



Fitting the relative seriality model on cardiac toxicity and dose to different parts of heart after radiation therapy for stage III non-small cell lung cancer

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Purpose

To determine which cardiac substructures are associated with radiation-induced cardiac symptoms following radiotherapy for stage III non-small cell lung cancer (NSCLC), and to estimate the corresponding dose–response relationships using a widely applied normal tissue complication probability (NTCP) model.

Materials and Methods

A total of 112 patients treated with 70–90 Gy across six prospective clinical trials were analyzed. Dose–volume histograms were generated for the left and right ventricles (LV, RV), left and right atria (LA, RA), left anterior descending artery (LAD), whole heart, and pericardium. Cardiac toxicity was categorized as ischemic, arrhythmic, pericardial, or a combination of these events. Baseline cardiac risk was evaluated using the WHO/ISH risk score. The Relative Seriality (RS) NTCP model was applied to fit the clinical data. Model performance was assessed using the area under the receiver operating characteristic curve (AUC) and odds ratios (ORs).

Table 1. Summary of the parameter values for the relative seriality (RS) model that best fitted the clinical data.

NTCP model	RS		
	D ₅₀	γ	s
Ischemic			
Heart	119.6	0.45	0.0001
LV	69.5	0.45	0.0001
LAD	97.0	0.50	0.0001
Arrhythmia			
Heart	111.1	0.43	2.14
LA	181.1	0.40	2.67
Pericardium	115.1	0.43	2.90
RA	137.5	0.38	1.15
RV	124.2	0.43	4.87
Pericardial			
Heart	91.0	0.51	1.04
LA	100.3	0.57	0.21
Pericardium	95.9	0.50	1.52
RA	114.3	0.47	0.71
RV	101.8	0.49	2.13
Combined			
Heart	46.7	0.34	0.92
LV	59.9	0.35	9.04

