Discover Oncology

Analysis

Simultaneous integrated dose reduction intensity-modulated radiotherapy improves survival in patients with locally advanced non-small cell lung cancer by reducing cardiac irradiation exposure

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Abstract
The study aimed to evaluate the safety and efficacy of simultaneous integrated dose reduction intensity-modulated radiotherapy (SIR-IMRT) in patients with locally advanced non-small-cell lung cancer (LA-NSCLC). In the SIR-IMRT conhort, the prescribed irradiation dose was 60 Gray (Gy) for the planning gross tumor volume (PGTV) and 54 Gy for the planning target volume (PTV), while in the conventional intensity-modulated radiotherapy (C-IMRT) cohort, it was 60 Gy for both PGTV and PTV. The SIR-IMRT group demonstrated better overall survival (OS) than the C-IMRT group, with a median OS of 37.7 versus 31.2 months. The SIR-IMRT group also experienced lower cardiac and esophagusal doses, along with a lower incidence of acute radiation esophagitis and ≥ grade 3 radiation pneumonitis. HeartV20 (the volume of the heart receiving at least 20 Gy) was the only independent risk factor associated with survival. SIR-IMRT significantly reduced cardiac irradiation exposure, improving patient survival and offering a new therapeutic direction for future studies.

Keywords Non-small-cell lung cancer (NSCLC) · Intensity modulated radiotherapy (IMRT) · Simultaneous integrity dose reduction · Radiation oncology

1 Background

Non-small-cell lung cancer (NSCLC) accounts for nearly 80% of all lung cancer cases, which approximately 30% of NSCLC patients belong to locally advanced stage [10] [2]. According to the National Comprehensive Cancer Network (NCCN) guidelines, definitive concurrent chemoradiotherapy is the standard of care (category 1) for unresectable locally advanced stage NSCLC (LA-NSCLC) [7]. Although there has been some debate over fractionation schedules

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and doses in recent years, it appears that these efforts have not resulted in a significant survival benefit in high radiation dose studies. The RTOG 0617 trial demonstrated that increasing dose had a negative effect on overall survival, possibly due to a higher incidence of grade 3 or worse adverse events, especially higher cardiac doses, which were associated with poorer overall survival [1]. Kong FM et al. explored the high dose radiotherapy of 86 Gy/30f with adaptive radiotherapy guided by Positron Emission Tomography/Computed Tomography (PET/CT) [14], whereas 28% patients in this trial experienced cardiac adverse events. Subsequent studies confirmed that increasing the cardiac and especially the pericardial dose was associated with worse survival [29]. For patients with LA-NSCLC, it is undeniable that the maintenance of immunotherapy showed excellent survival benefits, as demonstrated by the PACIFIC study [24]. Toxicities are still a problem in the immunotherapy era, as radiotherapy-related toxicities continue to be a key factor in patients' inability to receive consolidation immunotherapy, which may hinder long-term survival benefits. [23] For example, 38% and 19% in the KEYNOTE-799 study in cohort A and B, respectively, discontinued treatment due to treatment-related adverse events [12]. High-dose radiotherapy appears to be a bottleneck in the immunotherapy era, which opens up possibilities for intensity modulated radiotherapy based simultaneous integrated dose reduction radiotherapy (SIR-IMRT). In this approach, a conventional radiation dosage is administered to the planning gross tumor volume (PGTV) and a reduced dose was delivered to the planning target volume (PTV). Our previous study showed that simultaneous dose reduction radiotherapy can reduce cardiac dose and improve survival in patients with limited-stage small cell lung cancer [17]. However, it remains unclear whether this effect applies to patients with non-small cell lung cancer. Thus, this study retrospectively analyzed LA-NSCLC patients who received SIR-IMRT and hypothesized that SIR-IMRT may significantly reduce the dose to normal tissues especially cardiac, and the incidence of toxicities without increasing the risk of tumor recurrence.

2 Methods

2.1 Data source

The data in this study were obtained from Tianjin Medical University Cancer Hospital and included the baseline characteristics of patients and disease, the details of treatments, progression-free survival (PFS) and overall survival (OS). All procedures of the study were in accordance with the Declaration of Helsinki. Patient data were obtained from the hospital's medical record system, so informed consent forms were not required.

2.2 Patients selection

From July 2013 to February 2019, a total of 307 patients with pathologically diagnosed NSCLC and staged as advanced by tumor node metastasis (TNM) and American Joint Committee on Cancer (AJCC) staging, who received radiotherapy were enrolled in this study as the initial study population. The inclusion criteria were as follows: (I) aged 18 to 70 years; (II) pathologically confirmed NSCLC; (III) clinical stage of T_{any} N_{any} M_0 based on the 8th edition of the AJCC TNM stage classification based on chest computed tomography (CT), emission computed tomography (ECT), head magnetic resonance imaging (MRI) and type-B ultrasound or Positron Emission Tomography/Computed Tomography (PET-CT); (IV) LA-NSCLC that was unresectable or recurrent after surgery; (V) Karnofsky performance status (KPS) score ≥ 70; (VI) Complete and available clinical data. Patients were excluded if they met the following criteria: (I) pathologically confirmed non-NSCLC; (II) radiation dose (delivered to PTV) < 60 Gy; (III) physical condition that could not tolerate radiotherapy. Propensity score matching (PSM) was used based on the differences among factors including age, gender, stage of disease and chemotherapy. After matching, a total of 246 patients meeting the inclusion criteria were identified and included in the study and categorized into 2 groups based on different PGTV dose: 93 patients in the C-IMRT group, and 153 patients in SIR-IMRT group.

