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Original Report

Analysis of coronary artery dosimetry in the 3-dimensional era: Implications for organ-at-risk segmentation and dose tolerances in left-sided tangential breast radiation

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Abstract

Purpose: To evaluate the dose to the left anterior descending artery in patients receiving left-sided tangential breast radiation.

Methods and Materials: The study cohort consisted of 50 left-sided breast cancer patients who were sequentially simulated at our institution. The heart and left anterior descending (LAD) artery were contoured from its origin on the left main coronary artery down to the last visible segment of the vessel. Detailed dosimetry of the heart and LAD artery were obtained and analyzed.

Results: Excellent correlation between the dose to the heart and LAD artery was discovered. The mean LAD dose was 17.98 Gy. The mean dose to the proximal LAD was 2.46 Gy. The median V25 was 2.91% and the mean heart dose 3.10 Gy. For every 100 cGy increase in mean heart dose, mean LAD dose increased by 4.82 Gy. For every percent increase in the heart V10 and V25, there was a 2.23 Gy and 2.77 Gy increase in mean LAD dose, respectively. For every percent increase of heart V25, a 5.6% increase in the LAD V20 was demonstrated.

Conclusions: The LAD artery dose correlates very closely with all of the commonly measured heart dose constraints, and does not need to be contoured separately when standard tangential borders are used. Incidental LAD artery doses remain with supine breast tangential radiation therapy.

Introduction

Left-sided breast radiation therapy has historically been associated with a significant risk for radiation-induced coronary arthrosclerosis and cardiac-related deaths.[1] The

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wide-spread use of computed tomography (CT)-based treatment planning, along with the simultaneous development of improved treatment delivery techniques, have allowed for 3-dimensional visualization and delineation of normal tissue structures and enhanced methods for sparing normal tissue more effectively. While these developments in treatment planning and delivery have diminished the cardiac sequelae of left-sided radiation significantly,[2] the data on this topic are somewhat conflicting.[3] For example, several publications demonstrate persistent altered cardiac perfusion after left-sided radiation treatment for patients treated with modern techniques.[4] Furthermore, when analyzing radiated cardiac volumes with contemporary methods, the existing published data suggest that a fraction of left-sided breast cancer patients undergoing radiation are still receiving potentially significant doses of radiation to their heart and left ventricle. This calls into question whether radiation-induced coronary artery disease has truly been eliminated, or whether it has merely been reduced to the point where current studies are statistically underpowered to detect its presence.[5]

While the overall prevalence of cardiac irradiation has diminished with the use of modern radiation techniques, the characteristics of incidental cardiac exposure has now changed from previously described patterns. With increased awareness to reduce radiation-related cardiac sequelae, the use of internal mammary radiation has significantly diminished over the last several decades. Treatment of the internal mammary chain with a commonly utilized en face photon and electron field exposes a substantial portion of the proximal left anterior descending artery (LAD) to radiation, and an occlusion in this location (compared with more distal lesions) is associated with a fourfold increase in risk of death.[6,7] Modern radiation techniques have been shown to treat a relatively more distal portion of the LAD, which may be associated with a lower risk for clinically relevant radiation-induced coronary artery disease, as the distal LAD supplies a smaller amount of myocardium than the proximal LAD.[8] As such, the effects of cardiac irradiation from modern tangential radiation therapy may be more subtle than that seen with older techniques. Confounding these issues further, the dramatic advances in the field of cardiology have resulted in a steady decline of cardiac mortality in the overall population[9] with more widespread use of percutaneous interventions, aggressive pharmaceutical management, increased emphasis on lifestyle changes, and development of improved surgical coronary artery bypass techniques.[6,10]

Currently, the guidelines for cardiac dose constraints vary by institution, country, and personal philosophy. While recommendations regarding cardiac tissue tolerance in the setting of left-sided breast cancer have been published (ie, V_{25} <10%), no consensus guidelines have been developed to date to steer radiation oncologists during treatment planning.[11] Furthermore, a recent breast atlas developed by the Radiation Therapy Oncology Group recommends contouring of the whole heart. Thus, it remains unclear what cardiac effects the LAD dose may carry in a patient who is otherwise receiving a relatively small dose to the whole heart volume but a substantial dose to the LAD.

Unlike contouring of normal tissue structures (ie, whole heart, lung) which are routinely performed by the dosimetrist, contouring of the LAD artery requires physician-level expertise, a significant time commitment, and proficiency in contouring this often difficult-to-visualize structure. The current study was conducted to quantify LAD doses in patients treated with left-sided tangential breast radiation utilizing a physician-contouring protocol. Radiated volumes of whole heart, LAD, and proximal LAD were correlated to explore whether the more time-consuming contouring of the LAD is necessary in all patients to provide a better surrogate for determining likelihood of cardiac risk.

