Original Article

Heart V5 predicts cardiac events in unresectable lung cancer patients undergoing chemoradiation

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Background: Recent studies incorporating dose escalated radiation identified heart dose as a predictor of cardiac toxicity in unresectable lung cancer patients. Whether conventionally dosed radiation impacts cardiac events remains unclear.

Methods: Stage III lung cancer patients undergoing definitive chemoradiation to 60–70 Gy were analyzed. Clinical and dosimetric factors (mean heart dose, heart V5-60 in 5 Gy increments) were analyzed against freedom from ≥ grade 3 cardiac events and overall survival (OS) by log-rank test. Multivariable analysis (MVA) for factors significant on univariate analysis was performed by Cox proportional hazards.

Results: A total of 108 patients were identified. Median follow-up was 18.0 months. One- and two-year OS were 79% and 61%, respectively. On MVA, gross tumor volume (GTV) ≥98.6 cm^3 [hazard ratio (HR): 2.11, 95% confidence interval (CI): 1.15–3.93, P=0.02] and female gender (HR: 2.01, 95% CI: 1.09–3.73, P=0.03) predicted for worse survival. Twelve patients (11%) developed ≥ grade 3 cardiac events. One- and two-year freedom from cardiac events (FFCE) was 94% and 84% respectively. On MVA, heart V5 ≥49% predicted for cardiac events (HR: 11.44, 95% CI: 1.31–111.60, P=0.03) while female gender was nearly significant (HR: 3.49, 95% CI: 0.97–16.80, P=0.06). Females presented with similar comorbidity scores, GTVs, and relapse rates but experienced higher heart doses than their male counterparts.

Conclusions: Heart V5 ≥49% predicted for cardiac events after chemoradiation. However, cardiac dosimetry was not associated with survival. Rather, female gender and GTV ≥98.6 cm^3 led to worse survival. This study corroborates emerging data that low-dose radiation to the heart impacts cardiac toxicity.

Keywords: Cardiac toxicity; chemoradiation; unresectable lung cancer

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Introduction

It is well established that radiation therapy leads to increased risk of heart disease in long-term survivors of Hodgkin's lymphoma (1-3), breast cancer (4,5), and esophageal cancer (6). In lung cancer patients, the impact of thoracic radiation on cardiac toxicity was historically underappreciated as it was assumed that disease progression and its impact on life expectancy outpaced the development of cardiac events. Radiation Therapy Oncology Group (RTOG) 0617, a landmark study of unresectable stage III non-small lung cancer patients randomized to either standard-dose (60 Gy) or high-dose (74 Gy) chemoradiation with concurrent and consolidative carboplatin and paclitaxel with or without cetuximab, found that high-dose radiation was associated with a lower survival rate than the standard-dose arm and

identified that higher cardiac dose (heart V5 and V30) led to worse survival. However, specific heart toxicity outcomes were not tracked and the impact of pre-existing comorbidity on this finding remains unclear (7).

A significant interest in evaluating heart dose and cardiac events has followed. Recent single institution studies show that cardiac dosimetry predicts for cardiac events following thoracic radiation in locally advanced lung cancer patients (8-10). However, some of these studies did not corroborate the finding that heart dose adversely impacts overall survival (OS) (8,9). In addition, patients included in these studies were treated with doses up to 90 Gy or received only hypofractionated radiation (>2 Gy/fraction) on dose escalation protocols.

Due to the limited data in this setting, further validation is necessary to determine the effects of radiation therapy on cardiac events in lung cancer, particularly in the setting of standard radiation doses. We sought to determine if cardiac dose parameters may impact cardiac events following treatment and OS in patients with locally advanced lung cancer undergoing curative intent chemoradiation.

Methods

Patients were retrospectively identified from a database approved by an institutional review board (IRB) at two affiliated centers with unresectable stage IIIA/B (AJCC 7th edition) lung cancer who were treated with curative-intent radiation therapy and chemotherapy between 2010–2016. Waiver of consent was obtained. Exclusion criteria included patients with metastatic disease, omission of concurrent chemotherapy with radiation, surgically resected patients, or those with a prior course of thoracic radiation. Patients receiving altered fractionation, doses over 70 Gy or hypofractionated radiation (>2 Gy/day) were ineligible for this study.

