



Original Research Article

Dose to the cardio-pulmonary system and treatment-induced electrocardiogram abnormalities in locally advanced non-small cell lung cancer

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ABSTRACT

Introduction: High dose radiotherapy (RT) has been associated with unexpectedly short survival times for locally advanced Non-Small Cell Lung Cancer (LA-NSCLC) patients. Here we tested the hypothesis that cardiac substructure dose is associated with electrocardiography (ECG) assessed abnormalities after RT for LA-NSCLC.

Materials and methods: Pre- and post-RT ECGs were analyzed for 155 LA-NSCLC patients treated to a median of 64 Gy in 1.8–2.0 Gy fractions using intensity-modulated RT plus chemotherapy (concurrent/sequential: 64%/36%) between 2004 and 2014. ECG abnormalities were classified as new Arrhythmic, Ischemic/Pericardial, or Non-specific (A_{AECG} , I/P_{AECG} , or NS_{AECG}) events. Abnormalities were modeled as time to ECG events considering death a competing risk, and the variables considered for analysis were fractionation-corrected dose-volume metrics ($\alpha/\beta = 3$ Gy) of ten cardio-pulmonary structures (aorta, heart, heart chambers, inferior and superior vena cava, lung, pulmonary artery) and 15 disease, patient and treatment characteristics. Each abnormality was modelled using bootstrapping and a candidate predictor was suggested by a median multiple testing-adjusted p-value ≤ 0.05 across the 1000 generated samples. Forward-stepwise multivariate analysis was conducted in case of more than one candidate.

Results: At a median of eight months post-RT, the rate of A_{AECG} , I/P_{AECG} , and NS_{AECG} was 66%, 35%, and 67%. Both A_{AECG} and I/P_{AECG} were associated with worse performance status ($p = 0.007$, 0.03), while a higher superior vena cava minimum dose was associated with NS_{AECG} ($p = 0.002$).

Conclusion: This study suggests that higher radiation doses to the cardio-pulmonary system lead to non-specific ECG abnormalities. Reducing dose to this system, along with effective tumor control, is likely to decrease radiation-induced cardiac toxicity.

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1. Introduction

Lung cancer has been the leading cause of cancer death in the US for the last 25 years [1], and is among the cancer entities with the lowest 5-year relative survival rates for all stages (18%) [2]. The recently updated standard-of-care for locally advanced inoperable non-small cell lung cancer (LA-NSCLC) is concurrent chemotherapy and radiation therapy (RT) followed by adjuvant durvalumab [3]. However, most toxicity data have been based on the preceding standard of care, i.e., concurrent chemo-RT [4,5].

The most commonly observed acute effects involve the lungs and esophagus, while cardiac toxicity has typically been overlooked given that the overall survival (OS) times have in general been expected to be shorter than the manifestation of cardiac toxicity [6].

In view of earlier, encouraging data suggesting improved OS for LA-NSCLC with RT dose-escalation [7–11], the phase III RTOG 0617 trial compared high- to standard dose (74 Gy vs. 60 Gy) chemo-RT with or without Cetuximab [12]. Unexpectedly, the OS times in the high-dose arm were shorter, and increased heart dose was suggested an independent predictor to this finding. Based on these results, Faivre-Finn et al. hypothesized that under-reported cardiac toxicity might have contributed to the inferiority of the high-dose arm [13]. In general, radiation-induced cardiac toxicity has been considered a late effect as observed from breast cancer data [14,15] and Hodgkin's lymphoma data [16,17], but there are a

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few lung cancer studies suggesting that cardiac toxicity manifests already six months after completed RT [18,19]. Even though this has recently spurred increased recognition on cardiac toxicity in lung cancer RT [20–26], there is limited associated dose tolerance data [27–31] particularly for early cardiac toxicity assessed using electrocardiography (ECG) [32–35].

In this study, we explored the hypothesis that RT dose to the cardio-pulmonary system (including cardiac substructures) is associated with arrhythmic, ischemic/pericardial, or non-specific ECG abnormalities in stage III inoperable LA-NSCLC treated with intensity-modulated RT (IMRT).

