Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2019 March 15; 103(4): 985–993. doi:10.1016/j.ijrobp.2018.11.025.

Cardiac Substructure Segmentation and Dosimetry Using a Novel Hybrid Magnetic Resonance and Computed Tomography Cardiac Atlas

Eric D. Morris, BS^{a,b}, Ahmed I. Ghanem, MD^{a,c}, Milan V. Pantelic, MD^d, Eleanor M. Walker, MD^a, Xiaoxia Han, PhD^e, and Carri K. Glide-Hurst, PhD^{a,b,*}

^aDepartment of Radiation Oncology, Henry Ford Cancer Institute, Detroit, Michigan

^bDepartment of Radiation Oncology, Wayne State University School of Medicine, Detroit, Michigan

^cDepartment of Clinical Oncology, Alexandria University, Alexandria, Egypt

^dDepartment of Radiology, Henry Ford Cancer Institute, Detroit, Michigan

^eDepartment of Public Health Sciences, Henry Ford Cancer Institute, Detroit, Michigan

Abstract

Purpose: Radiation dose to the heart and cardiac substructures has been linked to cardiotoxicities. As cardiac substructures are poorly visualized on treatment planning computed tomography (CT), we employed the superior soft tissue contrast of magnetic resonance (MR) imaging to optimize a hybrid MR/CT atlas for substructure dose assessment using CT.

Methods: Thirty-one left breast cancer patients underwent a T2-weighted MR and non-contrast simulation CTs. A radiation oncologist delineated 13 substructures (chambers, great vessels, coronary arteries etc.) using MR/CT information via cardiac-confined rigid registration. Ground truth contours for 20 patients were input into an intensity-based deformable registration atlas and applied to 11 validation patients. Automatic segmentations involved employing majority vote and Simultaneous Truth and Performance Level Estimation (STAPLE) strategies with 1–15 atlas matches. Performance was evaluated via Dice similarity coefficient (DSC), mean distance to agreement (MDA), and centroid displacement. Three physicians evaluated segmentation performance via consensus scoring using a 5-point scale. Dosimetric assessment included measurements of mean heart dose (MHD), left ventricular volume receiving 5Gy (LV-V5), and left anterior descending artery mean and maximum doses (LADAm_{mean}, LADAm_{max}).

Results: Atlas approaches performed similarly well with 7/13 substructures (heart, chambers, ascending aorta, and pulmonary artery) having DSC>0.75, when averaged over 11 validation

*Corresponding author. Department of Radiation Oncology, Henry Ford Cancer Institute, 2799 W. Grand Blvd, Detroit, MI 48202. churst2@hfhs.org (C. Glide-Hurst).

Conflict of Interest Statement:

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

patients. Coronary artery segmentations were not successful with the atlas-based approach (mean DSC<0.3). STAPLE method with 10 matches (ST10) yielded highest DSC and lowest MDA for all high performing substructures (omitting coronary arteries). For ST10, >50% of all validation contours had centroid displacements<3.0mm, with largest shifts in coronary arteries. Atlas-generated contours had no statistical difference from ground truth for LADAmx, MHD, and LV-V5 ($p>0.05$). Qualitative contour grading showed that 8 substructures required minor modifications.

Conclusion: The hybrid MR/CT atlas provided reliable segmentations of chambers, heart, and great vessels for patients undergoing non-contrast CT, suggesting potential widespread applicability for routine treatment planning.

INTRODUCTION:

Increased risk of cardiotoxicity, including coronary artery disease and cardiomyopathy, has been linked to radiation therapy (RT) for many cancer sites in close proximity to the heart[1–3]. Moreover, major coronary events have been linked to radiation dose to the heart with a ~7%/Gy increase in rate of ischemic heart disease[4]. Radiation dose from breast cancer treatments specifically have also been correlated to myocardial infarction, congestive heart failure, and cardiovascular death more than 10 years after RT[5]. Therefore, minimizing cardiac dose due to RT treatments is critical and has been given recent attention[6,7].

Currently, organ at risk (OAR) dose limits for breast cancer radiation treatment planning (RTP) account for the entire heart volume. For example, according to a cooperative group trial for left-sided breast cancers, no more than 5% of the whole heart may exceed 20 Gy[8]. However, heart substructures are not routinely included in RTP as they are not visible on standard CT-simulation datasets and dose limits are not currently well established. Furthermore, dose to these cardiac substructures may have prognostic inferences. In left breast cancer patients, the left anterior descending coronary artery (LADA) is often exposed to the highest treatment-related radiation dose[4] and increased dose has been linked to increased risk of late radiation induced cardiac morbidity[9]. Additionally, measurements of radiation dose to cardiac substructures, like the left ventricle (LV), may be useful in the prediction of future acute coronary events[10]. By localizing these sensitive substructures within the heart, we can then estimate the dose to these regions. This may further our understanding of their potential roles in radiation-related cardiotoxicity.

