Original Article

Doses of intensity-modulated radiotherapy and its association with cardiac disease in esophageal cancer patients

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Background: No clear guidelines or available studies exist regarding the effects of intensity-modulated radiotherapy (IMRT) of esophageal cancer (EC) on the cardiovascular system. We therefore analyzed a wide range of cardiac vascular dosimetric parameters and clinical characteristics to assess the prognostic factors for EC patients treated with IMRT.

Methods: A total of 112 patients receiving IMRT at the Qianfoshan Hospital between July 2012 and May 2017 were retrospectively reviewed. The dose per fraction was 1.8–2.0 Gy, and the total dose range was 54–66 Gy. Kaplan-Meier analysis was used to estimate death due to heart disease. Univariate and multivariate logistic regression models were calculated to test for associations between patient characteristics and dose-volume histogram (DVH) parameters. A *t*-test and chi-squared or Fisher's exact test was used to analyze the comparisons.

Results: The maximum and mean doses received by the heart were 57.34±13.51 and 24.83±11.40 Gy, respectively. Among the parameters examined, which included the maximum dose received by the heart, the mean dose received by the right and left ventricle (RV and LV), and the maximum dose received by the right atrium (RA), the mean dose received by the RV predicted survival and was included in our multivariate analysis. The results indicated that patients with basic heart disease who were undergoing concurrent radiochemotherapy were more likely to have cardiac disease.

Conclusions: This is first study to examine the prognosis of cardiovascular vessels exposed to various radiation doses during the treatment of EC, the findings of which suggest that limiting radiation exposure may be an important measure in IMRT application. These findings of this study may provide theoretical support for prediction of radiation-induced heart disease (RIHD). Furthermore, to curb the risk of RIHD, the modality of chemotherapy also needs to be attentively monitored and managed.

Keywords: Cardiovascular radiation doses; radiation-induced heart disease (RIHD); intensity-modulated radiotherapy (IMRT); prognosis; esophageal cancer (EC)

Submitted Dec 10, 2020. Accepted for publication Jan 22, 2021.
doi: 10.21037/atm-21-184
View this article at: http://dx.doi.org/10.21037/atm-21-184

Introduction

The incidence of esophageal cancer (EC) is rapidly increasing compared to that of other malignancies, and EC is now the sixth leading cause of tumor mortality (1). In the treatment of EC, radiotherapy (RT) is a major modality for unresectable disease, but preoperative RT can contribute to operable disease as well (2). Intensity-modulated radiotherapy (IMRT) can be integral to reducing toxicity and sparing normal tissue (3). Radiation to the adjacent tissue typically occurs to the heart, which is a late-reacting organ. Radiation has been implicated in increasing the risk of cardiac toxicity in breast cancer and Hodgkin's disease (4,5), and correlated factors have been identified, including the heart volume, total amount of radiation, and fraction size (6-9). However, the clinical awareness of radiation-associated cardiovascular toxicity in esophageal carcinoma is unsatisfactorily low.

Cardiovascular insults resulting from radiation exposure usually manifest as a long latent period with subclinical changes, including coronary artery disease (CAD), ischemia, myocardial fibrosis, and valvular insufficiency with pericardial disease (10,11). There is a paucity of data regarding the cardiac complications resulting from the radiation treatment of EC, mainly due to the poor long-term survival of these patients. The articles that do exist report conflicting findings concerning the relationship between the radiation dose to the heart and the associated cardiac toxicity (11).

To our knowledge, no clear guidelines or available published studies currently exist regarding the prognosis of the cardiovascular system after patients are treated with IMRT for EC. In this study, we retrospectively analyzed a wide range of cardiac vascular dosimetric parameters to assess the prognostic factors for EC patients treated with IMRT. This is first study to examine the prognosis of cardiovascular vessels exposed to various radiation doses during the treatment of EC, the findings of which suggest that limiting radiation exposure may be an important measure in IMRT application. These findings of this study may provide theoretical support for prediction of radiation-induced heart disease. Our study showed the correlations between the radiation dose to the cardiac substructure and RIHD has not been reported in the past. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-184).