2. Materials and methods

2.1. Cohort data and inclusion criteria

From a total of 241 inoperable stage III LA-NSCLC patients treated with IMRT in combination with concurrent/sequential chemotherapy between 2004 and 2014 at the Memorial Sloan Kettering Cancer Center [36,37], this Institutional Review Board approved retrospective study included the 155 patients that had ECG acquired before and after RT. Among these patients, 65% received concurrent chemotherapy, while 35% received sequential chemotherapy. The population median prescribed dose was 64 Gy (range: 50–80 Gy) in 1.8–2.0 Gy fractions. Dose was prescribed to the primary tumor, and positron emission tomography positive lymph nodes. All dose distributions were re-calculated with our currently used dose-calculation algorithm (*Eclipse AAA v.13, Varian Medical Systems, Palo Alto, CA, US*). Patient characteristics and ECG reports were gathered from electronic medical records (EMRs), and records from all specialties were utilized to retrieve this information. A summary of the cohort data is depicted in [Table 1](#).

2.2. Electrocardiogram abnormalities

Electrocardiograms were retrospectively reviewed by A.H, and ECG abnormalities were defined as any new event after compared to immediately before RT. For the post-RT ECG readings, if a patient experienced a new ECG event at time point two and not at time point one, time point two was recorded. Any new ECG event was categorized into being primarily *Arrhythmic* (atrial fibrillation/flutter, atrioventricular block, left or right bundle branch block, prolonged/widened QRS, sinus bradycardia, and sinus tachycardia), *Ischemic/Pericardial* (anterior infarct, septal infarct etc., and Q/ST/T change), or *Non-specific* (left/right axis deviation, low voltage QRS, poor R wave progression, premature ventricular complex, atrial enlargement, and prolonged/short QT interval) [30,35].

2.3. Cardio-pulmonary structures and dose representation

Ten structures were considered for analysis: the aorta, heart, chambers (left and right atrium and ventricles, LA, RA, LV, RV), inferior and superior vena cava (IVC, SVC), lung, and the pulmonary artery (PA). Anatomical definitions followed those from Feng et al. [38]; further segmentation details are given in [Supplementary material S1 and S2](#).

The dose-volume histograms (DVHs) for each patient and structure were converted into equivalent doses in 2 Gy fractions ($\alpha/\beta = 3$ Gy). From these DVHs, the maximum, minimum, and the mean dose (Max[Gy], Min[Gy], and Mean[Gy]), and the minimum dose to the hottest x% volume, Dx%[Gy] ($x = 5-95$ in 5% steps) were extracted (dose-volume nomenclature according to TG 263 [39]). It was assumed that the DVH for each structure could be explained by Max[Gy], Min[Gy], and Mean[Gy], and that all remaining 19 Dx%[Gy] metrics were strongly correlated with any of these three

Table 1

Distribution of all disease, patient, and treatment characteristics investigated. *Pre-RT angina, arrhythmia, coronary artery disease, congestive heart failure, endocarditis, myocardial infarct, pericardial effusion, tamponade, and valve disease; **Pre-RT abdominal aortic aneurysm, cerebrovascular accident, deep vein thrombosis, middle cerebral artery syndrome, peripheral vascular disease, pulmonary embolism, and transient ischemic attack. ***Any ECG abnormality pre-RT. Abbreviations: COPD: Chronic obstructive pulmonary disease; KPS: Karnofsky performance status; LLL: Left lower lobe; LUL: Left upper lobe; RLL: Right lower lobe; RML: Right middle lobe; RUL: Right upper lobe.

Variable	N = 155 (% (n) or median (range))
Age at RT [y]	66 (25–86)
Cardiac disease*	29 (45)
Cardiovascular disease**	13 (20)
Chemotherapy timing	
Concurrent	65 (101)
Sequential	35 (54)
COPD	28 (43)
Diabetes	17 (27)
ECG abnormality***	61 (95)
Histology	
Adenocarcinoma	67 (104)
Squamous cell carcinoma	28 (44)
Other	5 (7)
Hyperlipidemia	35 (54)
Hypertension	48 (75)
KPS	80 (60–100)
Sex	
Female	49 (76)
Male	51 (79)
Smoking status	
Current	29 (45)
Former	61 (95)
Never	10 (15)
Stage	
IIIA	46 (71)
IIIB	54 (84)
Tumor location	
LLL	12 (19)
LUL	25 (39)
RLL	14 (22)
RML	9 (14)
RUL	55 (35)
N/A	4 (6)

metrics. This was, however, tested using an unsupervised approach prior to modeling: the dimensionality of each structure's DVH was assessed using principal component analysis (PCA). For each structure, the number of PCs accounting for $\geq 95\%$ of the explained variance in the DVH was assessed. In parallel, all Dx%[Gy] metrics were investigated for correlation with Max[Gy], Min[Gy], and Mean[Gy]. If the Spearman's rank correlation coefficient (R_s) exceeded 0.70 then a particular Dx%[Gy] metric was judged redundant. If, on the other hand, the R_s was below 0.70, the number of PCs was larger than three for a 95% explained variance, and Max[Gy], Min[Gy], or Mean[Gy] of that particular structure was a candidate predictor, that particular Dx%[Gy] was considered for modeling as well. Both the PCA and the correlation assessment were conducted with resampling (1000 bootstrap samples; median value over all samples is reported).