The current standard of care for radiation treatment planning is based on CT simulation (CT-SIM) to enable electron density mapping for dose calculation. However, cardiac substructures are not easily discernible on standard CT-SIM datasets. Some single modality atlas methods have employed contrast-enhanced CT[11–13]. For coronary arteries such as the LADA, contrast-enhanced CT may aid in localization although the majority of the structure is not discernible[14]. At present, contrast-enhanced CT (either diagnostic or for CT-SIM) is not widely available for breast cancer patients, nor are they included in the current National Comprehensive Cancer Network breast cancer recommendations[15] or cooperative clinical trial group guidelines for delineation [16–18]. Thus, developing atlas

solutions that can be applied to widespread, clinically available data, such as standard CT-SIMs, is advantageous.

Magnetic resonance imaging (MRI) also improves the visibility of cardiac substructures[19,20] as illustrated in Figure 1. Thus, numerous automatic segmentation methods have been established utilizing MR[21]. However, MRIs are not frequently acquired and integrated into routine RTP. Recently, a multi-scale patch method was used to generate a multi-modality atlas (e.g. cardiac MRI and contrast-enhanced CT) for automatic segmentation of 7 substructures[22]. The purpose of the current study is to develop and validate a novel hybrid MR/CT segmentation atlas with the overall goal of segmenting 13 sensitive cardiac substructures on standard, non-contrast, treatment planning CTs. The completion of this work offers potential for widespread implementation and may provide important information for dosimetric assessment for OAR sparing.

METHODS:

Image Acquisition

Thirty-one patients who underwent RT for left-sided whole-breast cancer were enrolled on an Institutional Review Board approved study to acquire cardiac MRI scans. T2-weighted acquisitions were performed on a 3T Philips Ingenia (Philips Medical Systems, Cleveland, OH) with images acquired at end-expiration (EE). Patients were positioned supine and imaged in a multi-coil configuration with a 32 channel dStream Torso coil (Philips Medical Systems, Cleveland, OH) and a 20-channel integrated posterior coil. Imaging parameters included an 8 mm slice thickness, in-plane resolution $0.7 \times 0.7 \text{ mm}^2$, and an echo time of 81 ms. This 2D acquisition involved a single breath hold at EE with an average total acquisition time across all patients of 22.1 ± 4.4 seconds (range: 15.1–31.0 seconds).

Non-contrast CT-simulation was performed on a Brilliance Big Bore CT Simulator (Philips Medical Systems, Cleveland, OH) with a 3 mm slice thickness. Eight patients underwent 4DCT while the other 23 patients underwent a CT-SIM under free-breathing conditions (FBCT) based on institutional practices. FBCT and 4DCT images were acquired with an in-plane resolution of $1.1 \times 1.1 \text{ mm}^2 - 1.4 \times 1.4 \text{ mm}^2$, 120–140 kVp, and 275–344 mAs. All patients were imaged in the supine position and immobilized on a Posiboard (Civco, The Netherlands) with their arms above their head.

Image Registration

A local, cardiac-confined, rigid registration was performed between the non-contrast CT and axial T2-weighted MR in MIM (version 6.7.12, MIM Software Inc., Cleveland, OH). Rigid registrations were conducted using normalized mutual information as the similarity metric, which has been shown to robustly align multi-modality images[23]. Visual inspection of the cardiac-confined rigid registration was performed by a radiation oncologist before completing manual segmentations. To compensate for respiratory motion, the 50% (EE) phase of the 4DCT was rigidly registered to the MR for 8 subjects. Despite 23 patients being imaged with FBCT at arbitrary phases of the breathing cycle, visual inspection of the locally

confined heart rigid registration by a physicist and Radiation Oncologist revealed that the registration quality was adequate for delineation purposes.

Contour Delineation

A radiation oncologist delineated 13 cardiac substructures, as outlined in Figure 1, with substructure selection based on CT and cardiac MRI auto-segmentation atlases [11,21,24]. Substructures were also selected based on their roles in major cardiac function and proximity to the radiation field.

A radiation oncologist followed a published cardiac atlas consensus contouring guideline[24] to delineate the substructures on the CT using a MR/CT rigid registration with a fixed window/level on CT (50/500 for large structures, 50/150 for cardiac vessels) and giving preference to MR anatomical information. However, as the epicardial border of the heart is visible on CT, the CT was used to generate the whole heart contour. Contours were verified by a radiologist with a cardiac subspecialty and 30 years of clinical experience.

Atlas Generation

Non-contrast CT ground truth delineations derived from MR/CT hybrid information for a subset of 20 patients were inputted into an intensity-based deformable registration atlas in MIM. To perform a sample size estimation, an initial test cohort of 5 subjects was evaluated. To achieve 80% power (medium effective size on a repeated measure ANOVA, alpha error of 0.05 to compare the difference between 8 means), 10 patient cases were required. However, because the DSC was not normally distributed and a non-parametric Friedman test was to be used for analysis, the sample size ($n=10$) was then divided by a correction factor of 0.955 (i.e. the asymptotic relative efficiency)[25], resulting in a required sample size of $n=11$ for the testing patient cohort. Thus, the deformable registration atlas was applied to 11 validation patients (i.e. test subjects).