Methods and materials

The study cohort consisted of 50 left-sided breast cancer patients who were sequentially simulated and treated for tangential breast radiation at our institution. Simulation was performed without contrast utilizing 2.5-mm slice thicknesses. The medial tangential border was midline, the lateral border was 2-cm posterior to palpable breast tissue, or the anterior latissimus dorsi muscle in mastectomy cases, the inferior border was 2-cm below palpable breast tissue, and the superior border was the inferior aspect of the clavicular head. Prescribed dose was 46-50 Gy. Heart blocks were used in most cases and were designed in parallel to the chest wall in the inferior third of the field to minimize cardiac exposure. A field-in-field technique (no more than 2 segments per field) was utilized to minimize breast hot spots >110% and was not used as a cardiac sparing maneuver. All patients were scanned in free breathing, with resting heart rates between 60-100 beats per minute. A cardiac atlas[12] with good interobserver concordance (variation of LAD mean dose was 2.6 Gy between observers) was utilized by the primary investigator (who had previous experience with cardiac contouring and, more specifically, LAD contouring) as a reference to contour all cases. The heart was contoured in accordance with the atlas.[12] The left LAD was contoured from its origin on the left main coronary artery down to the last visible segment of the vessel. After the initial 25 patients, the LAD was contoured de novo by the primary investigator to ensure reproducibility in all 25 cases. A 4-mm static brush was used for all cases as a standard diameter.[13] If the vessel was tortuous or positioned obliquely so that its visibility was obscured on 1 slice, the vessel was contoured in the anterior interventricular groove.[12,14] However, any case in which a vessel was not

Table 1 Anatomic and dosimetric parameters of the study population, n = 50 patients

Size parameter	Median (25th, 75th percentiles)	Range
Central lung distance	2.03 cm (1.62, 2.33)	1.07-3.19
Heart volume	611.75 cc (556.10, 699.60)	332.30-1087.90
V_{LAD}	1.00 cc (0.90, 1.10)	0.50-1.80
V_{pLAD}	0.40 cc (0.30, 0.50)	0.10-1.20
Mean dose pLAD (cGy)	246.2 (194.10, 336.60)	115.90-1897.80
Min dose pLAD (cGy)	148.45 (126.10, 182.60)	22.90-276.50
Max dose pLAD (cGy)	490.45 (316.60, 1368.80)	156.40-5034.80
Heart V5 (%)	7.83 (5.02, 10.50)	0.26-20.25
Heart V10 (%)	4.95 (2.63, 7.31)	0.00-15.73
Heart V15 (%)	4.13 (1.89, 6.06)	0.00-14.28
Heart V20 (%)	3.40 (1.48, 5.20)	0.00-13.28
Heart V25 (%)	2.91 (1.16, 4.61)	0.00-12.44
Heart V30 (%)	2.54 (0.87, 4.04)	0.00-11.63
Heart V40 (%)	1.56 (0.43, 2.71)	0.00-9.79
Heart V50 (%)	0 (0.0, 0.38)	0.00-4.47
Mean heart dose (cGy)	310.70 (209.1, 403.6)	89.40-778.50
Mean dose LAD (cGy)	1906.95 (867.20, 2343.90)	266.30-4462.60
LAD V10 (%)	46.20 (27.10, 56.80)	0.00-88.30
LAD V20 (%)	41.32 (17.00, 49.80)	0.00-87.00
LAD V30 (%)	33.10 (6.60, 43.90)	0.00-85.7
LAD V40 (%)	15.65 (0.43, 39.20)	0.00-84.50

LAD, left anterior descending artery; pLAD, proximal LAD.

visible for more than 1 sequential image was excluded from analysis. Based on published angiographic data suggesting typical LAD lengths of 10-12 cm, with the proximal (p)LAD segment defined as the initial segment of the artery before the first diagonal branch, the pLAD contour was approximated as the first 3 cm of the contoured LAD for the purposes of this study.[14] All dose-volume histograms and treatment planning were conducted using the Eclipse Treatment Planning System (Varian Medical Systems, Palo Alto, CA). The dose grid was 2.5 mm. Each volume parameter was defined as Vx (ie, V_5, V_{10}, V_{25}) and the volume of the organ (heart, LAD) that receives $\geq$X Gy. Perpendicular lung distance was measured in accordance with published methods.[15] Institutional review board approval was obtained for this study.

