

Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose

Radiation therapy is a critical component in the care of patients with non–small-cell lung cancer (NSCLC), yet cardiac injury after treatment is a significant concern. Therefore, we wished to elucidate the incidence of cardiac events and their relationship to radiation dose to the heart.

Patients and Materials

Study eligibility criteria included patients with stage II to III NSCLC treated on one of four prospective radiation therapy trials at two centers from 2004 to 2013. All cardiac events were reviewed and graded per Common Terminology Criteria for Adverse Events (v4.03). The primary end point was the development of a grade ≥ 3 cardiac event.

Results

In all, 125 patients met eligibility criteria; median follow-up was 51 months for surviving patients. Median prescription dose was 70 Gy, 84% received concurrent chemotherapy, and 27% had pre-existing cardiac disease. Nineteen patients had a grade ≥ 3 cardiac event at a median of 11 months (interquartile range, 6 to 24 months), and 24-month cumulative incidence was 11% (95% CI, 5% to 16%). On multivariable analysis (MVA), pre-existing cardiac disease (hazard ratio [HR], 2.96; 95% CI, 1.07 to 8.21; $P = .04$) and mean heart dose (HR, 1.07/Gy; 95% CI, 1.02 to 1.13/Gy; $P = .01$) were significantly associated with grade ≥ 3 cardiac events. Analyzed as time-dependent variables on MVA analysis, both disease progression (HR, 2.15; 95% CI, 1.54 to 3.00) and grade ≥ 3 cardiac events (HR, 1.76; 95% CI, 1.04 to 2.99) were associated with decreased overall survival. However, disease progression ($n = 71$) was more common than grade ≥ 3 cardiac events ($n = 19$).

Conclusion

The 24-month cumulative incidence of grade ≥ 3 cardiac events exceeded 10% among patients with locally advanced NSCLC treated with definitive radiation. Pre-existing cardiac disease and higher mean heart dose were significantly associated with higher cardiac event rates. Caution should be used with cardiac dose to minimize risk of radiation-associated injury. However, cardiac risks should be balanced against tumor control, given the unfavorable prognosis associated with disease progression.

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INTRODUCTION

Non–small-cell lung cancer (NSCLC) frequently presents with locally advanced, unresectable disease, and standard fractionation radiation has been the backbone of definitive treatment for more than 30 years.¹ Despite improved outcomes with the addition of concurrent chemotherapy,² locoregional relapse remains common and is associated with inferior overall survival (OS).³

Radiation dose escalation has been associated with increased tumor control,⁴ leading to a number of promising phase II trials.⁵⁻⁷ Ultimately, the Radiation Therapy Oncology Group (RTOG) 0617 (High-Dose or Standard-Dose Radiation Therapy and Chemotherapy With or Without Cetuximab in Treating Patients With Newly Diagnosed Stage III Non-Small Cell Lung Cancer That Cannot Be Removed by Surgery) phase III dose-escalation trial compared 74 Gy with the standard 60 Gy, both delivered with

ASSOCIATED CONTENT



Appendix

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concurrent chemotherapy.⁸ In an unexpected result, the high-dose arm had worse OS. On multivariable analysis, increasing radiation dose to the heart was independently associated with worse survival, and some hypothesize that under-reported cardiac events may have contributed to the inferior results in the experimental arm.⁹

The association of increasing exposure to ionizing radiation with long-term cardiac toxicity is well established. With decades of follow-up, increases in rates of cardiac disease with ionizing radiation exposure to the heart have been noted in long-term survivors of breast cancer^{10,11} and lymphoma.^{12,13} However, the subacute effects of radiation on the heart, such as those most likely to impact outcomes in patients with locally advanced NSCLC, have not been well elucidated. This is a research area of critical unmet need, especially given the uncertainty following RTOG 0617.

In this article, we analyzed the combined long-term results of four consecutive, prospective radiation therapy trials for locally advanced NSCLC. We hypothesized that the cardiac event rate in this population is higher than previously reported. We provide a comprehensive patient-level assessment of pretreatment cardiac status along with a detailed evaluation of cardiac events. We aimed to assess the patient- and treatment-related factors associated with clinically significant cardiac events and to determine the impact of these events on OS.

PATIENTS AND MATERIALS

Patients

Between 2004 and 2013, 125 patients with medically inoperable or unresectable stage II to III NSCLC were treated with informed consent on one of four consecutive trials approved by institutional review boards at two centers (University of Michigan and Ann Arbor Veterans Affairs Hospital). All patients had biopsy-confirmed NSCLC. Computed tomography (CT) of the chest and upper abdomen, positron emission tomography (PET)–CT scans and brain imaging (CT or magnetic resonance imaging) were required for staging. Eligible patients had Karnofsky performance score (KPS) \geq 60. Patients with any component of small-cell carcinoma, those with stage I disease, or those treated with stereotactic body radiation therapy were ineligible for this study.

Treatment

Details of the specific prospective trials are summarized in Appendix Table A1 (online only). All trials included patients treated with hypofractionated radiation ($>$ 2 Gy/fraction). Radiation was delivered over 6 weeks with concurrent chemotherapy as tolerated. Patients treated on the adaptive dose-escalation protocol underwent treatment on the basis of midtreatment PET-CT response similar to that in RTOG 1106 (Study of Positron Emission Tomography and Computed Tomography in Guiding Radiation Therapy in Patients With Stage III Non-Small Cell Lung Cancer).¹⁴ Heart constraints included volume receiving 40 Gy $<$ 100% (V40_{Gy} $<$ 100%) and V65_{Gy} $<$ 33%. All normal tissue constraints were evaluated in biologically equivalent 2-Gy fractions. Tumor planning target volume (PTV) coverage took priority over cardiac constraints. History, physical examination, and chest imaging (CT) were completed every 3 to 6 months after treatment. Response was determined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.¹⁵

End Points

The primary end point of this study was the development of a first grade \geq 3 cardiac event after treatment. Cardiac events were graded prospectively on each prospective trial on the basis of Common

Terminology Criteria for Adverse Events (CTCAE, version 3). In this study, all previous CTCAE cardiac events were reviewed, confirmed, and updated to the most recent version of the CTCAE (v4.03; Appendix Table A2, online only). In addition, cardiac events not previously attributed to radiation were documented, graded, and included in the analysis. All events were confirmed by two independent physicians without knowledge of the treatment plan or cardiac radiation dose. Secondary outcomes included grade \geq 2 cardiac events, progression-free survival (PFS) and OS.

