Dosimetric Predictors of Cardiotoxicity in Thoracic Radiotherapy for Lung Cancer

Jenna F. Borkenhagen,[1] Carmen Bergom,[1] Cooper T. Rapp,[1] Slade J. Klawikowski,[1] Lisa E. Rein,[2] Elizabeth M. Gore[1]

Abstract

When treating lung cancer with radiotherapy, higher cardiac doses are associated with worse overall survival, although the association with early cardiotoxicity is poorly understood. In this institutional retrospective review, the volume of ventricles receiving ≥45 Gy radiotherapy dose was associated with early cardiotoxicity. In practice, early cardiotoxicity is under-reported, supporting the need for detailed cardiac evaluations in high-risk patients.

Background: Higher cardiac radiotherapy (RT) doses when treating lung cancer are associated with worse overall survival (OS), although the direct association between cardiac dose and early cardiotoxicity is poorly understood. We hypothesized that RT doses to the heart and cardiac substructures are associated with under-reported early cardiotoxicity and worse OS. **Patients and Methods:** We conducted an institutional retrospective review of lung cancer patients treated with conventionally fractionated RT from 2010 to 2015. Collected data included pre-RT cardiac risk factors, post-RT cardiotoxicities, and dose-volume parameters for cardiac substructures. Univariate and multivariate analyses were performed to identify predictors of cardiotoxicity and OS. **Results:** Seventy-six cases were evaluated with 1.2 years median follow-up. Cardiotoxicities included atrial arrhythmia (n = 5), pericardial effusion (n = 16), and valvular disease (n = 1). In univariate analysis, significant dose-volume predictors for cardiotoxicity included mean RT dose to structure of interest, volume of structure of interest receiving ≥30 Gy RT dose, and volume of structure of interest receiving ≥45 Gy RT dose (V45) to the atria, ventricles, and pericardium. Higher ventricular V45 was associated with post-RT cardiotoxicity in multivariate analysis (hazard ratio [HR], 1.50; $P = .027$). Cardiotoxicity occurrence was a highly significant predictor of OS in multivariate analysis (HR, 12.7; $P < .001$), but higher ventricular V45 alone was not (HR, 0.78; $P = .450$). **Conclusion:** Early cardiac events were relatively common after lung cancer RT and associated with multiple cardiac dose-volume parameters. Occurrence of early cardiotoxicity was strongly associated with worse OS. In practice, early cardiotoxicity is under-reported, supporting the need for more detailed cardiac evaluations in high-risk patients to detect and address early cardiotoxicity.

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Introduction

The development of cardiotoxicity after thoracic radiotherapy (RT) is well established.[1-3] The spectrum of detrimental effects that might develop after radiation exposure includes coronary artery disease, valvular disease, cardiomyopathy, pericardial disease, and arrhythmias.[2] Considerable literature exists regarding radiation cardiotoxicity in patients with Hodgkin disease and breast cancer. Because these patients can survive many decades after treatment, these data focus primarily on cardiotoxicities years to decades after radiation.[4] Less is known regarding early radiation cardiotoxicity, which is relevant for patients with locally advanced lung cancer and limited long-term survival.[1] It is also noteworthy that contrary to the breast cancer and Hodgkin disease populations, the locally advanced lung cancer population might receive very high doses of radiation to regions of the heart that vary from patient to patient. Additionally, patients are likely to have numerous baseline risk factors for cardiac disease.