2.3 Treatment for the patients

A large-aperture spiral CT simulator was conducted to perform positioning scans with a 3-mm slice thickness. The scanned area extended from the mastoid process to L1 vertebral body, and the images were transferred to the 3D planning system (ADAC Pinnacle® 8.0 m^3; Philips Medical Systems, Bothell, W A). The gross tumor volume (GTV), defined based on

post-chemotherapy imaging, included any visible primary tumor and positive lymph nodes observed on CT images. The PGTV was established by adding 5 mm margins around the GTV. Clinical target volume (CTV) was extended 5–10 mm margin from GTV and included high-risk lymph nodal regions and adjacent regions, as well as the ipsilateral hilar. An additional 5–10 mm margin to the CTV was used to define PTV. In this study, heart contouring was performed in accordance with the Radiation Therapy Oncology Group (RTOG) guidelines. The heart was delineated from the level of the inferior border of the pulmonary artery to the apex of the heart. The contour included the entire pericardium but excluded the great vessels (such as the ascending aorta and the pulmonary veins) to ensure accurate representation of the heart tissue without incorporating adjacent vascular structures. The delineation was done using axial slices from the planning CT scan, and care was taken to ensure consistent contouring across all patients. All enrolled patients underwent intensity-modulated radiotherapy (IMRT) in the spine position with a thermoplastic mask covering the chest. In the SIR-IMRT group, the prescribed radiation dose was 60 Gy for PGTV with 2.0 Gy/day, 5 fractions/week and 54 Gy for PTV with 1.8 Gy/day, 5 fractions/week. While in the C-IMRT group, the prescribed radiation dose was 60 Gy with 2.0 Gy/day, 5 fractions/week for both PGTV and PTV. The prescription dose covered more than 95% of target volumes. The normal tissue constrains were as follows: (I) total lung; V_{lung} 5 (percentage of the total lung that received over 5 Gy) ≤ 60%; $V_{lung}20 \leq 35\%$; $V_{lung}40 \leq 30\%$ (II) $V_{heart}30 \leq 40\%$; $V_{heart}40 \leq 30\%$; $V_{heart}50 \leq 60\%$ (III) $V_{esophagus}$ maximum ≤ 60 Gy (IV) V_{spinal} cord maximum ≤ 45 Gy.

2.4 Definition and evaluation of treatment outcomes

Short-term efficacy was considered a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the Response Evaluation Criteria in Solid Tumors version 1.1(RECIST 1.1). Overall Survival (OS) is defined as the time from pathological diagnosis to the last follow-up or death, and progression-free survival (PFS) is defined as the time from treatment initiation to progression or death, or the last follow-up. Local recurrence free survival (LRFS) is defined as the time from treatment initiation to local relapse or death, or the last follow-up. Radiation-induced toxicities were defined according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Radiation pneumonitis (RP) was diagnosed based on clinical symptoms and imaging findings typically within 1 to 6 months after radiotherapy. Radiation esophagitis (RE) was assessed during treatment, manifesting 2–3 weeks after initiation, and was graded according to swallowing difficulty and esophageal injury. Myelosuppression was monitored through weekly blood counts during and up to 3 months post-treatment, with severity graded by reductions in hemoglobin, platelets, and leukocytes. Radiation-induced cardiac disease (RICD) was evaluated through routine cardiac imaging (ECG, echocardiography) and symptom tracking, with follow-up at 3 months, 6 months, and annually thereafter, capturing conditions like pericarditis, coronary artery disease, and cardiomyopathy. Based on the CTCAE version 4.0, all radiation-related cardiac, esophageal, and pulmonary toxicities, as well as myelosuppression, were observed by two or three oncologists to assess the toxicity type and severity.

2.5 Statistical analysis

The statistical analysis was carried out using SPSS software version 25.0 (SPSS, Inc., Chicago, IL, USA) and R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Propensity score matching (PSM) with 1:2 (C-IMRT:SIR-IMRT) was performed based on the factors including age, gender, stage of disease, KPS, chemotherapy, and GTV before treatment through logistic regression estimation algorithm with a caliper width of 0.2 of the standard deviation. Differences in baseline characteristics between the two groups were analyzed by chi-square test. Kaplan–Meier analyses were used to assess OS, PFS, and LRFS, while cumulative incidence was calculated and compared for event-specific outcomes. Log-rank tests were used to measure and compare survival outcomes. Univariate and multivariate Cox regression analyses were used to analyze the effect of the dosimetric parameters on survival. A p-value of < 0.05 was considered to represent statistical significance.

3 Results

3.1 Patient population and characteristic

After PS matching, 246 patients were included with 93 in C-IMRT group and 153 in SIR-IMRT. A total of 192 males (77.7%) and 54 females (22.3%) were included in the study with a median age of 61 years. All the participants who evolved were

not admitted to concurrent immunotherapy or targeted therapy. The basic characteristics of the eligible patients are summarized in Table 1. There were no significant differences among all basic characters ($P < 0.05$). Table S1 shows the details of before and after PSM.

3.2 Survival outcomes

With a median follow up of 45.8 months, the overall response rate (CR + PR) was 58.2% in SIR-IMRT group and 52.9% in C-IMRT group after thoracic radiotherapy. The details of the response outcomes are presented in Fig. 1A. The median survival of the entire cohort was 32.5 months (95% CI 26.5–38.5 months), and the median PFS was 10.1 months (95% CI 7.7–12.4 months) with 11.9 months (95% CI 8.8–15.0 months) of the median LRFS. In SIR-IMRT group, the median OS was 37.7 months (95% CI 28.9–46.5 months), while the median PFS and LRFS were 10.8 months (95% CI 7.1–14.5 months) and 13.6 months (95% CI 10.4–16.9 months), respectively. In the C-IMRT group, the median OS was 31.2 months (95% CI 21.8–40.7 months), while the median PFS and LRFS were 5.3 months (95% CI 0.3–10.4 months) and 8.0 months (95% CI 2.3–13.6 months), respectively. The 1-, 2-, 3- and 5-year OS rates in SIR-IMRT group were 83.0%, 65.3%, 51.8% and 40.8%, respectively. In the C-IMRT group the 1-, 2-, 3- and 5-year OS rates were 66.7%, 49.5%, 37.3% and 13.9%, retrospectively. To further analyze the survival outcomes obtained by C-IMRT, we performed a subgroup analysis based on whether patients received induction chemotherapy or not. As shown in Figure S1, there was no significant difference in survival outcomes between the groups. In the induction chemotherapy group, the 1-, 2-, 3-, and 5-year OS rates were 62.9%, 44.3%, 30.8%, and 12.9%, respectively. The 1, 2, 3 and 5 years of PFS rates of SIR-IMRT were 46.8%, 23.3%, 14.6% and 12.4%, retrospectively. For the C-IMRT group, the 1, 2, 3 and 5 years of PFS rates were 41.4%, 21.9%, 12.3% and 0%. The 1, 2, 3 and 5 years of LRFS rates of SIR-IMRT were 52.3%, 28.1%, 18.2% and 14.4%, retrospectively. And for C-IMRT group, the 1, 2, 3 and 5 years of LRFS rates of C-IMRT were 45.0%, 24.1%, 16.0% and 0%, retrospectively. For SIR-IMRT group, the OS was significantly higher than C-IMRT group ($P < 0.001$), while statistical differences were not found in PFS and LRFS ($P = 0.070$, $P = 0.079$). The survival outcomes were shown in Fig. 1B–D.

