



Short Communication

Development and evaluation of an auto-segmentation tool for the left anterior descending coronary artery of breast cancer patients based on anatomical landmarks



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ABSTRACT

This study describes the development and evaluation of an auto-segmentation tool for the left anterior descending coronary artery (LAD), on non-contrast planning computed tomography scans of breast cancer patients. The dosimetric parameters of the auto-segmented LAD contours are highly correlated with those of manual contours (R^2 -values ≥ 0.89).

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There is an increasing awareness of the importance of treatment-related cardiac toxicity in medical and radiation oncology. Several studies have highlighted the importance of the coronary arteries in the pathogenesis of radiation-induced cardiac toxicity in cancer patients, in particular the left anterior descending coronary artery (LAD) [1,2].

Manual contouring of the coronary arteries is time consuming, susceptible to intra- and inter-observer variation and often challenging due to the lack of intravenous contrast-enhancement and motion induced artifacts due to breathing and heart beating in planning computed tomography (CT) scans. These problems limit large scale contouring tasks necessary for research projects, such as the development of prediction models for radiation-induced cardiac toxicity. Recent studies have evaluated the accuracy of atlas based auto-segmentation (ABAS) for contouring the heart [3–6]. Accuracy was evaluated by measuring the geometric overlap between the auto-segmented and manual contours. These studies showed that auto-segmented contouring was successful for the whole heart (WH), but underperformed for the LAD [4,6].

In another recent study, endpoints were evaluated based on planned cardiac dose and geometry derived from an ABAS technique using breast cancer (BC) patient CT-scans [7]. The results revealed poor geometric overlap for the LAD, however there was

good agreement between radiation dose distributions of the auto-segmented and manual contours.

Due to the difficulty in creating an ABAS routine for small vascular structures on non-contrast CT-scans, we decided to develop an auto-segmentation tool for the LAD with the use of anatomical landmarks; WH, right ventricle (RV) and left ventricle (LV). The aim of this study was to develop and evaluate an auto-segmentation tool for the LAD in non-contrast planning CT-scans based on anatomical landmarks. Furthermore, we compared geometric and dosimetric endpoints between the auto-segmented and the manually contoured LAD of 105 BC patients.

Materials and methods

Patients

This study consisted of 105 female BC patients treated with postoperative radiotherapy (RT) following BC surgery from January 2005 to December 2011. Patients were included if they were diagnosed with BC stage I–III.

All 105 patients were treated with free breathing 3D conformal RT using non-contrast CT-based treatment planning (Somatom Sensation Open, Siemens; average voxel size $(0.88 \times 0.88 \times 3.7 \text{ mm})$ (range $[0.7–1.6] \times [0.7–1.6] \times [2.0–5.0]$); 100–140 kV). A dose of 50.4 Gy was prescribed to the whole breast in 28 fractions with a simultaneous integrated boost dose of 14.0 or 16.8 Gy in the same 28 fractions, depending on the pathologic risk factors.

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Auto-segmentation approach

For every patient, the WH, right atrium (RA), RV, left atrium (LA) and LV were contoured using an in-house generated atlas for free-breathing, non-contrast CT-scans based on the contours according to Feng et al. in the ABAS routine in Mirada RTx ([version 1.6]; Mirada Medical, Oxford, United Kingdom) [3,8]. The treatment position of the patients was the same for the study and for the development of the in-house ABAS. Details of the deep inspiration breath hold (DIBH) ABAS method have been described previously [3]. In short, DIBH planning CT-scans of 20 BC patients were randomly selected after breast irradiation. The planning CT-scans of the first ten patients were used to build the atlas with dedicated software. The remaining 10 planning CT-scans (validation group) were used to validate the ABAS by comparing the contours of the cardiac structures generated by the ABAS with those generated by four observers and the reference segmentation (generated by an expert panel). The ABAS for free breathing planning CT-scans was validated in the same way as for the DIBH planning CT-scans. For our study, the WH, RV and LV were used as anatomical landmarks for automatic segmentation of the LAD.

The LAD is the largest coronary artery and runs anterior to the interventricular septum in the anterior interventricular groove, extending from the base of the heart to the apex [9]. The anterior interventricular groove separates the RV and LV. Due to this anatomical positioning, auto-segmentation of the LAD is only feasible with distinguishable ventricles as landmarks. For this study, the LAD contour was bounded by the most caudal slice with at least one ventricle contoured, and the most cranial slice with contours of both ventricles.

