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Association of Sinoatrial Node Radiation Dose With Atrial Fibrillation and Mortality in Patients With Lung Cancer

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IMPORTANCE Atrial fibrillation (AF) can develop following thoracic irradiation. However, the critical cardiac substructure responsible for AF has not been properly studied.

OBJECTIVE To describe the incidence of AF in patients with lung cancer and determine predictive cardiac dosimetric parameters.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was performed at a single referral center and included 239 patients diagnosed with limited-stage small cell lung cancer (SCLC) and 321 patients diagnosed with locally advanced non–small cell lung cancer (NSCLC) between August 2008 and December 2019 who were treated with definitive chemoradiotherapy.

EXPOSURES Radiation dose exposure to cardiac substructures, including the chambers, coronary arteries, and cardiac conduction nodes, were calculated for each patient.

MAIN OUTCOMES AND MEASURES Main outcomes were AF and overall survival.

RESULTS Of the 239 and 321 patients with SCLC and NSCLC, the median (IQR) age was 68 (60-73) years and 67 (61-75) years, and 207 (86.6%) and 261 (81.3%) were men, respectively. At a median (IQR) follow-up time of 32.7 (22.1-56.6) months, 9 and 17 patients experienced new-onset AF in the SCLC and NSCLC cohorts, respectively. The maximum dose delivered to the sinoatrial node (SAN D_{max}) exhibited the highest predictive value for prediction of AF. A higher SAN D_{max} significantly predicted an increased risk of AF in patients with SCLC (adjusted hazard ratio [aHR], 14.91; 95% CI, 4.00-55.56; $P < .001$) and NSCLC (aHR, 15.67; 95% CI, 2.08-118.20; $P = .008$). However, SAN D_{max} was not associated with non-AF cardiac events. Increased SAN D_{max} was significantly associated with poor overall survival in patients with SCLC (aHR, 2.68; 95% CI, 1.53-4.71; $P < .001$) and NSCLC (aHR, 1.97; 95% CI, 1.45-2.68; $P < .001$).

CONCLUSIONS AND RELEVANCE In this cohort study, results suggest that incidental irradiation of the SAN during chemoradiotherapy may be associated with the development of AF and increased mortality. This supports the need to minimize radiation dose exposure to the SAN during radiotherapy planning and to consider close follow-up for the early detection of AF in patients receiving thoracic irradiation.

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Thoracic radiotherapy (RT) can increase the risk of cardiac adverse events.[1,2] Radiation-induced cardiac adverse events have been reported, mainly in patients with breast cancer or lymphoma.[3-6] The cardiac effect of RT in patients with lung cancer has also gained interest.[7-11] Although lung cancer is well known for its poor prognosis, the median survival has increased with the advancements in treatment strategies, indicating the need for achieving the appropriate balance between tumor control and cardiac toxic effects.[12-14]

Studies conducted on patients before the era of computed tomography (CT)-based planning estimated the cardiac dose based on a representative CT scan using virtual planning.[3-5] With CT simulation becoming a routine practice in RT planning, individual-based cardiac dose calculations have become possible. Not only the dose delivered to the whole heart, but also radiation dose delivered to cardiac substructures, can be calculated accurately.

Until now, studies on radiation-induced cardiotoxic effects have focused mainly on ischemic heart diseases.[1,2] Although the risk of atrial fibrillation (AF) in patients with intrathoracic cancers has been shown to be substantial,[7,9,11,15,16] to our knowledge a detailed study of AF in patients with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) receiving chemoradiotherapy (CRT) has not been conducted. Moreover, no specific dose constraint of a specific cardiac substructure has been suggested for predicting AF. To this end, we evaluated the dose-volume parameters of diverse cardiac substructures in patients with SCLC and NSCLC who received definitive CRT and investigated critical cardiac substructures associated with development of AF.

Key Points

Question What is the association between radiation dose exposure to cardiac substructures with cardiac toxic effects and survival in patients who received chemoradiotherapy for lung cancer?

Findings In this cohort study of 560 patients, individualized dose calculation for various cardiac substructures revealed that the maximum dose delivered to the sinoatrial node was an independent factor associated with atrial fibrillation and overall survival.

Meaning These findings suggest that incidental irradiation of the sinoatrial node may be associated with the development of atrial fibrillation and increased mortality, and indicate the need to minimize radiation dose exposure to the sinoatrial node during chemoradiotherapy and consider close follow-up for the early detection of atrial fibrillation.

Methods

Patients and Treatment

A total of 293 patients diagnosed with histologically confirmed limited-stage SCLC and 412 patients diagnosed with locally advanced NSCLC who were treated with definitive CRT between August 2008 and December 2019 were retrospectively analyzed. Patients with previously diagnosed cancer (n = 75), less than 3 months of follow-up (n = 36), premature termination of RT before reaching 45 Gy (n = 30), and nonrestorable RT plan (n = 4) were excluded, leaving a total of 239 patients with SCLC (SCLC cohort) and 321 patients with NSCLC (NSCLC cohort) for further analysis. None of the 36 patients with less than 3-month follow-up died due to cardiac events. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital (2021-2365-001), and the requirement for informed consent was waived owing to the retrospective nature of the research. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

All patients with SCLC received either etoposide with cisplatin or carboplatin for 4 to 6 cycles. Patients with NSCLC received weekly paclitaxel with carboplatin for up to 6 cycles. Radiotherapy was delivered using 3-dimensional conformal RT or intensity-modulated RT techniques. A total of 60 to 63 Gy in 1.8 to 2.1 Gy per fraction was delivered. None of the patients received up-front surgery. After treatment, the patients were followed up every 2 to 4 months for the first 3 years and then every 6 months for the next 2 years.