Statistical analyses

Physical characteristics and radiation exposures of the heart and LAD were described using summary statistics such as median and 25th and 75th percentiles. The trapezoid rule was used to calculate the area under the curve (AUC) in order to characterize the cumulative radiation levels in LAD and heart of each patient. The AUC calculation was derived from the first dose point measured (5 Gy for the heart, 10 Gy for the LAD) given the initial slope of the AUC, which is driven by the starting size of the segmented organ. The primary outcome of interest was volume of LAD radiated, which was correlated with various physical attributes of the heart and LAD, as well as cumulative and dose-specific radiation levels in the heart. The association between mean LAD doses and heart doses was determined using linear regression. Analysis was conducted using SAS 9.2 (SAS Institute, Cary, NC) software, with statistical significance achieved at .05.

Results

Of the 52 patients contoured, 2 patients had vessels not visible on more than 1 consecutive slice and they were excluded from analysis; 86% of the patients were breast conservation patients. Characteristics of the segmented organs within the patient population are shown in Table 1. Table 1 also details the dosimetric characteristics of the study population. Ninety-six percent (96%) of the subjects met the Quantitative Analysis of Normal Tissue Effects in the Clinic recommendation of heart V25 <10%. Of note, the mean dose to the proximal LAD was 3.10 Gy, and the mean dose to the LAD was 19.06 Gy. Significant

Table 2 Spearman correlation coefficients between heart dose parameters and mean, maximum, and minimum dose to the left anterior descending artery (LAD), n = 50 patients

Variable	Mean dose to LAD	Minimum dose to LAD	Maximum dose to LAD
Heart V5	0.83 $P < .0001$	0.43 $P < .002$	0.65 $P < .0001$
Heart V10	0.81 $P < .0001$	0.40 $P = .004$	0.69 $P < .0001$
Heart V15	0.80 $P < .0001$	0.40 $P = .004$	0.70 $P < .0001$
Heart V20	0.81 $P < .0001$	0.41 $P = .003$	0.71 $P < .0001$
Heart V25	0.80 $P < .0001$	0.40 $P = .004$	0.71 $P < .0001$
Heart V30	0.79 $P < .0001$	0.41 $P = .003$	0.71 $P < .0001$
Heart V40	0.79 $P < .0001$	0.44 $P = .002$	0.75 $P < .0001$
Heart V50	0.54 $P < .0001$	0.42 $P = .003$	0.72 $P < .0001$
Mean heart dose	0.80 $P < .0001$	0.50 $P = .0002$	0.70 $P < .0001$
Maximum heart dose	0.41 $P = .003$	0.28 $P = .053$	0.62 $P < .0001$

correlation was found between the sampled dose-volume heart parameters and the respective LAD doses, as shown in Table 2. Furthermore, correlation between the LAD volume with LAD dose and heart AUC with LAD dose were significant (Table 3). There was no significant association between the central lung distance or heart volumes and LAD dose (Table 4). Of the study population, 4 patients were identified as outliers, defined by their nonconformance to the models. Figure 1 illustrates the anatomy of 1 patient considered an outlier; note the axial image showing the nonstandard treatment borders utilized due to the patient's severe ptosis of the breast.

Correlations of the selected heart volume parameters with LAD dose parameters are shown in Figs e1-e5 (available online only at www.practicalradonc.org). All models demonstrate a highly significant relationship between radiation dose to the heart and LAD dose. The magnitude of the association between heart and LAD radiation doses are shown in Figs e1-e5. For example, for every 1 Gy increase in mean heart dose, mean LAD dose increased by 4.82 Gy (Fig e1). For every percent increase in the heart V_{10} and V_{25} there was a 2.23 Gy and 2.77 Gy increase in mean LAD dose, respectively (Figs e2, e3). For every percent increase in the heart V_{40} a 3.37 Gy increase in mean LAD dose was noted (Fig e4), and for every percent increase of heart V_{25} a 5.6% increase in the LAD V20 was demonstrated (Fig e5).

Of note, for mean heart doses <5 Gy, there was only 1 individual with a mean LAD dose >30 Gy; and for mean heart dose <2 Gy, mean LAD dose was <20 Gy (Fig e1). A heart V_{10} of ≤6% resulted in a LAD mean dose of ≤25 Gy in the vast majority of subjects (Fig e2). Similarly, a heart V_{25} of ≤5% resulted in a LAD mean dose of <30 Gy in the majority of cases (Fig e3). A heart V_{40} of ≤2% assured a LAD mean dose of <25 Gy (Fig e4), and a heart V_{25} of <4% (excluding outlier) assured that ≤50% of the LAD received more than 20 Gy (Fig e5).