To generate the hybrid segmentation atlas, a reference structure set was first generated from a predetermined patient with average anatomy to act as a template[26]. The template patient was selected based on a moderate habitus, minimal motion artifact, and standard heart geometry and anatomical position. A local, cardiac-confined, rigid registration was then performed between the template patient and the 20 subsequent patients, including the template patient. One of the 11 test subjects was then selected and a mutual information-based algorithm[27] was used to locate the atlas subject(s) that were deemed the best matches to the test subject. A free-form deformable image registration (DIR) was then completed between each selected atlas subject and the test subject. The commercially available free-form intensity-based DIR algorithm has limitless degrees of freedom and utilizes adequate regularity (i.e. penalty term weight) to ensure smooth deformation[28] and has been previously validated in CT/CT registrations yielding high segmentation accuracy[29]. Finally, the generated deformation vector field was used to propagate the ground truth segmentations from the best match to the test subject's CT.

To optimize atlas performance, three atlas approaches were evaluated (1) single-atlas method, and two multi-atlas segmentation approaches (2) majority vote (MV) and (3) Simultaneous Truth and Performance Level Estimation (STAPLE). The single-atlas method

deforms contours from the single best matching atlas subject to the test subject whereas multi-atlas approaches use various best matching atlas subjects. In MV, after multiple contours for the same substructure are deformably propagated to the test subject, the most frequent contour at each voxel is established as the true segmentation[30]. The STAPLE method uses a probability map to create an estimate of the true segmentation from a collection of contours by using an expectation-maximization algorithm[31]. The resultant segmentation is then formed by optimally combining the existing contours through assigning weights based on sensitivity and specificity[31].

To further optimize segmentation, the number of multi-atlas matches was iterated (3, 5, 10, and 15) for MV and STAPLE methods for the 11 validation datasets. Once final contours were obtained, post-processing including contour smoothing and filling was performed[30]. Image processing time was logged in MIM and tabulated for each approach for a representative validation patient. Image processing was conducted on a 64-bit Microsoft Windows PC with a quad-core Intel® Xeon® CPU-E5-1630 v4 at 3.70GHz and 16GB of memory.

Atlas Validation

Atlas performance was assessed via Dice similarity coefficient (DSC)[11,12,21] mean distance to agreement (MDA)[32], and centroid displacement between propagated and ground truth delineations for the 11 test cases. The DSC is used to measure the spatial overlap between two structures (Equation 1) and is a value from 0, representing no overlap, to 1, representing perfect agreement.

$$DSC = \frac{2|M \cap N|}{|M| + |N|} \quad (1)$$

Where M and N are the volumes of the manually delineated and propagated contour, respectively. MDA is used as a geometrical measure to assess the agreement between two contours by averaging the per voxel shortest distance from each point on the test contour to the reference contour, with an increased agreement yielding a lower MDA[32].

To evaluate clinical acceptance of the auto-segmented contours, qualitative consensus scoring was completed for 13 substructure contours on a subset of 5 of the 11 validation cases by 2 radiation oncologists and a radiologist with a cardiac subspecialty. Scores were assigned on a 5-point scale[33]: (1) clinically unacceptable, (2) major modifications required, (3) moderate modifications required, (4) minor modifications required, (5) clinically acceptable.

Dosimetric Assessment

A dosimetric assessment of left breast cancer patients was conducted to illustrate a potential clinical application of the validated atlas in the test cohort. For the 11 test subjects, the clinically approved and delivered treatment primary whole breast (tangential fields, 6–18 MV, 42.7–45.0 Gy) and boost (3D planned with 6–15 MV photons or 12 MeV electrons to

10.0–16.2 Gy) plans were exported from the Eclipse Treatment Planning System (Version 11.0, Varian Medical Systems, Palo Alto, CA) and into MIM for direct dose summation. Dosimetric evaluation of the cardiac substructures included measurements of the minimum, mean, and maximum dose to each substructure. The mean heart dose (MHD), left ventricular volume receiving 5 Gy (LV-V5) and left anterior descending artery mean and maximum doses ($LADA_{mean}$, $LADA_{max}$) are highlighted as they have been shown to be predictive of acute cardiac events[4,10] and are important indicators for ischemic heart disease[9,34].

Statistical Analysis

Data are presented as mean $\pm$ standard deviation (SD). Statistical analysis of DSC and MDA between atlas methods was performed using the Friedman test with a Wilcoxon signed ranks test for post hoc pairwise comparisons and were Bonferroni corrected. Statistical analyses between ground truth and auto-segmented volumes and doses were performed using 2-tailed Wilcoxon signed rank tests, with $P < .05$ considered statistically significant. All analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL, USA).