Treatment consisted of platinum-based chemotherapy delivered concurrently with radiation therapy. All patients underwent CT simulation on a 16 slice Brilliance CT scanner (Brilliance CT, Big Bore, Philips Medical Systems, Andover, MA, USA) with 4D CT for radiation planning. Patients were immobilized using standard upper and lower alpha cradles (Smithers Medical Products, North Canton, USA). Respiratory management was utilized for cases in which tumor motion was identified to be ≥1 cm on 4D CT. The gross tumor volume (GTV) was defined as the primary tumor and any regionally involved nodes identified clinically on staging CT (>1 cm) or PET scan, or identified pathologically by endoscopic bronchial ultrasound. An internal target volume (ITV) was generated from review of the 4D CT. A 0.5–1 cm clinical target volume (CTV) expansion was added for microscopic disease extension and an additional 0.5–1 cm planning target volume (PTV) margin was placed to account for setup uncertainty. Radiation therapy was delivered with 6–18 MV photons with either 3D conformal (3D CRT) or intensity-modulated radiation therapy (IMRT). Clinical and demographic information was obtained from electronic medical records. Charlson comorbidity index (CCI) (11) was determined for each patient although the diagnosis of lung cancer was excluded from the index. Patients whose primary tumor or nodes abutted the heart were characterized as having pericardial tumors. Dose-volume histogram data were extracted from the Pinnacle v7.6-10.2 planning system and the following dosimetric parameters were computed: heart V5–60 in 5 Gy increments, mean heart dose, lung V5, lung V20, and mean lung dose. All adverse events were graded by CTCAE Version 4.03. Patients were analyzed for grade 3 or higher cardiac events post-therapy defined as new arrhythmia, structural disease/valvulopathy, myocardial infarction, new or recurrent congestive heart failure, pericarditis or non-malignant pericardial effusion requiring intervention. Lung volume was defined as whole lung excluding GTV and cardiac volumes were recontoured if necessary to comply with RTOG organ at risk definition (12). Institutional planning goals included a whole lung-CTV V20 ≤37%, cord dose of ≤50 Gy, and heart V60 <33%, V45 <66% and V40 <100%.

OS was calculated from start date of radiation therapy to death from any cause. Disease-free survival was calculated from radiation start date to date of first disease recurrence or death. Freedom from cardiac events (FFCE) was calculated from start date of radiation therapy to date of grade 3 or higher cardiac event while disease recurrence and deaths unrelated to cardiac events were censored. Univariate analysis (UVA) was performed with log-rank tests. Continuous variables were dichotomized at their median values for survival analyses. The Cox proportional hazards model was used to run multivariable analyses on variables with P values ≤0.20 on UVA. When multiple dose variables were found to be significant on UVA, collinearity was assessed for highly correlated variables and dose variables were excluded from the multivariate model if variance inflation factors >10. OS, disease-free survival, and FFCE were estimated with the Kaplan-Meier method. Categorical variables were compared using Chi-

squared tests of independence while *t*-tests were performed for continuous variables. All analyses were done with JMP version 12 (SAS Institute Inc., Cary, NC, USA, 1989–2007).

Results

A total of 108 patients met inclusion criteria for this analysis. Median follow-up was 18.0 months (range, 3.3–84.6 months). Median OS was 30.7 months. One- and two-year OS for the entire cohort were 79% and 61%, respectively. One- and two-year disease-free survival were 59% and 42%, respectively. *Table 1* shows patient clinical and treatment characteristics. Median age was 67 years. A total of 90 (83%) patients presented with non-small cell lung cancer (NSCLC) of whom nearly half (49%) had squamous cell carcinoma while 18 patients (17%) presented with small cell lung cancer. A total of 62 (57%) patients had stage IIIA disease. The Eastern Cooperative Oncology Group (ECOG) performance status was 0, 1 and 2 in 32 (30%), 67 (62%), and 9 (8%) patients, respectively. CCI was <2 in 71 (66%) patients. Pre-existing comorbid heart disease, lung disease and diabetes mellitus were present in 29 (27%), 53 (49%), and 24 (22%) patients, respectively. Of the 29 patients with pre-existing cardiac comorbidities, prior diagnoses included 21 (72%) with coronary artery disease, 8 (28%) with congestive heart failure, 9 (31%) with arrhythmia (including atrial flutter and fibrillation, supraventricular tachycardia, and ventricular tachycardia), 2 (7%) with prior pericardial disease, and 8 (28%) with unspecified or other cardiac disease.

Nearly all (99%) patients underwent diagnostic positron emission tomography (PET) staging. Median GTV and PTV size was 98.6 and 495.3 cm^3, respectively. Median radiation dose was 64 Gy (range, 60–70 Gy). Induction chemotherapy was delivered in 20 patients (19%). The most common concurrent chemotherapy regimen was carboplatin/paclitaxel in 69 (64%) patients, followed by cisplatin/etoposide in 23 (21%) patients. Eight-five (79%) patients received 3D CRT while 23 (21%) patients received IMRT. Nearly all patients (98%) underwent treatment with image-guided radiotherapy.