The proposed auto-segmentation consisted of the following steps (Matlab, 2014a):

- (1) LV and RV were isotopically dilated by 2 voxels (Fig. 1A).
- (2) In slices with sufficient overlap of the dilated ventricles (>40 voxels, >35 mm²), the central voxels of this overlapping area were defined by skeletonization, a process to reduce an object to a single line (Fig. 1B).
- (3) By applying a linear regression to the skeletal points, a straight line was fitted between the ventricles and extrapolated to intercept the WH contour (Fig. 1C).
- (4) The LAD center point was defined on this fitted line, 2.5 mm (the LAD radius) away from the point of intercept of the fitted line and the WH.
- (5) For each relevant slice, the LAD contour was defined as an approximate 'circle' with a diameter of approximately 5 mm (2.5 voxel radius in Matlab), dilated from the LAD center point.

Steps 2 to 5 were repeated for all CT-slices with sufficient overlap between the dilated ventricles (Fig. 1A). Steps 6a–c were performed for CT-slices with insufficient overlap between the ventricles:

(6a) A linear fit between ventricles that intercept the WH described at step 3, was obtained by interpolation of the regression coefficient and intercept of the adjacent slices (defined as 25% of the slices already auto-segmented by steps 2–5).

(6b) Subsequently, steps 4 and 5 were performed on these slices.

(6c) For the top slices without overlap, the distance from the WH to the LAD center point was gradually increased to 5 mm and the LAD radius was increased to 3 voxels.

The auto-segmented LAD was finally post-processed in step 7:

(7) Regions of the auto-segmented LAD that overlap the ventricles were removed.

The completed LAD contour is shown in Fig. 1D. The time it takes to automatically contour the LAD, from start to finish, is on average 57.2 s (standard deviation: 25.6 s).

In the [Supplementary material Fig. 1](#), an example is shown of the agreement of the auto-segmented and manually contoured LAD for one patient, from the cranial surface to the caudal surface of the heart.

Manual contouring of the left anterior descending coronary artery

The manual contouring of the LAD was based on a recent cardiac contouring guideline published by Duane et al. [10], with alternative cranial limits, as described for the auto-segmented LAD. There were no constrictions for the caudal limits. Each LAD was contoured with a 4 mm diameter throughout its entire length, in accordance with the guideline from Duane et al. Contouring was performed by one observer, supervised by a cardiac radiologist. Manual contours were performed blinded, i.e. without knowledge of the auto-segmented contours. The time taken for the manual contours of the LAD was approximately 20–30 min per patient.

Analysis

To evaluate the performance of the auto-segmentation tool, the auto-segmented and manually contoured LADs were first compared using three geometric measures: (1) Dice Similarity Coefficient (DSC), (2) average centroid distance, and (3) the max-Hausdorff distance [5,11]. The DSC indicates the degree of spatial overlap between two contours. The DSC scores from 0 to 1, with 1 indicating a perfect overlap [12]. The average centroid distance

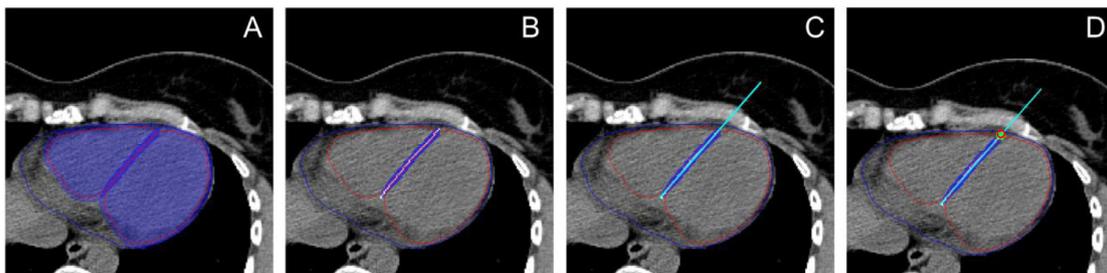


Fig. 1. Steps undertaken by the auto-segmentation tool for the contouring of the LAD. Step A) the dilations of the left ventricle and right ventricle. Step B) skeletonization, a process to reduce an object to a single line. Step C) a straight line fit with linear regression to the skeleton and extrapolated to intercept the whole heart (WH) contour. Step D) from a centroid point, positioned at a distance of the LAD radius away of the WH contour, a 'circle' was dilated to represent the final auto-segmented LAD. The manually contoured LAD was shown in red. Abbreviations: LAD, left anterior descending coronary artery.

is the average of the distances between the segmentation centroids per axial slice. The max-Hausdorff distance is the largest of all minimum distances between two contour points. This was performed per slice, for which an average was determined. A distance of 0 mm indicates a perfect overlap [11].