A contemporary phase III, multi-institutional study that evaluated standard versus high-dose RT for lung cancer, NRG (National Surgical Adjuvant Breast and Bowel Project [NSABP], Radiation

[1]Department of Radiation Oncology
[2]Department of Biostatistics, Medical College of Wisconsin, Milwaukee, WI

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Address for correspondence: Elizabeth M. Gore, MD, Department of Radiation Oncology, Medical College of Wisconsin, Froedtert Hospital, Third Floor-Specialty Clinics, 9200 W Wisconsin Ave, Milwaukee, WI 53226
E-mail contact: egore@mcw.edu

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Therapy Oncology Group [RTOG], and Gynecologic Oncology Group [GOG])/RTOG 0617, showed no survival benefit with increased tumor radiation dose, and it has been hypothesized this was at least partially related to cardiac toxicity.[5] NRG/RTOG 0617 lacked specific data on cardiotoxicity, making it challenging to evaluate this hypothesis. A secondary analysis of this study will examine the relationship between cardiac dose-volume relationship and overall survival (OS) as a surrogate for cardiotoxicity. Because the median follow-up for NRG/RTOG 0617 was just under 2 years, the cardiotoxicities of interest are presumably occurring months to a few years after treatment, much sooner than the classic cardiotoxicity literature suggests.[4]

Limited data exist regarding dose-volume predictors of cardiotoxicity. Moreover, the importance of limiting the dose to the heart has historically been regarded as secondary to limiting the dose to the lung and minimizing the risk of pneumonitis. Several retrospective series have been published on the spectrum of early cardiotoxicity of thoracic radiation for lung cancer, as well as dose-volume predictors of adverse outcome.[6,7] After the publication of the NRG/RTOG 0617, findings have included volume of structure of interest receiving $\geq$50 Gy RT dose (V50) to the heart as a predictor of worse OS,[7] mean heart dose as a predictor of cardiotoxicity, and cardiotoxicity as a predictor of worse OS,[6] and association of higher dose to the heart base with worse OS.[8]

In the current series, we review our institutional data from lung cancer patients treated with standard fractionation thoracic RT with curative intent to explore factors associated with development of cardiotoxicity. We hypothesized that cardiac dose-volume parameters correlated with the risk of cardiotoxicity and worse OS and sought to determine which dose-volume parameters might be the best predictors of adverse outcomes. We also explored the relationship between tumor location and adverse outcomes.

Patients and Methods

Data Collection

Approval was obtained from our institutional review board to conduct a retrospective review of patients who received thoracic RT from 2010 to 2015. The final cohort of 76 lung cancer patients was selected as outlined in Figure 1. The cohort included patients treated with conventionally fractionated thoracic RT with curative intent, BED_10 (biological equivalent dose with α-β ratio of 10) $>$ 39 Gy, excluding nonlung primary tumors and those receiving thoracic reirradiation. Patients whose treatment plans could not be restored for dose-volume analyses were also excluded.

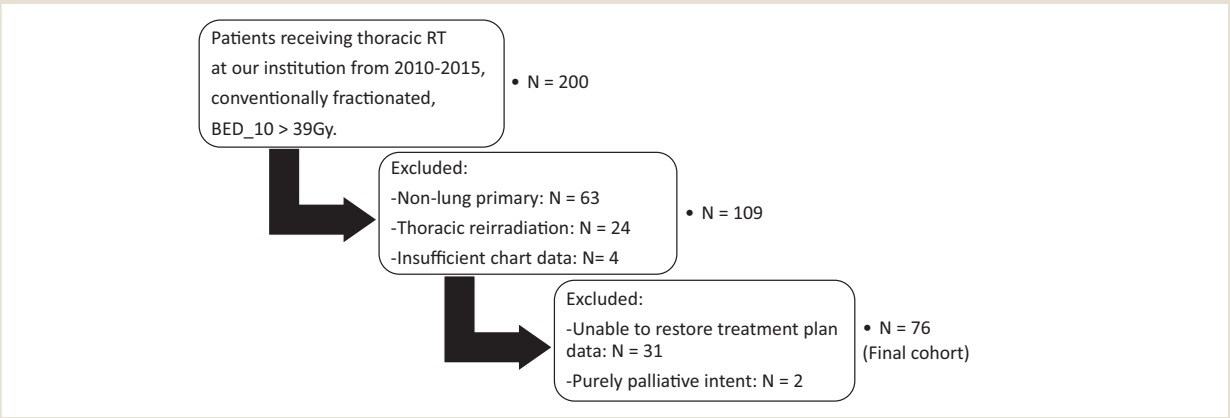
Progress notes, imaging, electrocardiograms, and echocardiograms were reviewed to identify cardiac events occurring after the start of RT. Cardiac events identified were categorized as arrhythmic, valvular, or pericardial effusion. Pericardial effusions were subdivided into trace, small to moderate, or large on the basis of descriptors used in the diagnostic study reports in the medical record. Treatment plans and standard structures contoured at the time of RT treatment planning were recovered using MIM software (MIM Software Inc, Cleveland, OH). Cardiac substructures including atria, ventricles, pericardium (the structure encompassing all cardiac substructures), and coronary space (base of heart) were contoured for each case using a previously published atlas.[9] We did not evaluate an additional "whole heart" structure as this was believed to be too similar to the pericardium structure. Dose-volume parameters of interest were extracted from MIM (MIM Software Inc).

