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Consolidation ICIs Alter cardiac subregion radiosensitivity in NSCLC patients treated with Chemo-Radiotherapy

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ABSTRACT

Purpose: he addition of immune checkpoint inhibitor (ICI) as consolidation therapy after chemoradiation (CRT) has improved survival rates in non-small cell lung cancer (NSCLC) patients. However, the cardiotoxicity of CRT combined with ICI remains underexplored. This study assesses if ICI exposure alters the critical cardiac subregion linked to radiation-induced heart disease (RIHD) following CRT.

Methods: We conducted a retrospective analysis of 321 locally advanced NSCLC patients treated with definitive CRT from August 2008 to December 2019, including 67 who received consolidation ICI. Cardiac contours include the entire heart, chambers, major coronary arteries, and conduction nodes. The primary endpoint was RIHD, defined as a major adverse cardiac event and atrial fibrillation. We used Fine-Gray analysis to investigate associations between RIHD and mean doses to cardiac subregions.

Results: In total, 53 patients (18.4 %) developed RIHD, with no significant difference between CRT and CRT + ICI groups. Doses to cardiac subregions were similar between the groups. In the CRT group, multivariable analysis shows that dose to the base of the heart, especially the sinoatrial node (SAN), correlated with increased RIHD risk (HR = 1.02 per 1 Gy, 95 %CI [1.01–1.03], $p < 0.001$). In the CRT + IO group, the left ventricle (LV) dose was a significant predictor (1.06 [1.06–1.1], $p = 0.006$).

Conclusions: Doses to the SAN and the base of the heart correlate with RIHD in CRT patients, while doses to LV in CRT + ICI patients. While the 2–6 % increased risk per Gy seems modest, it is clinically significant as the subregions, being small structures, can potentially be completely spared with a carefully optimized plan.

1. Introduction

Chemoradiation therapy (CRT) is the main treatment for inoperable locally advanced non-small cell lung cancer (NSCLC)[1]. Recently, the addition of immune checkpoint inhibitors (ICIs) as consolidation therapy after CRT has emerged as a new standard of care, markedly improving survival rates[2–4].

Cardiac toxicity has always been a significant concern for lung cancer patients undergoing CRT, as the heart is often exposed to high radiation doses[5–7]. The RTOG 0617 trial highlighted the delicate balance between improving tumor control and minimizing damage to surrounding healthy tissues, and the increased heart exposure in the higher dose (74 Gy) arm was linked to greater cardiac toxicity[8,9]. Following RTOG 0617, numerous studies have shown that higher doses

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to the heart and its substructures are associated with an increased risk of radiation-induced heart disease (RIHD)[10–14]. While the impact of CRT on cardiac toxicity has been thoroughly investigated, the addition of ICI to the treatment regimen necessitates a reevaluation of these risks for two reasons:

First, ICIs have been shown to induce cardiotoxicity independently [15,16]. The use of ICIs has been reported to cause cardiac side effects such as myocarditis, heart failure with left ventricular dysfunction, or heart fibrosis[17–20]. The mechanisms behind ICI-related cardiac toxicity are poorly understood. ICI drugs work by modifying the immune system's response to cancer, especially T cells, but this can inadvertently lead to inflammatory or autoimmune reactions affecting the heart[21]. CTLA-4, PD-1, and PD-L1 signaling appear to play important roles in cardiac-immune crosstalk, with disruptions potentially leading to heart failure. T-cell responses to cardiac antigens may also contribute to heart failure, involving myocardial inflammation and fibrosis[16]. When ICIs are used alongside thoracic CRT, the risk of cardiac adverse events could potentially increase. In addition to ICI-mediated T cell pathology, cardiac irradiation can trigger endothelial injury and immune cell infiltration, which may evolve into chronic inflammation and fibrosis beyond the acute phase[22,23]. A recent study has demonstrated that heart sparing radiotherapy also improves OS when using ICI as consolidation[24].

Second, the improved survival rates in NSCLC associated with consolidation ICI amplify the importance of monitoring and managing non-cancer comorbidities such as cardiac events [25,26]. Recent real-world data demonstrate that patients with unresectable stage III NSCLC treated with ICI following CRT have 3y-OS of 67 % [27], and even patients $>$ 75y have a median survival of almost 2 years[28]. As patients live longer, the potential for long-term cardiac toxicities, including RIHD, becomes an increasingly relevant concern. Addressing these issues is crucial for maintaining quality of life and ensuring overall patient well-being after anti-cancer treatment.