2.4. Modeling

The three ECG abnormalities were modelled as time to event accounting for death as the competing risk using a Fine and Gray sub distribution [40]. Variables considered for analysis were, unless otherwise specified, Max[Gy], Min[Gy], and Mean[Gy] for each of the ten structures, and 15 disease, patient and treatment characteristics (age, cardiac disease (baseline), cardiovascular disease (baseline), chemotherapy timing, COPD, diabetes, ECG abnormality (baseline), histology, hyperlipidemia, hypertension,

karnofsky performance status (KPS), sex, smoking status, stage, and tumor location; Table 1).

Each variable was first subject to univariate analysis using a same resampling approach as previously outlined. If a variable presented with a median p-value ≤ 0.05 across these samples ($p \leq 0.05$ also after adjusted for false discovery rate), that variable was considered a candidate predictor. If multiple DVH metrics of the same structure were candidate predictors only the metric with the lowest p-value was considered a candidate predictor. If there was more than one candidate predictor per ECG abnormality, these candidates were included in a bootstrapped multivariate analysis. However, preceding multivariate analysis, the correlation between candidate predictors was investigated and a candidate predictor presenting with $R_s \geq 0.70$ (over 1000 bootstrap samples) with any other candidate predictor with a lower p-value was considered redundant, and was not included in the multivariate analysis. The multivariate analysis was conducted using a forward-stepwise procedure minimizing the Bayesian Information Criterion (BIC) [41]. In each bootstrap sample, all candidate predictors with a BIC $\leq 0-2$ of the minimum BIC were considered final predictors [42], and the most frequently selected multivariate models across all samples were considered final.

The association between candidate predictors and predictors included in the final models of each ECG abnormality was plotted as cumulative incidence functions (CIFs). All statistical analyses were conducted in R version 3.5.1 using packages ‘cmprsk’ [40] and ‘crstest’ [41].

3. Results

The raw rate of *Arrhythmic*, *Ischemic/Pericardial*, and *Non-specific* abnormalities were 66%, 35%, and 67%, respectively. The corresponding median times to each abnormality (including all 155 patients) were seven, nine, and eight months (range: 0–96 months) after completed RT. The CIFs taking into account the competing risk of death for each abnormality is given in Fig. 1.

Three PCs explained a median of 97% (range: 92–99%) of the DVH variance, and only for the lung was the explained variance with three PCs $< 95\%$ (i.e., 92%), but four PCs accounted for more than 96% of the lung DVH variance (Fig. 2). Also, the correlation between the 19 Dx%[Gy] metrics and Min[Gy], Mean[Gy], or Max[Gy] was strong with R_s exceeding 0.70 for all metrics across all structures except for aorta D15%[Gy] and D20%[Gy], and lung D5%[Gy], D10%[Gy], and D40–90%[Gy] (Fig. 2). These 15 metrics were, therefore, also investigated univariately.

For *Arrhythmic* abnormalities, KPS, aorta Min[Gy] and lung Mean[Gy] were candidate predictors ($p = 0.007$, 0.008 , 0.02 ; Table 2). None of the additional 15 aorta or lung Dx%[Gy] metrics

predicted this abnormality better than aorta Min[Gy] and lung Mean[Gy] ($p = 0.02-0.47$). The correlation between KPS, aorta Min[Gy] and lung Mean[Gy] was at most modest with R_s reaching 0.56 between aorta Min[Gy] and lung Mean[Gy]. Thus, all three variables were considered candidate predictors and were passed on to multivariate analysis. The final multivariate model included KPS only (model frequency: 39%; Fig. 3). With a considerably lower frequency, two other single-variable models were selected that included either aorta Min[Gy] or lung Mean[Gy] (model frequency: 20%, 15%; Fig. 3), whereas non-single variable models were selected less frequently (model frequency: 5–8%).

