Original paper

Definition of the margin of major coronary artery bifurcations during radiotherapy with electrocardiograph-gated 4D-CT

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ABSTRACT

Purpose: The aim was to measure the cardiac motion-induced displacements of major coronary artery bifurcations utilizing electrocardiography (ECG)-gated four-dimensional computed tomography (4D-CT) and to determine the margin of coronary artery bifurcations.

Methods: Thirty-seven female patients who underwent retrospective ECG-gated 4D-CT in inspiratory breath hold (IBH) were enrolled. The left main coronary artery bifurcation (LM), the obtuse marginal branch bifurcation (OM), the first diagonal branch bifurcation (D₁), the second diagonal branch bifurcation (D₂), the caudal portion of the left anterior descending branch (APX), the first right ventricular artery bifurcation (V) and the acute marginal branch bifurcation (AM) were contoured. The center of the contour of the coronary arterial bifurcations at end systole was defined as the standard, and the margin were then calculated.

Results: The margin in the left–right (LR), cranio-caudal (CC), and anterior-posterior (AP) coordinates were as follows: **LM** 3, 3, and 3 mm; **D₁** 6, 3, and 3 mm; **D₂** 3, 3, and 3 mm; **APX** 4, 4, and 4 mm; **OM** 4, 6, and 5 mm; **V** 6, 8, and 7 mm; and **AM** 6, 8, and 7 mm, respectively.

Conclusion: Coronary artery bifurcations should be considered a separate organ at risk (OAR), and different margin should be provided due to the differences resulting from motion displacement. The maximum margin in the LR, CC, and AP coordinates of left coronary artery bifurcations were 6, 6, and 5 mm, and those of the right coronary artery bifurcations were 6, 8, and 7 mm, respectively.

1. Introduction

Radiotherapy improves the life expectancy of patients with thoracic malignant tumors; simultaneously, radiation-induced heart disease (RIHD) has been documented with the development of treatment-associated cardiac toxic effects. These effects could cause widespread concern about the problem of RIHD [1–3]. RIHD includes radiation-induced pericarditis, myocarditis, coronary artery disease (CAD), valvular heart disease, and conduction system disease [1–3]. Radiation-induced CAD generally has a long latent period of clinical toxicity and may significantly reduce the quality of patients' survival and even lead to death [4]. Mediastinal and breast radiotherapy involves inadvertent radiation to the heart and coronary artery, increasing the risk of ischemic heart disease [5,6]. Hahn et al. [7] suggested that a dose-volume index of the coronary artery (V₅, V₂₀) was more accurate than the heart mean dose in predicting the risk of ischemic heart disease. Epidemiological studies have revealed that the distribution of coronary atherosclerosis is inhomogeneous in different branches and in different segments of the same branch [8,9]. Atherosclerosis plaques were more

common near the side branches of coronary arteries, and Givchchi [10] et al. measured the accurate bifurcation angle to determine the correlation with plaque buildup. The development of atherosclerosis is closely related to endothelial cells and blood flow dynamics [11]. The permeability of endothelial cells to macromolecules in regions of arterial branching or curvature is increased, resulting in low-density lipoprotein accumulation and thus the formation of atherosclerosis plaques [12,13]. Atherosclerosis is accelerated by radiation in medium to large coronary arteries, and several studies have reported coronary arterial events after radiotherapy. The findings of Fuzellier et al. [14] indicated that the risk of radiation-induced CAD should be considered when the mediastinal radiation dose is greater than or equal to 30 Gy. Coronary artery bifurcations and proximal segments that are located in the irradiation field become preferential sites for lesion formation, whereas distal segments are usually unaffected [15]. The coronary artery is a late-responding organ; as a result of the complexity in delineation and inadequate knowledge of motion, it is not considered a routine organ at risk (OAR) during radiotherapy planning [16]. The marked movements of the coronary artery caused by cardiac motion

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include stretching, bending and torsion [9]. Organ motion leads to inaccurate contouring results that cause deviations between the planning dose and delivered dose; moreover, the magnitude of coronary motion caused by heartbeat could result in dosimetry variation [17]. Inaccurately contouring an OAR can have severe consequences; hence, it is important for a planner to precisely contour the OAR. To compensate for the difference in doses caused by organ movement, an appropriate margin should be provided for the OAR, and a similar margin should be provided for the coronary artery. To date, there has been no consensus on the study of the coronary artery margin. Different scholars have studied the influence of the setup and penumbra on the margin, while few publications describe the influence of organ motion.