A second measure to test the performance of the LAD auto-segmentation was to compare the differences in planned dose–volume histogram (DVH) parameters of the auto-segmented and manual LAD contours. The analysis included the mean dose, V5 (% volume of a structure receiving ≥ 5 Gy), V20 (% volume of a structure receiving ≥ 20 Gy), D5 (the maximum dose to at least 5% of the volume of a structure) and D95 (the minimum dose to at least 95% of the volume of a structure). These DVH-parameters were chosen based on previous research and cover a broad spectrum of the dose-distribution [7]. Correlations between the mean dose, V5, V20, D5 and D95 of the auto-segmented and manual LAD contours were analyzed with R^2 of the linear regression.

A high correlation does not necessarily mean that the agreement between the two methods is good, therefore the Bland–Altman plots were also created [13]. A Bland–Altman plot is a graphical method to compare two measurement techniques, and identifies any systematic difference between the measurements or possible outliers [14]. In this graphical method, the differences between the DVH-parameters of the auto-segmented and manual contours are plotted against the average values. The plot shows the limits of agreement estimated using the 2.5th and 97.5th percentiles, and the average bias estimated as the median of the differences.

Results

In total, 53 patients (50.5%) had left-sided BC and 52 patients (49.5%) had right-sided BC. The median mean heart dose for the total study population was 2.18 Gy (range: 0.61–11.34). For left-sided BC patients the median mean heart dose was 4.16 Gy (range: 1.07–11.34), and for right-sided BC patients 1.29 Gy (range: 0.61–4.14).

The DSC between the auto-segmented and manual contours of the LAD was 0.15. The median average centroid distance was

3.9 mm. The geometric overlap, as determined by the median max-Hausdorff distance, was 4.8 mm (shown in [Supplementary material Table 1](#)). The impact of the differences in agreement between the auto-segmented and manual contours of the LAD was visualized in a box-plot with the average centroid distance of all patients and illustrative CT-slices with the auto-segmented and manually contoured LAD shown ([Fig. 2](#)).

A high-level of correlation was measured between the dosimetric parameters of the auto-segmented contours and the manual contours. For the mean dose, V5, V20, D5 and D95 of the LAD, we found a R^2 -value of 0.99, 0.98, 0.99, 0.99 and 0.89, respectively (shown in [Fig. 3](#) and in [Supplementary material Table 1](#)).

The Bland–Altman plots in [Fig. 4](#) show the average of the two measurements (auto-segmented and manual contours) on the x-axis and the difference between the two measurements on the y-axis. The maximum bias was 0.01 Gy for the mean dose, D5 and D95 of the LAD, indicating the similarity in DVH-parameters of the two methods of contouring. Furthermore, the Bland–Altman plots show that the number of patients outside the limits of agreement (4 patients, 3.8% of the study population) was equally distributed above the upper limit and below the lower limit of agreement, indicating that for the vast majority, the two measurements were comparable.

Discussion

This technical note shows the development and evaluation of an auto-segmentation tool for the LAD based on free breathing non-contrast planning CT-scans of BC patients. This is the first auto-segmentation tool that uses anatomical landmarks for the contouring of the LAD. The dosimetric comparison showed a high-level of agreement between the auto-segmented and the manual contours. This agreement suggests that our method could be an efficient tool to help retrospectively calculate radiation dose to the LAD for BC patients for research purposes. The max-Hausdorff distance and the distance between centroids showed that overall the auto-segmented LAD was displaced approximately 4.4 mm from the manually segmented LAD. Due to the small size of the structures, the DSC values were low.