Only KPS was a candidate and, thus, final predictor for *Ischemic/Pericardial* abnormalities ($p = 0.03$; Table 2; Fig. 3). Among the DVH metrics, lung Mean[Gy] showed a predictive tendency ($p = 0.09$). In summary, a worse performance status, i.e. lower KPS, was associated with a higher probability of both *Arrhythmic* and *Ischemic/Pericardial* abnormalities.

The largest number of candidate predictors was observed for *Non-specific* abnormalities: four in total; all DVH metrics, i.e., IVC Min[Gy], lung Mean[Gy], PA Mean[Gy], and SVC Min[Gy] ($p = 0.0004-0.005$; Table 2). Given that the additional 13 lung Dx%[Gy] metrics were not better predictors than lung Mean[Gy] ($p = 0.01-0.52$ vs. $p = 0.005$), and that R_s was at most 0.42 between the four candidate predictors (IVC Min[Gy] and lung Mean[Gy]), these four metrics were passed on to multivariate analysis. The final multivariate model included SVC Min[Gy] (model frequency: 23%; Fig. 3) such that a higher minimum dose (i.e., less sparing) is associated with *Non-specific* abnormalities. The subsequent three most frequently selected models (model frequency: 11–14%) were single variable models and included any of the remaining three DVH metrics. The most frequently selected non-single variable model was that including lung Mean[Gy], and SVC Min[Gy], but this model presented with a frequency of only 8%.

4. Discussion

The underlying hypothesis of RT dose to the cardio-pulmonary system being associated with ECG abnormalities after RT for LA-NSCLC was confirmed between non-specific ECG abnormalities and high superior vena cava (SVC) dose. Also, the examined ECG abnormalities manifested at a median of eight months post-RT, which further adds to the growing evidence of early onset radiation-induced cardiac toxicity in NSCLC patients [12,18,19].

Pre-treatment cardiac toxicity is common in this patient population. Among our 155 patients, 61% experienced pre-treatment ECG abnormalities, which is considerably higher than reported for the general American population (adults; similar age

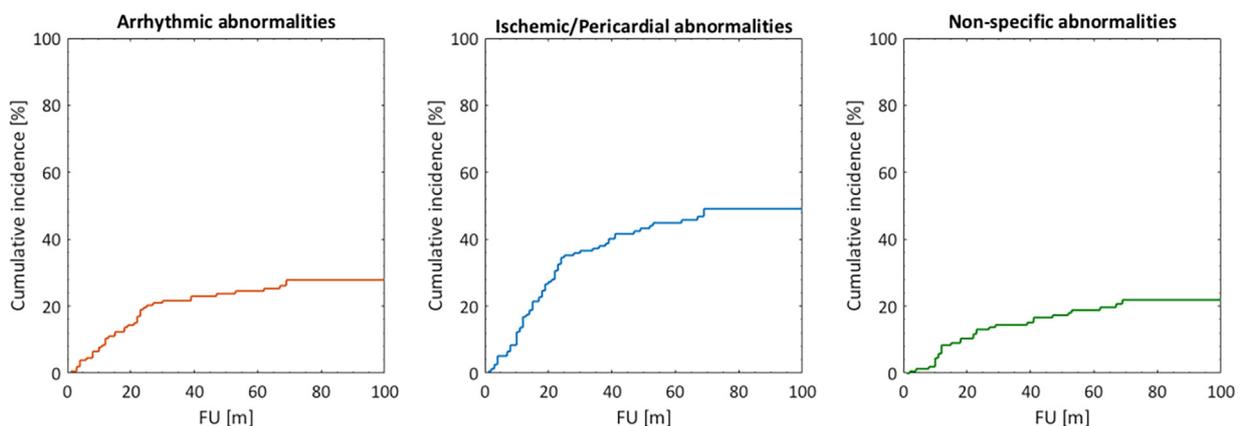


Fig. 1. Cumulative incidence functions for the three studied ECG abnormalities.