The present study aimed to quantify displacements of coronary artery main bifurcations in the left–right (LR), cranio-caudal (CC), and anterior-posterior (AP) coordinates and concluded that the external distance in the three directions would suggest an appropriate margin for radiotherapy planning.

2. Methods and materials

2.1. Patients and image acquisition

The study cohort consisted of 37 female patients who underwent retrospective enhanced electrocardiography (ECG)-gated four-dimensional computed tomography (4D-CT). ECG-gated 4D-CT scans were performed during an inspiration breath hold to eliminate the influence of respiration on cardiac motion. Images were obtained for two R waves and rebuilt at every 5% interval in the cardiac cycle, and the images were segregated into 0%-95% 20-phase sets with 0.75-mm slice thicknesses and a 0.5-mm interval (SOMATOM Definition Flash, SIEMENS, Germany).

2.2. Delineation of coronary artery major bifurcations

The left main coronary artery bifurcation (LM), the obtuse marginal bifurcation (OM), the first diagonal branch bifurcation (D_1), the second diagonal branch bifurcation (D_2) and the caudal portion of the left anterior descending branch (APX) in the left coronary artery, the first right ventricular artery bifurcation (V) and the acute marginal bifurcation (AM) in the right coronary artery were selected. Fig. 1 illustrates the selection of coronary bifurcations. The proximal left circumflex segment was defined as the initial segment of the artery before the obtuse marginal branch; the distal left circumflex segment was defined from the obtuse marginal branch to the tip of the circumflex. The proximal, middle, and distal segments of the left anterior

descending (LAD) artery were divided by D_1 and D_2 . The proximal, middle, and distal segments of the right coronary artery were divided by V and AM. All bifurcations were contoured 2 mm in CC coordinate on the cross-sectional image of the 20 phases using MIM Maestro 6.7.6 software (MIM Software Inc., USA). The software provided the center of the contour of the coronary arterial bifurcations for all three axes.

2.3. Measurement of bifurcation displacements

The maximum displacements of every bifurcation in every patient were calculated in three coordinates and were defined as the center of contour of the bifurcations between the maximum and the minimum values. The average maximum displacements were calculated for every bifurcation.

2.4. Margin calculation

During a complete cardiac cycle, 25–45% of the cycle is considered the end-systolic phase. Using the center of the contour of the coronary arterial bifurcation at the end of cardiac systole as the standard, we calculated the displacements of all structures referring to the standard. The means and standard deviations of the major bifurcations displacements of each patient were calculated. The standard deviation of the mean displacements was a systematic error called Σ , and the root-mean-square of the standard deviation was a random error called σ . The margin was calculated by the formula $1.3 \Sigma + 0.5\sigma$ [18].

2.5. Statistical analysis

Analysis was conducted using SPSS19.0 software; the data are in the form of $\bar{x} + s$.

3. Results

The displacements of left coronary arterial bifurcations for the LR, CC, and AP coordinates were as follows: LM 7.5, 6.2, and 6.2 mm; OM 11.8, 11.8, and 10.8 mm; D_1 5.7, 6.7, and 6.5 mm; D_2 5.3, 7.1, and 6.3 mm; and APX 6.4, 7.7, and 4.6 mm, respectively. The displacement of the left circumflex bifurcation OM varied slightly on all three axes. The left circumflex OM had more displacement than the LAD bifurcations D_1 , D_2 and APX in all three axes. The movement of LAD was predominantly in the CC coordinate. The proximal and middle segments of LAD bifurcations D_1 and D_2 had greater AP and less LR displacement than the distal segment bifurcation APX in the LR and CC coordinates.

Fig. 1. Coronary artery main bifurcation (LM = left main coronary artery bifurcation; OM = obtuse marginal bifurcation; D_1 = first diagonal branch bifurcation; D_2 = second diagonal branch bifurcation; APX = tip of the left anterior descending branch; V = first right ventricular artery bifurcation; AM = acute marginal bifurcation).