RESULTS:

Contour Generation

The average time for the manual delineation of 13 cardiac substructures was ~3 hours per patient. For a representative test subject, the atlas auto-segmentations took between 1–10 minutes depending on the selected amount of atlas matches. When applying the STAPLE method with 10 atlas matches to this same representative patient, the radiation oncologist required ~30 minutes of additional time to edit segmentations for all 13 substructures for clinical implementation.

Atlas Performance Evaluation

Figure 2 outlines atlas performance for single-atlas, MV, and STAPLE methods with 3, 5, 10, and 15 atlas matches for MV and STAPLE. Figure 2 (left) shows that median DSC values across all structures were between 0.71 and 0.80 for the single-atlas method and STAPLE method with 10 atlas matches (ST10), respectively. In general, atlas approaches performed similarly, yielding mean DSCs >0.75 for 7/13 substructures (heart, chambers, AA, and PA) over the 11 validation patients. Table 1 outlines DSC results for the single atlas method and select high performing multi-atlas methods. Across the 11 test subjects, all coronary artery segmentations had DSC values <0.42 . Figure 2 (right) summarizes the 11 validation patient mean DSC results after exclusion of the coronary arteries, where median DSC values range from 0.75 to 0.85 for the single-atlas and ST10 method, respectively. In comparing atlas methods, ST10 generated the highest mean DSC and lowest MDA values for all high performing substructures (i.e. heart, chambers, and great vessels). The post hoc pairwise comparisons (supplementary Table 2) revealed that ST10 outperformed the single-atlas for all substructures except the coronary arteries for both MDA and DSC ($p < 0.05$). However, the single atlas method's DSCs and MDAs performed similarly to STAPLE and Majority Vote when fewer than 5 atlas matches were used ($p > 0.05$, results not shown). Regarding MDA, ST10 outperformed ST3 and ST15 for > 8 high performing substructures.

Additionally, ST10 outperformed ST5 for the RV and PA DSCs at the expense of ~5 minutes processing time. Thus, all further analyses were conducted using ST10.

Segmentation Results for ST10

Figure 3 summarizes the mean MDA and DSC results between manually delineated ground truth contours and ST10 atlas generated contours over the 11 test cases. Over all 13 substructures, 10 had an MDA <2.1 mm and 9 had a mean DSC >0.70, suggesting excellent atlas performance. The coronary arteries performed the worst (mean DSC <0.3 and MDA between 3.1–4.2 mm). Additionally, across the 11 test cases, over half of all contours had centroid displacements <3.0 mm, with largest shifts in the coronary arteries. The greatest centroid displacements occurred in the superoinferior direction (predominantly superior). Three out of 13 substructures (LMCA, PV, and RCA) had statistically significant differences in volumes between ST10 and manually generated contours ($p < 0.05$). Figure 4 highlights agreement for all auto-segmented cardiac substructures as compared to ground truth.

Qualitative Contour Grading using ST10

Physician consensus scores for the heart, ventricles, PA, RA, SVC, IVC, and AA were found to require only minor modifications, typically at the inferior boundary (average score: 4.2 ± 0.5). The PV and LA scored between 3 and 4, requiring moderate modifications. Major modifications were necessary for the LADA (1.8 ± 0.8) and RCA (2.4 ± 0.9) although propagated contours were deemed useful for localization. LMCA yielded the lowest average score (1.4 ± 0.5), suggesting inadequate segmentation. The highest scoring segmentations occurred for the LVs and AAs, with 3 and 2 subjects requiring no modifications, respectively. Excluding the coronary arteries, average consensus scores across all validation patients were greater than 4 (Table 1), suggesting only minor modifications were necessary.

Dosimetric Assessment

Figure 5 shows a representative DVH for a test subject including the LV, LADA, and heart, as these structures fell within the tangential fields. All other cardiac substructures received negligible radiation dose (mean dose <1.5Gy, results not shown). The propagated contour yielded an LADA_{mean} of 23.1 Gy and an LADA_{max} of 44.9 Gy, which were within 3.4% and 0.1% of ground truth, respectively (LADA_{mean} of 22.4 Gy, LADA_{max} of 44.9 Gy).

The Wilcoxon signed rank test showed no statistically significant differences between ST10 and ground truth contours for the minimum, mean, and maximum dose to the chambers and great vessels ($p > 0.05$). Additionally, there were no statistically significant differences in LADA_{max}, MHD, and LV-V5 ($p > 0.05$). However, there was a significant difference in dose for the LADA_{mean} ($p < 0.05$). Excellent estimation of the dose to the heart and LV was observed across the 11 test subjects for the propagated contours proving them to be robust for dosimetric endpoints. The summation of the primary and boost treatment plans for the 11 validation subjects yielded no statistically significant differences in dosimetric endpoints between ST10 and ground truth contours for the LV-V5 ($14.9 \pm 7.0\%$ vs. $15.3 \pm 7.3\%$), MHD (2.7 ± 1.0 vs. 2.8 ± 1.0 Gy), and LADA_{max} (46.2 ± 6.9 vs. 43.2 ± 9.0 Gy) ($p > 0.05$). However, the difference in LADA_{mean} was statistically significant (22.5 ± 11.2 vs. 18.3 ± 10.0 Gy) ($p < 0.05$).