Dosimetric Analysis

All previous plans underwent uniform dose calculation using modern photon dose calculations (Analytical Anisotropic Algorithm, Varian Medical Systems). To account for variable fractionation schemes, biologic effective corrections to equivalent dose in 2 Gy fractions (EQD_{2Gy}) were performed by using the linear quadratic model (assuming α/β ratio = 2.5 for heart consistent with previous studies [2.0],¹⁶ experimental data on myocardium [2.4 to 2.9], capillary vasculature [1.8 to 2.8],^{17,18} and clinical estimates of pericardium [2.5]¹⁹). Heart contours were reviewed against a validated cardiac atlas and edited as necessary.²⁰

Covariables

Sex, diabetes, and current smoking status were analyzed as binary variables. KPS, age, and systolic blood pressure were analyzed as continuous variables. Pre-existing cardiac disease was defined as the presence or absence of either pre-existing ischemic heart disease (acute myocardial infarction, coronary artery bypass grafting procedure, angioplasty or stent placement, or a diagnosis of coronary artery disease [CAD]) or clinical diagnosis of congestive heart failure (CHF). For those without pre-existing cardiac disease, Framingham risk scores (hard coronary heart disease 10-year risk) were calculated and analyzed as a continuous variable.²¹ Cardiac radiation dose was analyzed as a continuous variable with a focus on parameters identified as clinically significant in RTOG 0617 (percent volume receiving 5 Gy [V5_{Gy}], 30 Gy [V30_{Gy}], and 50 Gy [V50_{Gy}], and mean heart dose).⁸

Statistical Analysis

Descriptive statistics were used to characterize baseline patient and treatment characteristics. Cumulative incidence curves of the development of a first grade \geq 3 cardiac event were generated accounting for noncardiac death as a competing risk. Univariable and multivariable Cox proportional hazard models were used to analyze the difference in the hazard of cardiac events by baseline patient- and treatment-related characteristics. Concordance index (C-index) values were calculated to quantify the discriminatory ability of cardiac dose terms with respect to cardiac events. Fine and Gray competing risk regression was used to generate models to predict cumulative incidence of grade \geq 3 cardiac events. The Kaplan-Meier method was used to estimate OS and PFS. For all analyses, two-sided *P* values of $<$.05 were considered statistically significant and values $<$.1 were considered a marginal association. Analyses were performed using R (version 3.3.1).

RESULTS

Baseline Patient and Treatment Characteristics

The median age was 66 years (range, 40 to 92 years), 98% had a KPS \geq 70, and the vast majority were current (52%) or former (42%) smokers (Table 1). Twenty seven percent of patients (*n* = 34) had pre-existing cardiac disease before treatment started; all 34 had CAD and five had concurrent CHF. For those without cardiac disease (*n* = 71), the median Framingham risk score was 13% (range, 0.2% to 37%), and 15% (*n* = 19) had a Framingham risk score \geq 20%.

Table 1. Patient, Tumor, and Treatment Characteristics

Characteristic	No.	%
Demographic characteristics		
Median age, years (range)	66 (40-92)	
Sex		
Male	95	76
Female	30	24
Karnofsky performance score		
90-100	66	53
70-80	56	45
60	3	2
Smoking history		
Current	65	52
Former	53	42
Never	4	3
Unknown	3	2
Pre-existing cardiac disease		
Yes	34	27
No	71	57
Unknown*	20	16
Framingham risk score, %		
Median (range)	13 (0.2-37)	
≥ 20	19	15
< 20	52	42
Not applicable	34	27
Unknown*	20	16
Tumor and treatment characteristics		
Histology		
Adenocarcinoma	39	31
Squamous cell carcinoma	36	29
NSCLC NOS	50	40
Stage		
II	16	13
III	109	87
IIIA	51	
IIIB	58	
Concurrent chemotherapy		
Yes	105	84
No	20	16
Radiation dose, Gy		
Median prescription dose (range)	70 (45-88)	
Median EQD2 _{Gy} dose (range)	70 (47-96)	
Technique		
3D	121	97
IMRT	4	3

NOTE. Some totals may not add to 100% because of rounding. Abbreviations: EQD2_{Gy}, equivalent dose in 2 Gy fractions; IMRT, intensity-modulated radiation therapy; NOS, not otherwise specified; NSCLC non-small-cell lung cancer.

*Detailed pretreatment cardiac information was unavailable for 20 patients treated on the 2003.073 and 2003.076 trials because those trials are permanently closed.

Eighty-four percent of the study population received concurrent chemotherapy and, assuming an α/β ratio of 10 for tumor, the median EQD2_{Gy} prescription dose was 70 Gy (range, 47 to 96 Gy). Ninety-seven percent of patients were treated with 3D-conformal radiation and 3% with intensity-modulated radiation therapy (IMRT). The median mean cardiac dose was 11 Gy (range, 0.3 to 46 Gy; interquartile range [IQR], 7 to 19 Gy). Cardiac volumetric dose parameters (V5_{Gy} to V50_{Gy}) were highly correlated (Appendix Fig A1, online only).

Cardiac Events

The median follow-up was 23 months for the entire cohort and 51 months for patients alive at last contact. Nineteen patients

experienced a grade ≥ 3 cardiac event after treatment at a median of 11 months (range, 0.4 to 63 months; IQR, 6 to 24 months) after treatment. Thirteen patients had a grade 3 cardiac event primarily consisting of acute coronary syndrome events ($n = 5$) or new diagnoses of CHF ($n = 5$). There were three grade 4 events: two patients underwent emergent surgical intervention for severe and symptomatic pericardial effusions 13 and 23 months after treatment, and one patient underwent emergent balloon valvuloplasty for severe aortic stenosis 19 months after treatment. There were three grade 5 events: two patients had fatal cardiac arrest 14 and 29 months after treatment, both in the setting of pretreatment multivessel CAD, and one patient had a fatal ventricular arrhythmia 1 month after treatment in the setting of pretreatment multivessel CAD and CHF. No patient with a grade ≥ 3 cardiac event had additional grade 4 or 5 esophageal or pulmonary events. Twenty-eight patients had grade 1 to 2 cardiac events, primarily asymptomatic pericardial effusions (Table 2).

Accounting for noncardiac death as a competing risk, the 12- and 24-month cumulative incidence of grade ≥ 3 cardiac events was 9% (95% CI, 3% to 12%) and 11% (95% CI, 5% to 16%), respectively (Fig 1A). Among those with pre-existing cardiac disease, the 12- and 24-month cumulative incidence was 15% (95% CI, 3% to 27%) and 21% (95% CI, 7% to 35%) compared with 4% (95% CI, 0% to 9%) and 7% (95% CI, 1% to 13%) in those without this history ($P = .08$; Fig 1B). The median mean heart dose was 11 Gy. The 12- and 24-month cumulative incidence of grade ≥ 3 cardiac events was 14% (95% CI, 5% to 24%) and 18% (95% CI, 8% to 28%) in those with mean heart dose above 11 Gy and 2% (95% CI, 0% to 5%) and 2% (95% CI, 0% to 5%) in those with mean heart dose below 11 Gy ($P < .01$; Fig 1C). Similar findings were noted for patients above and below median V5_{Gy} (40%) and V30_{Gy} (12%; Appendix Fig A2, online only).