Data on baseline characteristics for cardiac risk including preexisting cardiac disease, smoking, peripheral vascular disease, and diabetes were also collected. Clinical cancer stage was recorded according to the American Joint Commission on Cancer seventh edition staging manual.[10] Patients were counted as deceased either if documentation of death was found in the electronic medical record, or if they had been discharged to hospice with no subsequent encounters in the chart.

Statistical Analyses

Demographic characteristics, disease-related characteristics, and dosimetry data were described using frequencies and percentages for categorical variables and the mean, SD, median, and range for continuous variables. Data availability was reported for each

Figure 1 Patient Selection



Abbreviations: BED = biological equivalent dose; RT = radiotherapy.

variable. Missing values among analytic variables were rare and listwise deletion was used to handle missing values in all statistical tests.

Survival analysis methods were used to model cardiotoxicity and OS after the start of treatment. Event-free survival probabilities were estimated using Kaplan–Meier methods; patients were censored at last live follow-up for OS and at death or last follow-up for cardiotoxicity events. Univariate Cox proportional hazards regression was used to identify potential baseline predictors of each survival outcome; in addition to baseline predictors; cardiotoxicity was considered as a time-dependent covariate for OS.

Multivariable Cox proportional hazards models were developed for each outcome using the least absolute shrinkage and selection operator (LASSO) method for variable selection; a list of candidate predictors was selected on the basis of clinical expertise and LASSO was used for final selection. The LASSO method was chosen for its flexibility in dealing with collinearity among predictors. Collinearity among the dosimetric parameters was assessed graphically and many were observed to be highly correlated. Because of the limited sample size and high level of collinearity among the dosimetric features, a single feature ventricular V45 (volume of ventricles receiving $>$ 45 Gy RT dose) was selected for inclusion into the adjusted models. Presence of multicollinearity in an adjusted regression model might lead to large standard errors and difficulties with interpretation.

Additionally, each of the dose-volume parameters was compared between tumor locations (left vs. right and left lower lobe vs. all other locations) using Wilcoxon rank sum tests. All statistical analyses were performed using R, version 3.3.4 (R Foundation for Statistical Computing; http://www.R-project.org/). All P values were 2-sided and P value $<$.05 was considered statistically significant. No corrections were made for multiple testing.

Results

Median follow-up for the 76 patients was 1.2 years (range, 0.2-5.1 years). Baseline patient, tumor, and treatment characteristics are summarized in Table 1. Patient characteristics included a median age of 64 years, 45% (34) men, 96% (72) with a smoking history with a median of 41 pack-years, 37% (28) with previous cardiac disease, 22% (17) with diabetes, and 16% (12) with peripheral vascular disease. Tumor characteristics included 61% (45) clinical stage III, 38% (29) left-sided tumors, 12.5% (9) left lower lobe tumors, and histology of 39% (29) adenocarcinoma, 35% (26) squamous cell, 15% (11) small cell, and 13% (10) other.