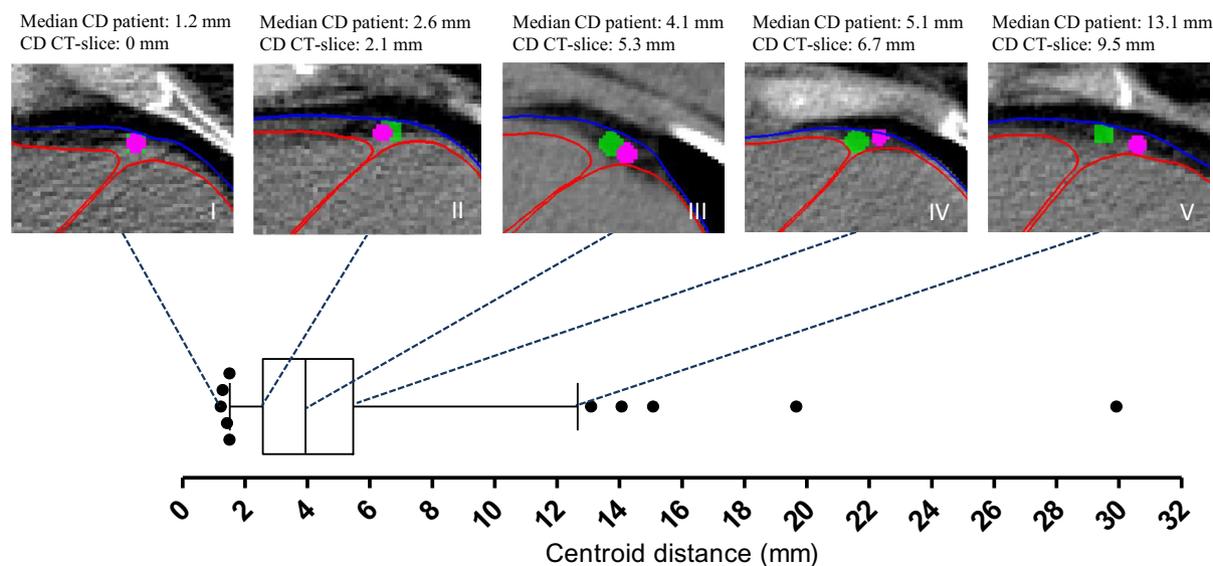


Fig. 2. Box-plot of the average centroid distance (CD) between the auto-segmented and manually contoured LAD of all patients and illustrative CT-slices with the auto-generated (green) and manual (pink) contours of the lowest CD (I), and the 25th (II), 50th (III), 75th (IV), and 95th percentile (V) of the average CD. Abbreviations: CD, centroid distance; LAD, left anterior descending coronary artery; CT, computed tomography.