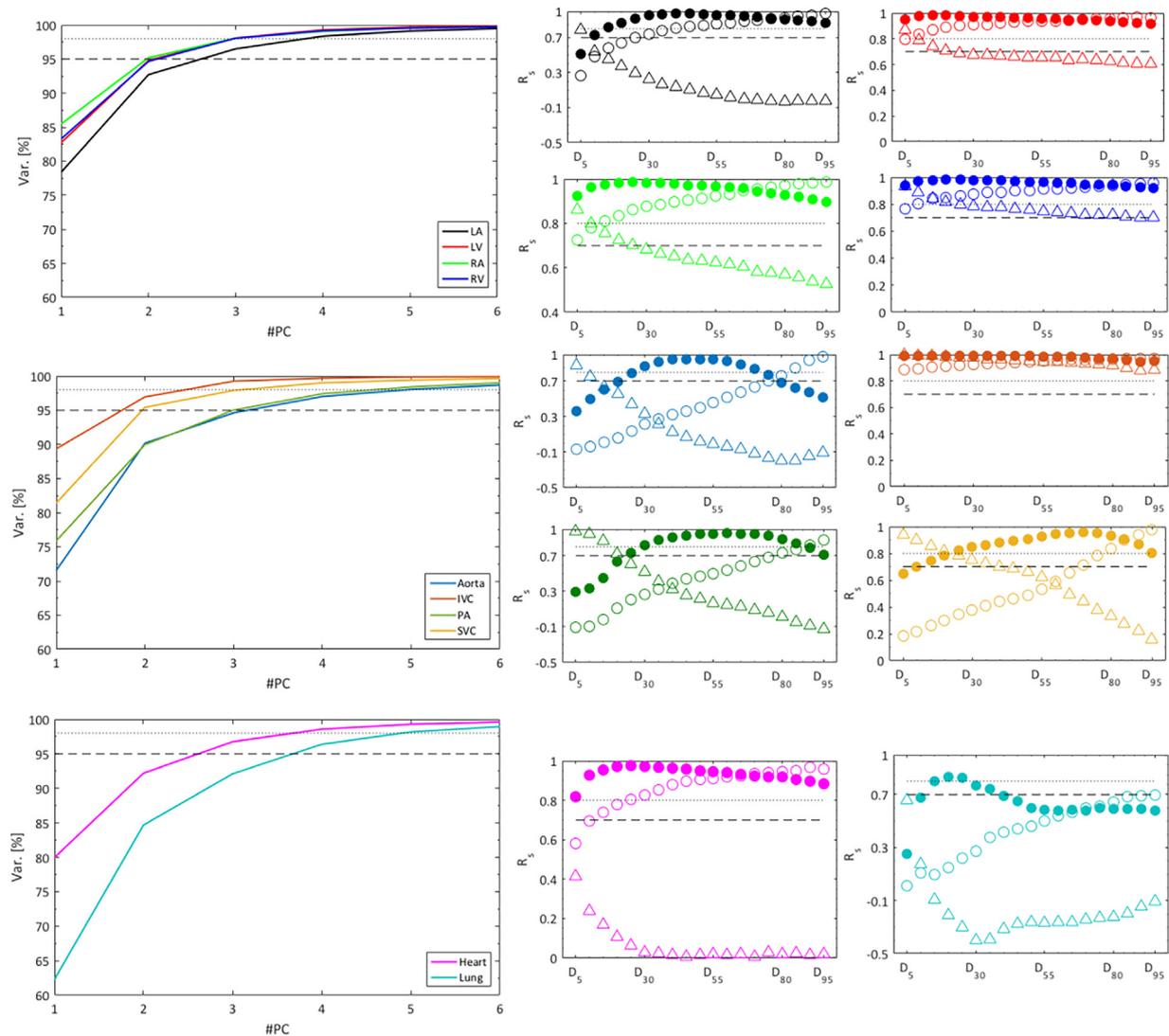


Fig 2. Left: Explained variance as a function of the number of principal components (#PC) based on the substructure DVHs for all patients. Dashed and dotted lines denote a 95% and 98% explained variance, respectively. Right: Spearman's correlation coefficients (R_s) between the min/mean/max dose (open circles/filled circles/open triangles) and D_x metrics ranging between D_5 and D_{95} (in 5 Gy intervals) with the same substructure color coding as on the left. Dashed and dotted lines denote $R_s = 0.70$, and $R_s = 0.80$. Abbreviations: IVC: Inferior vena cava; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; RA: Right atrium; RV: Right ventricle; SVC: Superior vena cava.