DISCUSSION:

This work has optimized and validated a hybrid MR/CT contouring atlas for cardiac substructure segmentation with the overarching goal of applying it to non-contrast enhanced CTs for RTP and dose assessment. After a promising segmentation approach was identified (i.e. ST10), accurate delineations were obtained for the heart, chambers, and great vessels (10 of 13 substructures), although the coronary arteries were not adequately segmented ($DSC < 0.3$). While the current retrospective dosimetric evaluation focuses on cardiac substructures for left-sided breast cancer RT, the atlas may be applied to other disease sites, such as advanced stage lung or esophageal cancer, which can be explored in future work.

Although cardiac substructure atlases have been described in the literature, to our knowledge, none have included hybrid MR/CT information for propagation to CT. STAPLE was recently applied to delineate heart chambers on non-contrast enhanced CT images via a fused contrast-enhanced CT[11]. With the introduction of MRI into our atlas, our work outperformed that of Zhou for the heart chambers (average improvements in DSC and MDA of 0.12 ± 0.02 and 2.8 ± 0.5 mm, respectively) (11). A multi-atlas MV method was used to automatically segment cardiac chambers on CT angiography scans from a large multicenter/multivendor database with little improvement in segmentation accuracy with >5 atlas matches[12]. When applying MV in our work, a slight improvement in median and IQR was observed when using up to 15 atlas matches (Figure 2, right) at the expense of computational time (~ 10 minutes/dataset). While Zhuang et al. did incorporate MRI into their cardiac substructure atlas, they focused mostly on the large structures such as the heart, chambers, AA, and PA[22] and also used contrast-enhanced CT. Our segmentation accuracy for ST10 was comparable for the same structures (DSC and MDA within 0.01 and 0.5 mm, respectively) after applying the MR/CT atlas to standard RTP CTs.

One limitation is that ground truth contours were generated by a single radiation oncologist. However, contour verification by a radiologist and our consensus scoring provided additional clinical interpretation by multiple observers. Another limitation of this work is that the performance of the atlas has yet to be evaluated for deep-inspiration breath hold, which has been shown to provide additional cardiac sparing for left-breast cancer cases[35]. Finally, the volumetric T2-weighted cardiac MRI scans were not optimized for RTP (slice thickness=8 mm) although in-plane resolution was 0.7×0.7 mm². Thinner slice thicknesses will improve contouring accuracy for small volumes, however at the expense of reduced signal-to-noise ratio.

The coronary arteries (i.e. LADA, RCA, and LMCA) were the most challenging for our atlas, which is consistent with other studies [11,13,36]. Potential causes of this include complex and low contrast anatomy and image resolution limitations. Although we accounted for respiratory motion by utilizing a local cardiac confined registration, cardiac motion may have adversely impacted the MR/CT fusion accuracy which may introduce additional uncertainty in small structures, such as the arteries. In these cases, manual segmentation was difficult and required expertise. Additionally, significant motion from respiration and the cardiac cycle may present challenges in identifying the coronary arteries as they can often appear indistinct or noncontiguous[24]. A recently reported contouring atlas using

landmarks like the atrioventricular and interventricular grooves has also shown to be useful in segmenting the coronary arteries without the use of contrast[36]. The 9 outliers (Figure 2 (right)) are due to PV segmentations from 2 validation patients where, in both cases, the atlas overestimated the volume and did not reach the inferior extent of the ground truth contours. Additionally, the 3 extreme outliers (DSC<0.4) (Figure 2 (right)) were attributed to an inadequate IVC segmentation on a single patient, likely due to the liver appearing homogeneous on non-contrast enhanced CT. Thus, artery and vein segmentation will be further addressed in future work via the application of deep convolutional networks, which have shown promise for ventricle segmentation[37].

The retrospective dosimetric evaluation revealed that for whole breast RT, few cardiac substructures may require assessment. Nevertheless, the maximum dose to the LADA (46.2 ± 6.8 Gy) was substantial, with possible consequences of acute cardiac events[10] and ischemic heart disease[9,34]. Future work may include the evaluation of treatment planning strategies and extend this work to other disease sites that may benefit from cardiac substructure sparing (e.g., esophagus, lung, or lymphoma). Additionally, further development of this atlas may incorporate the inclusion of cardiac valves and segments of the LV[36].

