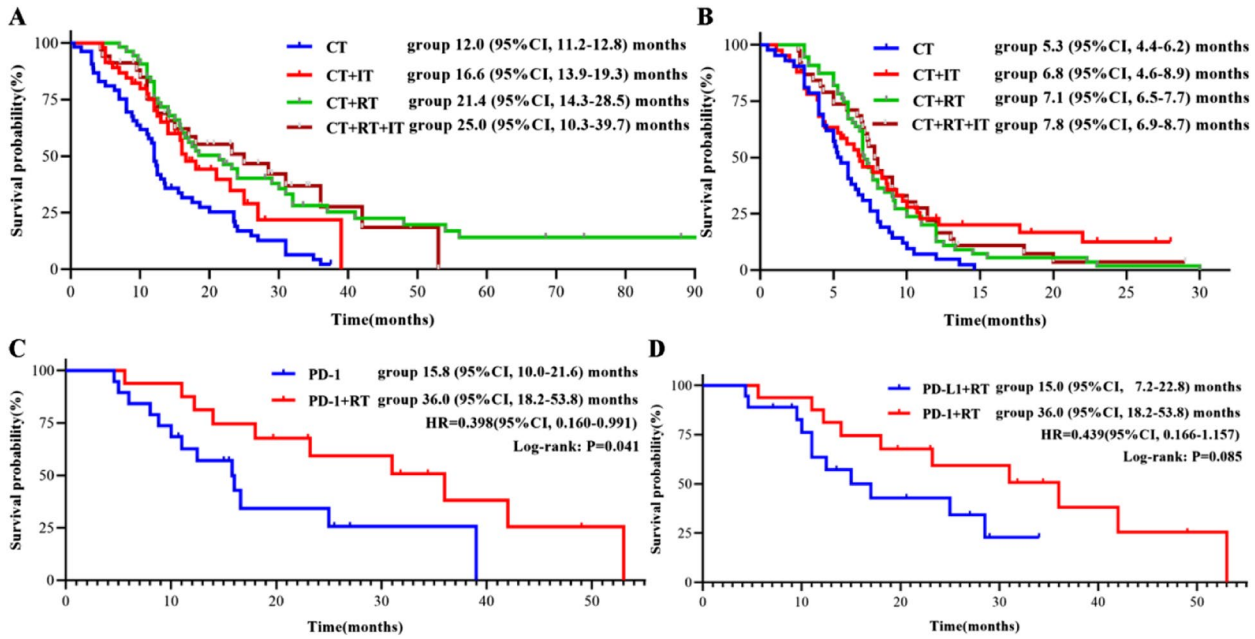

Fig. 4 **A** Kaplan-Mier curves showing OS about four groups. **B** Kaplan-Mier curves showing rwPFS about four groups. (**C**) Kaplan-Mier curves showing OS in the PD-1 group. **D** Kaplan-Mier curves showing OS based on radiotherapy combined with PD-1/PD-L1 inhibitors. Abbreviations: OS, overall survival; rwPFS, real-world progression-free survival; CT, chemotherapy; IT, immunotherapy; RT, radiotherapy; PD-1, Programmed death 1; PD-L1, programmed death ligand 1

Table 4 Survival outcomes of four groups

OS						rwPFS				
	N	mOS	RT	IT	CT	N	mrwPFS	RT	IT	CT
RT + IT	34	25.0	0.951	0.149	< 0.001	38	7.8	0.589	0.895	0.005
RT	53	21.4		0.148	< 0.001	55	7.1		0.571	0.005
IT	46	16.6			0.021	41	6.8			0.015
CT	53	12.0				42	5.3			

Abbreviations: OS overall survival, *rwPFS* real-world progression-free survival, *mrwPFS* median rwPFS, *CT* chemotherapy, *IT* immunotherapy, *RT* radiotherapy

Synchronous and sequential radiotherapy

For OS, a total of 87 patients received RT. After excluding 1 patient who received prophylactic cranial irradiation, the mOS for synchronous ($n=15$) and sequential ($n=71$) RT was 31.0 m versus 18.0 m ($p=0.854$). After excluding 21 patients who received brain radiation and 2 who received bone radiation, a total of 63 patients received thoracic radiotherapy (TRT), and the mOS for synchronous ($n=11$) and sequential ($n=52$) TRT was 32.0 m and 25.0 m, respectively ($p=0.955$). To eliminate the impact of IT on RT, we further analyzed the survival of patients who did not receive IT. The results also showed no statistically significant difference (32.0 m vs. 24.0 m, $p=0.925$). Similarly, in the analysis of the PFS population, no favorable outcomes were observed (Table 6).