Table 3 Spearman correlation coefficients of absolute heart volume dose parameters with mean dose to the left anterior descending artery (LAD) and area under the curve (AUC) analysis: Spearman correlation coefficients between cumulative heart exposure (heart AUC), cumulative LAD exposure (LAD AUC), and proximal LAD mean dose, LAD mean dose, and central lung distance

Heart volume dose parameters	Mean dose to LAD	
Heart V5 expressed as cc's of heart	0.77 $P < .0001$	
Heart V10 expressed as cc's of heart	0.78 $P < .0001$	
Heart V15 expressed as cc's of heart	0.77 $P < .0001$	
Heart V20 expressed as cc's of heart	0.77 $P < .0001$	
Heart V25 expressed as cc's of heart	0.77 $P < .0001$	
Heart V30 expressed as cc's of heart	0.76 $P < .0001$	
Heart V40 expressed as cc's of heart	0.74 $P < .0001$	
Heart V50 expressed as cc's of heart	0.47 $P < .0006$	
Area under the curve analysis		
	Heart AUC (5-50 Gy)	LAD AUC (10-40 Gy)
Central lung distance	0.23 $P = .107$	0.25 $P = .086$
Proximal LAD mean dose	0.52 $P = .0001$	0.52 $P < .0001$
LAD mean dose	0.81 $P < .0001$	n/a
AUC Heart (5-50Gy)	1.00	0.79 $P < .0001$

Table 4 Spearman correlation coefficients between volumes (left anterior descending artery [LAD], heart, and central lung distance) and dosimetry of LAD, n = 50 patients

Variable	Central lung distance	Heart volume	LAD volume
LAD Mean dose	0.20 $P = .160$	0.03 $P = .854$	−0.32 $P = .023$
Minimum dose to the LAD	0.07 $P = .613$	0.03 $P = .832$	−0.34 $P = .016$
Maximum dose to the LAD	0.13 $P = .356$	0.005 $P = .975$	−0.05 $P = .719$
LAD V10	0.16 $P = .281$	0.06 $P = .688$	−0.40 $P = .004$
LAD V20	0.21 $P = .152$	0.02 $P = .901$	−0.37 $P = .009$
LAD V30	0.26 $P = .067$	0.009 $P = .950$	−0.24 $P = .0903$
LAD V40	0.30 $P = .037$	−0.06 $P = .686$	−0.21 $P = .146$

Discussion

The current study was conducted to quantify LAD doses in patients treated with left-sided tangential breast radiation, to determine whether the LAD is a critical structure that needs to be independently contoured separate from the cardiac volume. This was achieved by analyzing LAD and heart dose and volume parameters to determine whether a significant correlation exists between the 2 structures. The potential implications of finding non-congruence between the LAD and heart volumes and doses would be potentially requiring contouring of the LAD, in addition to the heart and lung, in left-sided breast cancer cases to generate dose-volume histograms for clinical relevance. After consistent contouring of a series of 50 left-sided breast cancer patients, we demonstrated a

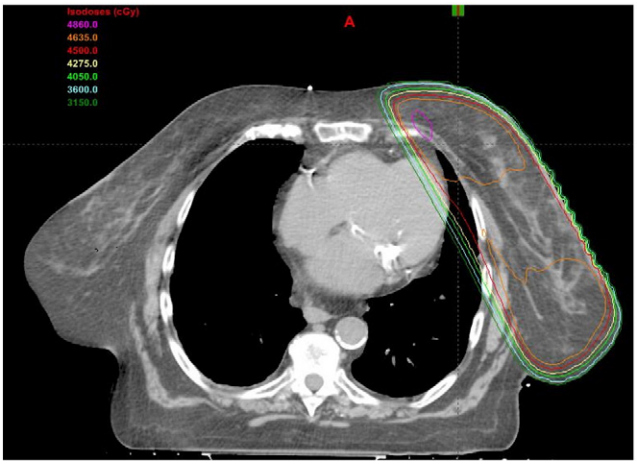

Figure 1 Subject No. 40, whose left anterior descending artery dose was lower than anticipated due to customized tangent entry and exit points.

significant correlation between whole heart dosimetry and LAD dosimetry does exist. For clinicians wishing to minimize LAD dose, any maneuver that limits heart dose while keeping standard tangent angles will decrease the LAD dose. These data suggest that specific LAD contouring or contrast-enhanced simulation are not necessary.