Predictors of Cardiac Events

On univariable analysis, male sex, diabetes, pre-existing cardiac disease, and Framingham risk score were at least marginally associated with increased risk of grade ≥ 3 cardiac events ($P < .1$). Moreover, mean heart dose, V5_{Gy} and V30_{Gy} were each significantly associated with an increased hazard of cardiac events ($P < .01$) with similar C-indices (approximately 0.7; Table 3).

Cox stepwise multivariable regression analysis (MVA) identified pre-existing cardiac disease (hazard ratio [HR], 2.96; 95% CI, 1.07 to 8.21; $P = .04$) and higher mean heart dose (HR, 1.07/Gy; 95% CI, 1.02 to 1.13/Gy; $P = .01$) as significant predictors of grade ≥ 3 cardiac events. No evidence of effect modification with cardiac dose and pre-existing cardiac disease was demonstrated ($P = .80$ for interaction). In a subpopulation MVA including only those without pre-existing cardiac disease ($n = 65$), increased mean heart dose remained significantly associated with grade ≥ 3 cardiac events (HR, 1.10/Gy; 95% CI, 1.02 to 1.18/Gy; $P = .01$) and Framingham risk score was marginally associated with an increased hazard (HR, 1.09 per 1% increase in Framingham risk score; 95% CI, 0.99 to 1.21 per 1% increase in Framingham risk score; $P = .08$). Similar to grade ≥ 3 cardiac events, grade ≥ 2 events were associated with pre-existing cardiac disease and radiation dose to the heart on MVA (Appendix Table A3, online only).

Table 2. Cardiac Event Detail (maximum grade experienced)

Cardiac Event	None	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 3-5
Acute coronary syndrome		0	0	5	0	0	5
New congestive heart failure		0	2	5	0	0	5
Arrhythmia		1	7	2	0	1	3
Cardiac arrest		0	0	0	0	2	2
Valvular disease		0	1	1	1	0	2
Pericardial effusion		0	17	0	2	0	2
Pericarditis		0	0	0	0	0	0
Total (n = 125)	78	1	27	13	3	3	19
Percent	62	1	22	10	2	2	15

Among patients with pre-existing cardiac disease, mean heart doses of 5 and 12 Gy associated with a Fine and Gray competing risk regression model predicted 24-month grade ≥ 3 cardiac event rates of 10% and 15%, respectively (Fig 2A). Among those without pre-existing cardiac disease, the model-predicted mean heart dose thresholds increased to 23 Gy and 29 Gy, respectively, for equivalent 24-month 10% and 15% cardiac event rates. Analysis of V_{5Gy} and V_{30Gy} provided similar results (Appendix Fig A3, online only). Among patients without pre-existing cardiac disease, model-predicted cardiac event rates were lower than those for patients

with overt cardiac disease, even with a Framingham risk score of 20% (Fig 2B).

Cardiac Events and OS

The median OS and PFS were 23.1 months and 14.6 months, respectively (Appendix Fig A4, online only). Younger age, higher pretreatment KPS, and female sex were associated with increased OS on MVA (Table 4). Cardiac dose was not significantly associated with OS, either on univariable

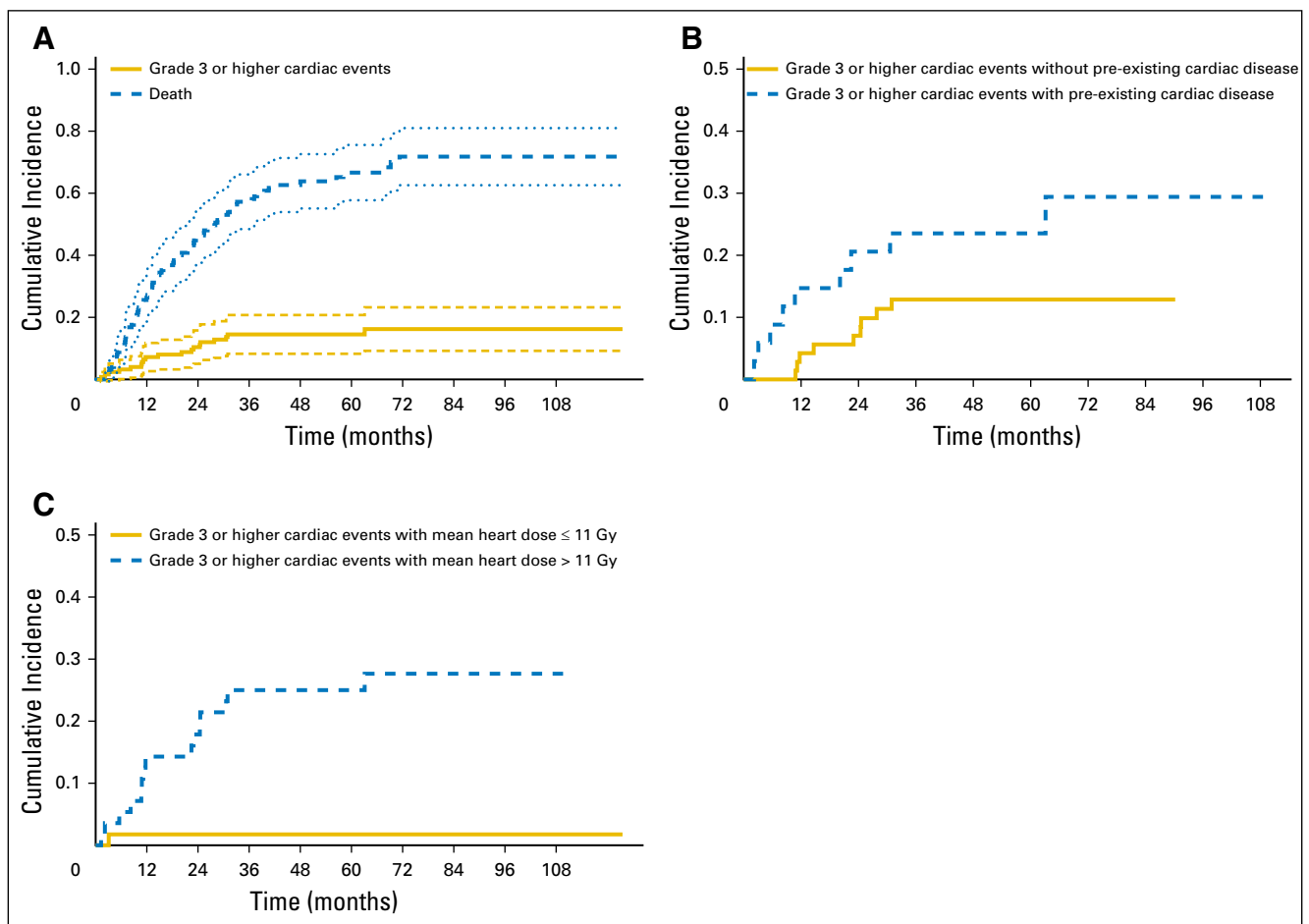


Fig 1. Cumulative incidence of grade ≥ 3 cardiac events. (A) Actual cumulative incidence of grade ≥ 3 cardiac events (with noncardiac death as competing risk) for the total cohort, (B) for those with and without pre-existing cardiac disease, and (C) for those with greater than or less than the median mean heart dose of 11 Gy.