Dosimetric Analysis

The cardiac substructures, including the right atrium, right ventricle, left atrium, left ventricle, left anterior descending artery, right coronary artery, and left circumflex artery, were contoured according to the cardiac contouring atlas[17] using a deep-learning based autosegmentation tool of the heart that was developed in-house.[18] Next, the contours were reviewed by 3 radiation oncologists (K.H.K., G.Y., and J.L.) who were blinded to the clinical factors. The sinoatrial node (SAN) and atrioventricular node were delineated manually according to the contouring atlas.[19] The maximum dose (minimum dose delivered to the hottest 0.035 cc), mean dose, and $V_{5\ Gy}$ to $V_{60\ Gy}$ in increments of 5 Gy were calculated ($V_{5\ Gy}$ to $V_{60\ Gy}$ refers to the percentage of the structure receiving at least the indicated dose).

Coronary Artery Calcium Measurement

Coronary artery calcium (CAC) score was automatically determined using a research prototype software (AVIEW CAC, Coreline Soft) and was expressed as Agaston score (eMethods in the Supplement).[20,21]

Cardiac End Points

Cardiac events were determined through in-depth reviews of the medical records by 2 independent cardiologists (J.O. and S.G.) who were blinded to the dosimetric data. The cardiac end points including cardiac death, unstable anginas, myocardial infarction, coronary revascularization, heart failure (HF), and AF were assessed after the initiation of RT.[22] Cardiac events other than AF were categorized as non-AF cardiac events. Patients with preexisting cardiac morbidities were considered to have had a cardiac event if they presented with the same cardiac event, but it was of a greater severity than that experienced during the 6-month interval preceding RT, or if the event was a different class of cardiac event. For AF, the baseline electrocardiogram (ECG) was compared with follow-up ECG to de-

termine new-onset AF. Chest CT scans and echocardiograms were reviewed to evaluate pericardial effusion following CRT.

Statistical Analysis

The predictive power of the dosimetric parameters was evaluated using time-dependent integrated area under the receiver operating characteristic curves (eMethods in the Supplement).[23] Time to cardiac event was estimated from the start date of RT to the date of the event or last observation. Overall survival (OS) was defined as the time from the initiation of the treatment to death from any cause or last observation. Fine and Gray regression and Cox proportional hazards regression were performed for the univariable and multivariable analyses (eMethods in the Supplement). A 2-sided *P* value less than .05 was considered to be statistically significant. All the analyses were performed using R, version 4.0.3 (R Foundation for Statistical Computing).

Results

Patient Characteristics

A total of 239 patients and 321 patients were included in the SCLC and NSCLC cohorts, respectively. The baseline patient characteristics of SCLC and NSCLC cohorts are summarized in **Table 1**. In the NSCLC cohort, 67 patients (20.9%) received consolidation durvalumab, pembrolizumab, or nivolumab following CRT. Following CRT, 1 patient and 8 patients received chest surgery after CRT in the SCLC and NSCLC cohorts, respectively. The patients underwent surgery for removal of empyema (n = 4) and local recurrence (n = 5).

Cardiac Events

In the SCLC cohort, 9 patients experienced new-onset AF, and 5 patients experienced non-AF cardiac events during a median (IQR) follow-up time of 25.7 (16.5-47.2) months. The 5 non-AF cardiac events included 2 patients who underwent coronary revascularizations, 1 patient who experienced an ST-segment elevation myocardial infarction, and 2 patients who were hospitalized with HF with reduced ejection fraction. In the NSCLC cohort, 17 patients experienced new-onset AF, and 6 patients experienced non-AF cardiac events during a median (IQR) follow-up time of 36.2 (26.9-60.2) months. The 6 non-AF cardiac events included 5 patients who underwent coronary revascularizations and 1 patient who experienced a non-ST-segment elevation myocardial infarction.