Treatment characteristics included 90% (68) who received chemotherapy, 22% (17) who underwent surgery, and a median RT dose/fractionation of 60 Gy in 30 fractions (range, 44-69 Gy in 14-34 fractions). Of the 90% of patients who received chemotherapy, all received platinum-based regimens with the most common being carboplatin/paclitaxel (40 patients), followed by cisplatin/etoposide (14 patients). Our data predates the National Comprehensive Cancer Network (NCCN) recommendations for adjuvant immunotherapy,[11] but 4 patients received either Epidermal Growth Factor Receptor- or Vascular Endothelial Growth Factor-targeted immunotherapy with their platinum-based regimen. Cardiac toxicities observed included 22 events occurring anywhere from 3 weeks to 102 weeks after initiation of RT (Table 2). There were 5 new atrial arrhythmias, 3 new trace pericardial effusions, 13 new small to moderate pericardial effusions, and 1 case of new valvular disease.

Table 1 Patient, Tumor, and Treatment Characteristics (n = 76)

Characteristic	Value
Median Age at Start of Radiation (Range)	64.0 (46.1-88.4)
Male Sex, n (%)	34 (44.7)
Smoker, n (%)	72 (96.0)
Median Pack-Years (Range)	39.0 (0.0-154.0)
Previous Cardiac Disease, n (%)	28 (36.8)
Diabetes, n (%)	17 (22.4)
Peripheral Vascular Disease, n (%)	12 (15.8)
Clinical stage, n (%)	
I	10 (13.5)
II	7 (9.5)
III	45 (60.8)
IV	12 (16.2)
Tumor Laterality, n (%)	
Right	44 (57.9)
Left	29 (38.2)
Nonlateralized	3 (3.9)
Left Lower Lobe Tumor, n (%)	9 (12.5)
Histology, n (%)	
Adenocarcinoma	29 (38.7)
Squamous cell carcinoma	26 (34.7)
Small cell carcinoma	11 (14.7)
Other	10 (13.2)
Chemotherapy, n (%)	68 (89.5)
Surgery, n (%)	17 (22.4)
Median Radiation Dose (Range), Gy	60.0 (44.0-69.0)
Median Radiation Fractions (Range)	30.0 (14.0-34.0)

In univariate analysis of nondosimetric variables (Table 3), no variable was a significant predictor of cardiotoxicity. Multiple variables were significant predictors of OS: clinical stage (hazard ratio [HR], 1.72; P = .040), local recurrence (HR, 2.95; P = .006), metastatic recurrence (HR, 4.16; P < .001), and left lower lobe tumor location (HR, 2.80; P = .021). Further, Wilcoxon rank sum analysis showed that patients with left lower lobe tumors had a higher V30 to the ventricles (median 33.9 Gy; range, 0.0-87.4) relative to patients with tumors in all other locations (median, 0.9 Gy; range, 0.0-75.7), with the P value for this comparison being

Table 2 New Cardiac Pathologies Observed

Event	Number Observed	Median Weeks From Radiation Start to Diagnosis (Range)
New Atrial Arrhythmia	5	6.7 (3.1-61.1)
Trace Pericardial Effusion	3	49.9 (9.1-90.6)
Small to Moderate Pericardial Effusion	13	26.1 (8.0-102.0)
Large Pericardial Effusion	0	–
New or Progressed Valve Disease	1	9.0

Table 3 Univariate Analysis for Association of Cardiotoxicity and Overall Survival With Nondosimetric Variables