Treatment-related adverse events (trAEs)

Among all eligible patients, 207 (80.5%) experienced at least one trAE, including 124 (48.2%) with grades 1–2 and 83 (32.3%) with grades 3–4. The rates of trAEs in the 4 groups were not significantly different ($p=0.385$). No patient exhibited grade 5 trAEs. Pneumonitis and esophagitis were the most common immune-related or radiation-related toxicities. Eleven patients developed grade 3 pneumonitis, and 4 patients developed grade 3 esophagitis (Table 7, Fig. 5).

Discussion

ES-SCLC represents a particularly challenging subset of lung cancer characterized by a poor prognosis and limited therapeutic options. Platinum-based chemotherapy

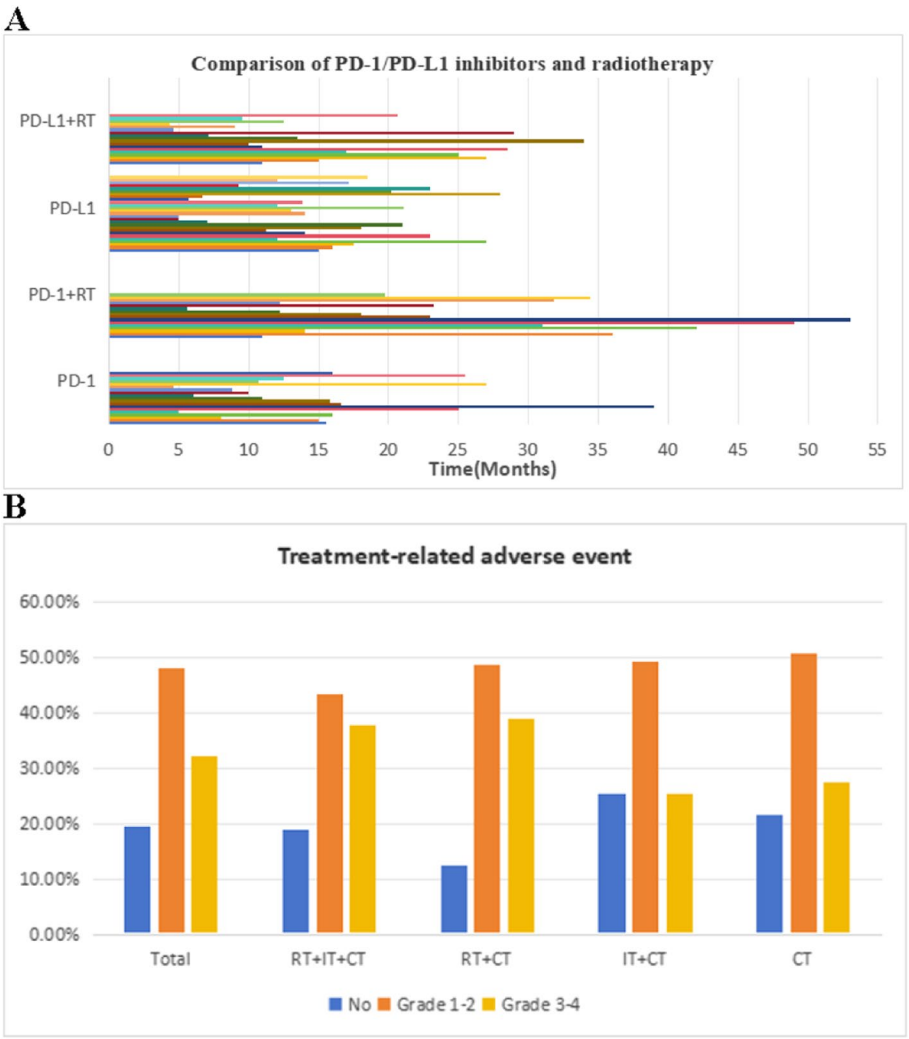

Fig. 5 **A** The bar chart showing OS comparison of PD-1/PD-LI inhibitors and radiotherapy. **B** Treatment-related adverse events in all ES-SCLC patients. Abbreviations: PD-1, Programmed death 1; PD-L1, programmed death ligand 1; CT, chemotherapy; IT, immunotherapy; RT, radiotherapy