Higher SAN D_{max} Predicts AF

Maximum dose (D_{max}) delivered to the SAN (SAN D_{max}) exhibited the highest C index (0.66; 95% CI, 0.56-0.74) for the prediction of AF in the combined cohort of SCLC and NSCLC (eTable 1 in the Supplement). The top 5 predictive SAN dosimetric variables, in both the SCLC and NSCLC cohorts, are shown in eTable 2 in the Supplement. A representative patient with NSCLC who experienced new-onset AF 7 months post-CRT is illustrated in eFigure 1 in the Supplement. The optimal SAN D_{max} cutoff level was 53.5 Gy (95% CI, 48.9-53.7 Gy) in the SCLC cohort. Patients who received a SAN D_{max} of 53.5 Gy or greater exhibited a significantly higher 3-year cumulative incidence of AF than those who received a SAN D_{max} less than 53.5 Gy (25.0%; 95% CI, 8.4%-74.1% vs 2.7%; 95% CI, 1.1%-6.7%; $P < .001$; **Figure 1**A). Patients who received a SAN D_{max} of 53.5 Gy or greater and a SAN D_{max} less than 53.5 Gy exhibited similar cumulative incidences of non-AF cardiac events ($P = .51$; Figure 1B). The significance of the SAN D_{max} of 53.5 Gy or greater in predicting AF was maintained in multivariable analysis (adjusted hazard ratio [aHR], 14.91; 95% CI, 4.00-55.56; $P < .001$; **Table 2**).

The optimal cutoff level of SAN D_{max} for prediction of AF in the NSCLC cohort was 20.0 Gy (95% CI, 2.5-43.5 Gy). The 3-year cumulative incidence of AF was significantly higher in patients who received a SAN D_{max} of 20.0 Gy or greater than in those who received a SAN D_{max} less than 20.0 Gy (9.9%; 95% CI, 5.9%-16.4% vs 0.7%; 95% CI, 0.0%-5.1%; $P < .001$; **Figure 2**A). Patients who received a SAN D_{max} of 20.0 Gy or greater and SAN D_{max} less than 20.0 Gy exhibited no significant difference in the cumulative incidence of non-AF cardiac events ($P = .13$; Figure 2B). The significance of a SAN D_{max} of 20.0 Gy or greater in predicting AF was maintained in multivariable analysis (aHR, 15.67; 95% CI, 2.08-118.20; $P = .008$; **Table 3**).

Pericardial effusion was observed in 14 and 18 patients in the SCLC and NSCLC cohorts, respectively, following CRT. None of the patients with new-onset AF had treatment-related pericarditis prior to AF. Moreover, pericardial effusion, chest surgery after CRT, presence of CAC, and extent of CAC were not significantly associated with new-onset AF in both cohorts (Tables 2 and 3).

Higher SAN D_{max} Predicts Poor Survival

The 3-year OS in patients with a SAN D_{max} of 53.5 Gy or greater was significantly lower than in those with a SAN D_{max} less than 53.5 Gy in the SCLC cohort (30.9%; 95% CI, 13.8%-69.0% vs 48.5%; 95% CI, 41.3%-57.0%; $P = .008$; Figure 1C). In the NSCLC cohort, the 3-year OS in patients with a SAN D_{max} of 20.0 Gy or greater was significantly lower than in those with a SAN D_{max} less than 20.0 Gy (35.0%; 95% CI, 28.3%-43.3% vs 54.5%; 95% CI, 46.5%-63.9%; $P < .001$; Figure 2C). The SAN D_{max} maintained a significant association with poorer OS in multivariable analysis in the SCLC cohort (aHR, 2.68; 95% CI, 1.53-4.71; $P < .001$; eTable 3 in the Supplement) and the NSCLC cohort (aHR, 1.97; 95% CI, 1.45-2.68; $P < .001$; eTable 4 in the Supplement).

Cardiac Substructures Associated With AF and Survival Other Than SAN

We analyzed the predictive value of maximal radiation dose delivered to the heart (eFigure 2 in the Supplement), left atrium (eFigure 3 in the Supplement), and right atrium (RA D_{max}; eFigure 4 in the Supplement), which also exhibited some predictive value (eTable 1 in the Supplement). Patients with higher RA D_{max} exhibited higher incidence of new-onset AF and poorer OS in both the SCLC and NSCLC cohorts (eFigure 4 in the Supplement). In multivariable analysis, higher RA D_{max} was associated with new-onset AF in the SCLC cohort (aHR, 20.54; 95% CI, 5.57-75.65; $P < .001$; eTable 5 in the Supplement) and