Methods

Patients

Between July 2012 and May 2017, the medical records of 112 patients receiving RT for EC at the Department of Radiation Oncology, Qianfoshan Hospital, were retrospectively reviewed following institutional review board approval. The evaluated patients had biopsy-confirmed clinical stage II–IV esophageal carcinoma that was managed with RT. To avoid underestimating the incidence of cardiac disease, we identified patients with a follow-up period of ≥60 months. Reasons for ineligibility included a previously treated malignancy and a history of thoracic radiation. All patients who participated in this study provided written informed consent for publication. This study was approved by the Board and Ethical Committee of Qianfoshan Hospital and was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Treatment

RT was administered with 6 MV photons 5 days per week. The doses per fraction were 1.8–2.0 Gy, and the total dose ranged from 56 to 60 Gy. The IMRT regimen was performed in all radiation treatment plans. None of the patients received further radiation in addition to the session included in the initial planned course. During this time, computed tomography (CT) scans using intravenous and oral contrast agents were obtained for all patients. Images were acquired with the participants in the supine position. All procedures were performed with the Eclipse 10.0 Treatment Planning System (Varian Medical Systems Inc., Palo Alto, CA, USA).

The gross tumor volume (GTV) was defined as the region of the primary tumor along with any related lymph nodes (>1 cm on the short axis) and was determined by the treating radiation oncologist. A 1.5-cm circumferential and 4-cm superior/inferior expansion of this area, including the involved contours of the GTV, was defined as the clinical target volume (CTV). After considering the daily setup error and motion, the planning target volume (PTV) was expanded by 0.5 cm in the radial dimension beyond the CTV to address these issues.

Dosimetric analysis

Two physicians contoured the whole external heart and

coronary border, while another radiation oncologist examined this area. Dose-volume histograms (DVHs) of the PTV, heart, and critical normal heart arteries were generated, and the risks to other organs (lungs, stomach, liver, and spinal cord) were calculated using the treatment planning system. The volumes of the heart's right coronary artery (RCA), left anterior descending artery (LAD), left circumflex artery (LCX), left ventricle (LV), left atrium (LA), right ventricle (RV), and right atrium (RA) were recorded for each patient.

Statistical analyses

All statistical analyses were performed with Statistical Package for the Social Sciences, version 21.0 (IBM Corp., Armonk, NY, USA). We employed standard descriptive statistics, including two-sided 95% confidence intervals (CI), to analyze the study population. Kaplan-Meier analysis was used to estimate death due to heart disease, which was considered the primary endpoint in the enrolled patients. The percentage of heart artery volume and the maximum and mean doses received by the heart were calculated from the DVHs. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff values for the DVH parameters. Furthermore, the areas under the ROC curves were calculated to assess the discriminative power of the models. Univariate and multivariate logistic regression models were used to test for associations between patient characteristics and DVH parameters. The explanatory variables were separately controlled to evaluate cardiac survival. A *t*-test and Chi-squared or Fisher's exact test were used to analyze the comparisons. A two-tailed P value less than 0.05 was defined as statistically significant.

Results

Patient and tumor characteristics

A summary of the baseline characteristics of the 112 EC patients treated with an RT modality is listed in *Table 1*. Among the patients, the median age was 67 years, and the age range was 49 to 85 years. In this cohort, patients were predominantly male (84%), while only 16% were female. Approximately 76% of patients had squamous cell carcinoma, and 24% had adenocarcinoma; 40 patients had stage II, 52 patients had stage III, and 20 had stage IV disease according to the database. The majority of patients did not have basic heart disease before treatment. The patients with and without radiation-induced heart disease (RIHD) were approximately equal in all groups. In terms of modality, 66 patients were treated with concurrent chemoradiotherapy, and a total of 38 patients had a history of consolidation chemotherapy after RT.