Fig. 2. The 55% and 70% phases delineation of left coronary artery bifurcations (A-E were 55% phase image of LM, OM, D₁, D₂ and APX, respectively. The delineation of LM, OM, D₁, D₂ and APX in 55% phase were revealed in red, and the delineation of them in 70% phase were revealed in green).

Fig. 3. The 30% and 35% phases delineation of right coronary artery bifurcations (F-G were 30% phase image of V and AM, respectively. The delineation of V and AM in 30% phase were revealed in red, and the delineation of them in 35% phase were revealed in green.)

Table 1
Displacements of main coronary artery bifurcations (mm).

Bifurcations	LR	CC	AP
LM	7.5 ± 2.6 (3.1–13.3)	6.2 ± 2.0 (3.0–11.0)	6.2 ± 2.3 (2.6–12.4)
OM	11.8 ± 4.0 (5.1–20.8)	11.8 ± 5.5 (5.0–28.5)	10.8 ± 4.1 (3.5–22.0)
D ₁	5.7 ± 1.9 (3.6–12.1)	6.7 ± 2.1 (3.0–12.4)	6.5 ± 4.4 (2.1–23.8)
D ₂	5.3 ± 1.9 (1.7–9.3)	7.1 ± 2.5 (2.8–18.0)	6.3 ± 3.6 (2.1–22.0)
APX	6.4 ± 3.4 (2.4–17.0)	7.7 ± 3.0 (3.4–15.5)	4.6 ± 2.4 (1.2–13.2)
V	15.4 ± 4.0 (7.0–22.8)	17.4 ± 6.1 (7.3–31.1)	18.4 ± 4.9 (8.9–30.5)
AM	15.4 ± 3.9 (8.1–22.5)	18.7 ± 6.2 (7.0–32.0)	21.8 ± 4.8 (13.9–30.5)

The displacements of right coronary arterial bifurcations for the LR, CC, and AP coordinates were V 15.4, 17.4, and 18.4 mm, respectively, and AM 15.4, 18.7, and 21.8 mm, respectively. The right coronary arterial bifurcations had obvious displacements in the three coordinates. The displacements were greater for the distal segment of the AM artery bifurcation than the proximal segment of the V artery bifurcation; the displacements of V and AM in the LR, CC, and AP coordinates were AP > CC > LR. Fig. 2 showed the 55% and 70% phases delineation of left coronary artery bifurcations. Fig. 3 showed the 30% and 35% phases delineation of right coronary artery bifurcations. We could

observe the motion of coronary bifurcations during the cycle of heart-beat. The displacements of the coronary artery main ostia are shown in Table 1.

The values of Σ and σ are shown in Table 2. The margin (rounded to the nearest mm) of the left coronary arterial bifurcations in the LR, CC, and AP coordinates were LM 3, 3, and 3 mm; OM 4, 6, and 5 mm D₁ 6, 3, and 3 mm; D₂ 3, 3, and 3 mm; and APX 4, 4, and 4 mm. The left coronary arterial bifurcation margin was homogeneous for the LR, CC, and AP coordinates, while the margin of D₁ for the LR coordinates was obviously greater than that for the CC and AP coordinates.

Table 2
Value of systematic error Σ and random error σ .

	Σ			σ		
	LR	CC	AP	LR	CC	AP
LM	0.1227	0.1050	0.1046	0.2048	0.2083	0.1991
OM	0.1438	0.3110	0.2510	0.3357	0.3630	0.3163
D ₁	0.3386	0.1144	0.0832	0.1786	0.2301	0.1919
D ₂	0.1155	0.1055	0.0983	0.1649	0.2366	0.1908
APX	0.2207	0.1612	0.1948	0.2115	0.2147	0.1289
V	0.2220	0.3828	0.2485	0.4783	0.5303	0.5919
AM	0.1947	0.3404	0.2635	0.4960	0.5546	0.6829

Table 3
Margin of main coronary artery bifurcations (mm).