Table 1. Patient Characteristics

Characteristic	No. (%) SCLC (n = 239)	NSCLC (n = 321)
Age, median (IQR), y	68 (60-73)	67 (61-75)
Sex		
Female	32 (13.4)	60 (18.7)
Male	207 (86.6)	261 (81.3)
BMI, median (IQR)	23.7 (21.4-25.8)	22.7 (20.8-25.0)
Hypertension		
No	124 (51.9)	187 (58.3)
Yes	115 (48.1)	134 (41.7)
Diabetes		
No	170 (71.1)	246 (76.6)
Yes	69 (28.9)	75 (23.4)
ECOG performance status		
0	23 (9.6)	46 (14.3)
1	208 (87.0)	262 (81.6)
2	8 (3.3)	13 (4.1)
Cardiovascular disease		
Atrial fibrillation	3 (1.3)	8 (2.5)
Valvular heart disease	1 (0.4)	1 (0.3)
Coronary artery disease	23 (9.6)	25 (7.8)
Complete atrioventricular block	1 (0.4)	0
Stroke	12 (5.0)	9 (2.8)
Peripheral vascular disease	3 (1.3)	5 (1.6)
None	196 (82.0)	273 (85.0)
Coronary artery calcification		
No	50 (20.9)	63 (19.6)
Yes	189 (79.1)	258 (80.4)
CAC score, median (IQR)	165.3 (3.9-712.1)	108.7 (3.8-428.2)
No. of coronary arteries with calcification		
0	50 (20.9)	63 (19.6)
1	50 (20.9)	64 (19.9)
2	21 (8.8)	38 (11.8)
3	34 (14.2)	51 (15.9)
4	94 (39.3)	98 (30.5)
Aortic valve calcification		
No	174 (72.8)	236 (73.5)
Yes	65 (27.2)	85 (26.5)
Mitral valve calcification		
No	226 (94.6)	294 (91.6)
Yes	13 (5.4)	27 (8.4)
Tobacco use		
Never	31 (13.0)	75 (23.4)
Current	54 (22.6)	57 (17.8)
Former	154 (64.4)	189 (58.9)
Pack-years, median (IQR)[a]	40 (25-50)	40 (27-50)
Alcohol use		
Never	81 (33.9)	116 (36.1)
Current	69 (28.9)	96 (29.9)
Former	89 (37.2)	109 (34.0)
Stage		
I-II	33 (13.8)	18 (5.6)
IIIA	70 (29.3)	89 (27.7)
IIIB	84 (35.1)	137 (42.7)
IIIC	52 (21.8)	77 (24.0)
Chemotherapy regimen		
Etoposide + carboplatin	102 (42.7)	0
Etoposide + cisplatin	137 (57.3)	0
Paclitaxel + carboplatin	0	291 (90.7)
Others	0	30 (9.3)
Maintenance IO agent		
None	0	254 (79.1)
Durvalumab	0	50 (15.6)
Pembrolizumab/nivolumab	0	17 (5.3)
RT dose, median (IQR)	60 (54.0-60.8)	63 (60.0-64.5)
RT fraction, median (IQR)	30 (30-30)	30 (30-30)
RT modality		
3D-CRT	116 (48.5)	110 (34.3)
IMRT	123 (51.5)	211 (65.7)

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CAC, coronary artery calcium; CVD, cardiovascular disease; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity-modulated radiotherapy; IO, immuno-oncology; NSCLC, non–small cell lung cancer; RT, radiotherapy; SCLC, small cell lung cancer; WHO, World Health Organization.

[a] Estimated among patients with history of tobacco use.

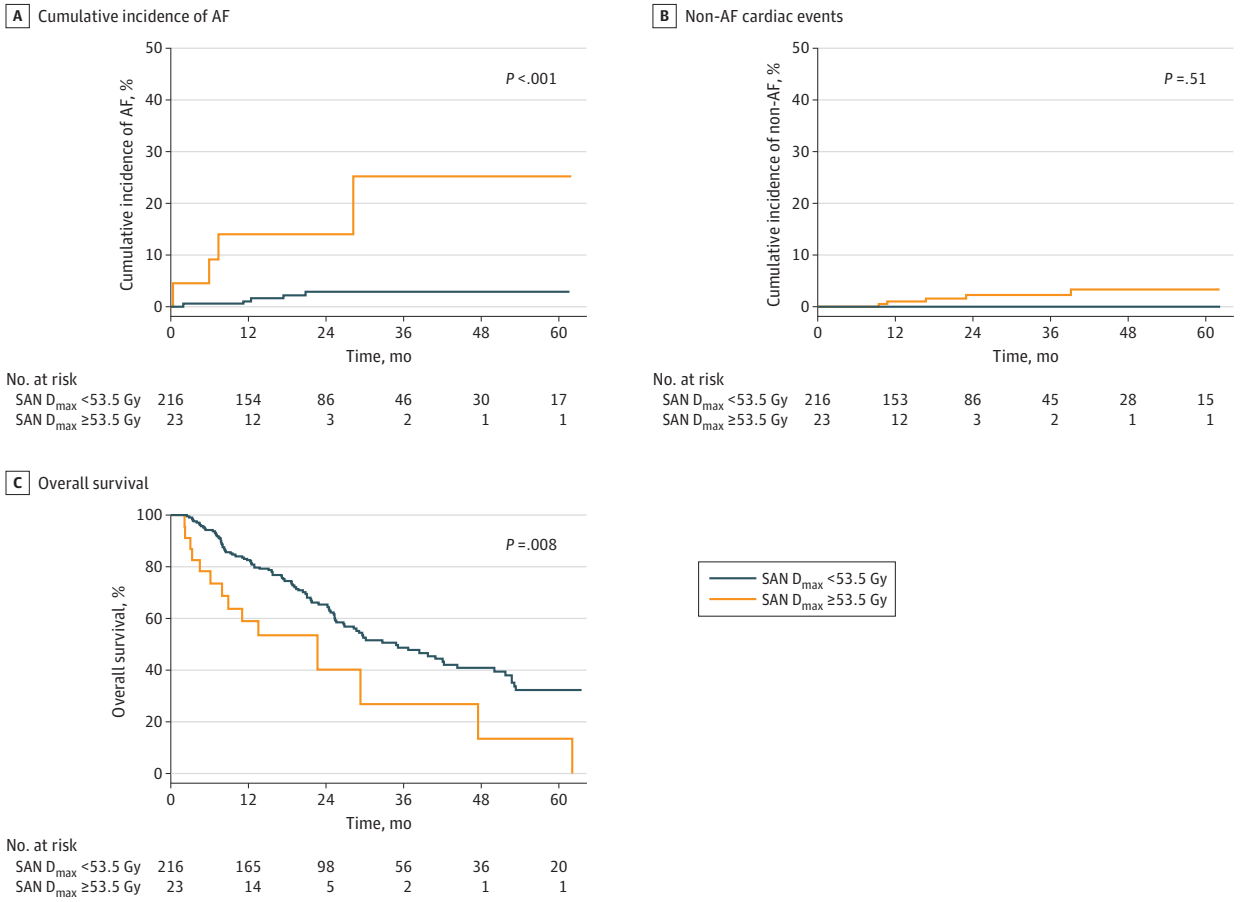
in the NSCLC cohort (aHR, 5.97; 95% CI, 1.34-26.57; P = .02; eTable 6 in the Supplement). The RA D_{max} maintained a significant association with poorer OS in the SCLC cohort (aHR, 2.29; 95% CI, 1.34-3.91; P = .002; eTable 7 in the Supplement) and the NSCLC cohort (aHR, 1.57; 95% CI, 1.14-2.17; P = .005; eTable 8 in the Supplement).