Table 1 Patient and tumor characteristics

Characteristic	No.	%
Age (years)		
≤65	48	43
>65	64	57
Sex		
Male	95	84
Female	17	16
Stage		
II	40	36
III	52	46
IV	20	18
Histology		
Squamous	85	76
Adenocarcinoma	27	24
Basic heart disease		
Yes	29	26
No	83	74
RIHD		
Yes	54	48
No	58	52
Concurrent chemotherapy		
Yes	66	59
No	46	41
Consolidation chemotherapy		
Yes	38	34
No	74	66

RIHD, radiation-induced heart disease.

DVH parameters

Patient descriptive dosimetric characteristics are presented in *Table 2*. Data are presented as the mean ± standard deviation (SD). The maximum (Dmax) and mean doses

Table 2 Doses in the target volume and heart for all patients undergoing IMRT

Site	Parameter	IMRT (mean ± SD)
Heart	Dmax (Gy)	57.34±13.51
	Dmean (Gy)	24.83±11.40
RA	Dmax (Gy)	40.98±22.64
	Dmean (Gy)	18.56±12.87
RV	Dmax (Gy)	36.61±22.11
	Dmean (Gy)	16.47±13.14
RCA	Dmax (Gy)	26.81±19.50
	Dmean (Gy)	22.24±16.58
LA	Dmax (Gy)	46.62±22.48
	Dmean (Gy)	35.17±20.43
LV	Dmax (Gy)	37.08±22.90
	Dmean (Gy)	12.61±10.84
LCX	Dmax (Gy)	31.43±23.37
	Dmean (Gy)	22.66±19.11
LAD	Dmax (Gy)	21.18±14.68
	Dmean (Gy)	12.68±11.21

IMRT, intensity-modulated radiotherapy; Dmax, maximum dose; Dmean, mean dose; SD, standard deviation; RA, right atrium; RV, right ventricle; RCA, right coronary artery; LA, left atrium; LV, left ventricle; LCX, left circumflex artery; LAD, left anterior descending artery.

received by the heart were 57.34±13.51 and 24.83±11.40 Gy, respectively. An overview of the RT process is summarized in *Figure 1*.

Univariate and multivariate analysis

Univariate analyses of patient demographics and heart dosimetric volumes are provided in *Table 3*. The Dmax of the heart, RA, RV, RCA, LA, LV, and LAD; the mean dose received by the heart; and the RCA, LA, and LAD dosimetric volumes were significantly different and affected cardiac toxicity. The Dmax and mean doses received by the RV and LV and the Dmax of the RA, RV, DVH were predictive of survival and thus were included in our multivariate analysis.

Association between RIHD and survival

The chi-squared test was used to compare patient variables with RIHD, which demonstrated that patients with both basic heart disease and concurrent radiochemotherapy were more likely to experience cardiac disease. The remaining factors, including age, sex, tumor stage, pathology, and consolidation chemotherapy were not correlated with the incidence of heart events and are described in detail in *Table 4*.

In the Kaplan-Meier analysis (*Figure 2*), aside from the mean dose received by the RA, RV, and LV, the remaining dosimetric factors exhibited significant differences in patient survival (all $P<0.05$).

Discussion

RT is an essential component of EC management. The heart of EC patients is affected by the irradiation, leading to myocardial fibrosis, coronary artery disease, and valvular lesions, which are considered radiation-induced heart diseases. Delayed cardiac injury especially myocardial fibrosis is prominent, and its incidence is as high as 20–80%. Myocardial fibrosis is the final stage of radiation-induced heart diseases, and it increases the stiffness of the myocardium and decreases myocardial systolic and diastolic function, resulting in myocardial electrical physiological disorder, incomplete heart function, or even death (12). The exact mechanism causing the occurrence of RIHD is unclear, the possible mechanism is direct damage from radiation is the most important cause. Rays can directly cause tissue ionization, cause local aseptic inflammation, and inhibit the growth of heart cells, causing cell lysis, apoptosis, and even necrosis. Repeated radiation damage can inhibit fibrosis around myocardial cells, so a large amount of cellulose deposited in the cells cannot be discharged, resulting in damage to the vascular endothelium, resulting in changes in vascular permeability, microthrombosis in the blood vessels and reduced blood flow. In addition, the biological effects caused by radiation may cause secondary damage to the heart, such as autoimmune changes in tissues and cells caused by radiation, gene mutations or abnormal gene expression, and obstruction of capillary and lymphatic return. These can aggravate or initiate continuous myocardial damage, accelerate myocardial fibrosis, and aggravate myocardial and pericardial exudation and thickening changes (12). For instance, one study reported that patients receiving RT treatment were 1.62 times more likely to die from heart disease than those without RT (13). Other researchers have reported that IMRT can mitigate the risk of cardiac sequelae (14). In addition, Beukema *et al.*