3.3 Patterns of failure

During follow-up periods, 156 patients experienced disease progression. 21.5% of the patients experienced first failure at the local site alone, while 23.2% of the patients developed distant metastasis as the first site of failure. The details of the failure patterns are shown in Table 2. No differences were observed in the failure patterns between the SIR-IMRT and C-IMRT groups ($P > 0.05$).

3.4 Toxicities

Then we analyzed the incidence of commonly observed treatment-related toxicities, including radiation pneumonitis, radiation esophagitis, radiation-induced cardiac disease, and myelosuppression. As shown in Fig. 2, the SIR-IMRT group had a significantly lower incidence of esophagitis than the C-IMRT group (56.9% vs 78.5%, $P = 0.001$). The SIR-IMRT group had a significantly lower incidence of grade ≥ 3 radiation pneumonia and myelosuppression (0.7% vs 5.4%, $P = 0.02$; 9.8% vs 19.4%, $P = 0.033$), but there was no difference in the incidence of radiation induced cardiac disease at any level, which could be attributed to the lower number of patients in each group who experienced adverse cardiac injury events. A further comparison of the cumulative incidence of radiation-induced cardiac disease between the C-IMRT and SIR-IMRT groups revealed no significant difference ($P = 0.13$; Fig. 3). The observed RICD events in this study included arrhythmias, coronary artery disease (CAD), pericardial effusion, and radiation-induced cardiomyopathy. Among these, arrhythmias were the most frequently observed, with a total of 25 cases recorded across the entire cohort. These arrhythmias encompassed conditions such as tachycardia, bradycardia, sick sinus syndrome, conduction blocks, and QT interval prolongation. The distribution of specific cardiac events between the two groups is detailed in Table S3.

3.5 Dose of organs at risk (OARs)

Dose–volume histogram (DVH) was used to evaluate the isodose distribution of dose of organs at risk (OARs). Lower normal tissue-sparing parameters were found in the SIR-IMRT group than that in the C-IMRT group. Comparison of dose of OARs between the two groups were shown in Table 3. The dose delivered to pulmonary and cardiac,

Table 1 Baseline characteristics of all the patients involved

Characteristics		Total (%)	SIR-IMRT (%)	C-IMRT (%)	P-value
Age, y	< 60	103 (41.9)	61 (39.9)	42 (45.2)	0.946
	≥ 60	143 (58.1)	92 (60.1)	51 (54.8)	
Gender	Male	192 (78.0)	117 (76.4)	75 (80.6)	0.438
	Female	54 (22.0)	36 (23.6)	18 (19.4)	
KPS	< 80	13 (5.3)	7 (4.6)	6 (6.5)	0.403
	≥ 80	233 (94.7)	146 (95.4)	87 (93.5)	
Clinical stage	IIIa	91 (37.0)	59 (38.6)	32 (34.4)	0.198
	IIIb	131 (53.3)	83 (54.2)	48 (51.6)	
	IIIc	24 (15.7)	11 (7.2)	13 (14.0)	
Tumor location	Left lobe	109 (44.3)	70 (45.8)	39 (41.9)	0.559
	Right lobe	137 (55.7)	83 (54.2)	54 (58.1)	
Tumor location	Upper lobe	166 (67.5)	101 (66.0)	65 (69.9)	0.530
	Lower lobe	80 (32.5)	52 (34.0)	28 (30.1)	
Operation	Yes	52 (21.1)	29 (19.0)	23 (24.7)	0.343
	No	194 (78.9)	124 (81.0)	70 (75.3)	
Induction chemotherapy	Yes	197 (80.0)	127 (83.0)	70 (75.3)	0.141
	No	49 (20.0)	26 (17.0)	23 (24.7)	
Cycle of induction chemotherapy	1–2	87 (44.2)	54 (42.5)	33 (47.1)	0.347
	3–4	87 (44.2)	59 (46.5)	28 (40.0)	
	5–6	23 (11.6)	14 (11.0)	9 (12.9)	
Details of induction chemotherapy	AP	73 (37.1)	48 (37.8)	25 (35.7)	0.761
	TP	78 (39.6)	53 (41.8)	25 (35.7)	
	DP	21 (10.7)	12 (9.4)	9 (12.9)	
	EP	3 (1.5)	1 (0.8)	2 (2.9)	
	GP	19 (9.6)	12 (9.4)	7 (9.0)	
	VP	3 (1.5)	1 (0.8)	2 (2.9)	
Concurrent chemotherapy	Yes	64 (26.0)	35 (22.9)	29 (31.2)	0.294
	No	182 (74.0)	118 (77.1)	64 (68.8)	
Cycle of Concurrent Chemotherapy	1–2	49 (76.6)	27 (77.1)	22 (75.9)	0.190
	3–4	15 (23.4)	8 (22.9)	7 (24.1)	
Details of concurrent chemotherapy	AP	16 (25.0)	8 (22.9)	8 (27.7)	0.280
	TP	20 (31.1)	11 (31.4)	9 (31.0)	
	DP	7 (10.9)	4 (11.4)	3 (10.3)	
	EP	6 (9.4)	2 (5.7)	4 (13.8)	
	GP	5 (7.8)	5 (14.3)	0 (0.0)	
	D	10 (15.6)	5 (14.3)	5 (17.2)	
GTV before treatment	< 65	153 (62.2)	95 (62.1)	58 (62.4)	0.913
	≥ 65	93 (37.8)	58 (37.9)	35 (37.6)	

SIR-IMRT simultaneous integrated dose reduction intensity-modulated radiotherapy, *C-IMRT* conventional intensity-modulated radiotherapy, *KPS* Karnofsky performance status, *AP* Pemetrexed plus cisplatin/carboplatin, *TP* Paclitaxel plus cisplatin/carboplatin, *DP* Docetaxel plus cisplatin/carboplatin, *EP* Etoposide plus cisplatin/carboplatin, *GP* Gemcitabine plus cisplatin/carboplatin, *VP* Vincristine plus cisplatin/carboplatin, *D* Docetaxel

esophageal and spinal cord for patients underwent SIR-IMRT were lower than that in C-IMRT group, the mean heart dose (MHD) ($P = 0.020$), Heart V20 ($P = 0.028$), Heart V50 ($P = 0.04$), Heart D50 ($P = 0.009$), maximum esophagus dose (ESO D_{max}) ($P = 0.007$), ESO V5-V10 ($P = 0.021$; $P = 0.048$) and ESO D5-D10 ($P = 0.001$; $P = 0.006$), especially, were significantly lower than that in C-IMRT group.