Results of UVA for OS are shown in *Tables 2,3*. GTV ≥98.6 cm^3 was associated with worse survival (P=0.02). Other factors associated with worse survival were lung V5 ≥59.8% (P=0.03) and heart V5 ≥49.4% (P=0.03). Age, performance status, race, current smoking, CCI, cardiac or lung comorbidity were not associated with OS. Female gender (P=0.12) and diabetes (P=0.09) were associated with a non-significant trend towards worse survival. Radiation dose and use of IMRT were not associated with OS. In addition, there were no significant differences in survival between patients with NSCLC *vs.* small cell lung cancer. On multivariable analysis (*Table 4*), covariates which were statistically significant for worse survival included larger GTV (HR: 2.11, 95% CI: 1.15–3.93, P=0.02) and female gender (HR: 2.01, 95% CI: 1.09–3.82, P=0.03). Diabetes trended toward significance (P=0.07) while heart V5 and lung V5 were not significant.

A total of 12 (11%) grade 3 or higher cardiac events developed at a median of 8.5 months (range, 2.8–40.2 months), leading to a 1- and 2-year FFCE rate of 94% and 84%, respectively. Four (33%) of these patients had pre-existing heart disease. Of these four patients, three patients had a prior diagnosis of coronary artery disease, 1 of whom also had co-existing congestive heart failure. The fourth patient had a prior diagnosis of diastolic congestive heart failure. Ten patients developed tachyarrhythmias of whom 3 developed arrhythmias in the setting of malignant pericardial effusions. Two of these 10 patients also experienced congestive heart failure or exacerbations. One patient developed heart failure secondary to diastolic dysfunction alone and another patient developed a large non-malignant pericardial effusion requiring pericardiocentesis. *Tables 5,6* show results of UVA for FFCE. Dosimetric variables significant for cardiac events include heart V5, V10, V15, and mean heart dose while heart V25 trended toward significance. Heart V5 <49.4% *vs.* >49.4% was most significant and was associated with a 2-year FFCE rate of 97% *vs.* 67%, P=0.005, respectively (*Figure 1*). Age, race, GTV, CCI, cardiac or lung disease, diabetes, current smoking, performance status, and use of IMRT were not significant for cardiac events while female gender trended towards statistical significance (2-year FFCE: 96% *vs.* 71%, P=0.06). There was also no statistically significant difference in cardiac events between those who relapsed *vs.* those who did not (2-year FFCE: 85% *vs.* 83%, P=0.67). Among the 53 (49%) patients who did not relapse, mean heart dose, heart V5, V10, V15, V25 remained significant for the development of cardiac events (data not shown). On multivariable analysis for FFCE, heart V5 and mean heart dose were among the significant cardiac metrics entered, along with gender, given the clinical relevance of these variables across multiple studies. In addition, heart V10, V15, V25 were found to be collinear (data not shown) and therefore excluded from the analysis to avoid overfitting. Only heart V5 (HR: 11.44, 95% CI: 1.31–111.60, P=0.03)

Table 1 Clinical and treatment related factors

Factors	N [%] or median (range)	HR (95% CI)	P value
Age, years	67 [40–85]	0.86 (0.48–1.52)	0.60
Gender			
Male	50 [46]	1.00	
Female	58 [54]	1.58 (0.89–2.86)	0.12
Race			
White	57 [53]	1.00	
Black or African-American	49 [45]	1.14 (0.65–2.02)	0.64
Other	2 [2]		
Smoking history			
Former smoker	81 [75]	1.00	
Non-smoker	2 [2]		
Current smoker	25 [23]	0.87 (0.41–1.68)	0.68
Pre-existing comorbid disease			
Cardiac	29 [27]	1.11 (0.58–2.04)	0.74
Pulmonary	53 [49]	1.04 (0.59–1.83)	0.89
Diabetes mellitus	24 [22]	1.74 (0.88–3.26)	0.11
AJCC stage			
IIIA	62 [57]	1.00	
IIIB	46 [43]	1.35 (0.77–2.38)	0.29
Histology			
Non-small cell lung cancer	90 [83]	1.00	
Adenocarcinoma	40 [44]		
Squamous	44 [49]		
Other	6 [7]		
Small cell lung cancer	18 [17]	1.21 (0.54–2.41)	0.62
GTV, cm^3	98.6 (3.8–891.1)	1.99 (1.12–3.63)	0.02
PTV, cm^3	495.3 (17.2–1388.0)	1.41 (0.79–2.52)	0.24
Radiotherapy technique			
3D CRT	85 [79]	1.00	
IMRT	23 [21]	0.97 (0.39–2.07)	0.95
ECOG performance status			
0	32 [30]	1.00	
1	67 [62]	1.22 (0.66–2.34)	0.53
2	9 [8]	0.75 (0.21–2.09)	0.61