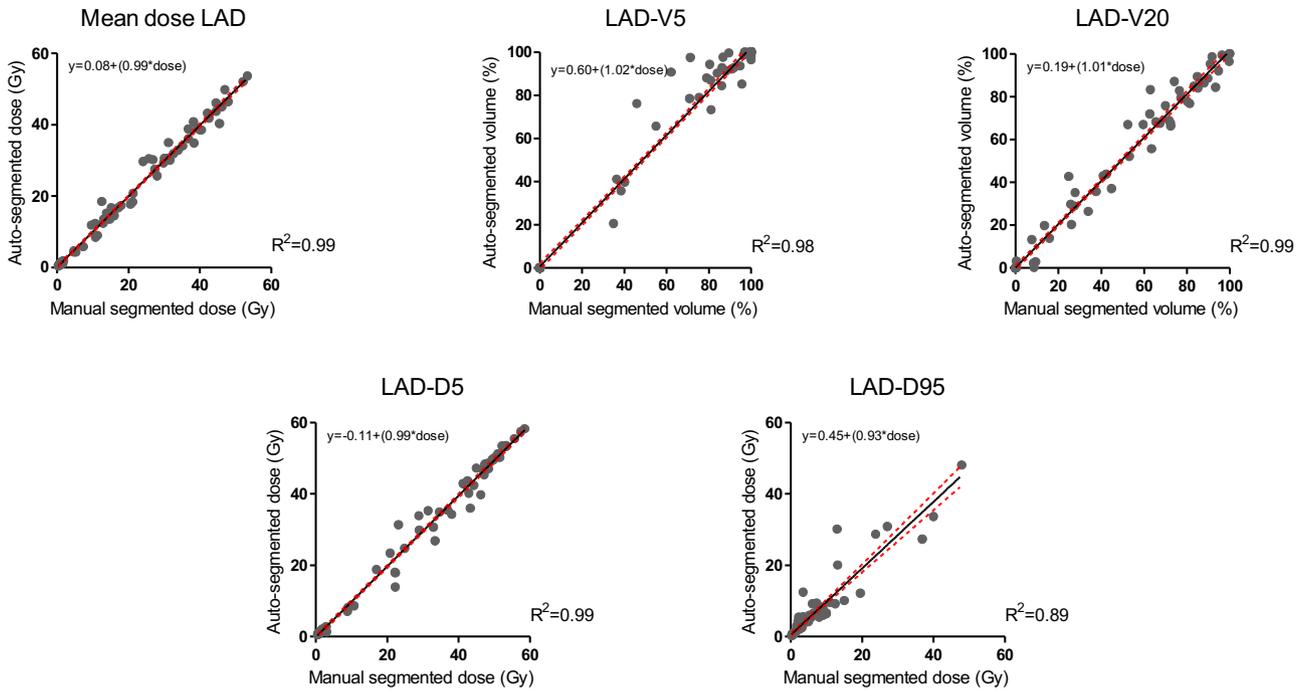


Fig. 3. Comparison of DVH parameters for the auto-segmented contours and the manual contours. This figure shows the mean dose to the LAD, V5 of the LAD, V20 of the LAD, D5 of the LAD and the D95 of the LAD. The black line represents the linear regression with confidence intervals (red lines). Abbreviations: DVH, dose–volume histogram; LAD, left anterior descending coronary artery.

Studies have shown that exposure of the heart to ionizing radiation during RT for BC increases the risk of ischemic heart disease [15,16]. The specific structures of the heart and the mechanisms that cause this radiation-induced cardiac toxicity are not fully understood. There are indications that the coronary arteries may play an important role in the pathophysiology of this type of cardiac toxicity, in particular the LAD [1,2,17]. Since the introduction of the CT-scan, 3D patient images and dose-distributions are widely available. However, the contouring of the LAD is time

consuming and often challenging due to lack of intravenous contrast-enhancement, as well as motion-related artifacts due to breathing and heart beating in planning CT-scans. To process imaging data on a large scale for research, an efficient and validated auto-segmentation tool has become necessary. With the contouring task automated, researchers can investigate possible relationships between DVH-parameters and cardiac endpoints for large groups of BC patients. For translation into clinical practice, validation in an independent cohort is still necessary.

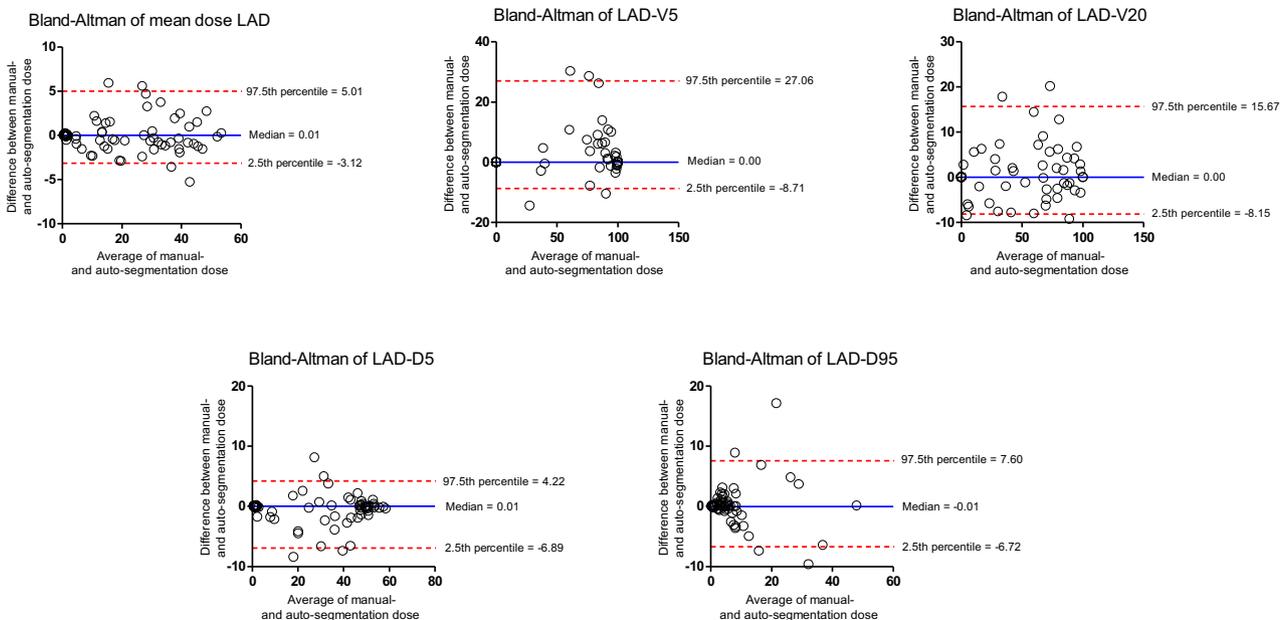


Fig. 4. Bland–Altman’s plots comparing the auto-segmented and manually contoured LADs, plotted against the averages of the two techniques. The blue line represents the average bias estimated as the median of the differences. The red lines represent the limits of agreement estimated using the 2.5th and 97.5th percentiles. Abbreviations: LAD, left anterior descending coronary artery.