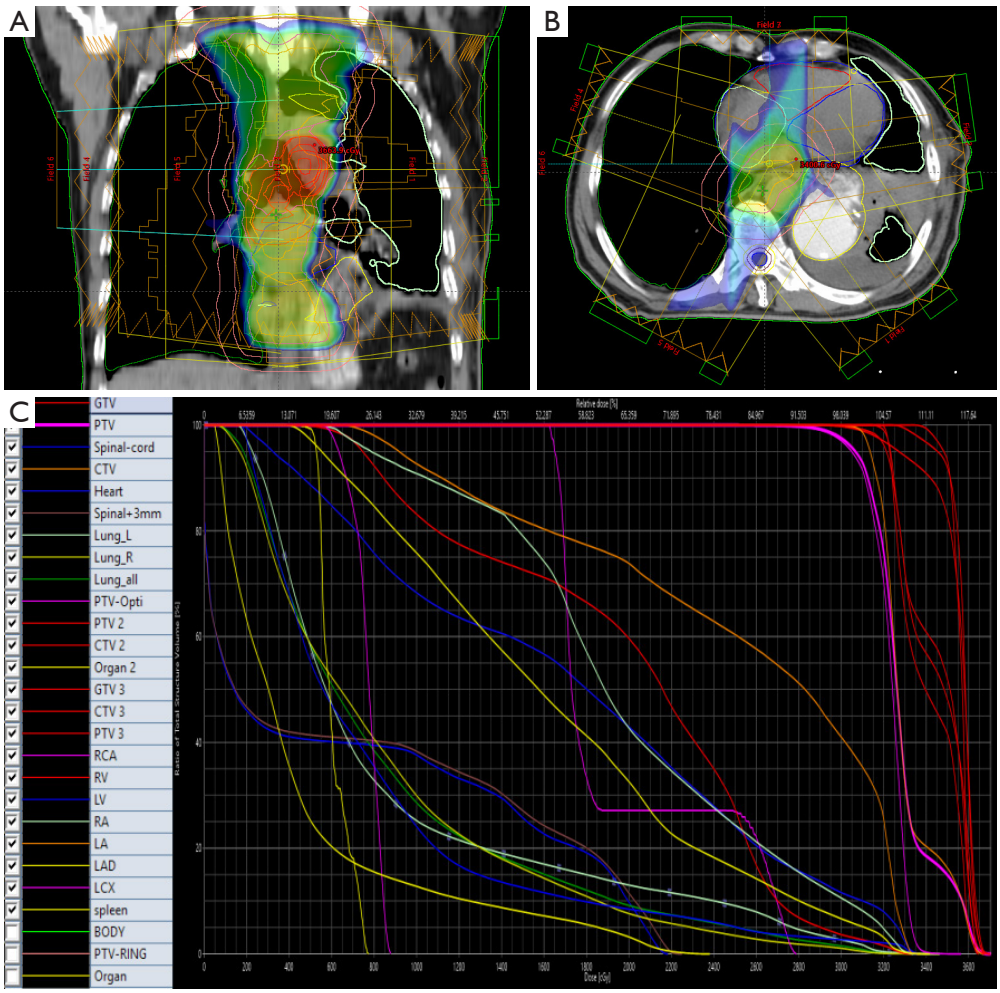

Figure 1 Treatment planning example: an image of a patient treated with radiation. (A,B) Dose distribution image; (C) dose-volume histograms showing the GTV (gold), CTV (dark blue), PTV (magenta), heart (green), lung-all (aqua), LA (orange), RCA (gray), RV (red), LV (blue), RA (light blue), LAD (pink), LCX (white), and spinal cord (yellow) in intensity-modulated radiotherapy (IMRT) treatment plans. GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; LA, left atrium; RCA, right coronary artery; RV, right ventricle; LV, left ventricle; LAD, left anterior descending artery; LAD, left anterior descending artery; LCX, left circumflex artery.