Table 1 *(continued)*

Table 1 *(continued)*

Factors	N [%] or median (range)	HR (95% CI)	P value
Charlson comorbidity index			
0	35 [32]	1.00	
1	36 [33]	1.36 (0.68–2.78)	0.39
2	19 [18]	1.18 (0.47–2.78)	0.72
3+	18 [17]	1.01 (0.40–2.37)	0.98
Radiation dose, Gy	64 [60–70]	0.79 (0.44–1.42)	0.42
Chemotherapy agents			
Carboplatin/paclitaxel	69 [64]	1.00	
Cisplatin/etoposide	23 [21]	1.99 (0.99–3.83)	0.90
Platinum/other	16 [15]	1.05 (0.46–2.16)	0.91

AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; GTV, gross tumor volume; PTV, planning target volume; 3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; ECOG, Eastern Cooperative Oncology Group; Gy, Gray.

Table 2 Univariate analysis of clinical factors for overall survival

Factors	HR (95% CI)	P value
Age (≥67/<67)	0.86 (0.48–1.52)	0.60
Gender (female/male)	1.58 (0.89–2.86)	0.12
Race (White/non-White)	1.14 (0.65–2.02)	0.64
Current smoker (yes/no)	0.87 (0.41–1.68)	0.68
Cardiac comorbidity (yes/no)	1.11 (0.58–2.04)	0.74
Lung comorbidity (yes/no)	1.04 (0.59–1.83)	0.89
Diabetes mellitus (yes/no)	1.74 (0.11–3.26)	0.09
Histology (SCLC/NSCLC)	1.21 (0.54–2.41)	0.62
GTV (≥98.6 cm^3/<98.6 cm^3)	1.99 (1.12–3.63)	0.02
PTV (≥495.3 cm^3/<495.3 cm^3)	1.41 (0.79–2.52)	0.24
Radiation dose (≥64 Gy/<64 Gy)	0.79 (0.44–1.42)	0.42
Radiotherapy technique (IMRT/3D CRT)	0.97 (0.39–2.07)	0.95
ECOG performance status (1–2/0)	1.13 (0.62–2.16)	0.69
Charlson comorbidity index (≥2/<2)	0.92 (0.49–1.66)	0.79

SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; GTV, gross tumor volume; PTV, planning target volume; 3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; ECOG, Eastern Cooperative Oncology Group; Gy, gray; HR, hazard ratio; CI, confidence interval.

Table 3 Univariate analysis of dosimetric factors for overall survival

Factors	Median (range)	Subcategory	HR (95% CI)	P value
MHD (Gy)	13.1 (5.5–48.7)	≥13.1 *vs*. <13.1	1.47 (0.83–2.63)	0.19
MLD (Gy)	19.1 (8.8–27.6)	≥19.1 *vs*. <19.1	1.39 (0.79–2.50)	0.29
Lung V5 (%)	59.8 (20.6–82.5)	≥59.8 *vs*. <59.8	1.87 (1.05–3.39)	0.03
Lung V20 (%)	32.0 (0–45.3)	≥32.0 *vs*. <32.00	1.00 (0.56–1.77)	0.99
Heart V5 (%)	49.4 (0–100.0)	≥49.4 *vs*. <49.4	1.90 (1.07–3.45)	0.03
Heart V10 (%)	39.4 (0–100.0)	≥39.4 *vs*. <39.4	1.44 (0.82–2.59)	0.21
Heart V15 (%)	31.0 (0–99.8)	≥31.0 *vs*. <31.0	1.48 (0.84–2.65)	0.18
Heart V20 (%)	22.7 (0–99.3)	≥22.7 *vs*. <22.7	1.26 (0.71–2.24)	0.43
Heart V25 (%)	18.3 (0–98.8)	≥18.3 *vs*. <18.3	1.22 (0.69–2.18)	0.49
Heart V30 (%)	15.6 (0–97.8)	≥15.6 *vs*. <15.6	1.13 (0.64–2.01)	0.66
Heart V35 (%)	11.8 (0–76.6)	≥11.8 *vs*. <11.8	1.30 (0.73–2.31)	0.37
Heart V40 (%)	9.1 (0–67.4)	≥9.1 *vs*. <9.1	1.30 (0.74–2.32)	0.37
Heart V45 (%)	6.8 (0–61.3)	≥6.8 *vs*. <6.8	1.34 (0.76–2.39)	0.32
Heart V50 (%)	5.3 (0–48.5)	≥5.3 *vs*. <5.3	1.38 (0.78–2.47)	0.27
Heart V55 (%)	3.5 (0–38.7)	≥3.5 *vs*. <3.5	1.47 (0.83–2.63)	0.18
Heart V60 (%)	1.9 (0–30.7)	≥1.9 *vs*. <1.9	1.63 (0.92–2.96)	0.09

MHD, mean heart dose; MLD, mean lung dose; HR, hazard ratio; CI, confidence interval.