Several studies have described ABAS for the heart and/or its substructures [4–7,18]. For contouring the WH, the geometric overlap scored well, all studies report a DSC >0.8. However, the reported DSC of the LAD was poor, between 0.09 and 0.15. Our study showed a DSC of 0.15, which is comparable and still disappointing. This could be because the DSC is heavily influenced by the volume of a structure. Evaluating the DSC for the small LAD volume might stress differences that are not clinically relevant. Therefore, for the geometrical endpoints, we want to emphasize the median average centroid distance of 3.9 mm and median max-Hausdorff distance of 4.8 mm. These results are comparable to, or in some cases better than, recently published results on LAD auto-segmentation [4,6,7,19].

One study investigated the impact of an automated contouring atlas on DVH-parameters of the heart and its substructures for BC patients [7]. The investigators stated that conventional geometric parameters, such as DSC, may not adequately illustrate whether an auto-segmented contour represents the actual radiation dose. In this study, we came to the same conclusion. The LAD showed a poor DSC, but had a high-level of agreement concerning DVH-parameters between the auto-segmented and the manual contours. The major difference between the studies is that the contours of the LAD in our study were based on anatomical landmarks. Using anatomical landmarks that are clearly distinguishable on CT-scans, such as the RV and LV, the problem of the poorly visible LAD was avoided.

There are several limitations in this study to address. The LAD is fully based on the anatomical landmarks defined in the ABAS tool. If the ventricles or WH is not contoured accordingly, the LAD will be automatically misplaced. As shown in Figs. 3 and 4, there are a few outliers present. These outliers were evaluated, and all were found to be misplaced due to an incorrect contouring by the ABAS tool. Therefore, it is necessary to visually check the ABAS contours of the whole heart and ventricles before using the LAD auto-segmentation tool. However, we have shown that our ABAS tool is overall a valid and reliable alternative to manually contouring major cardiac structures (WH, atria and ventricles) [3].

Furthermore, it is well established that manual contours are often prone to intra- and inter-observer variability and could therefore impact the calculated radiation dose. For the LAD, substantial variation was found in the estimated dose, which was not reduced with guidelines [20]. The coefficients of variation in the estimated mean dose to the LAD were 27% without, and 29% with guidelines. It is expected that the dose uncertainty using our automatic contouring method for the LAD is of the same order of magnitude as the intra- and inter-observer variability for manual contouring. Further research is necessary to verify this.

Another limitation is that, because the auto-segmentation tool uses the RV and LV to determine the anterior interventricular groove, the LAD can only start when both ventricles are first contoured. Therefore, the proximal 1/5th of the vessel may not always be fully contoured because the LAD originates from the end of the left main coronary artery passing anteriorly behind the pulmonary artery [10]. Since this proximal part of the LAD is likely to receive the lowest dose compared to the mid- and distal part, the auto-segmented LAD could give an overestimation of the mean LAD dose and the D95 [21]. However, it is expected that the D5 will hardly be influenced at all. Nevertheless, this method can be used in cohort studies regarding dose–effect relationships. Furthermore, a recently published study concluded that the minor differences in DVH-parameters on target structures between auto-segmented and manual contours are insignificant in a clinical setting [22]. However, caution is advised for comparing results with studies that contoured the entire LAD.

In conclusion, this technical note presents a method for the development of an auto-segmentation tool for the contouring of

the LAD of BC patients. This is the first auto-segmentation tool based on anatomical landmarks to avoid the challenge due to the lack of intravenous contrast-enhancement in planning CT-scans. The results concerning the dosimetric endpoints were satisfying, with R^2 -values all above 0.89. Furthermore, the Bland–Altman plots indicate that the two measurements are comparable and that the bias is minimal. This auto-segmentation tool could be made available for research purposes to enable automatic calculation of the radiation dose to the LAD for large groups of BC patients.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.03.013>.

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