Table 5 Comparison of PD-1 inhibitors, PD-L1 inhibitors and radiotherapy

		OS					rwPFS				
		N	mOS	*P*-Value	mOS	*P*-Value	N	mrwPFS	*P*-Value	mrwPFS	*P*-Value
PD-1	IT	19	15.8	0.041	23.2	0.380	16	5.9	0.505	8.3	0.785
	RT + IT	16	36.0				21	9.2			
PD-L1	IT	27	21.0	0.926	18.0		25	6.8	0.817	7.0	
	RT + IT	18	15.0				17	7.3			
RT + IT	PD-1	16	36.0	0.085	25.0	0.149	21	9.2	0.571	7.8	0.895
	PD-L1	18	15.0				17	7.3			
IT	PD-1	19	15.8	0.533	16.6		16	5.9	0.540	6.8	
	PD-L1	27	21.0				25	6.8			

Abbreviations: PD-1 Programmed death 1, *PD-L1* programmed death ligand 1, *CT* chemotherapy, *IT* immunotherapy, *RT* radiotherapy, *rwPFS* real-world progression-free survival, *mrwPFS* median rwPFS

Table 6 Synchronous and sequential radiotherapy

		N	mOS	*P*-Value	mOS	N	mrwPFS	*P*-Value	mrwPFS
RT	synchronous	15	31.0	0.854	22.0	13	7.3	0.806	7.4m
	sequential	71	18.5			79	7.4		
TRT	synchronous	11	32.0	0.955	28.5	11	7.3	0.466	8.0m
	sequential	52	25.0			56	8.0		
RT(no IT)	synchronous	10	23.2	0.913	18.5	7	7.0	0.722	7.0m
	sequential	42	18.0			47	7.1		
TRT(no IT)	synchronous	8	32.0	0.925	24.0	6	7.0	0.495	8.0m
	sequential	30	24.0			33	8.0		

Abbreviations: OS median overall surviva, *mrwPFS* median real-world progression-free survival, *IT* immunotherapy, *RT* radiotherapy, *TRT* thoracic radiotherapy

Table 7 Treatment-related adverse event

	Total(257)	RT + IT(53)	RT(72)	IT(63)	CT(69)	*P*-Value
No	50(19.5%)	10(18.9%)	9(12.5%)	16(25.4%)	15(21.7%)	0.385
Grade 1–2	124(48.2%)	23(43.4%)	35(48.6%)	31(49.2%)	35(50.7%)	
Grade 3–4	83(32.3%)	20(37.7%)	28(38.9%)	16(25.4%)	19(27.6%)	
Pneumonia	11(4.3%)	5(9.4%)	3(4.2%)	3(4.8%)	0	
Esophagitis	4(1.6%)	2(3.8%)	1(1.4%)	1(1.6%)	0	

Abbreviations: *CT* chemotherapy, *IT* immunotherapy, *RT* radiotherapy

(CT) has been the mainstay treatment for ES-SCLC patients. Despite the achievement of objective response rates ranging from 50–70%, the median survival time is limited to 9–12 months, with a dismal 5-year survival rate of less than 7% owing to rapid progression posttreatment resistance [11]. Recently, the most promising development in the treatment of ES-SCLC was the addition of immunotherapy (IT) to standard platinum-based first-line CT. Various clinical trials, including Checkmate032, Keynote028, IMpower133, ASTRUM005 and CASPIAN, have explored the safety and efficacy of anti-PD-1/PD-L1 therapy in SCLC patients, demonstrating encouraging outcomes marked by significant enhancements in survival metrics compared to historical data with CT alone [4, 5, 8, 12, 13]. Based on the results of these clinical studies, the relevant diagnosis and treatment guidelines approved PD-1/PD-L1 inhibitors combined with CT for the first-line treatment of ES-SCLC. However, the clinical benefits of IT in real-world patients with ES-SCLC are still worth exploring. Therefore, we conducted a real-world study to investigate the application of IT in patients with ES-SCLC.