Table 4 Multivariable analysis for overall survival

Factors	Hazard ratio	95% confidence interval	P value
Female gender	2.01	1.09–3.82	0.03
GTV ≥98.6 cm^3	2.11	1.15–3.93	0.02
Lung V5 ≥59.8%	1.55	0.72–3.39	0.26
Heart V5 ≥49.4%	1.25	0.58–2.73	0.56
Diabetes	1.87	0.94–3.54	0.07

GTV, gross tumor volume.

was predictive of cardiac events, while gender (HR: 3.49, 95% CI: 0.97–16.80, P=0.06) trended toward significance (*Table* 7). A total of 25 (23%) patients were found to have non-malignant pericardial effusions, classified as trace/minimal (18%), moderate (5%) or large/severe (1%). Only one patient required pericardiocentesis for non-malignant effusion. No cardiac variables were associated with the risk of pericardial effusion. Ultimately, the development of a cardiac event led to worse OS compared to those who did not experience a cardiac event (2-year OS: 38% *vs.* 64%, P=0.01).

On further analysis of gender differences, women and men presented with similar CCI scores and rates of heart and lung disease; however, women presented with lower rates of diabetes (14% *vs.* 32%, P=0.02) than men. Women also presented with similar GTVs, similar rates of relapse and were not more likely to experience treatment breaks or longer treatment lengths. However, women were more likely to have received higher mean heart doses and overall heart doses (V20–55) and experienced a higher trend in the presentation of pericardial tumors (64% *vs.* 46%, P=0.06) than men (*Table S1*).

Table 5 Univariate analysis of clinical factors for freedom from cardiac events

Factors	HR (95% CI)	P value
Age (≥67/<67 years)	0.94 (0.29–3.01)	0.92
Gender (female/male)	3.39 (1.00–15.42)	0.05
Race (White/non-White)	0.75 (0.22–2.35)	0.62
Current smoker (yes/no)	1.23 (0.39–4.15)	0.73
Cardiac comorbidity (yes/no)	1.44 (0.38–4.62)	0.56
Lung comorbidity (yes/no)	1.04 (0.33–3.33)	0.95
Diabetes mellitus (yes/no)	0.80 (0.12–3.06)	0.77
Histology (SCLC/NSCLC)	0.52 (0.03–2.72)	0.50
GTV (≥98.6 cm^3/<98.6 cm^3)	1.88 (0.60–6.38)	0.28
PTV (≥495.3 cm^3/<495.3 cm^3)	1.67 (0.53–5.65)	0.38
Radiotherapy technique (IMRT/3D CRT)	1.84 (0.40–6.51)	0.40
ECOG performance status (1–2/0)	1.53 (0.45–6.92)	0.52
Charlson comorbidity index (≥2/<2)	0.58 (0.13–1.96)	0.40

GTV, gross tumor volume; PTV, planning target volume; 3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; ECOG, Eastern Cooperative Oncology Group; Gy, gray.

Table 6 Univariate analysis of dosimetric factors for freedom from cardiac events

Factor	Median (range)	Subcategory	HR (95% CI)	P value
MHD (Gy)	13.1 (5.5–48.7)	≥13.1 *vs*. <13.1	3.59 (1.06–16.30)	0.04
Heart V5 (%)	49.4 (0–100)	≥49.4 *vs*. <49.4	6.69 (1.74–43.80)	0.005
Heart V10 (%)	39.4 (0–100.0)	≥39.4 *vs*. <39.4	6.13 (1.61–40.00)	0.008
Heart V15 (%)	31.0 (0–99.8)	≥31.0 *vs*. <31.0	6.08 (1.59–39.74)	0.009
Heart V20 (%)	22.7 (0–99.3)	≥22.7 *vs*. <22.7	2.23 (0.70–8.40)	0.18
Heart V25 (%)	18.3 (0–98.8)	≥18.3 *vs*. <18.3	3.26 (0.97–14.73)	0.06
Heart V30 (%)	15.6 (0–97.8)	≥15.6 *vs*. <15.6	2.16 (0.68–8.14)	0.20
Heart V35 (%)	11.8 (0–76.6)	≥11.8 *vs*. <11.8	2.29 (0.72–8.63)	0.17
Heart V40 (%)	9.1 (0–67.4)	≥9.1 *vs*. <9.1	2.29 (0.72–8.63)	0.17
Heart V45 (%)	6.8 (0–61.3)	≥6.8 *vs*. <6.88	1.50 (0.48–5.10)	0.48
Heart V50 (%)	5.3 (0–48.5)	≥5.3 *vs*. <5.3	1.57 (0.50–5.33)	0.44
Heart V55 (%)	3.5 (0–38.7)	≥3.5 *vs*. <3.5	1.67 (0.53–5.66)	0.38
Heart V60 (%)	1.9 (0–30.7)	≥1.9 *vs*. <1.9	1.58 (0.50–5.34)	0.43

MHD, mean heart dose; CI, confidence interval.