Table 3. Univariable and Multivariable Analysis for Time to Earliest Grade ≥ 3 Cardiac Event

Variable	Univariable Cox Regression Analysis				Cox Multivariable Regression					
	HR	95% CI	P	C-Index	All Patients (n = 96)*			No Pre-existing Cardiac Disease Only (n = 65)*		
					HR	95% CI	P	HR	95% CI	P
General										
Age	1.04	0.99 to 1.08	0.11	.619						
Male sex	3.53	0.82 to 15.38	0.09	.583						
Diabetes	2.38	0.92 to 6.18	0.07	.561						
Current smoker	1.91	0.71 to 5.12	0.20	.568						
Systolic blood pressure	1.00	0.98 to 1.02	0.91	.524						
Cardiac status										
Pre-existing cardiac disease	2.56	1.01 to 6.47	0.05	.650	2.96	1.07 to 8.21	.04			
Framingham risk score†	1.09	1.01 to 1.18	0.04	.699				1.09	0.99 to 1.21	.08
Cardiac dosimetry										
Mean heart dose (%)	1.08	1.03 to 1.13	<0.01	.730	1.07	1.02 to 1.13	.01	1.10	1.02 to 1.18	.01
V5 _{Gy}	1.03	1.01 to 1.05	<0.01	.725						
V30 _{Gy}	1.03	1.01 to 1.06	<0.01	.717						
V50 _{Gy}	1.05	1.00 to 1.10	0.06	.648						

Abbreviations: C-index, concordance index; HR, hazard ratio.
 *Of 125 patients, detailed pretreatment cardiac information was unavailable for 20 patients treated on the 2003.073 and 2003.076 trials because those trials are permanently closed. Nine additional patients had incomplete dose-volume histogram information (including six without pretreatment cardiac disease).
 †Framingham 10-year hard coronary heart disease was calculated only in patients without pre-existing cardiac disease (n = 71). Baseline age, systolic blood pressure, treatment of hypertension, and smoking status were available for all 71 patients. Cholesterol was available for 49 patients and was imputed based on the mean for 22 patients.

analysis or MVA with or without the inclusion of tumor dose. When analyzed as time-dependent variables in MVA analysis, both disease progression (HR, 2.15; 95% CI, 1.54 to 3.00; $P < .01$) and grade ≥ 3 cardiac events (HR, 1.76; 95% CI, 1.04 to 2.99; $P = .04$) were associated with increased hazard of death. Disease progression (n = 71), however, was far more common in the cohort than grade ≥ 3 cardiac events (n = 19). In contrast to grade ≥ 3 events, time-dependent grade ≥ 2 events were not significantly associated with OS on MVA (HR, 1.29; 95% CI, 0.90 to 1.84; $P = .17$).

DISCUSSION

In a detailed review of patients with locally advanced NSCLC treated on four prospective radiation therapy trials, clinically significant cardiac events were common and often within the window of median expected survival for this patient population. The 24-month cumulative incidence of grade ≥ 3 cardiac events was 11% (95% CI, 5% to 16%), with events occurring at a median of 11 months after treatment (IQR, 6 to 24 months). Our event rate

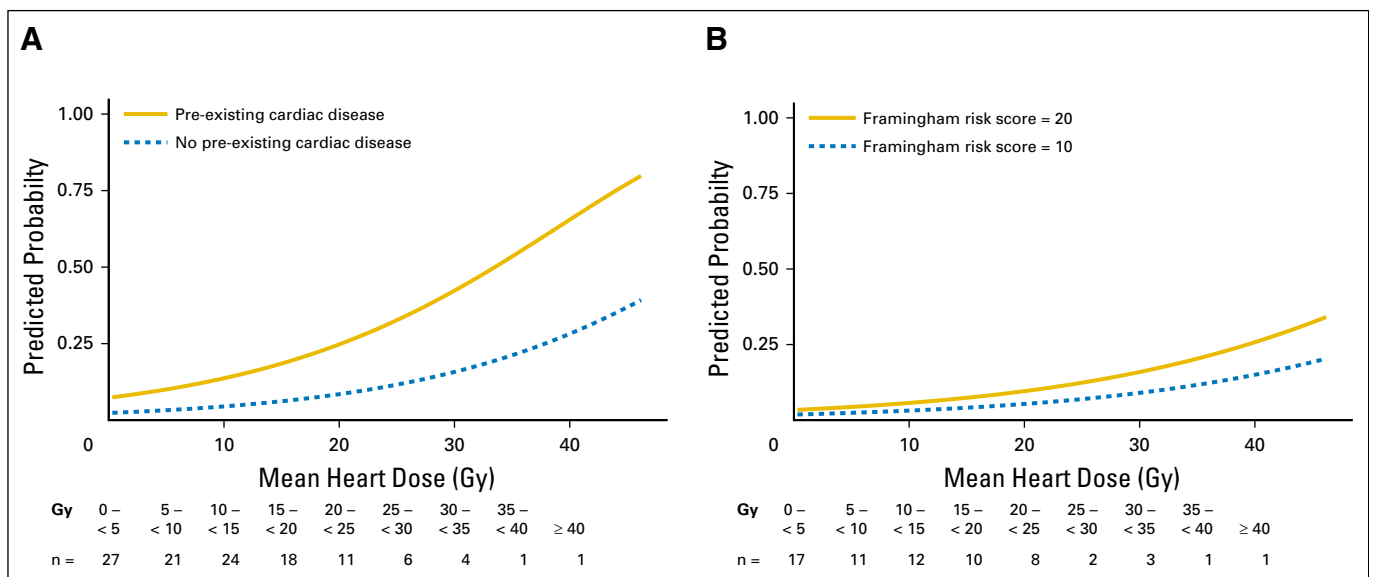


Fig 2. Model-predicted cumulative incidence of a grade ≥ 3 cardiac event within 24 months of treatment by increasing mean heart dose (A) for those with and without pre-existing cardiac disease and (B) for the subpopulation of only those without baseline cardiac disease. Representative patient Framingham risk scores of 10 and 20 are shown.