stated that further cardiac function parameters during follow-up were needed to identify the most important parts of the heart (15). Minimizing radiation exposure in normal tissue structures, especially the heart and coronary arteries, and increasing the long-term survival of EC patients is challenging. One of the strengths of our research that addresses this issue is the inclusion of a wide range of heart artery doses in our analysis. To the best of our knowledge, this is the first study to specifically investigate various heart artery radiation doses.

In our population-based analysis of EC survivors, accurate multivariable prediction models of radiation-induced toxicity showed that the Dmax and mean doses in the LV and RV and the Dmax in the RA and RV were significantly different. We determined the cutoff doses for the endpoints, and the risk of death increased with the increase of dosage.

An overview of the relevant randomized trials showed that RT contributed to reducing breast cancer mortality, but also increased cardiovascular mortality (16). In a retrospective study of 415 patients with Hodgkin's disease treated with RT. Hull *et al.* found that CAD occurred within 5 to 20 years (7). Furthermore, Beukema *et al.* found that modern RT contributed to increasing the morbidity

Table 3 Univariable and multivariable Cox regression analysis of treatment and dosimetric characteristics in patients

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Overall survival				
Age (years)		0.888		*
≤65	1			
>65	0.969 (0.623–1.506)			
Sex		0.790		0.006
Male	1		1	
Female	1.084 (0.598–1.967)		0.381 (0.193–0.753)	
TNM stage				
II	1	0.002	1	<0.001
III	1		1	
IV	2.812 (1.471–5.378)		3.553 (1.803–7.002)	
Histology		0.776		*
Squamous	1			
Adenocarcinoma	1.079 (0.639–1.822)			
Basic heart disease		0.033		0.004
Present	1		1	
Absent	0.579 (0.351–0.956)		0.004 (0.434–0.247)	
RIHD		0.063		*
Present	1			
Absent	1.525 (0.977–2.380)			
Concurrent chemotherapy		0.549		*
Present	1			
Absent	0.870 (0.553–1.371)			
Consolidation chemotherapy		0.367		*
Present	1			
Absent	1.234 (0.781–1.950)			
Heart				
Maximum dose (Gy)		0.004		<0.001
≤63.52	1		1	
>63.52	1.956 (1.238–3.093)		16.243 (6.913–38.164)	
Mean dose (Gy)		0.001		*
≤26.49	1			
>26.49	2.290 (1.435–3.655)			

Table 3 (*continued*)

Table 3 (*continued*)

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
RA				
Maximum dose (Gy)		<0.001		<0.001
≤48.11	1		1	
>48.11	0.337 (0.213–0.533)		0.234 (0.117–0.471)	
Mean dose (Gy)		0.161		*
≤24.68	1			
>24.68	1.373 (0.882–2.137)			
RV		0.002		<0.001
Maximum dose (Gy)				
≤44.85	1		1	
>44.85	0.497 (0.316–0.780)		0.055 (0.017–0.178)	
Mean dose (Gy)		0.076		<0.001
≤23.81	1		1	
>23.81	1.509 (0.958–2.377)		6.190 (2.223–17.237)	
RCA				
Maximum dose (Gy)		0.005		*
≤32.58	1			
>32.58	0.525 (0.334–0.824)			
Mean dose (Gy)		0.007		*
≤25.29	1			
>25.29	0.537 (0.343–0.841)			
LA				
Maximum dose (Gy)		<0.001		*
≤21.84	1			
>21.84	0.333 (0.202–0.550)			
Mean dose (Gy)		<0.001		*
≤38.04	1			
>38.04	0.432 (0.276–0.676)			