Rates of grade 2 or higher pneumonitis events were observed in 30 (28%) patients. Grade 2, 3, 4 and 5 pneumonitis were present in 23 (21%), 4 (4%), 1 (1%) and 2 (2%) patients, respectively. On UVA for median lung V5, V20 and mean lung dose, lung V20 <32% resulted in a trend towards a decrease in grade 2+ pneumonitis (20% *vs.* 35%, P=0.07). Gender, age, race, comorbid lung disease, use of IMRT, and GTV did not increase the risk of grade

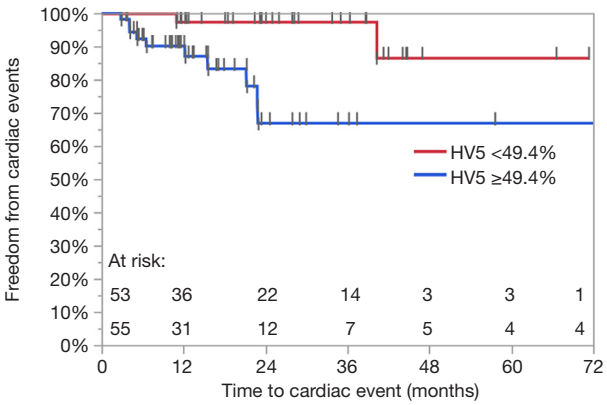

Figure 1 Kaplan-Meier freedom from cardiac event curve for Heart V5. P=0.005.

Table 7 Multivariable analysis for freedom from cardiac events

Factor	Hazard ratio	95% confidence interval	P value
Female gender	3.49	0.97–16.80	0.06
Heart V5 ≥49.4%	11.44	1.31–111.60	0.03
MHD ≥13.1 Gy	0.49	0.09–4.28	0.49

MHD, mean heart dose.

2 or higher pulmonary toxicity; however current smoking was protective against grade 2+ pulmonary toxicity (4% *vs.* 35%, P=0.0006) (*Table S2*). The development of grade 3 or higher, but not grade 2 or higher, pneumonitis was associated with a non-significant decrement in OS (2-year OS: 38% *vs.* 63%, P=0.06).

Discussion

Our findings suggest that while heart dose parameters are associated with cardiac events following radiation therapy, they are not independently associated with survival. While this finding conflicts with RTOG 0617 (7), it is consistent with several reports showing that the OS is driven by GTV and disease progression rather than cardiac dose (9,13). In a secondary analysis of the ESPATUE study (13) which randomized 161 patients with operable stage III NSCLC to resection versus continuation of chemoradiation following neoadjuvant chemoradiation, heart dose was not predictive of survival although cardiac events were not specifically assessed. Patients in the ESPATUE study were acknowledged to be healthier than those in RTOG 0617 given eligibility for operability which may account for the differences. It is possible that the relatively small cohorts in the current study and other negative studies are insufficiently powered to detect the influence of cardiac dose on survival despite the observation that cardiac events themselves predict for a higher risk of death (8,9,13).

An important finding was that crude grade 3 or higher cardiac events occurred in 11% of patients at a median follow-up of 18 months. This rate is similar to that reported by Dess *et al.* (9), who observed a 2-year cumulative incidence rate of 11% and by Wang *et al.* (8), who reported a 2-year event rate of 10% in patients with unresectable lung cancer treated with definitive chemoradiation. In addition, these studies also found that higher heart or substructure V5 predicted for cardiac events. This metric has also been validated in studies with patients with lymphoma or breast cancer (5,14). In a validation study to assess the findings set forth by Darby *et al.* (4), who found that patients with breast cancer treated with adjuvant radiation experience a relative increase in ischemic heart disease by 7.4%/Gy in mean heart dose with "no apparent threshold", left ventricular V5 appeared to be a better predictor of acute coronary events than mean heart dose (5). Potential mechanisms for cardiac injury from low-dose radiation include endothelial damage and atherosclerosis; however, the impact of low-dose radiation on other known sequela from radiation such as myocardial injury, conduction or perfusion related abnormalities is unclear (15). Finally, grade 1 or higher non-malignant pericardial effusions occurred in 23% of patients with only 1% requiring intervention. This relatively low grade 3+ pericardial effusion rate is similar to that (2.6%) reported by one recent series in which a prospectively followed cohort of unresectable lung cancer patients received proton beam or IMRT chemoradiation to 60–74 Gy (16).