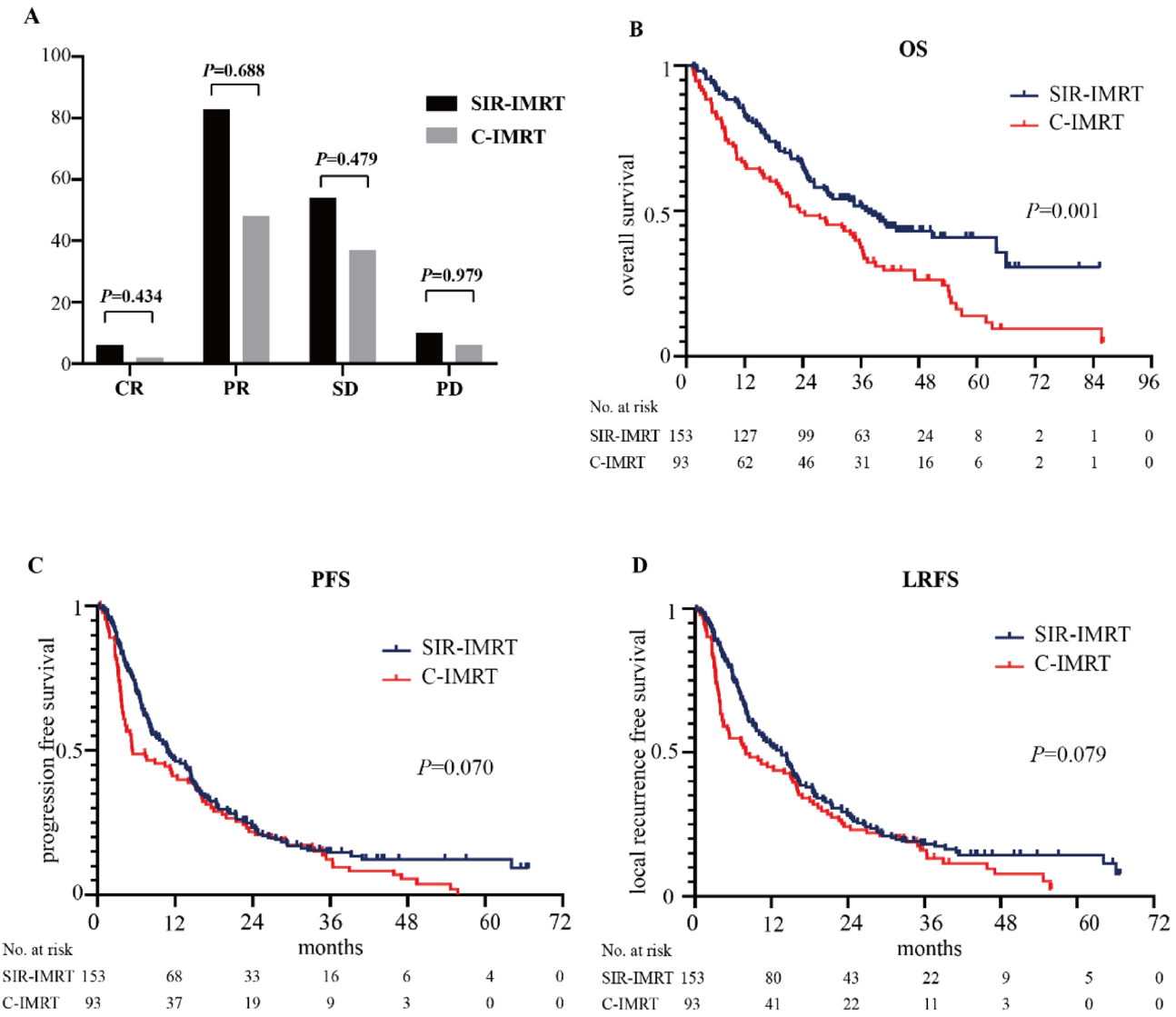

Fig. 1 Treatment response and survival outcomes. **A** Treatment response comparison between SIR-IMRT and C-IMRT groups; **B** Kaplan–Meier curves for overall survival (OS) in SIR-IMRT vs. C-IMRT; **C** Kaplan–Meier curves for progression-free survival (PFS) between the two groups; **D** Kaplan–Meier curves for locoregional recurrence-free survival (LRFS) between the two groups

Table 2 Comparison of patterns of failure in patients between C-IMRT and SIR-IMRT group

Failure site		Total, n = 246(%)	SIR-IMRT, n = 153(%)	C-IMRT, n = 93(%)	*P* value
Any failure		167(67.9)	102(66.6)	65(69.9)	0.599
Locoregional in field		64 (26.0)	40(26.1)	24(25.7)	0.953
Locoregional out of field		25(10.2)	18(11.8)	7(7.5)	0.286
Locoregional in and out of field		10(4.1)	8(5.2)	2(2.2)	0.327
Distant metastasis only	Bone	14(5.7)	6(3.9)	8(8.6)	0.157
	Brain	17(6.9)	11(7.2)	6(6.5)	0.825
	Liver	6(2.4)	4(2.6)	2(2.2)	0.819
	Adrenal	6(2.4)	2(1.3)	4(4.3)	0.203
	Others	14(5.7)	6(3.9)	8(8.6)	0.124
Locoregional and Distant metastasis		11(4.5)	7(4.6)	4(4.3)	0.920

SIR-IMRT simultaneous integrated dose reduction intensity-modulated radiotherapy, *C-IMRT* conventional intensity-modulated radiotherapy;