To better understand the impact of consolidation ICI on cardiac toxicity in NSCLC, we require patient cohorts treated with similar CRT regimen to disentangle the effects of CRT and ICI. Furthermore, given the complexity of cardiac toxicity, it is essential to analyze the impact on different subregions of the heart separately. In this study, we aim to explore the influence of cardiac subregion doses on the incidence of RIHD following CRT with or without consolidation ICI therapy.

2. Methods

2.1. Patient cohort

Patients with locally advanced NSCLC who underwent definitive chemo-radiation therapy (CRT) between August 2008 and December 2019 at a single institution were retrospectively analyzed Those with a prior cancer diagnosis, follow-up of less than three months, early termination of radiation therapy (before reaching 45 Gy), or an unrecoverable radiation data were excluded. Among these patients, those who were treated after 2015 and had PD-L1 expression levels of 1 % or higher received consolidation ICI following the completion of CRT. Cardiac dose constraints have not changed during the study period; assuring that whole heart and cardiac substructure doses were not different across cohorts. This study received approval from the Severance Hospital (IRB 4-2024-0791), and the need for informed consent was waived due to its retrospective nature.

2.2. Cardiac subregion contouring and dosimetric data

Cardiac subregions in this study include the entire heart, right atrium (RA), right ventricle (RV), left atrium (LA), left ventricle (LV), left circumflex artery (LCX), left anterior descending artery (LAD), and right coronary artery (RCA). Cardiac substructures were contoured per the cardiac atlas using an in-house deep learning–based autosegmentation tool[29], consistent with prior outcome-based studies[6]. The contours were reviewed by two radiation oncologists. The sinoatrial node (SAN) and atrioventricular node (AVN) were manually delineated according to the contouring atlas[30,31] by the same oncologists. Mean dose of the cardiac subregions was selected as the primary DVH summary metric, as it is less sensitive to outlier values than maximum dose and provides a stable measure for small cardiac substructures. Median dose and 25th (Quartile 1) to 75th percentile (Quartile 3) among patients were calculated to show the distribution of dosimetric data.

2.3. RIHD definition

In this study, we defined RIHD included cardiovascular death, unstable angina, heart failure, myocardial infarction, coronary revascularization and atrial fibrillation. RIHD was identified through thorough reviews of medical records conducted by two independent cardiologists blinded to the dosimetric data. The diagnosis of HFpEF, which accounted for the majority of RIHD cases, was established according to the 2021 ESC and 2022 AHA/ACC/HFSA guidelines, requiring (i) the presence of typical heart failure symptoms and/or signs, (ii) preserved left ventricular ejection fraction (LVEF $\geq$ 40 %), and (iii) objective evidence of diastolic dysfunction, structural cardiac abnormalities, or elevated natriuretic peptides (BNP/NT-proBNP).

2.4. Statistical analysis

Time to RIHD and overall survival (OS) was measured from the start of RT treatment to the last follow-up date or the date of RIHD occurrence or death respectively. To consider the baseline risk for RIHD, coronary artery calcification (CAC) score and history of coronary artery obstructive disease (CAD) were collected. Baseline CAC was calculated by was automatically determined using a research software (AVIEW CAC, Coreline Soft) and was expressed as Agaston score[32].

The cumulative incidence function was calculated using subdistribution hazard analysis to compare RIHD occurrence in the CRT/CRT + ICI groups. To determine the impact of clinical and dosimetric variables, uni- and multi-variable Fine-Gray models were fit to RIHD incidence, accounting for the competing risk of non-RIHD-related death. Among clinical variables, baseline CAC score was log-transformed to reduce the high variability of the data. Age, BMI, baseline CAC, and dosimetric variables including the cardiac subregion doses were treated as continuous variables whereas the remainders were treated as dichotomized or categorical variables. Multivariable Fine-Gray analyses considered clinical covariates with univariable $p < 0.05$ and, due to their collinearity, only included the most significant variable among cardiac subregion dose variables. Uni- and multivariable Cox regressions were used to evaluate the impact on overall survival, incorporating clinical variables with $p < 0.05$ from the univariable analysis and the most significant cardiac subregion dose variable for the multivariable analysis. To evaluate the relationship among dosimetric variables of cardiac subregions, correlation heat maps were created. Wilcoxon rank-sum and Chi-square tests were used to compare distributions of continuous and categorical variables between the CRT/CRT + ICI groups.