CONCLUSIONS:

Overall, applications of the hybrid MR/CT atlas offer future potential for robust cardiac substructure sparing using standard simulation CTs that are in routine use for treatment planning (i.e., non-contrast CT/4DCT) when an MRI is unavailable. As virtually all patients receiving radiation therapy have a CT simulation as needed for accurate dose calculation, our approach offers strong potential for widespread application. Our hybrid MR/CT atlas shows promise for cardiac substructure segmentation for use in routine treatment planning and dose assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors would like to thank the cardiac and radiation oncology teams at the University of Michigan for their consultation regarding the cardiac imaging protocol, including Dr. Lori Pierce, Dr. Venkatesh Murthy, and Robin Marsh.

Sources of support:

Data acquisition costs were supported by the Breast Cancer Research Foundation. Research reported in this publication was partially supported by the National Cancer Institute of the National Institutes of Health under award Number R01 CA204189-01A1. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

- [1]. Ng AK. Review of the Cardiac Long-Term Effects of Therapy for Hodgkin Lymphoma. British journal of haematology 2011;154:23–31. [PubMed: 21539537]

- [2]. Beukema JC, van Luijk P, Widder J, et al. Is Cardiac Toxicity a Relevant Issue in the Radiation Treatment of Esophageal Cancer? *Radiotherapy and Oncology* 2015;114:85–90. [PubMed: 25554226]
- [3]. Hardy D, Liu C-C, Cormier J, et al. Cardiac Toxicity in Association with Chemotherapy and Radiation Therapy in a Large Cohort of Older Patients with Non-Small-Cell Lung Cancer. *Annals of oncology* 2010;21:1825–1833. [PubMed: 20211871]
- [4]. Darby SC, Ewertz M, McGale P, et al. Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *New England Journal of Medicine* 2013;368:987–998. [PubMed: 23484825]
- [5]. Jacob S, Pathak A, Franck D, et al. Early Detection and Prediction of Cardiotoxicity after Radiation Therapy for Breast Cancer: The Baccarat Prospective Cohort Study. *Radiation Oncology* 2016;11:54. [PubMed: 27056179]
- [6]. Wright J Blitzblau R Cardiac Morbidity and Radiation Therapy for Breast Cancer. *International Journal of Radiation Oncology• Biology• Physics* 2018;100:283–286.
- [7]. Urbanic JJ, McGarry RC, Daly ME, et al. Locally Advanced Lung Cancer: Is It Time to Take Cardiac Protection Seriously in Radiation Planning? *International Journal of Radiation Oncology• Biology• Physics* 2018;100:1091–1094.
- [8]. Dmitriev I, Loo C, Vogel W, et al. Fully Automated Deformable Registration of Breast Dce-Mri and Pet/Ct. *Physics in medicine and biology* 2013;58:1221. [PubMed: 23369926]
- [9]. Poitevin-Chacón A, Chávez-Noguera J, Prudencio RR, et al. Dosimetry of the Left Anterior Descending Coronary Artery in Left Breast Cancer Patients Treated with Postoperative External Radiotherapy. *Reports of Practical Oncology & Radiotherapy* 2018;23:91–96. [PubMed: 29681771]
- [10]. van den Bogaard V, Ta B, van der Schaaf A, et al. Validation and Modification of a Prediction Model for Acute Cardiac Events in Patients with Breast Cancer Treated with Radiotherapy Based on Three-Dimensional Dose Distributions to Cardiac Substructures. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2017;35:1171. [PubMed: 28095159]
- [11]. Zhou R, Liao Z, Pan T, et al. Cardiac Atlas Development and Validation for Automatic Segmentation of Cardiac Substructures. *Radiotherapy and Oncology* 2017;122:66–71. [PubMed: 27939201]
- [12]. Kiri li H, Schaap M, Klein S, et al. Evaluation of a Multi-Atlas Based Method for Segmentation of Cardiac Cta Data: A Large-Scale, Multicenter, and Multivendor Study. *Medical physics* 2010;37:6279–6291. [PubMed: 21302784]
- [13]. Thor M, Yorke E, Jackson A, et al. Succesful Implementation of Atlas Segmentation for Cardiac Substructures. *International Journal of Radiation Oncology• Biology• Physics* 2017;99:E728.
- [14]. Vennarini S, Fournier-Bidoz N, Aristei C, et al. Visualisation of the Left Anterior Descending Coronary Artery on Ct Images Used for Breast Radiotherapy Planning. *The British journal of radiology* 2013;86:20120643. [PubMed: 23440165]
- [15]. Gradishar WJ, Anderson BO, Balassanian R, et al. Nccn Guidelines Insights: Breast Cancer, Version 1.2017. *Journal of the National Comprehensive Cancer Network* 2017;15:433–451. [PubMed: 28404755]
- [16]. Radiation Therapy Oncology Group. RTOG 1005 Protocol Information (updated August 28, 2018). Clinicaltrials.Gov Identifier: Nct01349322. Abstract. Available at: <https://clinicaltrials.gov/ct2/show/NCT01349322>. Accessed Sept 1, 2018.
- [17]. Radiation Therapy Oncology Group. Rtog 1014 Protocol Information (Updated June 18, 2018). Clinicaltrials.Gov Identifier: Nct01082211. Available at: <https://clinicaltrials.gov/ct2/show/NCT01082211>. Accessed Sept 1, 2018.
- [18]. White J, Tai A, Arthur D, et al. Radiation Therapy Oncology Group Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definitions. Available at: <https://www.rtog.org/corelab/contouringatlas/breastcanceratlas.aspx>. Accessed Feb 1, 2018.
- [19]. Attili AK, Schuster A, Nagel E, et al. Quantification in Cardiac Mri: Advances in Image Acquisition and Processing. *The international journal of cardiovascular imaging* 2010;26:27–40.