distribution), which has been estimated to be at most 37% (accumulation of all possible ECG abnormalities) for Afro-American men older than 65 years [43]. However, in that national population study only major ECG abnormalities were addressed and as such some of the ECG abnormalities included in the current study (e.g., sinus tachycardia/bradycardia, axis deviation, wide QRS, and poor R wave progression) were not. Further in [43], the prevalence of ECG abnormalities was associated with the presence of hypertension, diabetes, high blood pressure, and advanced age. A similar pattern was also found in the current cohort with 42% presenting with pre-existing cardiovascular disease, 57% with hypertension, and 19% with diabetes among the 95 patients with pre-existing ECG abnormalities. The corresponding rates for the remaining 60 patients with no ECG abnormalities prior to RT were 27%, 35%, and 15% for pre-existing cardiovascular disease, hypertension, and diabetes, respectively. Also, patients with pre-RT ECG abnormalities were slightly older (population averages: 67 vs. 62 years). Thus, our data indicate a higher prevalence of ECG abnormalities among LA-NSCLC patients compared to the general population, motivating the need for closer monitoring and follow-up of cardio-pulmonary status in this patient population.

Following RT for breast cancer and Hodgkin's lymphoma, primarily long-term severe ECG abnormalities, such as arrhythmias and conduction blocks, have been reported [44]. However, Strender et al. described earlier ECG abnormalities and found that 45% of their 197 breast cancer patients had conduction abnormalities six months after treatment; among the left-sided patients, the major ECG event was T-wave abnormalities [45]. Furthermore, in a limited-sized prospective study including 25 patients treated to a median of 50 Gy in 2 Gy fractions for primary thoracic malignancies including lung cancer, Gomez et al. observed that approximately every other patient presented with ECG abnormalities during or near the end of treatment (i.e., end of RT or 1–2 months post-RT) with most abnormalities being non-specific; however, no ECG assessments were made later than 1–2 months post-RT [35]. In another small cohort including only LA-NSCLC patients, Vivekanandan et al. instead observed that ischemic/pericarditis like ECG abnormalities were most common (N = 53; rate: 14%) at the six months post-RT assessment [30]. Unlike in [30], the rate of ECG abnormalities in the current study was the lowest for ischemic/pericardial abnormalities (35%) compared to 53% for arrhythmic, and 89% for non-specific abnormalities six months

Table 2

Univariate analysis results for the three investigated ECG abnormalities based on all investigated disease, patient and treatment characteristics, as well as the DVH metrics. Note: P-value refers to the median p-value across the 1000 Bootstrap samples; Final candidate predictors for each ECG abnormality are denoted by *. Abbreviations: AR: Arrhythmic; I/P: Ischemic/Pericardial; NS: Non-specific; SCC: Squamous cell carcinoma.

Variable	AR p-value	I/P p-value	NS p-value
Age at RT [y]	0.47	0.47	0.40
Cardiac disease	0.37	0.06	0.38
Cardiovascular disease	0.09	0.07	0.13
Chemotherapy timing (Ref: Sequential)	0.47	0.25	0.40
COPD	0.43	0.42	0.25
Diabetes	0.21	0.23	0.29
ECG abnormality	0.49	0.33	0.41
Histology (Ref: Adenocarcinoma)	0.22	0.20	0.45
(Ref: SCC)	0.05	0.37	0.41
Hyperlipidemia	0.17	0.45	0.35
Hypertension	0.47	0.37	0.36
KPS	0.007*	0.03*	0.24
Sex (Ref: Female)	0.26	0.46	0.03
Smoking status (Ref: Current)	0.40	0.43	0.47
(Ref: Former)	0.39	0.47	0.40
Stage (Ref: IIIA)	0.10	0.39	0.50
Tumor laterality (Ref: Left)	0.41	0.52	0.19
(Ref: Right)	0.44	0.52	0.07
Tumor inferiority (Ref: Inferior)	0.29	0.24	0.47
(Ref: Superior)	0.52	0.10	0.16
Aorta Min[Gy]	0.008*	0.48	0.10
Mean[Gy]	0.40	0.40	0.03
Max[Gy]	0.47	0.48	0.45
Heart Min[Gy]	0.43	0.46	0.10
Mean[Gy]	0.22	0.46	0.05
Max[Gy]	0.45	0.29	0.15
IVC Min[Gy]	0.20	0.31	0.0004*
Mean[Gy]	0.08	0.30	0.23
Max[Gy]	0.22	0.35	0.22
Lung Min[Gy]	0.47	0.40	0.34
Mean[Gy]	0.02*	0.09	0.005*
Max[Gy]	0.29	0.30	0.35
LA Min[Gy]	0.48	0.32	0.35
Mean[Gy]	0.43	0.51	0.02
Max[Gy]	0.49	0.28	0.03
LV Min[Gy]	0.33	0.25	0.44
Mean[Gy]	0.49	0.43	0.46
Max[Gy]	0.46	0.34	0.01
PA Min[Gy]	0.41	0.50	0.02
Mean[Gy]	0.42	0.25	0.005*
Max[Gy]	0.48	0.29	0.44
RA Min[Gy]	0.35	0.24	0.11
Mean[Gy]	0.04	0.50	0.07
Max[Gy]	0.04	0.49	0.04
RV Min[Gy]	0.45	0.16	0.45
Mean[Gy]	0.35	0.35	0.44
Max[Gy]	0.33	0.40	0.14
SVC Min[Gy]	0.11	0.27	0.002*
Mean[Gy]	0.15	0.46	0.11
Max[Gy]	0.32	0.50	0.47