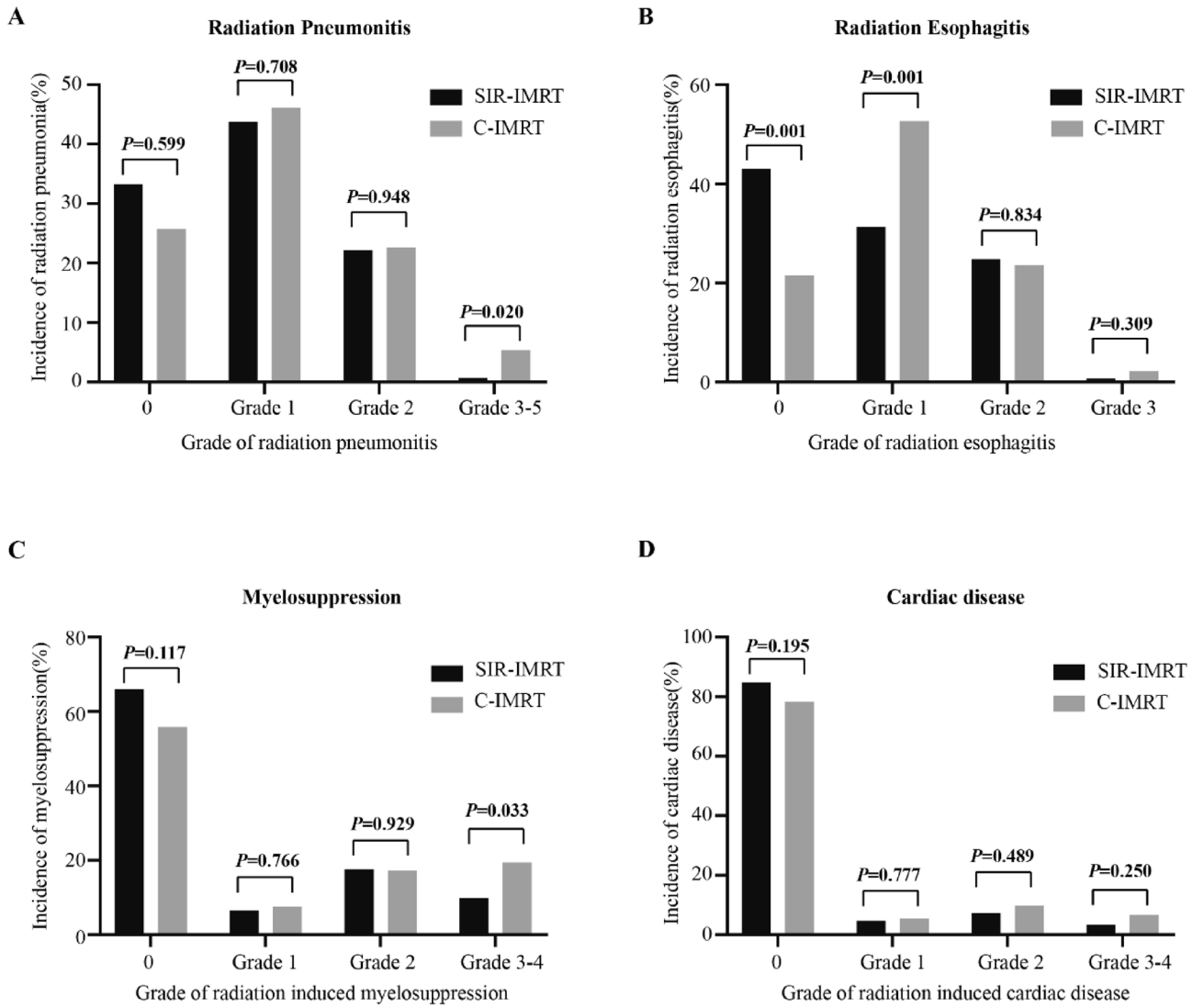

Fig. 2 Comparison of radiation induced toxicities between the C-IMRT and SIR-IMRT groups. **A** Radiation pneumonitis, **B** Radiation esophagitis, **C** Radiation induced myelosuppression, and **D** Radiation induced cardiac disease

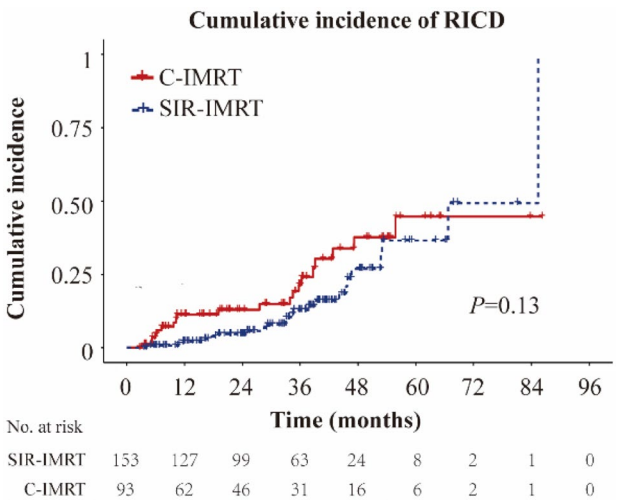

Fig. 3 Cumulative incidence of radiation-induced cardiac disease (RICD) in C-IMRT and SIR-IMRT groups

Table 3 Comparison of dose of organs at risk between the SIR-IMRT and C-IMRT group