Additionally, we performed a sensitivity analysis including on patients treated after 2015, i.e. after the introduction of consolidation ICI, to ensure the observed effects are not due to shift in outcomes with time.

All statistical analyses and survival curve generation were performed using R 4.4, employing publicly available libraries such as *survival* and *cmprsk* [33], for statistical analyses and Python 3.8 for image preprocessing.

3. Results

In total 321 patients were collected where the CRT group contained 254 patients treated with CRT only, whereas the CRT + ICI group

consisted of 67 patients treated with CRT followed by durvalumab (n = 50) or pembrolizumab/nivolumab(n = 17). The median follow-up was 23.7 and 36.6 months respectively in the CRT and CRT + ICI groups, providing adequate follow-up in both cohorts. As shown in Table 1, the CRT group was slightly older (67.3vs 64.2y, p = 0.05), but had a lower proportion of advanced T stage tumors ([8, 37, 37, 19 %] vs [12, 25, 27, 36 %] for T stages 1 to 4, p = 0.008), and lower baseline coronary artery calcification (CAC) scores (346 vs 459, p = 0.05). In total, 53 patients had RIHD after treatment, including 45/8 from CRT/CRT + ICI group respectively. Detailed subcategories of RIHD incidence are summarized in Supplementary Table 1.

The two-year estimated cumulative incidence of RIHD in the CRT and CRT + ICI groups was 18.1 % [95 % CI 12.5–23.4 %] and 13.2 % [4.2–21.4 %] respectively, with no significant difference between the two groups (log-rank p = 0.43, Fig. 1). The cumulative incidence of non-RIHD related death in the two groups also showed no significant difference (Fig. 1). However, Fine-Gray analysis showed differences in the impact of clinical variables and cardiac subregion doses on RIHD between the CRT and CRT + ICI groups (Table 2). Among clinical variables, age (HR 1.02, 95 %CI [1–1.03]), diabetes mellitus (DM, HR 1.85, [1.33–2.58]), T stage (HR 1.21, [1.02–1.44]), N stage (HR 1.24, [1.04–1.47]) and AJCC stage (HR 1.43, [1.05–1.95]) were significant predictors in the CRT group. In the CRT + ICI group, age and BMI trended towards significance. Regarding cardiac subregion dose variables, strong differences emerged: mean heart dose and structures around the base of the heart, which is defined as the posterior, superior aspect of the heart; housing part of atria, pulmonary veins, the proximal coronary arteries, and nearby conduction nodes in the right atrium, were significant predictors of RIHD in the CRT group. In the CRT + ICI group, regions around the LV and LCX showed significant associations (Table 2).

The doses delivered to cardiac subregions did not differ significantly between the two groups, as shown in Supplementary Table 2. Additionally, the intercorrelation among cardiac subregion doses was examined using a correlation heat map in Supplementary Fig. 1. The results show that the structures showing the strongest association to RIHD in the two groups, SAN and LV, demonstrated low correlation coefficients with each other, 0.19 and 0.12 for the CRT and CRT + ICI groups, respectively, supporting their identification as independent structures associated with RIHD in each group.

Fig. 2A demonstrates that mean doses to the heart, SAN, and LV show no significant difference between the two groups. The median doses and 25–75 % interquartile ranges to the SAN and LV in the CRT/CRT + ICI groups are 17.7 Gy [6.0–34.8 Gy] and 3.8 Gy [1.1–8.9 Gy], respectively. Fig. 2B presents the multivariable Fine-Gray analysis of RIHD, accounting for the competing risk of non-RIHD-related death in the CRT and CRT + ICI groups. Variables for each group were selected based on the results of the univariable analysis shown in Table 2. When considering the multivariable effect, all five variables, including SAN, remained significant predictors of RIHD in the CRT group, while LV was the only significant variable for RIHD in the CRT + ICI group.

Fig. 3A illustrates the impact of mean SAN and LV doses, the strongest predictors of RIHD, on OS in the CRT and CRT + ICI groups when dichotomized at the median. In the CRT group, patients receiving SAN < 14 Gy exhibited significantly improved survival compared to those with higher SAN (p < 0.0001). On the other hand, in the CRT + ICI group, patients receiving LV < 2 Gy demonstrated superior survival compared to their counterparts (p = 0.03). In Fig. 3B, uni- and multivariable Cox analyses demonstrate that significant clinical variables in the CRT group included age, sex, DM, smoking history (smoking hx) and baseline CAC. Among dosimetric variables, doses to all cardiac subregions, including the heart itself, were significant. In CRT group, age, DM, N stage, and dose to the SAN remained as significant variables whereas in CRT + ICI group, LV dose was the only variable correlated with survival. A sensitivity analysis, conducted by subsampling patients who started treatment after 2015, reaffirmed the primary findings of this

Table1
Patient characteristics.