Our study demonstrated that in terms of OS, there was no significant improvement in the CT + IT group compared to the CT-alone group in the entire cohort (18.0 m vs. 15.7 m, $p = 0.208$). Due to the baseline imbalance between the two groups, we conducted PSM and ultimately matched 60 pairs of data. Further analysis revealed a significant increase of 9.8 months in survival time for the CT + IT group compared to the CT-alone group (23.2 months vs. 13.0 months, $p = 0.008$). Regarding rwPFS, there was a significant improvement in the CT + IT group compared to the CT-alone group in the overall cohort (7.7 m vs. 6.8 m, $p = 0.043$), and IT tended to improve rwPFS in the matched cohort (7.3 m vs. 6.2 m, $p = 0.096$). It is worth noting that our OS outcomes in patients treated with CT + IT were numerically better than those in some prospective studies, such as the IMpower133, CASPIAN, CAPSTONE-1 and ASTRUM-005 studies [4, 5, 8, 14], and retrospective studies (17.3 m vs. 13.4 m; $p = 0.001$) [15]. Similarly, our study data surpass those of several prospective studies on the mrwPFS, such as the mPFS of the IT group and CT group, which were 4.5–5.8 months and 4.3–5.6 months, respectively. This could be attributed to approximately half of the patients receiving RT in our study.

Previously, the CREST trial showed that thoracic radiotherapy (TRT) after first-line CT could increase local control rates and improve OS [9]. In the era of CT, several prospective studies and meta-analyses have demonstrated that consolidative TRT offers survival benefits in comparison with CT alone [16, 17]. Moreover, studies have shown that RT can prolong the survival of patients with SCLC [18, 19]. Our research revealed that in terms of OS, both in the overall population and in the 61 matched pairs, RT significantly extended the OS

of patients with ES-SCLC (22.0 m vs. 13.6 m, $p<0.001$; 21.4 m vs. 12.5 m, $p<0.001$). These findings are consistent with previous research. Regarding rwPFS, no significant benefit was observed in either the overall cohort (7.4 m vs. 6.0 m, $p=0.175$) or the matched cohort (7.3 m vs. 5.2 m, $p=0.220$), which may be due to the heterogeneity in the timing of RT in our retrospective study. Furthermore, subgroup analysis suggested that synchronous RT may confer greater benefits with or without IT for ES-SCLC patients, although this difference did not reach statistical significance (31.0 m vs. 18.5 m; $p=0.854$).

Previous studies have demonstrated that both PD-1 and PD-L1 inhibitors combined with CT can prolong the survival of patients with ES-SCLC. One meta-analysis suggested that anti-PD-1 agents and anti-PD-L1 agents are likely to have comparable effectiveness [20]. Another meta-analysis revealed that compared with anti-PD-L1 agents, anti-PD-1 agents were linked to favorable survival results [21]. For anti-PD-1 agents, the RATIONAL-312 study suggested that the OS of patients treated with tislelizumab combined with CT reached 15.5 months [22]; in the ASTRUM-005 study, the OS of patients treated with serplulimab reached 15.4 months [8]; in the EXTENTORCH study, the OS of patients treated with toripalimab reached 14.6 months [23]. Regarding anti-PD-L1 agents, the IMpower133 study showed that the OS of patients treated with atezolizumab reached 12.3 months [5]; in the CASPIAN study, the OS of patients treated with durvalumab reached 12.9 months [4]; and in the CAPSTONE-1 study, the OS of patients treated with adebrelimab reached 15.3 months [15]. The first large prospective real-world study The ORIENTAL study was the first large, prospective, real-world study on this topic and reported that theOS of ES-SCLC patients treated with durvalumab reached 14.8 months. These studies suggest that there is a trend toward stronger improvement with anti-PD-1 agents than with anti-PD-L1 agents [24]. According to our findings, no significant difference was observed between patients who received anti-PD-1 agents and those who received anti-PD-L1 agents, although the survival was longer in the PD-1 group (23.2 m vs. 18.0 m, $p=0.380$). However, after controlling for the effect of RT, we found that there appeared to be a greater survival benefit with anti-PD-L1 agents than with anti-PD-1 agents (21.0 m vs. 15.8 m, $p=0.533$). A similar trend was observed for rwPFS.