variables	SIR-IMRT (n = 153)	C-IMRT (n = 93)	P values
Mean lung dose (Gy)	12.36 ± 2.71	13.08 ± 2.91	0.055
Lung V5 (%)	43.88 ± 9.95	44.54 ± 11.19	0.640
LungV10 (%)	33.36 ± 7.69	33.47 ± 9.10	0.920
LungV20 (%)	22.99 ± 4.94	22.92 ± 5.94	0.926
Lung V30 (%)	16.09 ± 3.99	16.37 ± 4.46	0.628
Lung V40 (%)	10.88 ± 3.76	10.66 ± 4.50	0.686
Lung V50 (%)	6.42 ± 3.05	6.91 ± 3.21	0.233
Lung D5(Gy)	50.56 ± 10.29	49.99 ± 11.88	0.692
Lung D10(Gy)	42.25 ± 10.11	39.72 ± 12.16	0.080
Lung D20(Gy)	24.82 ± 7.71	23.45 ± 8.10	0.192
Lung D30(Gy)	13.77 ± 5.14	14.46 ± 5.15	0.307
Lung D40(Gy)	7.67 ± 3.48	8.36 ± 3.30	0.125
Lung D50(Gy)	4.19 ± 2.11	4.77 ± 2.37	0.052
Mean heart dose (Gy)	13.02 ± 8.79	15.48 ± 7.44	0.020*
Heart V5 (%)	43.41 ± 23.31	46.84 ± 27.26	0.296
Heart V10 (%)	33.24 ± 20.38	36.78 ± 24.45	0.222
Heart V20 (%)	24.95 ± 18.19	30.34 ± 18.68	0.028*
Heart V30 (%)	17.26 ± 12.29	20.40 ± 13.11	0.064
Heart V40 (%)	11.17 ± 8.67	12.80 ± 8.90	0.162
Heart V50 (%)	5.63 ± 4.90	7.01 ± 5.19	0.040*
Heart D5(Gy)	42.62 ± 15.11	42.84 ± 17.32	0.916
Heart D10(Gy)	30.04 ± 13.46	33.00 ± 16.86	0.130
Heart D20(Gy)	19.78 ± 11.69	22.22 ± 15.35	0.162
Heart D30(Gy)	14.01 ± 10.71	14.89 ± 12.50	0.574
Heart D40(Gy)	8.58 ± 7.57	10.10 ± 9.81	0.177
Heart D50(Gy)	4.86 ± 4.55	6.94 ± 7.84	0.009*
Esophagus D_{max} (Gy)	58.75 ± 13.33	70.28 ± 7.21	0.007*
Esophagus V5 (%)	61.34 ± 21.40	67.37 ± 18.68	0.021*
Esophagus V10 (%)	55.67 ± 21.19	60.85 ± 18.91	0.048*
Esophagus V20 (%)	49.48 ± 21.00	52.85 ± 17.83	0.180
Esophagus V30 (%)	44.12 ± 20.71	46.35 ± 18.32	0.378
Esophagus V40 (%)	38.18 ± 20.24	39.57 ± 18.60	0.582
Esophagus V50 (%)	29.57 ± 18.45	30.44 ± 18.01	0.716
Esophagus D5(Gy)	54.13 ± 13.52	59.04 ± 7.39	0.001*
Esophagus D10(Gy)	52.21 ± 13.72	56.63 ± 8.61	0.006*
Esophagus D20(Gy)	51.55 ± 13.47	51.93 ± 11.61	0.918
Esophagus D30(Gy)	45.35 ± 24.87	44.87 ± 15.82	0.922
Esophagus D40(Gy)	34.35 ± 19.67	36.12 ± 18.59	0.487
Esophagus D50(Gy)	25.03 ± 19.94	25.58 ± 18.81	0.827
Trachea (Gy)	61.61 ± 8.26	61.06 ± 12.41	0.724
Spinal cord D_{max} (Gy)	36.60 ± 6.65	37.57 ± 9.79	0.363

SIR-IMRT simultaneous integrated dose reduction intensity-modulated radiotherapy, *C-IMRT* conventional intensity-modulated radiotherapy;

Lung V5: Percentage of the total lung that received over 5 Gy;

Lung D5: Dose received by 5% volume of the total lung;

Additionally, when analyzing the dosimetric parameters across different tumor locations, there were no significant differences between left and right lobes in both overall patients and within the SIR-IMRT and C-IMRT groups (Table S2). However, when comparing upper vs. lower lobes, significant differences were observed. Specifically, doses to the lung V5 ($P = 0.003$, SIR-IMRT group) and lung V10 ($P = 0.007$, SIR-IMRT group) were significantly higher in upper lobe tumors. Similarly, heart doses, including heart V5 ($P < 0.001$) and heart V10 ($P < 0.001$), were also higher in lower lobe tumors across all patients and within the SIR-IMRT group.

Table 3 (continued) Esophagus D_{max}: Maximum esophagus dose;
*Means there was significant differences between the two group

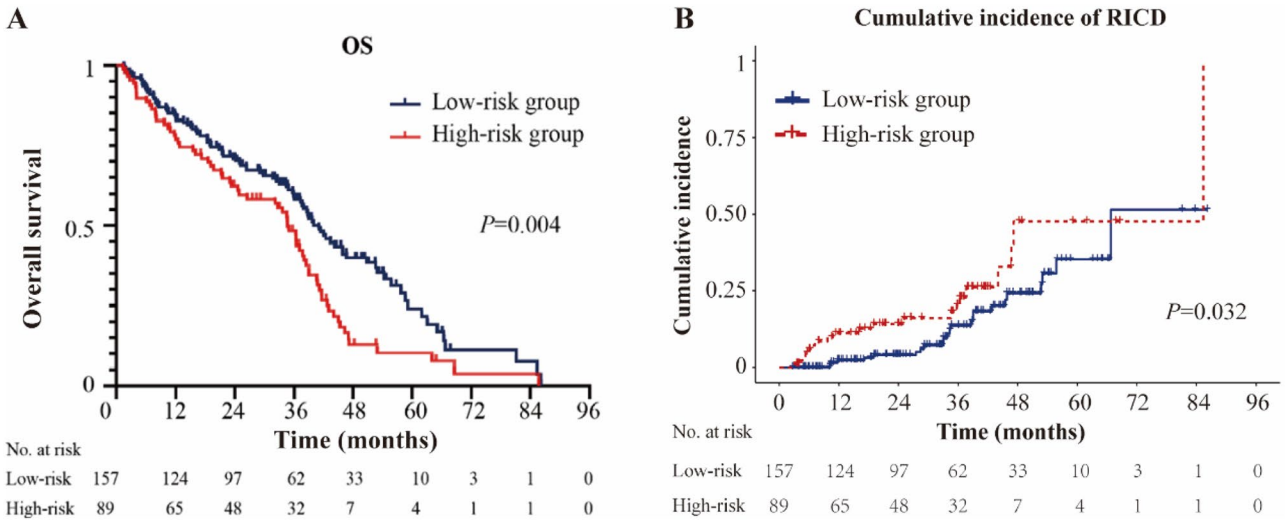

Fig. 4 Comparison of overall survival (OS) and cumulative incidence of radiation-induced cardiac disease (RICD) between low-risk and high-risk groups based on Heart V20. **A** OS, **B** Cumulative incidence of RICD

3.6 The effect of the dosimetric parameters on survival

To determine whether dosimetric parameters have an impact on survival in patients with LA-NSCLC, we use univariate Cox regression analysis, and showed that Lung V5, Lung V20-30, Lung D5, Heart V20-V40 were risk factors associated with patient survival. Other factors were not significantly correlated with survival (Table S4). Multivariate Cox regression analysis showed that Heart V20 was the only independent risk factor associated with patient survival with Hazard ratio of 1.008 (> 1) suggesting that increasing Heart V20 may raise the risk of disease progression or patient death (Table S4).