Table 3 (*continued*)

Table 3 (*continued*)

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
LV				
Maximum dose (Gy)		0.004		*
≤43.11	1			
>43.11	0.519 (0.332–0.812)			
Mean dose (Gy)		0.082		0.009
≤15.98	1		1	
>15.98	0.632 (0.377–1.059)		3.521 (1.378–9.001)	
LCX				
Maximum dose (Gy)		0.055		*
≤23.15	1			
>23.15	0.650 (0.419–1.009)			
Mean dose (Gy)		0.055		*
≤14.68	1			
>14.68	0.650 (0.419–1.009)			
LAD				
Maximum dose (Gy)		0.020		*
≤12.86	1			
>12.86	0.589 (0.376–0.921)			
Mean dose (Gy)		0.001		*
≤10.13	1			
>10.13	0.474 (0.300–0.749)			

* indicates a variation not in the model. RIHD, radiation-induced heart disease; HR, hazard ratio; 95% CI, 95% confidence interval; TNM, tumor-node-metastasis; RA, right atrium; RV, right ventricle; RCA, right coronary artery; LA, left atrium; LV, left ventricle; LCX, left circumflex artery; LAD, left anterior descending artery.

and mortality of EC due to CAD (15). Previous experience has shown that epicardial CAD is the deadliest complication after radiation but rarely occurs and is treatable (17). In addition, management of radiation-induced CAD, which is commonly included in RIHD, appears similar to the that of normal CAD. These findings led us to examine the arteries of the heart after radiation treatment. Although many RIHD studies of Hodgkin's disease and breast cancer exist, reports of RIHD after radiation for EC are lacking, and the risk factors are unclear. It is possible that the prognosis of EC is worse and the heart radiation doses are higher, resulting in the differences among EC, breast cancer, and lymphoma patients. We searched the database and compiled information regarding heart radiation doses and RIHD. Notably, Lorenzen *et al.* showed that, compared with the dose received by the LAD coronary artery, the mean dose received by the heart had increased risk of ischemic events; however, they did mention that further confirmation of this findings was needed through further study (18).

Several decades ago, Gyenes *et al.* showed that cardiac mortality occurs in a dose-volume–dependent manner by demonstrating higher incidences in a highest dose-volume study group than in a low dose-volume group (19). More recently, researchers have attempted to quantify the survival of EC patients according to heart radiation dose and cardiac physiological results. Moreover, Frandsen *et*

Table 4 Relationships between RIHD and clinical characteristics

Characteristic	With RIHD	Without RIHD	P value
Age (years)			0.113*
≤65	19	29	
>65	35	29	
Sex			0.528*
Male	47	48	
Female	7	10	
Stage			0.083*
II	24	16	
III	24	28	
IV	6	14	
Histology			0.078*
Squamous	37	48	
Adenocarcinoma	17	10	
Basic heart disease			<0.001*
Yes	28	1	
No	26	57	
Concurrent chemotherapy			<0.001*
Yes	20	46	
No	34	12	
Consolidation chemotherapy			0.354*
Yes	16	22	
No	38	36	

*, two-sided χ^2 test. RIHD, radiation-induced heart disease.

al. indicated that a minimized cardiac dose in RT planning was crucially important (13). Unfortunately, based on the available literature alone, it remains impossible to determine the most appropriate dose parameter, mainly due to the discrepancies in reported outcomes. Several articles examining the correlation between the dose-volume parameters of the heart and coronary disease have found heart V30 to be a significant predictor of radiation-induced pericardial effusion (9), while Tait *et al.* reported V40 as a possible predictive factor (20). In a study of 102 patients treated with concurrent chemoradiotherapy for locally advanced EC, Konski *et al.* predicted that the lowest significant cutoff values of V20, V30, and V40 were 70%, 65%, and 60%, respectively (8). Similarly, in a study of long-term EC survivors, the thresholds for cardiac toxicity of V45, V50, and V55 were greater than 70%, 65%, and 60%, respectively (21). Compared with IMRT, proton beam therapy resulted in significantly lower mean heart dose (MHD) and heart V5, V10, V20, V30, and V40 as well as lower radiation exposure to the four chambers and four coronary arteries. Proton beam therapy results in significantly lower radiation exposure to the whole heart and cardiac substructures than IMRT (22).