Variables		all patients (n = 321)	CRT (n = 254)	CRT + ICI (n = 67)	p
Age		66.7 ± 10.2	67.3 ± 9.9	64.2 ± 11.2	0.05
Sex					0.85
	Men	261	206 (81.1 %)	55 (82.1 %)	
	Women	60	48 (18.9 %)	12 (17.9 %)	
BMI		23.0 ± 3.8	22.9 ± 4.0	23.2 ± 3.2	0.20
HTN					0.79
	No	187	147 (57.9 %)	40 (59.7 %)	
	Yes	134	107 (42.1 %)	27 (40.3 %)	
DM					0.24
	No	246	191 (75.2 %)	55 (82.1 %)	
	Yes	75	63 (24.8 %)	12 (17.9 %)	
T stage					<0.01
	1	28	20 (7.9 %)	8 (11.9 %)	
	2	111	94 (37.0 %)	17 (25.4 %)	
	3	111	93 (36.6 %)	18 (26.9 %)	
	4	71	47 (18.5 %)	24 (35.8 %)	
N stage					0.67
	0	26	20 (7.9 %)	6 (9.0 %)	
	1	29	24 (9.4 %)	5 (7.4 %)	
	2	126	104 (40.9 %)	22 (32.8 %)	
	3	140	106 (41.7 %)	34 (50.7 %)	
AJCC Stage					0.11
	I-II	18	18 (7.1 %)	0 (0 %)	
	IIIA	89	70 (27.6 %)	19 (28.4 %)	
	IIIB	137	109 (42.9 %)	28 (41.8 %)	
	IIIC	77	57 (22.4 %)	20 (29.9 %)	
Histology					0.67
	Adenocarcinoma	139	107 (42.1 %)	32 (47.8 %)	
	Squamous Cell Carcinoma	169	136 (53.5 %)	33 (49.3 %)	
	Others	13	11 (4.3 %)	2 (3.0 %)	
ECOG					0.18
	0	46	33 (13.0 %)	13 (19.4 %)	
	1	262	208 (81.9 %)	54 (80.6 %)	
	2	12	12 (4.7 %)	0 (0 %)	
	3	1	1 (0.4 %)	0 (0 %)	
Smoking Hx					0.36
	Never	75	59 (23.2 %)	16 (23.9 %)	
	Current	57	49 (19.3 %)	8 (11.9 %)	
	Ex-smoker	189	146 (57.5 %)	43 (64.2 %)	

(continued on next page)

Table1 (*continued*)

Variables		all patients (n = 321)	CRT (n = 254)	CRT + ICI (n = 67)	p
Alcohol Hx					0.14
	No	116	97 (38.2 %)	19 (28.4 %)	
	Yes	205	157 (61.8 %)	48 (71.6 %)	
Baseline CAC		369.5 ± 647.3	345.8 ± 625.5	458.8 ± 717.0	0.05
Baseline CAD					0.07
	No	269 (84 %)	208 (81.9 %)	61 (91.0 %)	
	Yes	52 (16 %)	46 (18.1 %)	6 (9.0 %)	

Categorical variables are described in counts whereas continuous variables are described with mean ± standard deviation. P value is calculated for the difference in patient characteristics between CRT vs CRT + ICI using the Wilcoxon or χ^2 test for continuous or categorical variables respectively.
(Abbreviations: BMI = body mass index; HTN = hypertension; DM = diabetes mellitus; AJCC = America Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group performance; Hx = history; CAC = coronary artery calcification; CAD = coronary artery obstructive disease; RT = radiotherapy).