The finding that GTV is an independent prognostic factor for OS has been shown by multiple studies in patients with lung cancer (17-19). Higher GTV leads to increased disease progression and worse survival. Our study cohort presented with similar GTVs and PTVs (median of 99 and 495 cm^3, respectively) to those of RTOG 0617 (median GTV and PTV size were 75–110 and ~500 cm^3, respectively). Despite increasing GTV being significant for worse survival on UVA in RTOG 0617, this specific factor was not assessed in a multivariable model. Rather, PTV volume was marginally significant for the radiation endpoint (7).

The finding that gender was associated with worse survival and a non-significant trend toward higher rates

of cardiac events was unexpected. We did not observe differences in baseline characteristics between females and males with the exception of lower rates of pre-existing diabetes in women (*Table S1*). Total treatment duration and relapse rates were also similar between women and men. However, women received significantly higher mean heart and overall heart doses. This finding may be attributed to tumor location but regardless underscores the link between cardiac doses and cardiac events despite a comparable, if not better, comorbid background in women versus men in this study. Limited data suggest that females may be more sensitive to treatment related cardiac injury. This finding has been observed in at least one study of 102 patients treated with chemoradiation for esophageal cancer in which heart V20, V30, V40 and female gender were predictive of cardiac toxicity (20). Aside from radiation, gender differences in cardiac injury from anthracycline based chemotherapy is also well documented in childhood survivors of lymphoma (21,22).

In addition, we found that grade 3 pneumonitis, present in 6.5% of the cohort, was associated with higher risk of death which is similar to other studies (23,24). We did not observe an association between whole lung V5 and pulmonary toxicity but did see a non-significant trend towards higher lung V20 and development of grade 2+ pneumonitis. This finding is similar to that of RTOG 0617 in which higher lung V20, but not lung V5, was associated with heightened risk of (grade 3+) pneumonitis (25). Current smoking was found to be associated with decreased risk of development of grade 2+ pneumonitis. Similar findings of the protective effects of current smoking on radiation pneumonitis have been reported in other studies, and one hypothesis is that there is a diminished inflammatory response in smokers *vs.* non-smokers (26). This finding could be used to improve the accuracy of predictive models for determining patients at risk of developing radiation pneumonitis (27). We could not evaluate the impact of prior versus no smoking on outcomes as 98% of our study cohort had a history of tobacco use.

This study has a number of limitations. First, the analysis included a relatively small patient cohort which led to limited statistical power. The cohort included 17% of patients with small cell lung cancer who received conventional daily radiation therapy. Such patients historically present with similar median survival (23–30 months) and 2-year OS rates (46–53%) after chemoradiation to those of NSCLC patients (28,29). In fact, we observed no difference in survival between these subgroups. We acknowledge that the inclusion of these patients results in heterogeneity in the patient sample and may have impacted study results owing to different outcomes and therapies. Additional limitations of this study include the retrospective data collection and limited follow-up which led to potential underestimation of adverse events. This study also included 79% of patients who received 3D CRT. The use of 3D CRT has been found to be associated with higher heart doses than IMRT in patients with locally advanced NSCLC and therefore may be less likely to be utilized (25). However, we observed no difference in OS or FFCE in these patients. The cause of cardiac events could not be characterized as events related to general decline, disease progression, salvage therapy, pre-existing medical comorbidities or radiation therapy-induced injury. Nonetheless, the study population received relatively homogeneous radiation doses (60–70 Gy) and treatment parameters as all patients eligible for this analysis received concurrent chemoradiation. This study provides further validation to the growing evidence that cardiac dose predicts early cardiac events in this patient population.

Conclusions

Heart V5 ≥49% predicted for cardiac events after chemoradiation. However, cardiac dosimetry was not associated with survival. Rather, female gender and GTV ≥98.6 cm^3 led to worse survival. This study corroborates emerging data that low dose radiation to the heart impacts cardiac toxicity.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Patients were retrospectively identified from a database approved by an institutional review board (IRB) at two affiliated centers. Waiver of consent was obtained. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Clinical and dosimetric variable associations with gender

Characteristic	All patients		Female		Male		P value
	No.	%	No.	%	No.	%	
Total No. of patients	108	100.0	58	54	50	46	–
Age							0.17
<67 years	53	49	32	55	21	42	
≥67 years	55	51	26	45	29	58	
Race							0.53
Caucasian	57	53	29	50	28	56	
Other	51	47	29	50	22	44	
Smoking status							0.79
Current smoker	25	23	14	24	11	22	
Non-current smoker	83	77	44	76	39	78	
ECOG PS							0.36
0	32	30	15	26	17	34	
1–2	76	70	43	74	33	66	
CCI							0.24
0–1	71	66	41	71	30	60	
2+	37	34	17	29	20	40	
Pre-existing diabetes							0.02
Yes	24	22	8	14	16	32	
No	84	78	50	86	34	68	
Pre-existing cardiac disease							0.49
Yes	29	27	14	24	15	30	
No	79	73	44	76	35	70	
Pre-existing lung disease							0.55
Yes	53	49	30	52	23	46	
No	55	51	28	48	27	54	
Relapse							0.86
Yes	55	51	30	52	25	50	
No	53	49	28	48	25	50	
Gross tumor volume							0.08
<98.6 cm^3	55	51	34	59	21	42	
≥98.6 cm^3	53	49	24	41	29	58	
Tumor location							0.06
Pericardial	60	56	37	64	23	46	
Non-pericardial	48	44	21	36	27	54	