The mean dose to the LAD in this study was 19.07 Gy. While Taylor et al[16] reported a mean LAD dose of 7.6 Gy for left-sided breast radiation, their findings may differ from ours partially due to their use of accelerated, hypofractionated radiation and thus a total lower dose to the whole breast. Another explanation for this difference in mean LAD dose may be their technique of using a 1-cm expansion on the coronary artery to account for localization uncertainty of the vessel. In contrast, in our study we segmented the vessel without expansion. Their findings demonstrated that the distal LAD received the highest dose, which was consistent with our current data. As resting heart rates were a minimum of 60 beats per minute, there was certainly some cardiac motion from systole represented on our images, which lessens the need for accounting for localization uncertainty due to the cardiac cycle.

Other series have attempted to correlate dosimetric and field metrics with LAD dose. Taylor et al[17] attempted to correlate maximum heart distance to LAD dose, with only weak correlations. Storey et al[15] examined changes in coronary artery doses with increases in perpendicular lung distance. They found a relationship between perpendicular lung distance and LAD dose that we were not able to demonstrate in our current study. It is likely that the widespread use of cardiac blocking at our institution may be contributing to the difference in this finding. Importantly, the correlations between heart dose and LAD dose in our series outperform these earlier 2-dimensional metrics. Furthermore, one must consider that the above noted studies predated the standardization of contouring using a heart atlas[12] and, therefore, the segmentation techniques were likely significantly different between studies.

We acknowledge one of the major limitations of the present study was limited visualization of the artery due to lack of contrast during simulation. While the LAD volume and LAD mean dose were found to be inversely correlated, these differences may be attributed to the following causes: (1) there may be true differences in the LAD volume due to variation in vessel length; and (2) there may be limitations of CT visualization. Alternatively, this finding may represent a type I statistical error (falsely positive). The LAD could exhibit a more tortuous course upon branching from the left main coronary artery, traversing over myocardium in a dome before descending into the interventricular groove, causing a truly longer vessel length and larger LAD volume. Those who have a tortuous proximal LAD course would have a greater portion of the vessel's volume located away from the field edge, leading to a true lower mean dose. Variations in anatomy that are more difficult visualize on CT imaging include a natively small caliber LAD or the presence of a myocardial bridge (vessel embedded in myocardium for a portion of its course). Most patients have a long LAD that wraps around the apex of the left ventricle. A minority of patients have a shorter LAD, with the left ventricular apex supplied by the right coronary artery or the left circumflex coronary artery. It is important to recognize that these individual variations in anatomy are an existing occurrence and must be reported as such. Failure to segment the distal portion of a small caliber vessel might overestimate the mean dose by decreasing its volume; however, the distal vessel is often a high-dose region and it remains unclear whether the mean dose would truly vary significantly.

This study is also limited in that it studied only the relationship of cardiac dose and LAD dose in patients treated with standard tangential breast radiation. Therefore, these data cannot be applied to patients treated with nonstandard tangent borders, partial breast radiation, or regional nodal radiation. Likewise, these data are only

informative for the initial relationship between cardiac dose and LAD dose. Given the anterior location of the LAD these relationships may not hold in patients treated with extraordinarily deep tangents resulting in large irradiated cardiac volumes. It is likely, in those patients, further escalations in irradiated cardiac volume do not increase LAD dose once the LAD is fully included within the beam.

Despite these limitations, the data obtained in the current study provide clinically useful information regarding the potential efforts at reducing the long-term toxicities of modern techniques. The Danish and Swedish reported a risk ratio of 1.09 for heart disease with a mean heart dose of 6.3 Gy in their left-sided radiated cases,[3] which was dramatically less than that seen in women irradiated in the 1950s (23 Gy)[18] but nearly double the mean heart dose in our current study (3.3 Gy). However, the critical value to acknowledge in this study is the mean LAD dose of 19.07 Gy, which suggests that despite the low mean heart dose there remains potentially significant dose to this critical vessel. There was also a fraction of individuals whose mean LAD dose approached 46 Gy. Notably, this was the mean dose LAD in the Stockholm cohort that experienced an elevated risk of cardiac mortality.[18] Our findings suggest cardiac morbidity remains an issue in a small number of left-sided breast cancer patients treated with modern techniques and, as such, efforts to identify these patients and reduce their risks remains a valuable endeavor.

In conclusion, we found excellent correlation between cardiac doses and LAD doses, suggesting that for the vast majority of patients, contouring of the heart and utilization of stringent dose constraints to minimize the volume and dose delivered to the heart clinically correlates to minimization of dose to the LAD. However, in patients with nonstandard tangent borders, LAD doses are not well estimated by the heart contour, and contouring of the LAD should be considered in these patients.

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