Bifurcations	LR	CC	AP
LM	3	3	3
OM	4	6	5
D ₁	6	3	3
D ₂	3	3	3
APX	4	4	4
V	6	8	7
AM	6	8	7

The margin (rounded to the nearest mm) of the right coronary arterial bifurcations for the LR, CC, and AP coordinates were V 6, 8, and 7 mm, respectively and AM 6, 8, and 7 mm, respectively. The right coronary arterial bifurcation margin was inhomogeneous for the LR, CC, and AP coordinates, i.e., LR < AP < CC. The margin of the coronary artery main bifurcations are shown in Table 3.

The standard margin of the coronary artery major bifurcations indicated that the coverage rate of margin was $93\% \pm 3.2\%$ (90%–100%).

4. Discussion

The coronary artery is adjacent to irradiation fields, and its cardiac motion-induced movements are complex; thus, the coronary artery receives a high dose during mediastinum and breast radiotherapy, and severe RIHD can occur. Handler et al. [19] proved that radiotherapy can result in coronary stenosis. Several studies have shown a marked dependency between the risk of coronary artery injury and dose. Darby et al. [5] found that the rate of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray for breast cancer radiotherapy. Moignier et al. [20] found the rate of major coronary events increased with the mean dose to the coronary artery by 4.9% per gray in Hodgkin's lymphoma patients who received mediastinal radiation. Our study calculated the displacements of the coronary artery caused by heartbeat and then defined the coronary artery margin, which provided support for the prediction and protection of the radiation-induced injury of the coronary artery in radiation therapy of thoracic tumor, which held clinical significance for future studies.

In the current study, the displacements of the left coronary artery bifurcations were predominantly in the CC coordinate; the right coronary artery bifurcations had obvious AP movement during a complete cardiac cycle. The right coronary artery bifurcations had various displacements for the three coordinates. These findings reminded us that the motion of the coronary arteries caused by cardiac activity is more complex than three-dimensional motion. Johnson et al. [21] observed coronary motion using ECG-gated biplane angiography films. The movement of the left circumflex and LAD were predominantly in the CC coordinate and accounted for 48% and 59%, respectively, of the movement. The movement of the right coronary artery was predominantly in the LR coordinate, accounting for 48% of the movement. We observed notable displacements of the LAD bifurcations D₁, D₂, and

APX in the CC coordinate, accounting for 35.4%, 38.0% and 41.2%, respectively. The variation in left circumflex bifurcation OM displacements for three coordinates was not obvious. The displacements of the right coronary artery bifurcations were obvious for the AP coordinate, accounting for 35.9% and 39.0%, respectively. These findings disagreed with our study and may be related to differences in the selection of mark points.

The right coronary artery bifurcations had larger movement than the left coronary artery bifurcations, and the range of left circumflex bifurcation OM motion was at a maximum because the left circumflex and right coronary artery both run through the atrioventricular sulcus in the basal plane of the heart, and studies have shown that cardiac motion increases from the apex to the base [22,23]. Similarly, Lu et al. [24] concluded that the left circumflex and right coronary artery had the same movement characteristics, which was consistent with our findings. Kataria et al. [16] calculated the average displacement at end systole and end diastole for the LR, CC, and AP coordinates; specifically, the LAD displacements were 3.0 ± 1.6 , 2.8 ± 1.5 , and 3.6 ± 2.0 mm, respectively, the left circumflex displacements were 4.9 ± 1.6 , 2.9 ± 1.3 , and 5.1 ± 1.9 mm, respectively, and the right coronary artery displacements were 6.6 ± 2.2 , 3.6 ± 2.1 , and 5.9 ± 2.2 mm, respectively. The displacements of bifurcations that we observed were larger than these values, likely due to an averaging effect. The overall movement of the coronary arteries is not as significant as that of the bifurcations.