Variable	n	Cardiotoxicity			Overall Survival		
		HR	95% CI	*P*	HR	95% CI	*P*
Age at Start of Radiation	76	0.988	0.946-1.031	.578	1.018	0.977-1.061	.392
Histology: Squamous Cell vs. Adenocarcinoma	55	2.520	0.928-6.843	.070	1.054	0.428-2.595	.910
Clinical Stage	74	0.886	0.555-1.414	.612	1.719	1.026-2.882	.040
Previous Cardiac Disease, Yes vs. No	76	0.663	0.269-1.632	.371	1.337	0.628-2.847	.451
Pack Years	76	1.001	0.987-1.014	.943	1.012	1.000-1.024	.056
Initial Radiation Dose, Gy	76	1.071	0.992-1.156	.081	0.991	0.939-1.045	.728
Local Recurrence, Yes vs. No	74	0.848	0.313-2.298	.745	2.951	1.361-6.396	.006
Metastatic Recurrence, Yes vs. No	76	1.663	0.705-3.923	.245	4.164	1.900-9.122	<.001
Tumor Location, Left vs. Right	73	1.620	0.697-3.763	.262	1.711	0.789-3.711	.174
Left Lower Lobe Tumor vs. Other	72	1.721	0.581-5.101	.327	2.800	1.167-6.720	.021

Abbreviation: HR, = hazard ratio.

.009. When left lower lobe tumors were compared with tumors in all other locations, pericardial V30 was not significantly different ($P = .099$), nor was atrial V30 ($P = .824$). Of note, chemotherapy regimen was not included in the analyses for cardiotoxicity and OS because 90% of patients received platinum-based regimens.

In univariate analysis of dose-volume parameters (Table 4), the following were predictors for cardiotoxicity: Dmean to the pericardium (HR, 1.05; $P = .015$), pericardium V30 (HR, 1.03; $P = .010$), pericardium V45 (HR, 1.05; $P = .004$), atria Dmean (HR, 1.03; $P = .024$), atria V30 (HR, 1.01; $P = .039$), atria V45 (HR, 1.02; $P = .022$), ventricles Dmean (HR, 1.05; $P = .012$), ventricles V30 (HR, 1.02; $P = .008$), and ventricles V45 (HR, 1.05; $P = .001$). Dmax to pericardium, atria, and ventricles, however, were not significant cardiotoxicity predictors. In univariate analysis for OS, no cardiac parameter was a significant predictor. However, cardiotoxicity itself was a time-dependent predictor of worse OS (HR, 3.28; $P = .002$).

In multivariate analysis (Table 5), ventricular V45 was a significant predictor for cardiotoxicity (HR, 1.50; $P = .027$). Other parameters in the multivariate model for cardiotoxicity were nonsignificant, including age (HR, 0.90; $P = .718$), previous cardiac disease (HR, 0.78; $P = .656$), smoking pack-years (25-49 vs. 0-24 pack-years: HR, 1.49 [$P = .495$]; ≥50 vs. 0-24 pack-years: HR, 1.13 [$P = .853$]), diabetes (HR, 1.62; $P = .335$), peripheral vascular disease (HR, 1.69; $P = .432$), left lower lobe tumor location (HR, 1.43; $P = .584$), and clinical stage (HR, 1.07; $P = .824$).

In multivariate analysis for OS, ventricular V45 was initially significant for OS in our first model, which did not yet include cardiotoxicity (HR, 1.63; $P = .034$). However, when cardiotoxicity was added to this model, ventricular V45 was no longer significant (HR, 0.779; $P = .450$), and cardiotoxicity was highly significant (HR, 12.7; $P < .001$). Additional significant predictors of OS in the final multivariate model included metastatic recurrence (HR, 10.1; $P < .001$), local recurrence (HR, 2.72; $P = .043$), diabetes

Table 4 Univariate Analysis for Association of Cardiotoxicity and Overall Survival With Dosimetric Variables (n = 76)