To further assess whether the higher dosimetric parameters observed for lower lobe tumors, particularly higher heart doses, would translate into worse survival outcomes, we performed Kaplan–Meier survival analysis comparing outcomes by tumor location (Figure S2-S4). Despite significantly higher lung and heart doses for lower lobe tumors—especially in the SIR-IMRT group (lung V5, P = 0.003; lung V10, P = 0.007; heart V5, P < 0.001; heart V10, P < 0.001)—there were no significant differences in OS, PFS, or LRFS between upper and lower lobes or between left and right lobes in either the SIR-IMRT or C-IMRT groups. These findings indicate that, although heart doses are higher for lower lobe tumors compared to upper lobe tumors, the survival benefit observed in the SIR-IMRT group is unlikely to be influenced by tumor location.

3.7 Predictive value of heart V20 in the prognosis of LA-NSCLC patients

Finally, to determine the accuracy and stability of Heart V20 prognosis prediction for LA-NSCLC patients, we divided the 246 patients into two groups (high risk or low risk group) based on the cut off value (Heat V20 > 29.5 Gy or < 29.5 Gy) obtained from the Heart V20 ROC curves (Figure S5). The Kaplan–Meier analysis (Fig. 4A) showed that the 1-, 2-, 3-, 5-year OS rates of the low-risk group (n = 157) were 83.7%, 71.0%, 59.4% and 24.0%, respectively, which were significantly better than those for high-risk group 76.9%, 62.3%, 48.4%, 12.8% ($P = 0.004$). The cumulative incidence of RICD at 1-, 2-, 3-, 5-year was 2.17%, 4.0%, 13.6% and 35.3% in low-risk group and 11.2%, 14.2%, 20.4% and 47.7% in high-risk group ($P = 0.032$; Fig. 4B). This analysis demonstrates a significant correlation between higher Heart V20 values and increased cumulative incidence of RICD, reinforcing the impact of heart dose on cardiac events.

4 Discussion

From RTOG 7301[21], which proposed radiation therapy's key role in the treatment of LA-NSCLC, to GALGB 8433 [6] and RTOG 9410 [4], which indicated that concurrent chemo-radiotherapy is more beneficial than sequential chemo-radiotherapy. Concurrent radiotherapy, on the other hand, has a higher incidence of cardiac and pulmonary damage than radiotherapy alone [4], limiting its value for some patients. Furthermore, it is consensus that increasing the absolute dose of radiotherapy may improve efficacy, while trials with increasing doses do not improve efficacy due to increased adverse effects, particularly cardiac and pulmonary damage [1]. In the LUNG ART study, 16% of patients experienced cardiopulmonary toxicity and thus did not improve overall survival [15]. While both immune maintenance therapy, (PACIFIC [24] and ETOP NICOLAS [22] studies), and neoadjuvant immunotherapy, (KEY-NOTE799 [12] and DETERRED studies [16]), face challenges with the high rate of treatment-related adverse events. As a result, in the age of immunotherapy, reducing the incidence of adverse events, particularly cardiopulmonary adverse events, is a hot topic of radiotherapy, which brings new opportunities for SIR-IMRT attempts. In SIR-IMRT, a conventional radiation dose of 60 Gy was administered to the PGTV and a reduced dose of 54 Gy was delivered to the PTV, and the study found that SIR-IMRT may reduce the radiation dose to normal tissues and thus limit damage while maintaining good local control and survival benefits; however, further confirmation in randomized controlled trials is warranted.

Our study discovered that the SIR-IMRT group had better OS than the C-IMRT group, with median OS 37.7 vs 31.2 months ($P = 0.001$), while PFS and LRFS did not show statistically significant differences between in the two groups, indicating that SIR-IMRT is not only satisfactory in terms of local control, but also has some survival advantage compared to conventional 60 Gy radiotherapy.

This result is also better than any other cohort in the RTOG 0617 trial [1], with mOS of 20.3 months vs. 28.7 months for each group, suggesting that SIR treatment is more likely to benefit LA-NSCLC patients than high doses or even regular doses of radiation. However, the results were poorer than in the PACIFIC trial. Although the median OS of the C-IMRT group was similar to the results of the PACIFIC study at 29.1 months [24], its 1-, 3-, and 5-year survival rates were still inferior. To examine such discrepancies, we performed a subgroup analysis and found that 70 of the C-IMRT patients received induction chemotherapy. According to the CALGB8433 [6] and RTOG9410 trials [4], concurrent chemo-radiation is more effective than induction radiotherapy, which might explain why the C-IMRT group had a lower survival rate in our study even though the survival between induction chemotherapy and non-induction chemotherapy group was not statistically different in this study, probably contributing to the limited sample size. The 5-year survival rate in the sequential chemotherapy group was 12.9%, which is comparable to the 5-year survival rates of 13.7% in the CALGB 8433 trial [6] and 14.6% in RTOG 9410 [4], further suggesting the low survival rate might be attributed to the large number of patients who underwent induction chemotherapy. Furthermore, the patients in the PACIFIC study were all stage IIIA patients in good health quality, but only around one-third of the patients in our study were stage IIIA, and only 23 patients underwent concurrent chemo-radiotherapy, which may result in lower results than the PACIFIC data [24]. In this study, the five-year survival rate in the SIR-IMRT group was 40.8%, which might be attributed to the fact that some patients received immunotherapy and targeted treatment during the follow-up period, as well as the fact that some patients did not reach the 5-year endpoint. Although there was no statistically significant difference in PFS and LRFS between the two groups, the SIR-IMRT group had more patients with PFS or LRFS > 60 months than the C-IMRT group, with two patients benefiting from EGFR-TKI and two achieving CR after chemo-radiotherapy. Therefore, we speculate that SIR-IMRT may offer patients the opportunity to better combine targeted therapy or immunotherapy compared to conventional radiotherapy.