There are both systematic and random errors in the processes of radiotherapy preparation and delivery, such as uncertainty in CT-guided laser aiming, setup error, and organ motion [18][25]. In the present study, the formula for margin calculation mainly referred to the methods proposed by McKenzie [18] et al. Systematic errors are persistent, while random errors have more uncertainty. Therefore, it is necessary to consider both types of error when calculating the margin. The movement of the heart is repeated cyclically in three dimensions, and the movement displacement of each axis is consistent with the Gaussian distribution. The dose distribution was shifted closer to or further away from an organ at risk due to systematic errors, and the magnitude Σ determines the feasibility of the coronary margin encompassing the coronary mean position during radiotherapy [18]. McKenzie et al. [18] thought that adding 1.3Σ in width to the margin of the OAR could ensure inclusion of 90% the mean position of the OAR in any single direction. The coronary effects of the random error caused by organ movement and setup errors during radiotherapy may lead to serious radiation-induced damage [26]. Thus, the prudent course of action was to add a 0.5σ coronary margin to the systematic margin to control the coronary dose within a safe range [18].

In the present study, we found that the coverage rate of the margin was $93\% \pm 3.2\%$, which was superior to the study by McKenzie et al. [18]. The coverage of the major bifurcation margin in the CC direction shows a slight advantage compared with the coverages obtained in the LR and AP directions for two reasons; specifically, the cardiac motion-induced coronary movement in the CC direction is more complicated and the main bifurcations of the coronary artery were delineated only at 2 mm in the CC direction in this study, resulting in the calculation of a small bifurcation margin in the CC direction.

The LAD is adjacent to the radiation field during mediastinal and breast radiotherapy; thus, the margin of the LAD should be more conservative [27]. Taylor et al. [28] reported that the dose varied among different LAD segments for left breast radiotherapy; the dose at the proximal segment was less than 4 Gy (10% of the tumor dose) because outside of the field, the middle segment and the distal segment were affected by the tangential beam, and the distal segment dose was greater than 30 Gy (75% of the tumor dose). As a result of the various doses among different segments of the LAD, the margin of bifurcations should be diverse. In the present study, the margin of LAD bifurcations increased from D₁, D₂ to APX in the left coronary artery, and the margin of D₂ and APX is homogeneous for the three coordinates. The margin of

D₁ for the LR coordinate was clearly more than that of the CC and AP coordinates. This finding may be related to the individual differences in the diagonal branches that are usually 3–5 branches, and sometimes the first diagonal branch comes directly from the left main coronary artery.

Few publications describe the contribution of cardiac activity to coronary artery movement; those that do have mostly focused on the respiratory activity that affects the heart and the cardiac substructure movement. The main reason lies in the fact that the coronary artery has irregular lumens, quantifying coronary artery movement afterward is difficult, and the study of the respiration activity that induces coronary motion cannot eliminate the influence of cardiac activity. Thus, some conclusions need further confirmation. Studying the margin of major bifurcations based on a respiratory and electrocardiography-gated technique is more accurate. However, the time of the single phase in the respiratory-gated technique is notably longer than that in the electrocardiography-gated technique. Therefore, dividing the cardiac cycle completely with the respiratory gate is difficult. Furthermore, there are no reports of the combination of these two gating technologies online. In this study, all patients were scanned while performing an inspiration breath hold to minimize the influence of respiration on coronary motion. The scanning time of conventional 3D-CT is longer, and confirming the specific phase of the coronary artery in various slices during the cardiac cycle is difficult. 4D-CT was usually used to estimate the internal organ motion [29]. For ECG-gated 4D-CT, the method of volume scanning combined with cardiac cycle tracking was adopted, and the images were analyzed retrospectively based on the electrocardiography curve. The temporal resolution of a single phase in the ECG-gated sequence is sufficient for this study, resulting in high quality with minimal blurring and increasing the accuracy of all bifurcation data, and this information cannot be obtained by 3D-CT.

Rigorous dose constraint and optimization of the radiotherapy plan design and delivery can reduce the risk of RIHD; these conditions are closely related to the accurate delineation of the organs and the use of an appropriate margin for the organs. In this study, the proposed margin should also be constantly adjusted and optimized in practice to protect coronary artery main bifurcations to avoid high-dose irradiation.

5. Conclusion

In summary, there are significant differences among the bifurcation displacements; thus, varying margin should be provided for coronary artery bifurcations. The maximum margin in the LR, CC, and AP coordinates of the left coronary artery bifurcations were 6, 6, and 5 mm, respectively, and those for the right coronary artery bifurcations were 6, 8, and 7 mm, respectively.

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