Table 4. Univariable and Multivariable Overall Survival Models

Variable	Univariable Regression			Multivariable Regression					
	HR	95% CI	P	HR	95% CI	P	HR*	95% CI*	P*
General									
Age	1.03	1.01 to 1.05	.01	1.02	1.00 to 1.04	.02	1.02	1.01 to 1.04	.01
KPS	0.95	0.93 to 0.98	<.01	0.95	0.93 to 0.97	<.01	0.97	0.95 to 0.98	<.01
Male sex	1.80	1.07 to 3.01	.03	1.82	1.07 to 3.11	.03	1.80	1.20 to 2.70	<.01
Stage II v III	1.28	0.72 to 2.25	.40						
Concurrent CRT	0.51	0.31 to 0.85	.01						
Tumor dose (D90)	0.99	0.96 to 1.01	.26						
Cardiac dosimetry									
Mean heart dose (%)	1.01	0.98 to 1.03	.65						
V5 _{Gy}	1.00	0.99 to 1.01	.98						
V30 _{Gy}	1.01	0.99 to 1.02	.29						
V50 _{Gy}	1.01	0.98 to 1.04	.59						
Time-dependent variables									
Any progression†							2.15	1.54 to 3.00	<.01
Grade ≥ 3 cardiac event†							1.76	1.04 to 2.99	.04

Abbreviations: CRT, chemoradiation therapy; D90, minimum dose received by 90% of the planning target volume; HR, hazard ratio; KPS; Karnofsky performance score.
*Including time-dependent variables.
†Time-dependent variables.

exceeds the baseline coronary risk of approximately 2% to 3% per year in a population with a similar Framingham risk score distribution and prevalence of pre-existing CAD. To the best of our knowledge, this represents one of the largest detailed studies performed to date of cardiac morbidity and mortality in patients with locally advanced NSCLC treated on prospective protocols with dose-escalated radiation therapy. Our data provide useful insight regarding patient- and treatment-related factors associated with increased risk of developing clinically significant cardiac events.

On MVA, pre-existing cardiac disease was significantly associated with a near three-fold increase in the likelihood of developing a grade ≥ 3 cardiac event. Pre-existing cardiac disease was common in our cohort. More than one in four patients (27%) had overt CAD, a finding consistent with other studies. Janssen-Heijnen et al²² reviewed nearly 4,000 patients in the Netherlands with lung cancer and noted that a diagnosis of concomitant cardiovascular disease was 23%, nearly twice that of the general population. In our patients with pre-existing cardiac disease, the 24-month cumulative incidence of grade ≥ 3 cardiac events after treatment was 21% (95% CI, 7% to 35%). Such a rate far exceeds thresholds for aggressive preventative treatment in the general population, which range from 7.5% to 20% risk of composite cardiac or cardiovascular events over 10 years.^{21,23} Thus, patients with pre-existing cardiac disease may warrant establishment of care with a cardiologist with frequent, close monitoring after treatment. Further investigation into preventive management strategies should be explored in this high-risk population. Moreover, individualized, more stringent cardiac dosimetric constraints may be needed in those with pre-existing cardiac disease, especially given our finding of the cardiac dose-effect on grade ≥ 3 cardiac events.

Independent of pretreatment cardiac status, cardiac radiation dose was significantly associated with increased risk of grade ≥ 3 cardiac events on MVA with a hazard of 1.07/Gy increase in mean heart dose. A recent retrospective series from Washington University in St. Louis²⁴ and preliminary data from University of North

Carolina prospective trials have suggested a similar cardiac dose-response relationship with cardiac events.²⁵ In retrospect, our previous heart dose constraints were liberal; V40_{Gy} < 100% exceeds our model-predicted thresholds for a 15% incidence of grade ≥ 3 cardiac events at 24 months. By comparison, cardiac constraints in ongoing trials such as RTOG 1308 (Comparing Photon Therapy To Proton Therapy To Treat Patients With Lung Cancer) are more stringent (eg, V30_{Gy} < 50%), and achieving these lower targets may lead to lower cardiac event rates.

Our patients were treated almost exclusively with 3D-conformal radiation therapy. In a recent secondary analysis, the RTOG 0617 group reported that patients treated with IMRT had significantly lower cardiac doses compared with those treated with 3D-conformal treatment (eg, V40_{Gy}, 6.8% v 11.4%; *P* < .01) and that V40_{Gy} was inversely associated with OS on adjusted analysis.²⁶ It is therefore possible that IMRT may be an attractive treatment option for reducing risk of cardiac events. Proton therapy may also be an attractive treatment option because cardiac dosimetry benefits have previously been demonstrated.²⁷ It is important to note that in addition to mean heart dose, V5_{Gy} and V30_{Gy} were essentially equally valid parameters on the basis of the C-indices, and clinicians should focus on these metrics as well.

It is increasingly evident that radiation-induced cardiac mortality has an earlier time course than previously appreciated.^{28,29} We now understand that dose-escalated radiation therapy can have a detrimental effect on survival in locally advanced NSCLC,⁸ especially in the context of concurrent chemotherapy.³⁰ In our cohort, time-dependent MVA suggests that grade ≥ 3 cardiac events negatively impact survival (HR, 1.76) after accounting for age, KPS, sex, and disease progression. We provide several plausible explanations by which an increased yet under-reported cardiac event rate on the 74 Gy arm of RTOG 0617 may have led to a decreased OS. A lack of stratification by pre-existing cardiac disease may have led to treatment arm imbalances, thus negatively impacting survival. Moreover, higher heart dose on the dose-escalated arm may have directly increased the cardiac event

rate and contributed to the inferior results. Of note, similar to RTOG 0617, certain cardiac dose metrics increased hazard of death in our series, but the association was not statistically significant (eg, V30_{Gy}; HR,1.01; $P = .29$) likely a result of the limited power of our study.

Our study has several other limitations. It is possible that not all cardiac events were completely captured. However, all patients were enrolled on prospective clinical trials with regularly scheduled follow-up. In addition, 75 of 125 patients were treated in the Veterans Affairs Health System which offers comprehensive medical care, thus increasing the likelihood of reliably capturing cardiac events. We acknowledge that the incidence of cardiac events will likely continue to rise with further follow-up. We also recognize that others have estimated a slightly higher α/β ratio for heart than 2.5.³¹ Using an α/β of 3.5 does not change our associations, but does increase our reported EQD2_{Gy} heart doses by approximately 3%. Finally, larger confirmatory studies with uniform fractionation and chemotherapy are required to confirm and broadly interpret our findings.

In conclusion, we have demonstrated that the cumulative incidence of grade ≥ 3 cardiac events exceeds 10% within 24 months among patients with locally advanced NSCLC treated with definitive radiation therapy. Pre-existing cardiac disease markedly increased the risk of post-treatment cardiac events. Moreover, higher mean heart doses, V5_{Gy} and V30_{Gy}, were each independently associated with an increased cardiac event rate. In light of these findings, future studies of thoracic radiation therapy should stratify on the basis of pre-existing cardiac status to enable a more meaningful analysis of cardiac events. Our results also suggest that stricter cardiac dose constraints may be necessary, especially among patients with pre-existing cardiac disease.