post-RT. In our cohort, non-specific abnormalities were more prevalent than both arrhythmic and ischemic/pericardial abnormalities within the studied follow-up period, which spanned from the end of RT up to nine years after completed RT. The pattern of non-specific ECG abnormalities being most prevalent was also observed within the much shorter 1–2 months time period studied in [35]. Thus, the high rate of non-specific ECG abnormalities observed in the current study, which includes to the best of our knowledge by far the largest number of LA-NSCLC with ECG data published so far, suggest that these ECG abnormalities are more related to radiation-induced cardiac toxicity than are arrhythmic and ischemic/pericardial abnormalities. The role as the primary radiation-induced cardiac toxicity is also supported by the identified cardio-pulmonary dose-response relationship, which was only established for non-specific ECG abnormalities.

The dose-response relationship identified for non-specific ECG abnormalities suggests that higher minimum SVC doses are likely to generate higher incidences of non-specific ECG abnormalities. More specifically, reducing the minimum SVC dose from 35 Gy to 10 Gy would lead to a 4% reduction (from 16% to 12%) in the cumulative incidence of non-specific ECG abnormalities two years post-RT according to this model (Fig. 3). The three residual candidate predictors for non-specific ECG abnormalities involved IVC, lung and pulmonary artery dose, but our multivariate analysis demonstrated that the minimum SVC dose was the final predictor. Similarly, Stam et al. found that near minimum (D90%[Gy]) SVC doses were significantly correlated with non-cancer death (*i.e.*, cause of death not indicated to be related to the disease) in patients treated with stereotactic body RT for early stage NSCLC patients [28]. Their multivariate model also included left atrial maximum dose, which we did not observe. In a subsequent analysis we established a significant association between the non-specific ECG abnormalities and OS (Fig S3; Authors' note: OS was chosen as endpoint over non-cancer death given that patients were lost to follow-up and scoring of cause-specific mortality is, therefore, questionable): we demonstrated that higher SVC doses lead to non-specific ECG abnormalities and shorter survival times. Thus, conforming the IMRT dose distributions to maximally avoid irradiation of the SVC should be warranted.

While the pathophysiologic mechanism on how RT affects SVC is not clear, radiation-induced toxicity on vessels in the short- and long-term have been described: initially, irradiation causes endothelial dysfunction, which ultimately leads to intimal hyperplasia [46]. In parallel, RT activates nuclear factor-kappa B, which can cause inflammation due to oxidative stress [47]. In the later phase, vasa vasorum damage (*i.e.*, microvasculature that nourishes the walls of large blood vessels) produces focal necrosis of the media, which results in fibrosis [48]. Additionally, case reports of SVC obstruction caused by vascular fibrosis due to RT years earlier have been described [49]. Rather than slowly progressing fibrosis explaining our SVC results, other potential mechanisms are microvascular damage or disturbances of the conduction system given that the sinoatrial node is located at the junction between the right atrium and the SVC. Also, accounting for organ motion uncertainty (including that from the heart) nearby located structures such as the RA, origin of the coronary artery origin and/or the sinoatrial node may also play a role to our SVC finding. Monitoring SVC pathological conditions may be further improved using *e.g.* MRI venography imaging [49].