Table S1 *(continued)*

Table S1 *(continued)*

Characteristic	All patients		Female		Male		P value
	No.	%	No.	%	No.	%	
Treatment length							0.61
<45 days	49	45	25	43	24	48	
≥45 days	59	55	33	57	26	52	
Treatment break							0.77
Yes	14	13	7	12	7	14	
No	94	87	51	88	43	86	
Mean heart dose							0.01
<13.1 Gy	53	49	22	38	31	62	
≥13.1 Gy	55	51	36	62	19	38	
Heart V5							0.18
<49.4%	53	49	25	43	28	56	
≥49.4%	55	51	33	57	22	44	
Heart V10							0.18
<39.4%	53	49	25	43	28	56	
≥39.4%	55	51	33	57	22	44	
Heart V15							0.08
<31.0%	53	49	24	41	29	58	
≥31.0%	55	51	34	59	21	42	
Heart V20							0.01
<22.7%	53	49	22	38	31	62	
≥22.7%	55	51	36	62	19	38	
Heart V25							0.01
<18.3%	53	49	22	38	31	62	
≥18.3%	55	51	36	62	19	38	
Heart V30							0.03
<15.6%	53	49	23	40	30	60	
≥15.6%	55	51	35	60	20	40	
Heart V35							0.01
<11.8%	53	49	22	38	31	62	
≥11.8%	55	51	36	62	19	38	
Heart V40							0.01
<9.1%	53	49	22	38	31	62	
≥9.1%	55	51	36	62	19	38	

Table S1 *(continued)*

Table S1 *(continued)*

Characteristic	All patients		Female		Male		P value
	No.	%	No.	%	No.	%	
Heart V45							0.03
<6.8%	53	49	23	40	30	60	
≥6.8%	55	51	35	60	20	40	
Heart V50							0.03
<5.3%	53	49	23	40	30	60	
≥5.3%	55	51	35	60	20	40	
Heart V55							
<3.5%	54	50	24	41	30	60	0.05
≥3.5%	54	50	34	59	20	40	
Heart V60							0.25
<1.9%	54	50	26	45	28	56	
≥1.9%	54	50	32	55	22	44	
Mean lung dose							0.57
<19.1 Gy	55	51	31	53	24	48	
≥19.1 Gy	53	49	27	47	26	52	
Lung V5							0.34
<59.8%	55	51	32	55	23	46	
≥59.8%	53	49	26	45	27	54	
Lung V20							0.84
<32.0%	55	51	29	50	26	52	
≥32.0%	53	49	29	50	24	48	

ECOG PS, Eastern Cooperative Oncology Group performance status; CCI, Charlson comorbidity index.

Table S2 Clinical and dosimetric variable associations with grade 2+ lung toxicities

Characteristic	All patients		Pneumonitis grade <2		Pneumonitis grade ≥2		P value
	No.	%	No.	%	No.	%	
Total No. of patients	108	100.0	78	72	30	28	–
Age							0.24
<67 years	53	49	41	77	12	23	
≥67 years	55	51	37	67	18	33	
Gender							0.63
Female	58	54	43	74	15	26	
Male	50	46	35	70	15	30	
Race							0.22
Caucasian	57	53	44	77	13	23	
Other	51	47	34	67	17	33	
Smoking status							0.0006
Current smoker	25	23	24	96	1	4	
Non-current smoker	83	77	54	65	29	35	
Radiotherapy technique							0.41
3D CRT	85	79	63	74	22	26	
IMRT	23	21	15	65	8	35	
Pre-existing lung disease							0.16
Yes	53	49	35	66	18	34	
No	55	51	43	78	12	22	
Gross tumor volume							0.91
<98.6 cm^3	55	51	40	73	15	27	
≥98.6 cm^3	53	49	38	72	15	28	
Mean lung dose							0.16
<19.1 Gy	55	51	43	78	12	22	
≥19.1 Gy	53	49	35	66	18	34	
Lung V5							0.16
<59.8%	55	51	43	78	12	22	
≥59.8%	53	49	35	66	18	34	
Lung V20							0.07
<32.0%	54	50	44	81	11	20	
≥32.0%	54	50	34	63	19	35	

3D CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; Gy, gray.