Variable	Cardiotoxicity			Overall Survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Pericardium: Dmax, Gy	1.017	0.976-1.059	.415	1.000	0.966-1.034	.983
Pericardium: Dmean, Gy	1.052	1.010-1.097	.015	1.024	0.986-1.063	.226
Pericardium: V30	1.026	1.006-1.046	.010	1.014	0.996-1.033	.126
Pericardium: V45	1.051	1.016-1.087	.004	1.021	0.988-1.055	.211
Atria: Dmax, Gy	1.013	0.990-1.036	.277	1.019	0.996-1.042	.099
Atria: Dmean, Gy	1.031	1.004-1.059	.024	1.016	0.991-1.042	.204
Atria: V30	1.014	1.001-1.027	.039	1.008	0.995-1.020	.219
Atria: V45	1.022	1.003-1.041	.022	1.007	0.987-1.026	.510
Ventricles: Dmax, Gy	1.018	0.997-1.039	.100	1.016	0.998-1.035	.087
Ventricles: Dmean, Gy	1.047	1.010-1.085	.012	1.015	0.978-1.052	.433
Ventricles: V30	1.021	1.005-1.037	.008	1.008	0.991-1.024	.357
Ventricles: V45	1.049	1.019-1.080	.001	1.029	0.993-1.067	.115

Abbreviations: Dmax = maximum radiation dose to specified structure; HR = hazard ratio; V*x* = volume of structure of interest receiving a dose of at least *x* Gy.

Table 5 Multivariate Models for Cardiotoxicity and Overall Survival (n = 70)

	Cardiotoxicity			Overall Survival		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Metastatic Recurrence (Time-Dependent), Yes vs. No				10.132	3.204-32.043	<.001
Local Recurrence (Time-Dependent), Yes vs. No				2.717	1.032-7.152	.043
Cardiotoxicity (Time-Dependent), Yes vs. No				12.686	3.006-53.542	<.001
Ventricles: V45, Units of 10%	1.503	1.047-2.157	.027	.779	0.408-1.489	.450
Age at Start of Radiation, Units of 10 Years	0.895	0.490-1.635	.718	.997	0.467-2.127	.993
Previous Cardiac Disease, Yes vs. No	0.782	0.264-2.311	.656	3.110	0.872-11.098	.080
Smoking Pack-Years						
25-49 vs. 0-24	1.488	0.476-4.655	.495	1.204	0.336-4.317	.776
≥50 vs. 0-24	1.128	0.315-4.045	.853	4.149	0.824-2.893	.085
Diabetes, Yes vs. No	1.619	0.608-4.316	.335	.170	0.035-0.827	.028
Peripheral Vascular Disease, Yes vs. No	1.691	0.456-6.266	.432	.584	0.099-3.433	.552
Tumor Location, Left Lower Lobe vs. Other	1.434	0.395-5.214	.584	2.381	0.640-8.860	.196
Clinical Stage	1.065	0.611-1.855	.824	3.185	1.241-8.176	.016

Abbreviations: HR = hazard ratio; V45 = volume of ventricles receiving a dose of at least 45 Gy.

(HR, 0.17; $P = .028$), and clinical stage (HR, 3.19; $P = .016$). The following variables were not predictors of OS in the final multivariate model: age (HR, 0.997; $P = .993$), previous cardiac disease (HR, 3.11; $P = .080$), smoking pack-years (25-49 vs. 0-24 pack-years: HR, 1.20 [$P = .776$]; ≥50 vs. 0-24 pack-years: HR, 4.15 [$P = .085$]), peripheral vascular disease (HR, 0.58; $P = .552$), and left lower lobe tumor location (HR, 2.38; $P = .196$).

Discussion

Although historically significant radiation-induced cardiotoxicity has been thought to occur years to decades after RT,[4] our data suggest that early cardiac events are common and associated with worse OS in lung cancer patients. Patients in our study cohort had cardiac findings after RT that were not documented as or understood to be a side effect of RT. With careful chart review, we documented cardiac events in 22 of 76 total patients with a median follow-up of 1.2 years. NRG/RTOG 0617[5] showed a relationship between cardiac dose and OS although not a strong correlation with treatment-related cardiotoxicity. A logical hypothesis is that cardiotoxicity was under-reported in this large multicenter trial. This has prompted investigators to retrospectively perform detailed reviews of clinical records to identify early treatment-related cardiotoxicity. These reviews have consistently shown an association between treatment-related cardiotoxicity and cardiac dose,[6,7,12,13] and in 2 large trials an association was seen between OS and cardiac dose-volume parameters, specifically high heart V50 and V40, respectively.[7,14] Most single-institution and retrospective reviews have not shown a direct correlation between cardiac dose and OS and this is likely because of the size of the studies.[6,12,13]