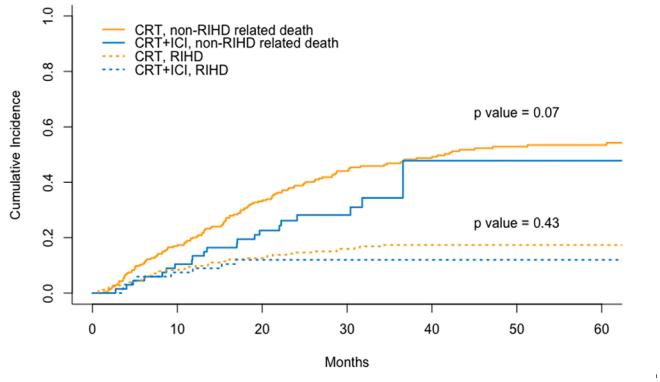

Fig. 1. Cumulative Incidence Function (CIF) plot of RIHD with competing risk of non-RIHD related death for CRT/CRT + ICI groups considering subdistribution hazard ratios.

study (see Supplementary Table 3 and Supplementary Fig. 2).

4. Discussions

Among 321 NSCLC patients treated with CRT, 53 (17 %) developed new-onset RIHD following treatment. When comparing patients who received ICI with those who did not, the incidence of RIHD was not significantly different between the two groups. However, Fine-Gray competing risk analysis highlighted distinct differences in how cardiac subregion doses influenced RIHD differently in the two groups, suggesting that ICI use may markedly shift the cardiac toxicity pattern associated with radiotherapy. Specifically, in patients not receiving ICI, higher dose to the sinoatrial node (SAN), which is at the base of the heart, was correlated with death (Fig. 3A), consistent with findings in previous studies[10,34,35]. In contrast, in patients treated with ICI after CRT, higher doses to the LV, which includes the left side of the heart's apex, emerged as strong predictors of RIHD.

Notably, as shown in Supplementary Table 1, heart failure with preserved ejection fraction (HFpEF) was dominant among RIHD subcategories, potentially reflecting the known association of heart failure with ICI exposure[36,37]. Endpoint-specific substructure associations,

Table 2
Univariable Fine-Gray analysis of RIHD for CRT and CRT + ICI groups accounting for the competing risk of non-RIHD-related death using subdistribution hazard ratio. For dosimetric parameters, hazard ratios are for change of 1 Gy.

Variables	CRT (N = 254) Univariable HR (95 % CI)	p	CRT + ICI (N = 67) Univariable HR (95 % CI)	p
Age	1.02 (1.00–1.03)	0.017	1.04 (1.00–1.09)	0.063
Sex	0.75 (0.50–1.12)	0.160	0.66 (0.22–1.96)	0.449
BMI	0.98 (0.94–1.01)	0.210	0.88 (0.75–1.02)	0.092
DM	1.85 (1.33–2.58)	<0.001	0.33 (0.09–1.27)	0.106
T stage	1.21 (1.02–1.44)	0.032	1.12 (0.75–1.67)	0.572
N stage	1.24 (1.04–1.47)	0.014	1.03 (0.61–1.74)	0.911
AJCC stage	1.43 (1.05–1.95)	0.022	1.49 (0.64–3.50)	0.356
Histology	0.93 (0.68–1.27)	0.669	0.86 (0.38–1.94)	0.709
ECOG	1.14 (0.75–1.74)	0.537	4.96 (0.65–37.97)	0.123
Smoking Hx	1.08 (0.90–1.30)	0.410	1.15 (0.71–1.86)	0.576
Alcohol Hx	0.97 (0.71–1.32)	0.832	1.28 (0.50–3.30)	0.604
Baseline Heart Hx	1.16 (0.79–1.70)	0.444	1.13 (0.23–5.41)	0.881
Baseline CAC	1.02 (0.96–1.08)	0.619	1.09 (0.89–1.33)	0.402
Baseline CAD	1.16 (0.79–1.72)	0.443	1.46 (0.29–7.39)	0.651
Mean heart dose	1.02 (1.00–1.03)	0.041	1.04 (0.99–1.10)	0.139
RA	1.01 (1.00–1.03)	0.050	1.00 (0.96–1.04)	0.979
RV	1.01 (0.99–1.03)	0.240	1.04 (0.98–1.11)	0.184
LA	1.01 (1.00–1.03)	0.030	1.02 (0.99–1.06)	0.181
LV	1.00 (0.99–1.02)	0.530	1.05 (1.01–1.09)	0.008
SAN	1.01 (1.00–1.02)	0.003	1.00 (0.98–1.02)	0.958
AVN	1.01 (1.00–1.02)	0.159	1.04 (1.00–1.07)	0.07
LAD	1.01 (1.00–1.02)	0.243	1.03 (0.99–1.08)	0.144
LCX	1.00 (0.99–1.01)	0.719	1.03 (1.00–1.05)	0.03
RCA	1.01 (1.00–1.03)	0.124	0.99 (0.96–1.04)	0.809

(Abbreviations: RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; SAN, sinoatrial nose; AVN, atrioventricular node; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery).