At our own institution, we are evaluating the use of cardiac magnetic resonance imaging to noninvasively identify early pathologic changes in cardiac function and to investigate the utility

of novel imaging biomarkers. We are also evaluating potential blood biomarkers of cardiac damage or stress such as troponin and N-terminal prohormone brain natriuretic peptide.³² Finally, our ongoing adaptive definitive lung protocol incorporates more stringent cardiac dose constraints on the basis of pretreatment cardiac status to evaluate the feasibility and outcomes of personalized dose escalation. Although this study focused on grade ≥ 3 cardiac events, progression of disease was far more common in our study population. By minimizing cardiac and other toxicities, the full benefit of intensive chemoradiation can be realized.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Appendix

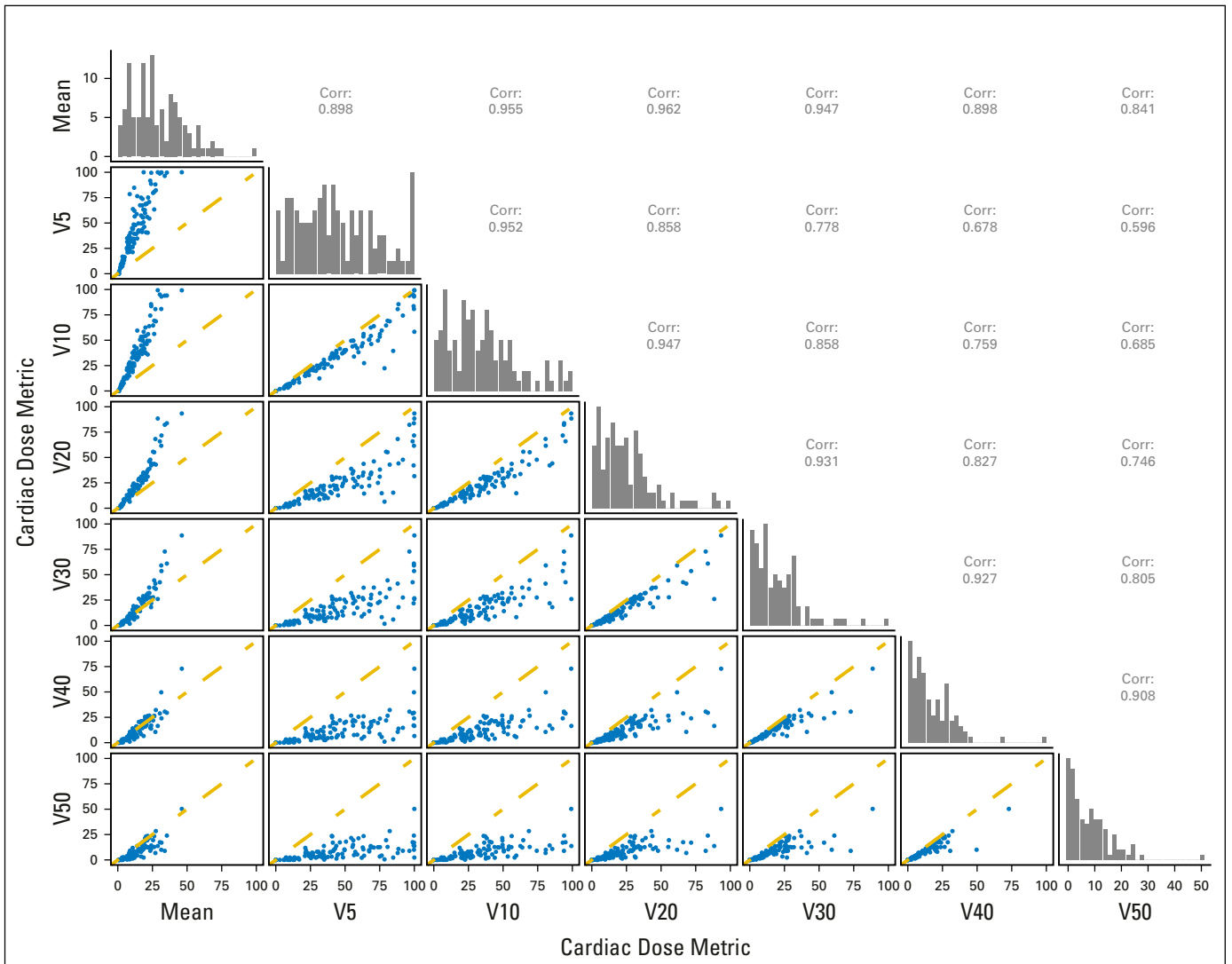


Fig A1. The cardiac dose correlation (Corr.) matrix demonstrates the correlation between mean heart dose and volume receiving 5 Gy ($V5_{Gy}$) to $V50_{Gy}$ (%). The distribution of each variable is shown on the diagonal.

Cardiac Events and Radiation Therapy for Locally Advanced NSCLC

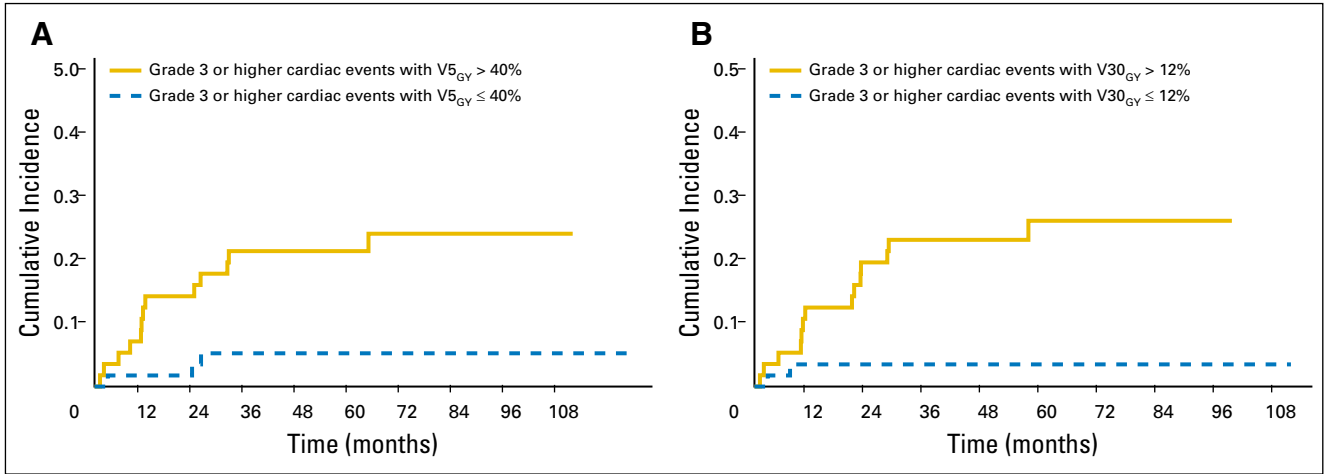


Fig A2. Cumulative incidence of grade ≥ 3 cardiac events (volume receiving 5 Gy [$V5_{Gy}$] and $V30_{Gy}$). Actual cumulative incidence of grade ≥ 3 cardiac events (with noncardiac death as competing risk) (A) for those greater than or less than the median $V5_{Gy}$ of 40% ($P < .01$) and (B) for those greater than or less than the median $V30_{Gy}$ of 12% ($P < .01$).