In the current series Dmean, V30, and V45 to the pericardium (the structure encompassing all cardiac substructures), the atria, and the ventricles were associated with early post-treatment cardiotoxicity in univariate analysis. Ventricular V45 was selected for multivariate analysis and maintained significance. Studies have reported on a variety of parameters associated with cardiotoxicity and/or worse OS in multivariate analysis including heart Dmean, V5, V30, V45, and V50.[5-7,13,15] Additionally, Wang et al[12,15] evaluated 112 subjects and showed that cardiac event rates increased with increasing mean heart dose in 10-Gy increments and that cardiac event types were each associated with distinct heart subvolume doses. We did not have sufficient data to show an association between the structure treated and type of toxicity, although this is important information. Understanding the type of cardiotoxicity for which a patient is at risk is essential for prescribing appropriate interventions and post-therapy monitoring. Much larger studies with detailed dose and cardiac assessments are needed to understand relationship between dose to substructures, associated toxicity, and treatment outcomes.

Current NCCN guidelines for conventionally fractionated treatment of lung cancer recommend cardiac dose-volume constraints of whole heart V50 ≤25% and a mean dose ≤20 Gy.[11] The QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) reports suggested cardiac V30 ≤ 46% to achieve a pericardial effusion risk <15%, or a more conservative constraint of

limiting the cardiac V25 ≤10% to achieve a long-term cardiac mortality risk <1%.[16] Yegya-Raman et al[13] reported higher cumulative incidence of symptomatic cardiac events with whole-heart mean dose >20 Gy. Our series suggests ventricular V45 is an important parameter, but because of the small size of our data set we were statistically unable to provide a specific cutoff for use in clinical practice. The cardiac dose should be kept as low as reasonably achievable while adequately covering the target and respecting other normal tissue dose constraints. There is a tradeoff between toxicity risks to critical organs and tumor control resulting in cases in which the cardiac dose exceeds guideline recommendations. These patients should undergo surveillance and monitoring. The American Society of Clinical Oncology guideline recommends surveillance and monitoring for high-risk patients, which includes those with radiation to ≥30 Gy with the heart in the treatment fields.[17]

Our multivariate model showed other established prognostic factors[11] as significant for OS, including clinical stage, local recurrence, and metastatic recurrence (Table 5). Interestingly, the diagnosis of diabetes is associated with a significantly lower risk of death in our data. It is possible that patients with diabetes were actively being counseled on lifestyle and medical interventions that optimized their health and survival. Previous cardiac disease and smoking ≥50 versus 0 to 24 pack-years were marginally significant predictors of OS.

Cardiotoxicity itself is multifactorial. Patients likely have higher cardiac sensitivity to radiation on the basis of underlying risk factors, including pre-existing cardiovascular disease, smoking, diabetes, hypertension, dyslipidemia, obesity, advanced age, and treatment with cardiotoxic chemotherapy agents. In light of this, a new field termed, "cardio-oncology" has emerged with focus on cardiac disease as it relates to chemotherapy and radiation.[18]

In the current study, we examined the relationship between cardiotoxicity and established risk factors including age, previous cardiac disease, smoking, diabetes, and peripheral vascular disease. Contrary to our expectations, these variables were not significant in our multivariate model for cardiotoxicity, suggesting that dose to the ventricles was more significant than underlying risk factors. Patients with a pre-existing cardiac diagnosis and/or other risk factors were possibly monitored closely and had toxicity mitigated by prevention and early intervention. Increased risk of radiation-induced cardiotoxicity and association with baseline risk factors for cardiotoxicity is likely more relevant for late toxicity and possibly at lower radiation doses. This is consistent with breast cancer data and will likely become more relevant in lung cancer because patients with advanced disease are living longer.[19] This supports the need to monitor high-risk patients to detect subclinical effects of radiation, allowing early intervention to improve outcomes.[17]

