Dose to the Left Anterior Descending Artery Correlates with Cardiac Events after Irradiation for Breast Cancer

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Introduction

- Radiation therapy is an established treatment for breast cancer that reduces recurrence and mortality in select patients. However, cardiac toxic effects after irradiation have become increasingly well characterized.
- Although global heart dose has been associated with cardiac toxic effects, there are limited data to date establishing a relationship between cardiac substructure dosimetry and cardiac morbidity.[1] The left anterior descending artery (LAD) is particularly vulnerable during irradiation due to its position along the anterolateral surface of the myocardium, which is near the posterior edge of radiation fields when treating the left breast or chest wall, especially when partially deep tangents are used to cover the internal mammary lymph node region.
- This work aims to delineate a relationship between LAD dosimetry and cardiac toxic effects.[2]

Aims and Objectives

- Correlate dose to the LAD with adverse cardiac events in patients receiving left whole breast or chest wall irradiation with or without regional nodal irradiation.
- Propose dose constraints for the LAD which can be used in treatment plans.

Methods

- Retrospectively identified 375 female patients with left-sided breast cancer who were treated with breast-conserving surgery or mastectomy and adjuvant radiation therapy between 2012 and 2018.
- Performed query of cardiac-specific ICD-10 codes to assess for cardiac events. Major cardiac events were defined as cardiogenic death, myocardial infarction, coronary revascularization, unstable angina, or development of heart failure. Any cardiac events were defined as major cardiac events as well as valvular disease requiring surgical intervention, dysrhythmias, and pericarditis.
- Collected baseline characteristics for patients. Calculated the Charlson Comorbidity Index based on preexisting cardiac disease, hypertension, diabetes, hyperlipidemia, or obstructive lung disease with a point assigned to each comorbidity.
- Mean and maximum LAD and heart doses were calculated and converted to 2-Gy equivalent doses (EQD_2) to account for differences in fractionation between patients. Performed univariate and multivariable Cox regression analyses to determine association with cardiac toxic effects.
- Generated ROC curves to identify potential dose constraints for mean and maximum heart and LAD EQD_2 doses. Performed Kaplan-Meier analysis to compare cardiac event-free survival (EFS) for patients.

Results

Table 1: Summary of cardiac dosimetry

Dosimetric index*	All patients† (N = 375)	Breast/CW RT alone† (n = 291)	Breast/CW and RNI† (n = 84)
LAD D_{mean}	1.9 (1.4, 3.2)	1.7 (1.3, 2.2)	3.4 (2.4, 5.1)
LAD D_{max}	4.0 (3.0, 11.0)	4.0 (3.0, 8.0)	11.0 (6.0, 18.0)
Heart D_{mean}	0.8 (0.6, 1.1)	0.7 (0.6, 0.9)	1.1 (1.0, 1.4)
Heart D_{max}	9.0 (5.0, 25.0)	7.0 (5.0, 23.0)	18.0 (10.0, 36.0)

Abbreviations: CW = chest wall; D_{max} = maximum dose; D_{mean} = mean dose; LAD = left anterior descending artery; RNI = regional nodal irradiation; RT = radiation therapy.
* Dose presented in grays as adjusted 2-Gy equivalent doses.
† Data are presented as median (IQR).

Median dosimetric indices for the LAD and the heart were greater for patients receiving regional nodal irradiation as opposed to those receiving whole breast or chest wall irradiation alone.

Table 2: Univariate analyses for any and major cardiac events

	Any cardiac events			Major cardiac events		
Covariate†	HR	95% CI	*P* value	HR	95% CI	*P* value
LAD D_{mean}	1.09	1.03, 1.15	.005	1.09	1.02, 1.17	.01
LAD D_{max}	1.02	1.01, 1.04	.003	1.02	1.00, 1.04	.036
Heart D_{mean}	1.63	1.03, 2.60	.039	1.73	1.17, 3.19	.01
Heart D_{max}	1.02	1.01, 1.04	.009	1.02	1.00, 1.04	.11
Age at diagnosis	1.05	1.02, 1.08	.003	1.06	1.02, 1.10	.005
Race						
Black	-	-		-	-	-
White	0.7	0.30, 1.62	.4	1.25	0.37, 4.25	.7
Other	1.32	0.38, 4.51	.7	3.32	0.74, 14.9	.12
Charlson Comorbidity Index						
0	-	-		-	-	-
1	2.28	0.78, 6.66	.13	2.68	0.69, 10.4	.2
2+	7.65	2.88, 20.3	<.001	9.29	2.69, 32.1	<.001
Anthracycline or Herceptin						
No	-	-		-	-	
Yes	1.59	1.21, 3.67	.034	1.47	1.38, 3.67	.035
History of smoking						
No	-	-		-	-	-
Yes	2.2	1.12, 4.30	.021	2.07	0.93, 4.60	.075
Body mass index	1.35	0.70, 2.61	.4	1.23	0.65, 2.21	.3

Abbreviations: CI = confidence interval; D_{max} = maximum dose; D_{mean} = mean dose; HR = hazard ratio; LAD = left anterior descending artery.