These inconsistencies suggest that the variations in dose and fractionation, the definition of cardiac volumes with regard to radiation dosimetry, and the radiation technique used are important and cannot be ignored.

In our study, RIHD was more likely to occur in patients with basic heart disease, including CAD, pericardial disease, and myocardial disease. Furthermore, of the chemotherapy

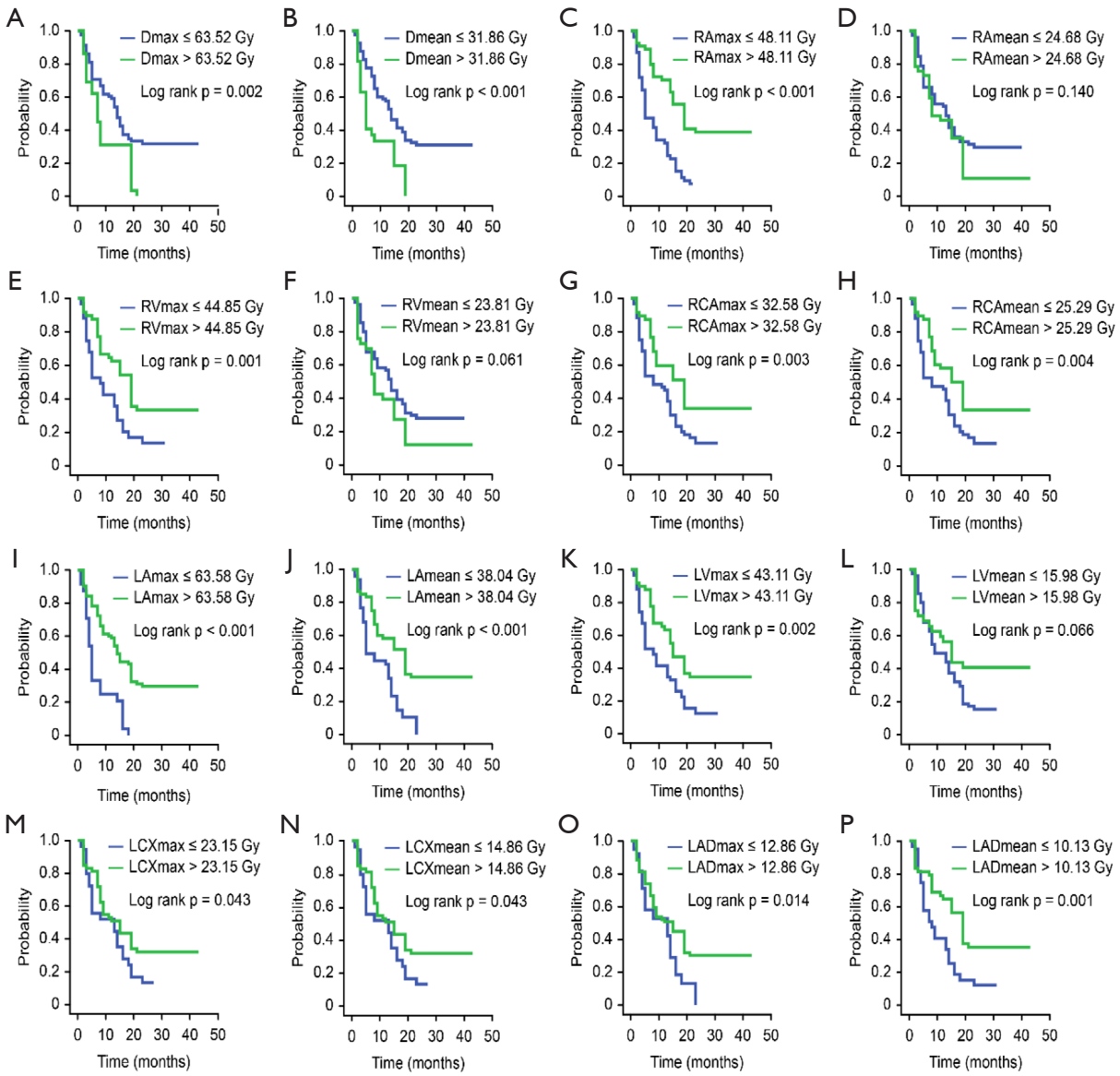

Figure 2 Kaplan-Meier curves for overall survival for various heart radiation dose parameters in advanced non-small cell lung cancer patients. (A) Dmax ≤63.52 Gy (blue) *vs.* Dmax >63.52 Gy (green). (B) Dmean ≤31.86 Gy (blue) *vs.* Dmean >31.86 Gy (green). (C) RAmax ≤48.11 Gy (blue) *vs.* RAmax >48.11 Gy (green). (D) RAmean ≤24.68 Gy (blue) *vs.* RAmean >24.68 Gy (green). (E) RVmax ≤44.85 Gy (blue) *vs.* RVmax >44.85 Gy (green). (F) RVmean ≤23.81 Gy (blue) *vs.* RVmean >23.81 Gy (green). (G) RCAmax ≤32.58 Gy (blue) *vs.* RCAmax >32.58 Gy (green). (H) RCAmean ≤25.29 Gy (blue) *vs.* RCAmean >25.29 Gy (green). (I) LAmax ≤63.58 Gy (blue) *vs.*

regimens examined, concurrent chemoradiotherapy was associated with cardiac injury. This is in line with a study by Shapiro *et al.*, who found chemoradiotherapy to be associated with an increased risk of cardiovascular adverse effects (23). Lee *et al.* also noted that concurrent chemotherapeutic agents, especially anthracyclines, were likely to potentiate a series of clinically notable myocardial diseases (17). Additionally, Stavrev *et al.* observed a higher incidence of pericardial effusion after chemoradiotherapy for EC, and Stavrev also found fraction size, bio-average and bio-maximum dose of heart are the risk factors for pericardial effusion (24,25).

Although we obtained notable outcomes in our study, some limitations of this research should be mentioned.