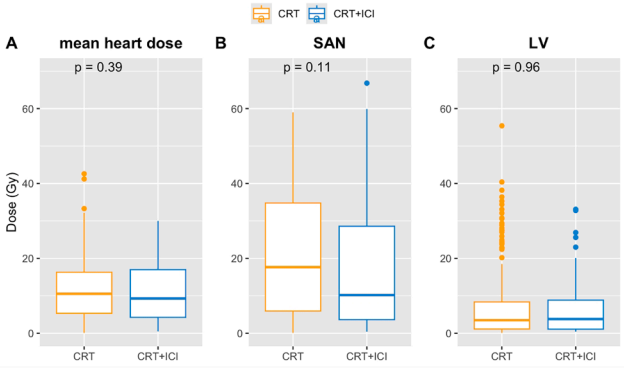

Fig. 2A. Boxplot of important heart subregion mean dose for CRT vs CRT + ICI groups with student *t* test results.

Variables	CRT HR (95% CI)	CRT p	CRT+ICI HR (95% CI)	CRT+ICI p
Age	1.03 (1.01-1.05)	0.002	1.05 (1-1.1)	0.038
BMI			0.91 (0.79-1.05)	0.21
DM	1.77 (1.28-2.46)	<0.001		
T stage	1.28 (1.08-1.53)	0.005		
N stage	1.36 (1.15-1.61)	<0.001		
LV			1.06 (1.06-1.1)	0.006
SAN	1.02 (1.01-1.03)	<0.001		

Fig. 2B. A multivariable Fine-Gray analysis of RIHD considering the competing risk of non-RIHD-related death for the CRT and CRT + ICI groups. Variables for each group were selected based on the univariable Fine-Gray analysis results presented in Table 2.

such as LV dose with HFpEF or HFrEF and LA dose with A-Fib, may be physiologically relevant. Although our study was not powered to fully address these associations in terms of number of events and mechanistic

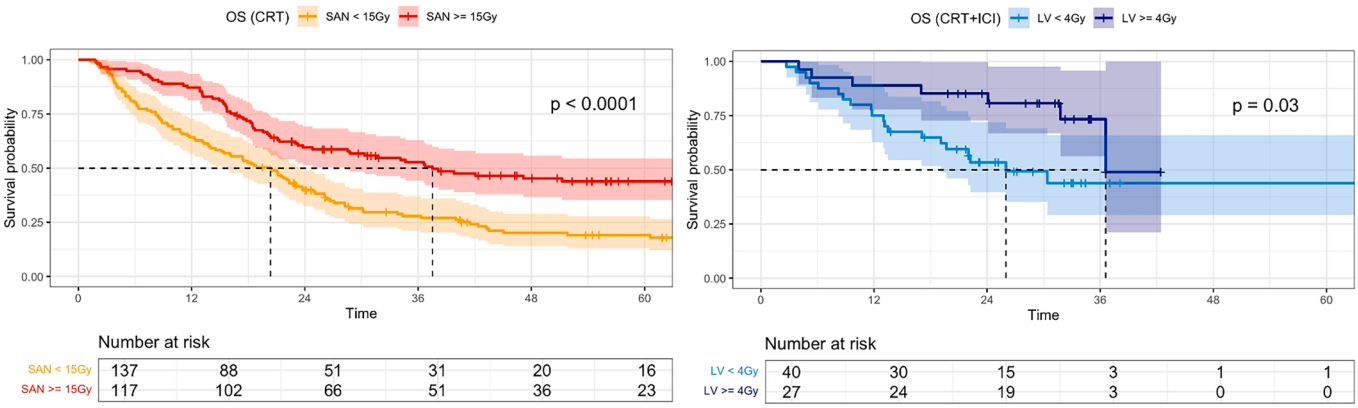

Fig. 3A. Kaplan-Meier curve of overall survival for CRT vs. CRT + ICI groups stratified by mean SAN and LV doses respectively.

evidence remains limited, this represents an important direction for future research. Overall, the stronger statistical signals observed in the CRT group (N = 254) compared to the CRT + ICI group (N = 67) are possibly due to the larger sample size in the former. In the CRT + ICI cohort, attenuation of associations for baseline variables such as diabetes may reflect limited power as well as a shift in cardiotoxicity phenotype with ICI exposure (relatively more HFpEF and A-Fib and fewer ischemic events), which could weaken expected links with traditional risk factors.