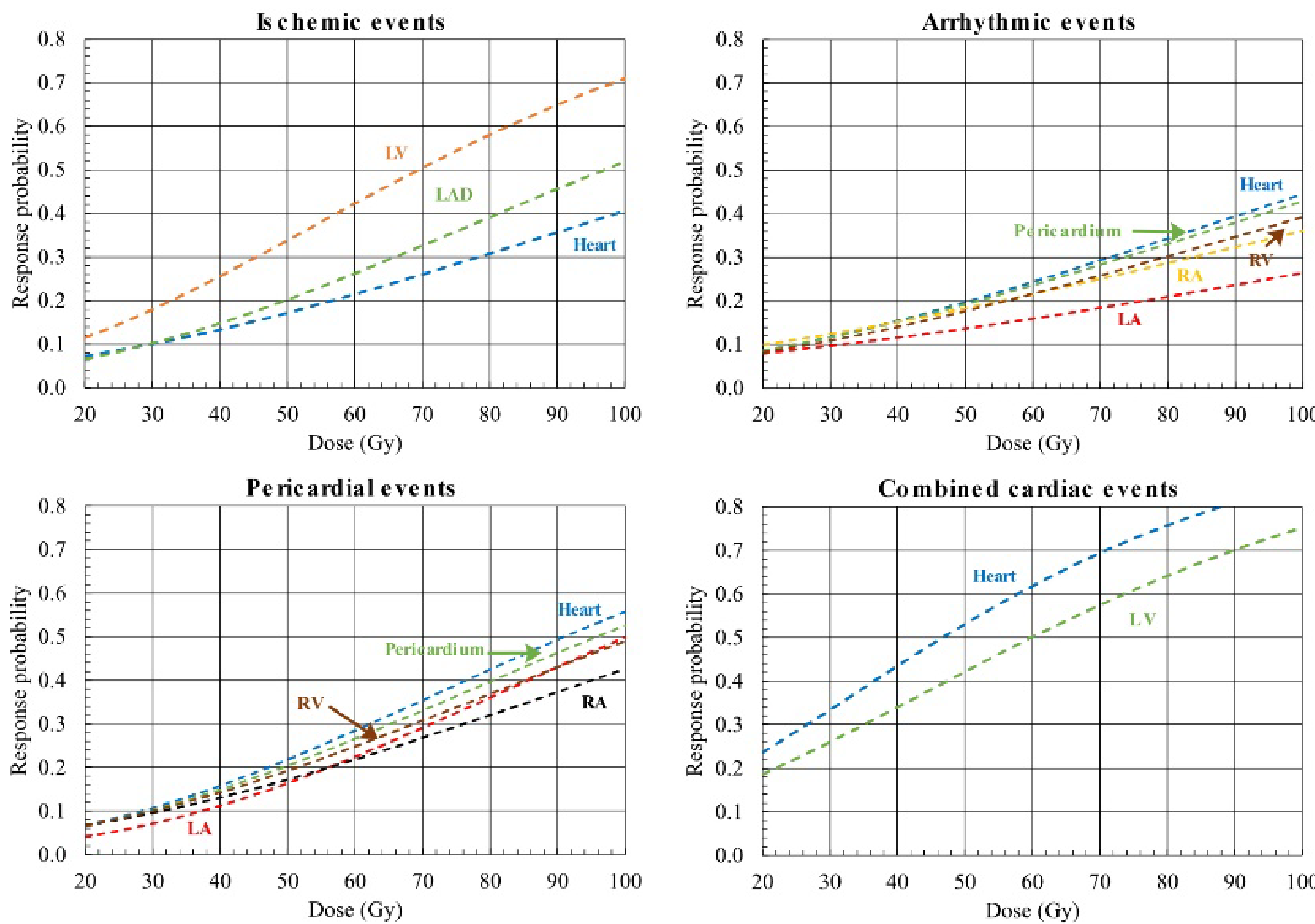


Fig. 1. The dose response curves for different cardiac structures and clinical endpoints (upper left: ischemic events, upper right: arrhythmic events, lower left: pericardial events, lower right: combined cardiac events). Toxicity was defined as a ≥20 point worsening in the Michigan score, or a ≥2 point worsening in both score (from baseline). The lines correspond to the Relative Seriality NTCP model.

Results

After a median follow-up of 26 months post-radiotherapy, ischemic, arrhythmic, pericardial events and at least one cardiac event occurred in 6.3%, 10.7%, 8.0% and 22.3% of the patients, respectively. Combined cardiac events were correlated with dose to heart (AUC = 0.71, OR = 3.3 (1.1-9.3), p = 0.03) and LV (AUC = 0.68, OR = 3.6 (1.4-9.6), p = 0.01). The corresponding biological dose constraints were 31Gy for heart and 21Gy for LV, respectively. The RS model parameters for heart were D₅₀ = 46.7 Gy (32.7-74.7 Gy), gamma = 0.34 (0.21-0.49) and s = 0.92 (0.09-6.43), whereas for LV they were 59.9 Gy (44.2-93.6 Gy), 0.35 (0.19-0.49) and 9.04 (4.97-63.26), respectively (Table 1).

Table 2 shows the statistical associations between dosimetric parameters and events. Fig.1 illustrates the dose response curves of the different combinations of organ doses and cardiac events. The resulting parameter sets may be applied as NTCP-based objectives in radiotherapy treatment plan optimization.

Table 2. Summary of the results from the fit of the relative seriality normal tissue complication probability model for the different cardiac events. AUC = area under the curve. Predicted response rate is the average of the response rates predicted by the model. OR = Odds ratio.

	Obs. rate (%)	Pred. rate (%)	AUC	OR	gEUD thres.	p-value
Ischemic						
Heart	6.3	6.3	0.68	4.9 (0.8-29.1)	36	0.08
LV		6.3	0.76	8.0 (1.2-51.9)	30	0.03
LAD		6.3	0.72	4.9 (1.0-24.1)	34	0.05
Arrhythmia						
Heart	10.7	10.6	0.69	6.0 (1.7-21.6)	24	0.01
LA		10.7	0.62	3.1 (0.9-10.6)	42	0.07
Pericardium		10.7	0.68	3.8 (1.1-12.9)	39	0.03
RA		10.7	0.66	3.5 (1.0-12.1)	32	0.04
RV		10.6	0.68	6.3 (1.8-22.9)	43	<0.01
Pericardial						
Heart	8.0	8.0	0.72	5.9 (1.4-24.2)	33	0.01
LA		8.1	0.77	5.9 (1.2-28.3)	59	0.03
Pericardium		8.0	0.74	5.9 (1.4-24.2)	36	0.01
RA		8.0	0.74	9.5 (1.4-66.7)	67	0.02
RV		8.0	0.72	5.9 (1.4-24.2)	39	0.01
Combined						
Heart	22.3	22.2	0.71	3.3 (1.1-9.3)	31	0.03
LV		22.4	0.68	3.6 (1.4-9.6)	21	0.01

Conclusions

Specific cardiac substructures were identified as being significantly associated with distinct radiation-induced cardiac symptoms. The RS NTCP model demonstrated a statistically significant fit to the clinical data in most cases. The resulting parameter sets may be applied as NTCP-based objectives in radiotherapy treatment plan optimization.