First, the records were derived from a retrospective cohort, and additional prospective studies are needed to confirm our findings. Second, the number of patients diagnosed with EC was relatively small, and larger, longer duration studies are required to validate these findings. Third, due to the small number of people with basic heart disease, subgroup analysis was not performed. The survival differences between patients with a previous history of heart disease and those with no history still needs further confirmation.

Conclusions

While RT plays an important role in the current treatment paradigm for EC, the use of RT in EC patients likely results in an increased risk of RIHD. Considering the cardiac toxicity, clinicians should monitor the doses received by the arteries of the heart. With regard to the probability of RIHD occurrence, other cardiac risk factors and the modality of chemotherapy should be subsequently monitored and managed. Limitation of the RT dose to the arteries of the heart should be carefully considered, and further work is necessary to minimize the risk of heart disease after RT for the treatment of EC.

Acknowledgments

Funding: This work was supported by grants from the National Natural Science Foundation of China (no. 81672974) and the Shandong Province Science Fund (no. SQ20170004).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-184

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-21-184

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-184). The authors have no conflicts of interest to declare.

Ethical Statement: 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. All patients who participated in this study provided written informed consent for publication. This study was approved by the Board and Ethical Committee of Qianfoshan Hospital and was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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(English Language Editor: J. Gray)

Cite this article as: Zhang J, Lv Y, Chen F, Wang X, Zhang L, Zhang X. Doses of intensity-modulated radiotherapy and its association with cardiac disease in esophageal cancer patients. Ann Transl Med 2021;9(2):166. doi: 10.21037/atm-21-184