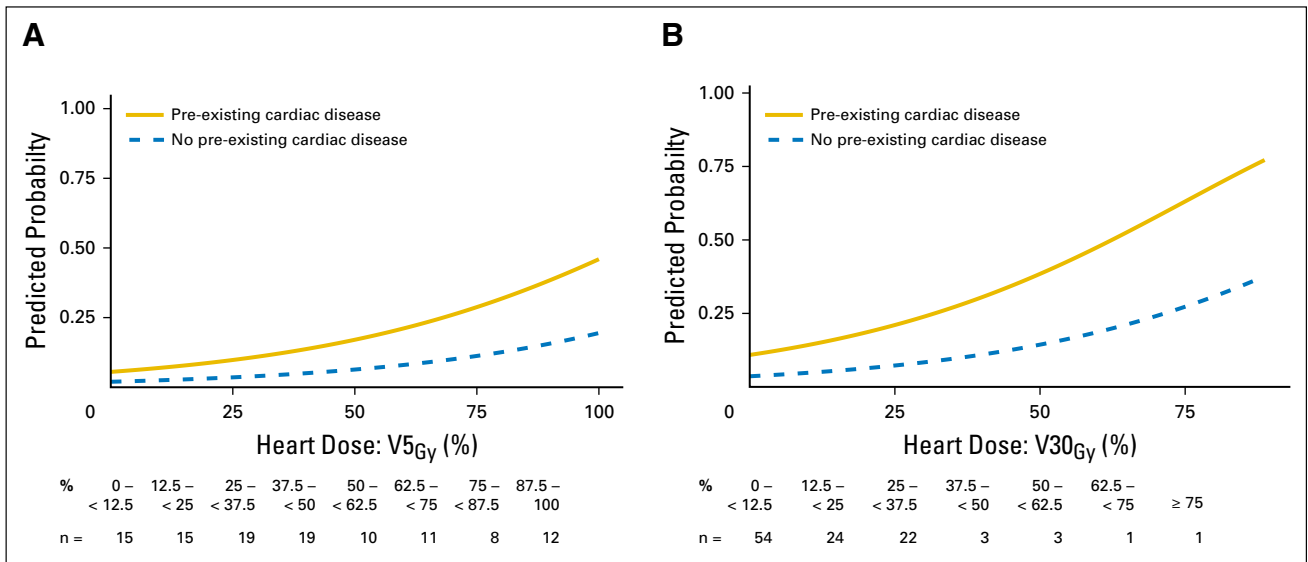


Fig A3. Predicted probability of grade ≥ 3 cardiac events within 24 months. Model-predicted cumulative incidence of a grade ≥ 3 cardiac event within 24 months of treatment for those with and without pre-existing cardiac disease with increasing (A) $V5_{Gy}$ and (B) $V30_{Gy}$.

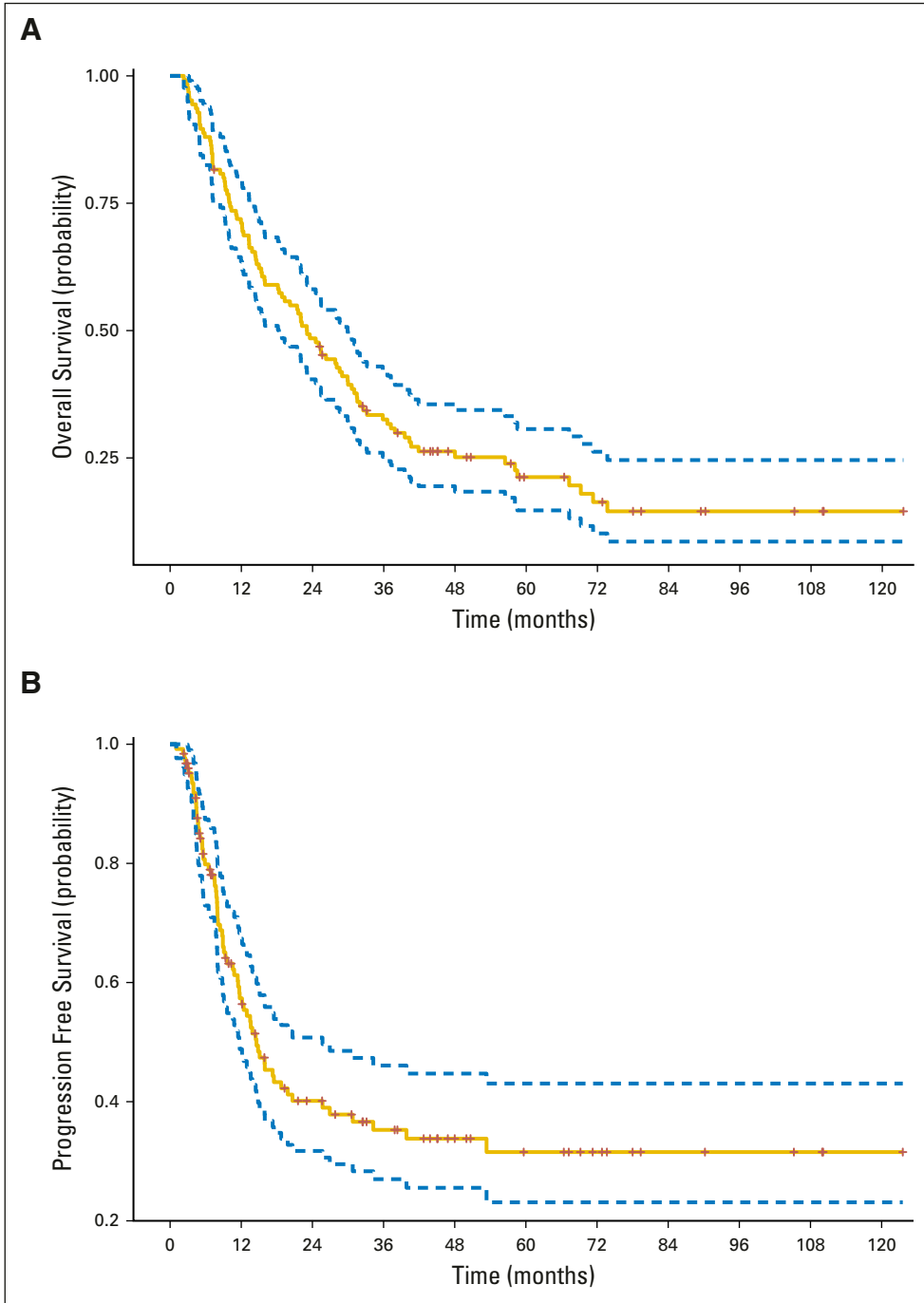


Fig A4. K-M estimated for (A) overall survival and (B) progression-free survival.