Each dosimetric parameter independently correlated with statistical significance in predicting any cardiac events, while only LAD D_{mean}, LAD D_{max}, and heart D_{mean} correlated with prediction of major cardiac events. Age, CCI score ≥2, receipt of anthracycline-based chemotherapy or Herceptin, and smoking history all correlated with predicting any and major cardiac events on UVA (smoking history only for any, but not major, cardiac events).

Table 3: Multivariable analyses for each dosimetric parameter versus cardiac toxic effects

	Any cardiac events			Major cardiac events		
Dosimetric index†	HR	95% CI	*P* value	HR	95% CI	*P* value
LAD D_{mean}	1.09	1.02, 1.17	.006	1.08	1.01, 1.17	.022
LAD D_{max}	1.02	1.01, 1.04	.009	1.02	1.00, 1.04	.12
Heart D_{mean}	1.86	1.12, 3.08	.016	1.68	1.24, 3.77	.007
Heart D_{max}	1.02	1.00, 1.04	.016	1.01	0.99, 1.04	.2

Abbreviations: CI = confidence interval; D_{max} = maximum dose; D_{mean} = mean dose; HR = hazard ratio; LAD = left anterior descending artery.

Each of the 4 dosimetric indices independently predicted the risk for developing any cardiac events. Only LAD D_{mean} and heart D_{mean} independently predicted major cardiac events. The risks of any cardiac event or major cardiac event were increased by 9% and 8%, respectively, per 1 Gy of LAD D_{mean}.

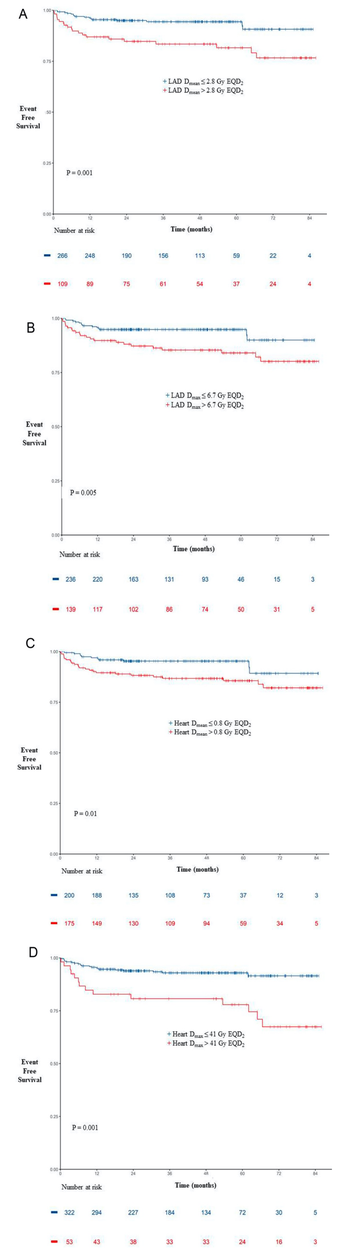

Figure 1: Event-free survival analysis for any cardiac events
EFS analyses were performed using ROC-suggested dose thresholds, stratifying patients who had cardiac dosimetric parameters above or below each threshold. These demonstrated significant improvements in EFS for each suggested threshold.

Conclusions

- The results are consistent with large-population studies which show a correlation between mean heart dose and the incidence of both a major cardiac event and any cardiac event on multivariable analysis.[1]
- The data also support a strong correlation between mean and maximum LAD dose and adverse cardiac events. Our results add to the growing recognition that, in addition to global heart dose, distribution of dose within cardiac substructures plays a critical role in predicting adverse cardiac events.
- The ROC curve analysis suggests limiting the mean and maximum LAD dose to 2.8 Gy EQD_2 and 6.7 Gy EQD_2, respectively, to minimize cardiac toxic effects. There does not appear to be a threshold below which there is no risk of toxic effects. As such, doses to these organs at risk should be kept as low as reasonably achievable. Use of treatment techniques to spare the LAD should be considered and balanced with a patient's anatomy, cancer characteristics, receipt of cardiotoxic systemic therapy, and baseline risk for cardiac disease.
- Limitations of the study include the ability to capture cardiac events based on abstracting select diagnosis codes from institutional electronic medical record. Additionally, the cohort sample size of 375 patients is relatively small compared with previous population-based analyses aimed at detecting correlations between dosimetry and cardiac toxic effects. The limited sample size precluded separate analyses of women receiving regional nodal irradiation or whole breast or chest wall irradiation alone. Ongoing, prospective studies, including larger patient samples sizes will help elucidate the incidence of cardiac events and the importance of cardiac substructure dosimetry.

References

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