The adjusted HRs for SAN and LV indicate a 2/6% increased relative risk of RIHD per 1 Gy and have to be put in context of the wide dose ranges to these small structures (IQR of 28.8 [6.0–34.8] Gy for the SAN and 7.8 [1.1–8.9] Gy for the LV). This indicates clinical importance, particularly because the SAN and LV are small structures that can potentially be spared to a large degree with a carefully optimized radiotherapy plan. In CRT patients, higher SAN dose was associated with worse overall survival (Fig. 3A). This finding is consistent with the results of McWilliam et al.[10], who identified the heart base region as radiosensitive and predictive of early mortality. Despite differences in methodology and patient population, the concordance supports the importance of cardiac regions near the heart base in determining survival outcomes after CRT. We also extended this analysis to patients receiving consolidation ICI therapy, identifying a correlation between dose to the LV and survival, a subregion distant from the base of the heart and SAN. This difference highlights the complex and potentially varied impact of ICI treatments on cardiac outcomes, depending on the specific cardiac subregion affected by radiation.

Cardiac subregion doses are thought to be highly correlated to each other in general. However, as shown in the correlation heat map in Supplementary Fig. 1, doses to the SAN and LV did not demonstrate a meaningful correlation with each other (coefficients of 0.12 and 0.19 for the CRT and CRT + ICI groups, respectively). Also, dose to SAN and LV were not statistically different between the two groups as shown in Supplementary Table 2 (Wilcoxon's p = 0.63 and 0.52). These results suggest that, despite similar delivered doses between the two groups with weak correlation between SAN and LV, the impact on RIHD differs between the CRT and CRT + ICI groups. These results further confirm existing literature that mean heart dose is not sufficiently representative of radiation-induced cardiac toxicity[38–40] and demonstrate for the first time that different cardiac substructures might be involved when addition a checkpoint inhibitor to CRT.

Among patients who underwent thoracic CRT, cardiac toxicity has predominantly been explored in breast cancer or Hodgkin lymphoma patients, due to their relatively longer survival compared to lung cancer patients[14,22,41]. In breast cancer and lymphoma, it is known that radiation causes heart disease many years after treatment[14,22,42]. In this study, patients developed new-onset RIHD in relatively short time after treatment. Out of 53 patients in this study who had post-RT RIHD after a median of 10 months, 30 (57 %) had RIHD within 12 months and 45 (85 %) within 24 months. This may be due to the larger irradiation field and/or higher delivered dose in lung cancer treatment compared to breast cancer and lymphoma. Studies in these cancers also emphasize the importance of dose inhomogeneity in the heart as a predictor of cardiac toxicity, mentioning that considering only mean heart dose might be an obsolete way to estimate cardiotoxicity[41–43]. This emphasizes the need to consider cardiac subregion irradiation to better understand the exact mechanisms of cardiotoxicity, which align with the findings in this study.

Our findings complement the recent study from University of Pennsylvania (UPenn)[44] concluding that there was no significant correlation between heart dose and RIHD. While on the surface our findings challenge their conclusion, our results indeed agree well with theirs when considering the large differences in dose to the heart: UPenn implemented strict institutional constraints in 2017, demonstrated by the lower cardiac doses in their study (8.7 and 2.3 Gy for mean heart and LV dose) compared to ours (11.5 and 7.1 Gy). This is backed up by the lower observed RIHD incidence in the UPenn study (9.5 % vs 17 % in our data). These higher cardiac doses were likely caused to some extent by the more advanced tumors in our cohort (65 % vs 47 % AJCC II/III) driven by higher nodal involvement (43 % vs 22 % N3). This suggests that there is indeed a correlation between RIHD and dose to cardiac subregions in contemporary patients treated with consolidation ICI and that stricter dose constraints help to lower RIHD incidence to levels where this correlation is exceedingly hard to observe.