Discussion

The present study demonstrated, to our knowledge, a previously undescribed association between the radiation dose exposed to the SAN and new-onset AF in patients with lung cancer who received CRT. Higher SAN D_{max} was also associated with an increased risk of mortality. However, it did not predict non-AF cardiac events, indicating the specific association between SAN D_{max} and AF.

Studies on radiation-induced cardiac adverse events have mainly focused on ischemic heart diseases.[1,3,8,24] However, arrhythmia is one of the most common cardiac adverse events following CRT in patients with lung cancer.[7,9,10,16] Nevertheless, dose-volume parameters of cardiac substructures associated with AF have not been properly studied. Most previous studies have focused on the 4 chambers of the heart and coronary arteries with little emphasis on the conduction nodes.[8-10] In these studies, either the left ventricle doses or left anterior descending artery doses were associated with acute coronary syndromes or HF, which are known to be caused by occlusion of the coronary artery or dysfunction of the left ventricle. However, the pathophysiology of AF is distinct from either acute coronary syndromes or HF, and thus, cardiac substructures other than the chambers or coronary arteries should be evaluated.[25]

Figure 1. Incidence of Cardiac Adverse Events and Overall Survival According to SAN D_{max} in the SCLC Cohort



Cumulative incidence of AF (A), non-AF cardiac events (B), and overall survival (C) in patients with SAN D_{max} of 53.5 Gy or greater and SAN D_{max} less than 53.5 Gy. AF indicates atrial fibrillation; SAN D_{max}, maximum radiation dose exposed to sinoatrial node; SCLC, small cell lung cancer.

The pathophysiology of AF is complex and has not been fully elucidated. It frequently coexists with SAN dysfunction, which is considered as a predisposing condition for AF.[26] Patients with SAN dysfunction are known to be more susceptible to develop AF, and AF may newly develop in 1 of 4 patients receiving cardiac pacing.[27,28] More recently, genetic variants significantly associated with AF and SAN dysfunction were identified by genome-wide association studies.[29-31] The common variants between AF and SAN dysfunction imply a shared genetic background of these 2 conditions. Moreover, in mendelian randomization analysis, AF was associated with SAN dysfunction, suggesting causality.[31] Dysfunction of the SAN can be mediated by degenerative fibrosis and electrical remodeling of the atrium, especially in SAN. Radiotherapy has been known to induce fibrosis or remodeling of the heart.[32] Therefore, it may be hypothesized that iatrogenic SAN dysfunction by RT may facilitate AF. We took advantage of a recently published contouring atlas for cardiac conduction node delineation to estimate the irradiated dose to the SAN and atrioventricular node in each individual patient.[19]

The optimal cutoff SAN D_{max} values in the SCLC and NSCLC cohorts were different. A lower cutoff of 20.0 Gy was determined in the NSCLC cohort, compared with 53.5 Gy in the SCLC cohort, and the confidence intervals of the cutoff values did not overlap. The incidence of new-onset AF was higher in the NSCLC cohort than in the SCLC cohort despite similar SAN D_{max} values between both cohorts (eTable 1 in the Supplement). Therefore, the lower cutoff value of SAN D_{max} and higher incidence of AF in the NSCLC cohort than in the SCLC cohort indicate that patients in the NSCLC cohort may have been more sensitized to the effect of radiation compared with the SCLC cohort. Such difference may be partially explained through the different chemotherapy regimen used in the 2 cohorts. Previous studies have demonstrated the arrhythmogenic effect of chemotherapeutic agents and the effect of paclitaxel on AF has been better defined compared with etoposide.[33,34] However, whether paclitaxel, compared with etoposide, may further sensitize the cardiac conduction system to RT needs further investigation. Cardiomyocytes generated from human-induced pluripotent stem cell lines may be the proper platform to test the hypotheses.[35] Despite the difference in cutoff values, results of the current study indicate a common process involving the SAN in RT-induced AF across different types of cancers.