The high risk of adverse events is one of the problems with immune combination therapy. The PACIFIC study reported a 33.9% incidence of any grade of pneumonia, with a 3.6% incidence of grade III or more severe pneumonia [24]. In real world study of durvalumab, the incidence of pneumonia was even higher with 33.9% incidence of any grade and 6% in grade III or more severe pneumonia [27]. In KEY-NOTE 799 study, the adverse event rates did not decrease with grade 3–5 adverse event rates of 64.3% in cohort A and 50.0% in cohort B [12]. The ETOP NICOLAS study had an even higher incidence of grade 3 and higher pneumonia at 11.7% [22]. Several studies have now proven that radiation pneumonia has a direct impact on patients' outcomes and quality of life [18, 28]. This study found that the SIR-IMRT group had a lower incidence of grade 3 or more severe pneumonia compared to the control group. Although no statistically significant differences in lung dosimetric parameters were found between the two groups, the lung dose was still lower in the SIR-IMRT group than in the control group. MLD is now thought to be the most prevalent and effective risk factor for radiation pneumonia [13]. In this study, the SIR-IMRT group had a lower MLD, which might explain why the SIR-IMRT group had a

reduced incidence of grade 3 or higher pneumonia. Furthermore, the SIR-IMRT group showed lower rates of radiation esophagitis. This is consistent with the findings for dosimetric parameters, which showed that SIR-IMRT significantly lowered ESOmax, ESOV5-10, and ESOD5-10.

Although there was no significant difference in the incidence of adverse cardiac events between the two groups, we discovered that SIR-IMRT significantly reduced MHD and HeartV20, and subsequent Cox analysis revealed that Heart V20 was the only independent risk factor for LA-NSCLC. According to the results of RTOG0617 [1], a high cardiac dose was associated with a lower survival rate. Several subsequent retrospective studies on breast cancer, esophageal cancer, and lymphoma have also identified the relationship between severe cardiac events and poor prognosis [5, 9, 25]. Immunosuppression from cardiac irradiation may now be one of the key determinants of poor prognosis in the era of immunotherapy. According to current research, increasing vascularized volumes exposed to long courses of fractionated radiation increase lymphopenia [3, 11], and this decrease in lymphocytes, as well as an increase in neutrophil count, are linked with a poor prognosis in the treatment of non-small cell lung cancer [3, 19]. According to a recent study, significant lymphopenia following concurrent radiotherapy is related to faster disease progression in patients with NSCLC treated with immunotherapy [8]. Since immune checkpoint inhibitors rely on T-cells for their anticancer action, reducing the amount of cardiac irradiation may minimize the incidence of lymphopenia and therefore achieve higher immunotherapy efficacy. This may potentially give an opportunity to investigate the combination of SIR-IMRT and immunotherapy, though the ideal modalities for combining radiation and immunotherapy are still not fully understood [28]. We observed significant differences in dosimetric parameters between upper and lower lobes, particularly in the SIR-IMRT group, where lower lobe tumors received higher heart doses. However, the results showed no significant differences in OS, PFS, or LRFS between upper and lower lobes or between left and right lobes in either the SIR-IMRT or C-IMRT groups. The lack of survival differences, despite higher heart doses in lower lobe tumors, suggests that the heart-sparing strategies employed in SIR-IMRT effectively mitigate the impact of increased radiation exposure. This aligns with our earlier findings, where heart V20 was identified as an independent predictor of survival. The results indicate that, although tumor location influences dosimetric parameters, it does not significantly affect survival outcomes when heart doses are adequately controlled.

A number of studies have been conducted to investigate dose reduction for PTV; nevertheless, the majority of them are SIB-IMRT, with higher doses for PGTV over 60 Gy and lower doses for PTV below 60 Gy. [20, 26] However, because these studies had small sample sizes or were limited by short-term follow-up time and lacked long-term follow-up data, it is unclear if higher dose to affect the the tumor immune microenvironment and the patient's subsequent maintenance treatment. Our findings show that giving standard doses of 60 Gy to PGTV and reduced doses to PTV is enough to provide a good survival benefit. Many prospective clinical trials such as NCT04500145 and NCT04398199 for dose reduction to subclinical lesions are now ongoing, and it is believed that these prospective data will give some support for new therapy concepts for patients with LA-NSCLC.

This study still has some limitations. While we implemented PSM to reduce bias, the retrospective nature of the study inevitably introduces some variability, particularly in the chemotherapy regimens used across groups. Differences in treatment protocols, though minimized through PSM, may still affect the outcomes and introduce potential bias. Future prospective studies with standardized treatment protocols are necessary to more accurately evaluate the efficacy and safety of the therapeutic interventions used. Although the SIR-IMRT group had a superior survival benefit and lower radiation exposures to OARs such as the heart, lung, and esophagus, further prospective studies are needed to evaluate the efficacy and safety of SIR in combination with immunotherapy. Additionally, the relatively low incidence of cardiac events observed in this cohort underscores the need for further investigation. This may be partly due to the variability in baseline cardiac conditions among patients and incomplete historical data, which limited our ability to conduct a more detailed competing risk analysis. Furthermore, the long latency of radiation-induced cardiac damage, typically taking 10–15 years to manifest, means that many cardiac events may not have appeared yet. As overall survival improves with the advent of immunotherapy, long-term cardiac effects are becoming more apparent, emphasizing the importance of future studies to clarify the impact of heart dose and its interaction with immunotherapy on long-term cardiac outcomes. In conclusion, this study discovered that SIR-IMRT considerably reduced the dose of radiation to the heart, improving patient survival and giving a new therapeutic idea for future research into immune-combined radiotherapy.

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Author contributions Chang Xu & Jiehan Wu: Conceptualization, Formal analysis, Writing—Original Draft; Bingxin Liu: Statistical analysis and Manuscript language editing; Hanheng Meng: Methodology, Writing—Original Draft; Lujun Zhao& Ping Wang: Data Collection and Curation, Project administration; Jifeng Sun: Data Collection and Curation; Jun Wang& Ningbo Liu: Supervision, Validation, Writing—Review & Editing.

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Data availability The datasets generated and analyzed during the current study are not publicly available due to patient privacy concerns, as the data were obtained from a hospital setting. However, the data are available from the corresponding author upon reasonable request, in compliance with institutional and ethical guidelines.

Declarations

Ethics approval and consent to participate All participants in this study provided informed consent, fully understanding the study's purpose, procedures, and their rights. Consent for publishing anonymized results was also obtained. This research was carried out in strict adherence to the protocol established by the Ethics Committee of Central Lab- oratory, College of Public Health, Cancer Hospital of Tianjin Medical University, National Cancer Clin-ical Medical Research Center, Tianjin, China. All the experimental procedures in this study were in accordance with the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

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