This suggests that there is an interaction effect between RT and IT in the treatment of ES-SCLC. Daher et al. showed that patients who underwent TRT after IT had a significantly longer OS (27.7 m vs. 13.2 m, $p<0.007$) and PFS (8.5 m vs. 5.6 m, $p<0.003$), with an acceptable safety profile in patients with ES-SCLC [25]. In addition, studies have demonstrated that RT has the potential to increase the expression of tumor antigens on the surface of tumor cells and enhance the binding of antibodies to tumor cells, and IT could enhance the abscopal effect of RT [26, 27]. Several preclinical and clinical investigations have indicated that the combination of RT and IT can bolster local control and improve systemic antitumor immune responses through synergistic mechanisms [27, 28]. The LEAD study, presented at this year's ELCC, highlighted the feasibility and potential application of combining systemic therapy with local treatments in clinical practice [29]. According to our subgroup analysis, the mOS was 25.0 m for the RT + IT + CT group, 21.4 m for the RT + CT group, 16.6 m for the IT + CT group and 12.0 m for the CT group. Moreover, our research revealed that the combination of anti-PD-1 agents with RT significantly improved survival (36.0 vs. 15.8 m, $p=0.041$). Conversely, the combination of anti-PD-L1 agents with RT not only failed to confer benefits but also had detrimental effects on patients (15.0 m vs. 21.0 m, $p=0.926$). A similar trend was observed for rwPFS. These findings suggest a potentially greater synergistic effect between RT and anti-PD-1 agents. However, whether anti-PD-1 and PD-L1 agents combined with RT cause different clinical outcomes remains unclear, and additional research is needed.

Recent retrospective studies have assessed the safety and efficacy of the combination of IT with TRT in patients with ES-SCLC and revealed that the addition of TRT to IT did not exhibit an apparent association with increased toxicity in patients with SCLC [30]. Furthermore, the occurrence of TRT-related adverse events was in line with previous findings from other studies and was considered manageable [18, 19]. Our retrospective study, which was conducted across three medical centers, revealed similar rates of adverse events across the four cohorts, confirming the safety of combining IT with RT in ES-SCLC patients.

The main strength of this article is that it not only confirms the efficacy and safety but also further validates the synergistic effects of RT and IT in patients with ES-SCLC. Additionally, the combination of anti-PD-1 agents with RT resulted in significant survival benefits, and anti-PD-L1 agents without RT seemed to be more effective. This will be the focus of our subsequent research. However, our study has some limitations worth considering. First, as the study design was retrospective, PSM could not completely exclude confounding variables and selection bias. Second, In the PSM analysis, we did not include the number of transfers in the covariate, it has the potential to influence the outcomes and the interpretation of the results. Third, although half of the total patients underwent RT, it included TRT, brain RT, and bone RT, which also affected the results of our analysis. Last, the

small number of patients receiving IT, along with the use of multiple anti-PD-1/PD-L1 agents, was likely to have impacted the analysis outcomes. Therefore, further large-scale studies are warranted to validate our results.

Conclusions

An increasing number of treatment options are being explored for ES-SCLC, and chemotherapy is the cornerstone. Our study demonstrated that both IT and RT can prolong survival in patients with ES-SCLC and have excellent safety profiles. In addition, these data reflect a synergistic effect between RT and anti-PD-1 agents. Despite some limitations, this combination therapy is worthy of further investigation for optimizing treatment strategies in patients with ES-SCLC.

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Authors' contributions
MS and HJ drafted the manuscript. YL and HJ were involved in conception and design. MS and HJ were involved in analysis and interpretation of data. MS, HJ, FD and NX were involved in data collection. JL provide comprehensive information about radiotherapy. All authors contributed in review, revise and approve the manuscript; and agree to be accountable to all aspects of the work.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due these data will be prepared for further studies, we will release relevant data when all the studies are completed, but are available from the corresponding author on reasonable request. To request data please contact Huaijun Ji (email: sdhzcxjhj@sina.com).

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee in Weihai Municipal Hospital of Shandong University. Because this study was retrospective, informed consent from the included patients was not required after the approved by the Medical Ethics Committee in Weihai Municipal Hospital of Shandong University, and patient information was anonymized. This study was conducted in accordance with the World Medical Association Declaration of Helsinki, Good Clinical Practices, and local ethical/legal requirements.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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