Table 2. Competing Risk Regression Analysis for Atrial Fibrillation in SCLC Cohort

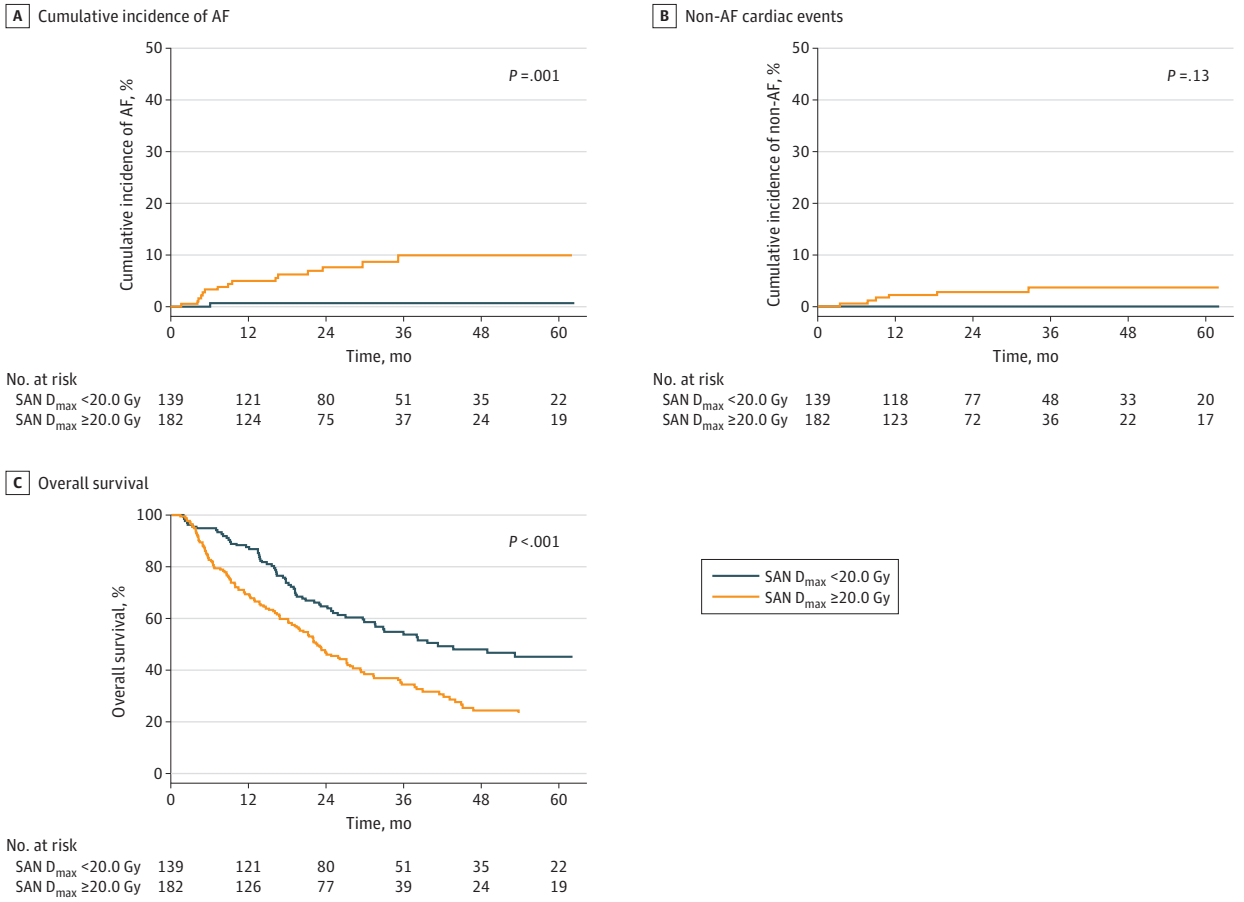
	Univariable		Multivariable	
Variable[a]	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
SAN D_{max}, Gy				
<53.5	1 [Reference]		1 [Reference]	NA
≥53.5	8.90 (2.40-32.96)	.001	14.91 (4.00-55.56)	<.001
Age, y	1.05 (0.99-1.11)	.12	1.08 (1.00-1.17)	.04
Tobacco use				
Never	1 [Reference]	NA	NA	NA
Ever	2.14 (0.45-10.21)	.34	NA	NA
Alcohol use				
Never	1 [Reference]	NA	1 [Reference]	NA
Ever	4.24 (0.55-32.83)	.17	6.09 (0.97-38.47)	.06
Hypertension				
No	1 [Reference]	NA	NA	NA
Yes	1.32 (0.35-4.96)	.68	NA	NA
Diabetes				
No	1 [Reference]	NA	NA	NA
Yes	0.71 (0.15-3.44)	.67	NA	NA
Cardiovascular disease				
No	1 [Reference]	NA	NA	NA
Yes	2.12 (0.53-8.53)	.29	NA	NA
Coronary artery calcium score				
No	1 [Reference]	NA	NA	NA
Yes	0.96 (0.20-4.75)	.96	NA	NA
CAC score	1.00 (1.00-1.00)	.61	NA	NA
No. of coronary arteries with calcification				
0	1 [Reference]	NA	1 [Reference]	NA
1-2	2.34 (0.45-12.3)	.31	1.66 (0.30-9.20)	.56
3-4	0.39 (0.05-2.83)	.35	0.21 (0.03-1.55)	.13
Aortic valve calcification				
No	1 [Reference]	NA	NA	NA
Yes	1.40 (0.35-5.63)	.64	NA	NA
Mitral valve calcification				
No	1 [Reference]	NA	NA	NA
Yes	2.32 (0.28-19.0)	.43	NA	NA
BMI	1.18 (1.00-1.39)	.05	1.37 (1.09-1.72)	.007
AJCC stage				
I-IIIA	1 [Reference]	NA	NA	NA
IIIB-IIIC	0.61 (0.16-2.26)	.46	NA	NA
Chemotherapy				
Etoposide + cisplatin	1 [Reference]	NA	NA	NA
Etoposide + carboplatin	0.92 (0.25-3.42)	.91	NA	NA
RT dose, Gy	0.99 (0.89-1.10)	.83	NA	NA
RT modality				
3D-CRT	1 [Reference]	NA	NA	NA
IMRT	0.32 (0.06-1.65)	.18	NA	NA