- [20]. Dweck MR, Puntmann VO, Vesey AT, et al. Mr Imaging of Coronary Arteries and Plaques. *JACC: Cardiovascular Imaging* 2016;9:306–316. [PubMed: 26965732]
- [21]. Peng P, Lekadir K, Gooya A, et al. A Review of Heart Chamber Segmentation for Structural and Functional Analysis Using Cardiac Magnetic Resonance Imaging. *Magnetic Resonance Materials in Physics, Biology and Medicine* 2016;29:155–195.
- [22]. Zhuang X Shen J Multi-Scale Patch and Multi-Modality Atlases for Whole Heart Segmentation of Mri. *Medical image analysis* 2016;31:77–87. [PubMed: 26999615]
- [23]. Pluim JP, Maintz JA Viergever MA. Mutual-Information-Based Registration of Medical Images: A Survey. *IEEE transactions on medical imaging* 2003;22:986–1004. [PubMed: 12906253]
- [24]. Feng M, Moran JM, Koelling T, et al. Development and Validation of a Heart Atlas to Study Cardiac Exposure to Radiation Following Treatment for Breast Cancer. *International Journal of Radiation Oncology* Biology* Physics* 2011;79:10–18.
- [25]. Salkind NJ and Rasmussen K, *Encyclopedia of measurement and statistics*. 2007, Thousand Oaks, Calif.: SAGE Publications.
- [26]. Horvat M, Nelson A Pirozzi S. Time Savings of a Multi-Atlas Approach for Liver Segmentation. *Journal of Nuclear Medicine* 2014;55:1523–1523.
- [27]. Young AV, Wortham A, Wernick I, et al. Atlas-Based Segmentation Improves Consistency and Decreases Time Required for Contouring Postoperative Endometrial Cancer Nodal Volumes. *International Journal of Radiation Oncology* Biology* Physics* 2011;79:943–947.
- [28]. Piper J Su-Ff-I-68: Evaluation of an Intensity-Based Free-Form Deformable Registration Algorithm. *Medical Physics* 2007;34:2353–2354.
- [29]. Kirby N, Chuang C, Ueda U, et al. The Need for Application-Based Adaptation of Deformable Image Registration. *Medical physics* 2013;40.
- [30]. Iglesias JE Sabuncu MR. Multi-Atlas Segmentation of Biomedical Images: A Survey. *Medical image analysis* 2015;24:205–219. [PubMed: 26201875]
- [31]. Warfield SK, Zou KH Wells WM. Simultaneous Truth and Performance Level Estimation (Staple): An Algorithm for the Validation of Image Segmentation. *IEEE transactions on medical imaging* 2004;23:903–921. [PubMed: 15250643]
- [32]. Thomson D, Boylan C, Liptrot T, et al. Evaluation of an Automatic Segmentation Algorithm for Definition of Head and Neck Organs at Risk. *Radiation Oncology* 2014;9:173. [PubMed: 25086641]
- [33]. Kumarasiri A, Siddiqui F, Liu C, et al. Deformable Image Registration Based Automatic Ct-to-Ct Contour Propagation for Head and Neck Adaptive Radiotherapy in the Routine Clinical Setting. *Medical physics* 2014;41.
- [34]. Sato K, Mizuno Y, Fuchikami H, et al. Comparison of Radiation Dose to the Left Anterior Descending Artery by Whole and Partial Breast Irradiation in Breast Cancer Patients. *Journal of contemporary brachytherapy* 2015;7:23. [PubMed: 25829933]
- [35]. Remouchamps VM, Letts N, Vicini FA, et al. Initial Clinical Experience with Moderate Deep-Inspiration Breath Hold Using an Active Breathing Control Device in the Treatment of Patients with Left-Sided Breast Cancer Using External Beam Radiation Therapy. *International Journal of Radiation Oncology* Biology* Physics* 2003;56:704–715.
- [36]. Duane F, Aznar MC, Bartlett F, et al. A Cardiac Contouring Atlas for Radiotherapy. *Radiotherapy and Oncology* 2017;122:416–422. [PubMed: 28233564]
- [37]. Tran PV. A Fully Convolutional Neural Network for Cardiac Segmentation in Short-Axis MRI; 2016 Available at: <https://arxiv.org/abs/1604.00494>. Accessed Feb 1, 2018.