Even though no dose-response relationship was established for arrhythmic or ischemic/pericardial ECG abnormalities, the identified association between these and KPS could be used as an indicator to precautionous planning involving more stringent dose/volume

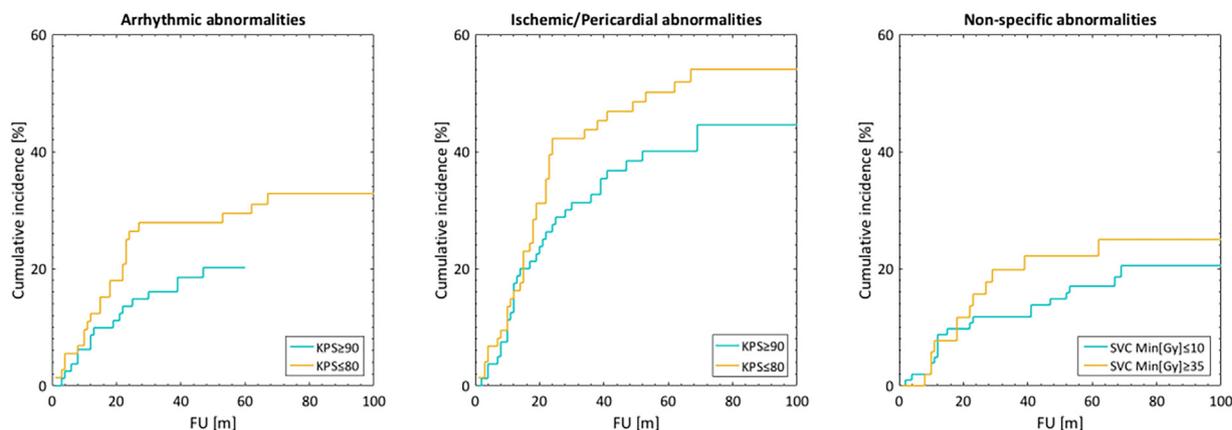


Fig 3. Cumulative incidence functions stratified by the tertiles of the three predictors included in the final model for each ECG abnormality.

constraints to structures of the cardio-pulmonary system for patients presenting with a $KPS \leq 80$ (Fig. 3), also given that ischemic/pericardial ECG abnormalities were associated with worse OS (Fig S3). In [30], an association was found between ‘any’ ECG abnormality six months post-RT and OS, but this relationship did not persist as the ECG abnormalities were studied separately as ischemic/pericardial or conduction changes, yet again, this inconclusiveness may be hampered by the size of their cohort ($N = 53$). As for arrhythmic abnormalities, the superior heart region (including the SVC) is where arrhythmias are more likely to originate and high dose can ablate cardiac conductive tissue [50]. Thus, further studies are needed to better understand how RT affects the cardiac conduction system and more specifically, arrhythmias.

This study is associated with a couple of limitations: ECGs were identified retrospectively from the EMRs and patient selection bias is likely, *i.e.*, patients presenting with symptoms are more likely to have an ECG acquired. Therefore, the true ECG rate in this population may have been misjudged. Detailed data on all such symptoms was not available, however, comparing the 86 patients from the original cohort ($N = 241$) that were not included in this study with the 155 included patients, did not indicate any significant difference in either mortality rate or follow-up time (mortality rate: 71% vs. 77% ($p = 0.32$); median follow-up time: 20 months vs. 20 months ($p = 0.13$)). Additionally, to assess ECG abnormalities we relied on reports, which are mainly used as a screening tool in clinical practice. Also, reversible and irreversible ECG abnormalities post-RT were not differentiated. Lastly, given that the 155 patients were treated at only one institution, we advise others to externally validate our results and assess the treatment planning feasibility of the SVC minimum dose before routinely implementing such a dose-volume constraint.

In conclusion, this study indicates that non-specific ECG abnormalities are more common after RT for LA-NSCLC than ECG abnormalities related to arrhythmic or ischemic/pericardial abnormalities, and that these are caused by dose to the superior vena cava (SVC). Prior to adopting a minimum SVC dose-volume constraint (except for As Low As Reasonably Achievable), this finding should be explored externally. In addition, patients with $KPS \leq 80$ may also benefit from a lowered SVC dose, and may constitute a subgroup that could also profit from additional and close cardiac monitoring. Lastly and due to heterogeneity in cardiac toxicity ranging from myocardial to vascular, thrombotic, or metabolic, using ECG in combination with biomarkers (*e.g.*, troponins, BNP) and advanced imaging, such as cardiac MRI may provide more insight into radiation-induced cardiac toxicity.

Declaration of Competing Interest

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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.2019.09.003>.

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