In this study, we also examined the relationship between tumor location and outcome. Our findings showed that left lower lobe tumors are associated with higher ventricular dose and worse OS in univariate analysis (Table 3), but not in multivariate analysis (Table 5). This is consistent with an NRG/RTOG 0617 secondary analysis that showed cardiac dose was higher in patients with left lower lobe tumors. Although left lower lobe location was associated with worse OS, this was independent of cardiac dose. A Surveillance, Epidemiology, and End Results database review of patients with locally advanced non–small-cell lung cancer showed that left-sided tumors were associated with worse cardiac mortality than right-sided tumors.[20] A group from the United Kingdom has used a complex dose-modeling computer algorithm to identify the base of the heart as a dose-sensitive region in lung cancer patients, with higher dose to the base being associated with worse survival.[8]

Limitations of the current series include the retrospective nature, small study size, and relatively short median follow-up of 1.2 years. Placing this in the context of a median follow-up of just under 2 years for the NRG/RTOG 0617, we have likely captured the most likely timeframe for occurrence of early cardiac events that might have led to decreased survival in that trial. In addition, we only evaluated one dose-volume parameter in our multivariate analysis because of the close inter-relatedness of the various dose-volume parameters for the different cardiac substructures. Ventricular V45 was selected after consideration of the exiting literature and unanswered questions.

There are noteworthy strengths of this study. First, these data encompass the contemporary experience at our institution over a 5-year period. Modern technologies that can influence cardiac dose, including image-guided RT and 4-dimensional planning, would have been used as indicated per our institutional practices. In addition, cardiac substructures were reliably contoured by 3 of the authors using a published cardiac atlas.[9] Finally, individual patient charts and treatment plans were available for data extraction, allowing for assessment of many more variables than would be feasible with use of one of the large national databases.

Conclusion

Early treatment-related cardiotoxicity is common after curative intent, conventionally fractionated RT for lung cancer and is strongly associated with worse OS. More information is needed to understand the effect of radiation on the heart and cardiac substructures, as well as the interaction with baseline patient risk factors and systemic therapies. This is an area of active research. The dose to the heart and cardiac substructures should be kept as low as reasonably possible, with patient risk factors for cardiotoxicity documented and monitored. Our findings support a role for dedicated cardiac evaluations pre-RT and as part of follow-up in high-risk patients to detect and address early cardiotoxicity, because it is currently underappreciated in clinical practice.

Clinical Practice Points

- The development of cardiotoxicity after thoracic RT for lung cancer is well established and can encompass a broad spectrum of cardiac pathologies. Recent data suggest cardiotoxicity occurs earlier after RT than previously believed and is under-reported. Cardiotoxicity is clearly associated with worse OS, but the relationship between early cardiotoxicity and RT dose to specific regions of the heart is less well understood.
- The current study showed that the volume of the ventricles receiving ≥45 Gy RT dose was associated with development of early cardiotoxicity, and early cardiotoxicity was associated with worse OS. In the developing field of cardio-oncology, there is

interest in exploring the multifactorial nature of cardiotoxicity as it relates to cancer therapies as well as underlying patient risk factors.
- Our findings support a role for dedicated cardiac evaluations before lung cancer treatment and as part of follow-up in high-risk patients as part of multidisciplinary cancer care, with the goal of detecting and addressing early cardiotoxicity.
- Practicing radiation oncologists should remain cognizant of the dose to the heart and cardiac substructures, keeping this as low as reasonably possible, and be cognizant of patient-specific risk factors for cardiotoxicity.

Disclosure

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