Despite these significant findings, our study is not without limitations. Multi-institutional validation is required to confirm our that our conclusions derived from single-institution data are generalizable. The underlying biological mechanisms how the use of ICI following CRT affect radiation-induced cardiac toxicity remain unclear. Understanding the interplay between these treatments at a biological level is critical for advancing cardioprotective strategies in this patient population. Additionally, considering subtypes of RIHD could yield further insights. RIHD, the primary endpoint of this study, encompasses myocadiac infarction, atrial fibrillation, pericarditis, and heart failure (Supplementary Table 1). Although these conditions are grouped under the term RIHD, the underlying mechanisms of each disease differ significantly[14]. Therefore, further research on each of these RIHD subtypes larger cohorts are required. Furthermore, the CRT + ICI cohort was relatively small, and multiple heterogeneous RIHD endpoints were assessed. Pre-existing cardiac events were not systematically captured, and cardiology work-up was largely symptom-driven, which may have contributed to underestimation of RIHD incidence. Unmeasured confounders such as cardioprotective medications, cardio-oncology co-management, and treatment-era effects may also have diluted baseline associations since these variables were not systematically captured. Finally, we could not formally adjudicate immune-mediated myocarditis

VARIABLES	CRT				CRT+ICI			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.02 (1.01-1.04)	0.007	1.03 (1.01-1.04)	0.002	1.04 (1-1.09)	0.055	1.04 (0.99-1.08)	0.056
Sex	0.66 (0.44-0.99)	0.045	0.74 (0.43-1.28)	0.280	0.45 (0.14-1.52)	0.200		
BMI	0.98 (0.94-1.01)	0.234			0.88 (0.77-1.01)	0.060		
DM	1.77 (1.28-2.46)	0.001	1.72 (1.23-2.40)	0.002	0.4 (0.12-1.35)	0.141		
T stage	1.14 (0.96-1.35)	0.128			1.16 (0.8-1.67)	0.429		
N stage	1.25 (1.05-1.48)	0.011	1.38 (1.15-1.67)	<0.001	1.07 (0.7-1.65)	0.754		
AJCC stage	1.17 (0.85-1.6)	0.330			1.53 (0.7-3.34)	0.287		
Histology	0.96 (0.71-1.29)	0.775			0.73 (0.34-1.58)	0.424		
ECOG	1.25 (0.88-1.77)	0.217			2.98 (0.71-12.6)	0.137		
Smoking Hx	1.29 (1.07-1.56)	0.008	1.1 (0.86-1.43)	0.433	1.43 (0.87-2.35)	0.155		
Alcohol Hx	0.96 (0.71-1.3)	0.797			1.44 (0.58-3.58)	0.436		
Baseline Heart Hx	1.09 (0.75-1.6)	0.640			2.59 (0.89-7.54)	0.080	2.63 (0.86-8.05)	0.092
Baseline CAC	1 (1-1)	0.048	1 (1-1)	0.083	1 (1-1)	0.076		
Baseline CAOD	1.03 (0.7-1.52)	0.881			2.17 (0.65-7.24)	0.208		
Mean heart dose	1.05 (1.03-1.07)	<0.001			1.04 (0.99-1.09)	0.125		
RA	1.02 (1.01-1.03)	0.002			1 (0.97-1.04)	0.823		
RV	1.05 (1.03-1.07)	<0.001			1.04 (0.99-1.1)	0.113		
LA	1.03 (1.02-1.04)	<0.001			1.02 (0.99-1.04)	0.286		
LV	1.03 (1.01-1.05)	<0.001			1.04 (1-1.08)	0.081	1.06 (1.01-1.11)	0.020
SAN	1.01 (1.01-1.02)	0.001	1.02 (1.01-1.03)	<0.0001	1 (0.98-1.02)	0.996		
AVN	1.04 (1.02-1.05)	<0.001			1.03 (0.99-1.07)	0.130		
LAD	1.02 (1-1.03)	0.021			1.03 (0.99-1.08)	0.094		
LCX	1.01 (1-1.02)	0.021			1.02 (1-1.04)	0.096		
RCA	1.02 (1.01-1.04)	0.004			1 (0.96-1.04)	0.865		

Fig. 3B. Uni- and multi-variable Cox proportional hazard analysis for overall survival.

in our retrospective dataset; nonetheless, it remains a plausible contributor to the observed cardiac events and represents an important area for prospective evaluation.

In conclusion, our study provides important evidence that cardiac subregion dose to the base of the heart for CRT patients and to the LV region for CRT + ICI patients are correlated with new onset post-RT RIHD. These findings underscore the necessity for further research into the dose-dependent effects on specific cardiac subregions and the potential mechanisms by which ICI therapies may intensify these effects. Understanding these relationships will be crucial for optimizing treatment strategies and improving patient outcomes and quality of life.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2025.101069.

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