Abbreviations: 3-DCRT, 3-dimensional conformal radiotherapy; AJCC, American Joint Committee on Cancer; aHR, adjusted hazard ratio; BMI, body mass index; CAC, coronary artery calcium; CVD, cardiovascular disease; HR, hazard ratio; HTN, hypertension; IMRT, intensity-modulated radiotherapy; NA, not applicable; RT, radiotherapy; SAN D_{max}, maximum radiation dose exposed to sinoatrial node; SCLC, small cell lung cancer; WHO, World Health Organization.

[a] Categorical variables that had no events in 1 of the subgroups and were not applicable for regression analysis were sex, Eastern Cooperative Oncology Group performance status, pericardial effusion after chemoradiotherapy, and chest surgery after chemoradiotherapy.

The SAN D_{max} maintained its predictability of AF even after adjustments for well-known clinical risk factors of AF, such as age, body mass index, tobacco use, and hypertension.[36] We also incorporated CAC, which has been reported as a risk factor for AF,[37,38] as an adjusting factor in the multivariable model. The association between CAC score and cardiac adverse events has been previously demonstrated in patients with breast cancer receiving RT.[39] In the current study, a trend of increased

Figure 2. Incidence of Cardiac Adverse Events and Overall Survival According to SAN D_{max} in the NSCLC Cohort



Cumulative incidence of AF (A), non-AF cardiac events (B), and overall survival (C) in patients with SAN D_{max} of 20.0 Gy or greater and SAN D_{max} less than 20.0 Gy. AF indicates atrial fibrillation; NSCLC, non–small cell lung cancer; SAN D_{max}, maximum radiation dose exposed to sinoatrial node.

risk of new-onset AF in patients with CAC was observed but was not statistically significant. Further studies are needed to confirm the association of CAC with new-onset AF in the context of patients with lung cancer receiving CRT.

The high doses delivered to the SAN were significantly associated not only with AF, but also with poor survival, even after adjustments for other clinical variables. A recent population-based study among patients with breast cancer has also demonstrated that new-onset AF increased all-cause mortality.[40] Moreover, numerous studies have demonstrated the association between higher cardiac doses and worse OS.[7-9,41-45] In the current study, the patients were not tested routinely for arrhythmias, and those with higher SAN doses may have had undiagnosed and untreated AF leading to mortality. The SAN dose also inevitably correlates with mean heart dose, and higher SAN D_{max} may serve as a surrogate of higher mean heart dose. Higher mean heart dose is known to correlate with more severe lymphopenia, which leads to inferior survival.[46] Although the association seems clear, further studies are needed to elucidate the underlying mechanisms of increased mortality due to higher cardiac doses.

Cardiac parameters other than SAN D_{max}, such as RA D_{max}, also exhibited comparable C indices, indicating that SAN D_{max} is not the only predictor for new-onset AF. Considering the proximity of SAN and RA, the strong correlation between SAN D_{max} and RA D_{max} may have led to the similar results between the 2 parameters. The current study data imply that if there are limitations in defining SAN, RA D_{max} may be able to serve as an alternative. In addition, the radiation dose delivered to the atrium may have caused structural changes in the atrium, such as fibrosis, and facilitate AF. Atrial fibrosis, remodeling, and myopathy can be visualized with cardiac magnetic resonance imaging.[47,48] Prospective studies that use cardiac magnetic resonance imaging following thoracic RT may uncover the role of RT-induced structural changes in the development of AF.

Because of the different optimal cutoff points of SAN D_{max} in the SCLC and NSCLC cohorts, clear dose constraints cannot be currently recommended. Further validation studies are required to confirm the optimal cutoff value. We suggest keeping SAN D_{max} as low as reasonably allowable while satisfying the dose constraints to other organs at risk and maintaining tumor coverage. In addition, we suggest establishing a screening protocol for subclinical or clinical AF in the multidisciplinary team. Patients with cancer receiving thoracic RT may be screened using regular ECG or Holter monitoring.