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Table A1. Detail of Prospective Trials

Trial	Title	Radiation	Concurrent Chemotherapy	Adjuvant Chemotherapy
2003.073 (NCT: NA)	A Phase I/II Randomized Trial in Radiation Dose Escalation and Timing of Concurrent Chemotherapy for Patients with Stage III Unresectable/Inoperable Non-Small Cell Lung Cancer	2 Gy Monday through Wednesday	Paclitaxel 45 mg/m ²	Per treating physician
		2.35-3.8 Gy Thursday and Friday for 6 weeks ≤ 15% NTCP for grade ≥ 3 pneumonitis (EQD _{2Gy} between 64 and 86 Gy in 30 fractions)	Carboplatin AUC 2 (17 of 17 received chemotherapy)	
2003.076 (NCT: NA)	A Pilot Study to Evaluate the Impact of Multiple Functional Images and Molecular Markers on Radiation Treatment Planning and Radiation Outcome and Lung Toxicity Prediction	Determined by radiation oncologist (EQD _{2Gy} between 64 and 86 Gy in 30 fractions)	Yes, per treating physician (two of four received chemotherapy)	Paclitaxel 200 mg/m ²
2006.040 (NCT00603057)	Using Functional Image and Circulating Molecular Markers to Predict Tumor Response and Lung Toxicity in Treatment of Lung Cancer	Determined by radiation oncologist (EQD _{2Gy} between 60 and 96 Gy in 30 fractions)	Yes, per treating physician (48 of 62 received chemotherapy)	Carboplatin AUC 6 Per treating physician
2007.123 (NCT01190527)	Using FDG-PET Acquired During the Course of Radiation Therapy to Individualize Adaptive Radiation Dose Escalation in Patients with Non-Small Cell Lung Cancer	2.1-2.85 Gy per day	Paclitaxel 45 mg/m ²	Paclitaxel 200 mg/m ²
		≤ 17.2% NTCP for normal lung (EQD _{2Gy} between 64 and 92 Gy in 30 fractions)	Carboplatin AUC 2 (37 of 42 received chemotherapy)	Carboplatin AUC 6

NOTE. All patients underwent a computed tomography (CT) simulation. Patients were immobilized by using a thorax board, and CT scans were obtained with intravenous contrast. Depending on institutional standard at time of treatment, respiratory motion was managed by acquiring both inspiratory and expiratory CT scans or by a respiration-correlated CT (4D-CT). Target delineation included the gross tumor volume (GTV) as defined by the primary tumor plus clinically involved lymph nodes (fluorodeoxyglucose avidity above mediastinal blood pool on positron emission tomography-CT or those greater than 1 cm on contrast-enhanced CT). A clinical target volume (CTV) was created by using a 0.5 cm anatomically confined expansion of the GTV to account for occult disease and a 0.5- to 1.0-cm uniform expansion was applied to the CTV to create a planning target volume to account for setup uncertainty. Elective nodal irradiation was not used.

Abbreviations: AUC, area under the (time-concentration) curve; EQD_{2Gy}, equivalent dose in 2 Gy fractions; FDG, fluorodeoxyglucose; NA, not applicable; NCT, National Clinical Trial; NTCP, noninvasive transcutaneous cardiac pacing; PET, positron emission tomography.

Table A2. Detail of Common Terminology Criteria for Adverse Events (version 4.03) Cardiac Event Grading

Adverse Event	Cardiac Event Grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute coronary syndrome	—	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction; cardiac enzymes abnormal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction; cardiac enzymes abnormal; hemodynamically unstable	Death
Cardiac arrest	—	—	—	Life-threatening consequences; urgent intervention indicated	Death
Systolic and diastolic dysfunction Congestive heart failure	Asymptomatic with laboratory (eg, B-natriuretic peptide) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest of minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)	Death
Pericardial disease Pericardial effusion	—	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Pericarditis	Asymptomatic, electrocardiogram or physical findings (eg, rub) consistent with pericarditis	Symptomatic pericarditis (eg, chest pain)	Pericarditis with physiologic consequences (eg, pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Valvular disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (eg, valve replacement, valvuloplasty)	Death
Arrhythmia	Asymptomatic, intervention not indicated	Nonurgent medical intervention indicated	Symptomatically and incompletely controlled medically, or controlled with device (eg, pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death

Cardiac Events and Radiation Therapy for Locally Advanced NSCLC

Table A3. Univariable and Multivariable Analysis for Time to Earliest Grade \geq 2 Cardiac Event

	Univariable Cox Regression				Multivariable Cox Regression					
	HR	95% CI	P	C-Index	All Patients (N = 96)*			No Pre-existing Cardiac Disease Only (n = 65)*		
					HR	95% CI	P	HR	95% CI	P
General										
Age	1.03	1.00 to 1.06	0.05	.58						
Male sex	2.95	1.24 to 7.01	0.01	.60						
Diabetes	2.03	1.09 to 3.78	0.02	.57						
Current smoker	0.96	0.54 to 1.73	0.90	.51						
Systolic blood pressure	1.02	1.00 to 1.03	0.05	.58						
Cardiac status										
Preexisting cardiac disease	2.22	1.21 to 4.07	0.01	.59	2.34	1.23 to 4.45	< .01			
Framingham risk score†	1.07	1.02 to 1.12	< 0.01	.69				1.06	1.01 to 1.12	.02
Cardiac dosimetry										
Mean heart dose (%)	1.06	1.03 to 1.10	< 0.01	.68	1.07	1.03 to 1.11	< .01	1.07	1.03 to 1.12	< .01
V5 _{Gy}	1.02	1.01 to 1.03	< 0.01	.67						
V30 _{Gy}	1.03	1.02 to 1.05	< 0.01	.69						
V50 _{Gy}	1.06	1.03 to 1.10	< 0.01	.65						

Abbreviations: C-index, concordance index; HR, hazard ratio.

*Of the 125 patients, detailed information on pretreatment cardiac status was unavailable for 20 patients treated on the 2003.073 and 2003.076 trials because those trials are permanently closed. Nine additional patients had incomplete dose-volume histogram information (including six without pretreatment cardiac disease).

†Framingham 10-year hard coronary heart disease was calculated only in patients without pre-existing cardiac disease (n = 71). Baseline age, systolic blood pressure, treatment of hypertension, and smoking status were available for all 71 patients. Cholesterol was available for 49 patients and imputed on the basis of the mean for 22 patients.