Table 3. Competing Risk Regression Analysis for Atrial Fibrillation in NSCLC Cohort

	Univariable		Multivariable	
Variable[a]	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
SAN D_{max}, Gy				
<20.0	1 [Reference]	NA	1 [Reference]	NA
≥20.0	13.15 (1.73-99.82)	.01	15.67 (2.08-118.20)	.008
Age, y	1.03 (0.97-1.09)	.30	NA	NA
Sex				
Male	1 [Reference]	NA	NA	NA
Female	0.53 (0.13-2.25)	.39	NA	NA
ECOG performance status				
0	1 [Reference]	NA	NA	NA
1-2	2.64 (0.35-19.96)	.35	NA	NA
Tobacco use				
Never	1 [Reference]	NA	1 [Reference]	NA
Ever	5.15 (0.71-37.7)	.11	5.07 (0.74-34.71)	.10
Alcohol use				
Never	1 [Reference]	NA	NA	NA
Ever	0.63 (0.25-1.63)	.34	NA	NA
Hypertension				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	3.38 (1.19-9.56)	.02	3.74 (1.24-11.20)	.02
Diabetes				
No	1 [Reference]	NA	NA	NA
Yes	3.08 (1.18-8.02)	.02	NA	NA
Cardiovascular disease				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	0.69 (0.16-2.95)	.61	0.33 (0.09-1.28)	.11
Coronary artery calcium				
No	1 [Reference]	NA	NA	NA
Yes	4.16 (0.56-31.1)	.16	NA	NA
CAC score	1.00 (1.00-1.01)	.03	NA	NA
No. of coronary arteries with calcification				
0	1 [Reference]	NA	NA	NA
1-2	2.97 (0.34-26.3)	.33	NA	NA
3-4	4.96 (0.65-37.8)	.12	NA	NA
Aortic valve calcification				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	4.24 (1.64-11)	.003	3.18 (1.17-8.67)	.02
Mitral valve calcification				
No	1 [Reference]	NA	NA	NA
Yes	2.45 (0.69-8.64)	.16	NA	NA
Pericardial effusion after CRT				
No	1 [Reference]	NA	NA	NA
Yes	0.80 (0.11-5.85)	.82	NA	NA
BMI	1.01 (0.90-1.12)	.89	NA	NA
AJCC stage				
II-IIIA	1 [Reference]	NA	NA	NA
IIIB-IIIC	0.94 (0.35-2.54)	.90	NA	NA
Chemotherapy				
Others	1 [Reference]	NA	NA	NA
Paclitaxel + carboplatin	0.71 (0.16-3.11)	.65	NA	NA

(continued)

Table 3. Competing Risk Regression Analysis for Atrial Fibrillation in NSCLC Cohort (continued)

Variable[a]	Univariable		Multivariable	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
Maintenance ICI				
No	1 [Reference]	NA	NA	NA
Yes	0.91 (0.26-3.15)	.88	NA	NA
RT dose, Gy	1.05 (0.94-1.17)	.39	NA	NA
RT modality				
3D-CRT	1 [Reference]	NA	NA	NA
IMRT	1.50 (0.55-4.14)	.43	NA	NA

Abbreviations: 3D-CRT, 3-dimensional conformal radiotherapy; AJCC, American Joint Committee on Cancer; aHR, adjusted hazard ratio; BMI, body mass index; CAC, coronary artery calcification; CVD, cardiovascular disease; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HTN, hypertension; ICI, immune checkpoint inhibitor; IMRT, intensity-modulated radiotherapy; NA, not applicable; NSCLC, non–small cell lung cancer; RT, radiotherapy; SAN D_{max}, maximum radiation dose exposed to sinoatrial node; WHO, World Health Organization.

[a] The categorical variable of chest surgery after CRT had no events in 1 of the subgroups and was not applicable for regression analysis.

In addition, a recent pragmatic study demonstrated the usefulness of smartwatch application in identifying subclinical AF.[49] Monitoring patients using smartwatches may be feasible for early detection of AF.

Limitations

Several limitations of this study stem from its retrospective nature. Patients were not prospectively followed up for cardiac toxic effects, which limited the estimation of the true incidence of cardiac adverse events. In addition, the small number of cardiac events underpowered the results of multivariable analysis. However, 2 cardiologists who were blinded to the dose-volume parameters reviewed the patients' medical records thoroughly. Prospective studies including proper cardiac screening protocols, such as use of cardiac biomarkers, echocardiogram, and ECG, should be pursued. The results of several ongoing prospective studies (eg, NCT04361240, NCT04674501, NCT04867564, NCT04896242) are awaited.

Conclusions

In this cohort study, results suggest that incidental irradiation of the SAN during CRT may be associated with the development of AF and increased mortality. Although further validation is required, the results indicate that SAN may need to be considered as an organ at risk during RT planning and that patients receiving higher doses to the SAN may need close monitoring for earlier recognition and treatment of AF.

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