Radiation dose to sensitive cardiac substructures has been linked to cardiac toxicity. However, substructures cannot be adequately visualized on standard CT treatment planning scans. This work generated and validated a novel MR/CT atlas for cardiac substructure segmentation. High similarity to ground truth was achievable for the heart, great vessels, and chambers. Consensus scoring confirmed the clinical applicability of the segmentations. Overall, the atlas offers potential for cardiac sparing for treatment planning when MRI is unavailable.

Figure 1:
Left: Axial planning CT, axial T2-weighted MRI, and contoured axial T2-weighted MRI, shown at 4 different axial locations. Right: List of cardiac substructures assessed in this study.

Figure 2:

Validation patient Dice Similarity Coefficient (DSC) results over all substructures (Left) and all high performing substructures (i.e. heart, cardiac chambers, and great vessels) (Right). Boxplots and line indicate the interquartile range (IQR) and median, respectively. Whiskers indicate the minimum and maximum, with data points >1.5 times the IQR and >3 times the IQR marked by circles and stars, respectively.

Figure 3:
Mean distance to agreement (MDA) (Left) and Dice similarity coefficient (DSC) (Right) between ground truth and ST10 contours for all delineated substructures ($n = 11$). Error bars represent the standard error of the mean.

Figure 4:

Three-dimensional rendering of substructures showing agreement between manually drawn ground truth (GT) contours and STAPLE 10 (ST) generated contours.

Figure 5:

Left: Axial cross section of a treatment planning CT for a representative validation patient showing contours generated from STAPLE 10 (ST10) and ground truth, as well as percentage dose delivered to the left breast (substructure colors not represented in the dose volume histogram (DVH): Dark Blue-RA, Denim Blue-RA_ST10, Pink-RV, Magenta-RV_ST10). Right: Corresponding DVH for the same validation patient.

Table 1:

Mean and standard deviation (SD) results for select atlas methods showing the Dice Similarity Coefficient (DSC) per substructure and across all high performing substructures for the validation population (heart, chambers, and great vessels). Consensus scores from physician grading of the STAPLE 10 (ST10) method are also shown. Abbreviations defined in text.

	DSC from Atlas Application			Consensus Score
	Single	MV10	ST10	ST10
Per Structure Mean $\pm$ SD				
Heart	0.92 $\pm$ 0.03	0.94 $\pm$ 0.01	0.95 $\pm$ 0.01	4.2 $\pm$ 0.4
Left Ventricle	0.83 $\pm$ 0.04	0.88 $\pm$ 0.01	0.91 $\pm$ 0.01	4.6 $\pm$ 0.5
Right Atrium	0.80 $\pm$ 0.05	0.84 $\pm$ 0.04	0.87 $\pm$ 0.03	4.2 $\pm$ 0.4
Left Atrium	0.77 $\pm$ 0.03	0.84 $\pm$ 0.03	0.86 $\pm$ 0.03	3.8 $\pm$ 0.4
Pulmonary Artery	0.74 $\pm$ 0.07	0.81 $\pm$ 0.03	0.84 $\pm$ 0.03	4.0 $\pm$ 0.0
Ascending Aorta	0.73 $\pm$ 0.09	0.79 $\pm$ 0.07	0.84 $\pm$ 0.03	4.4 $\pm$ 0.5
Right Ventricle	0.71 $\pm$ 0.06	0.80 $\pm$ 0.05	0.83 $\pm$ 0.03	4.2 $\pm$ 0.4
Superior VC	0.67 $\pm$ 0.09	0.66 $\pm$ 0.08	0.80 $\pm$ 0.04	4.0 $\pm$ 0.7
Inferior VC	0.46 $\pm$ 0.23	0.55 $\pm$ 0.11	0.70 $\pm$ 0.07	4.0 $\pm$ 0.7
Pulmonary Vein	0.47 $\pm$ 0.13	0.50 $\pm$ 0.06	0.64 $\pm$ 0.06	3.2 $\pm$ 0.4
Average over Heart, Chambers, and Great Vessels	0.71 $\pm$ 0.08	0.76 $\pm$ 0.05	0.82 $\pm$ 0.03	4.1 $\pm$ 0.5
LAD Artery	0.15 $\pm$ 0.14	0.04 $\pm$ 0.04	0.27 $\pm$ 0.09	1.8 $\pm$ 0.8
RT Cor. Art.	0.14 $\pm$ 0.10	0.03 $\pm$ 0.05	0.22 $\pm$ 0.10	2.4 $\pm$ 0.9
LT Main Cor. Art.	0.05 $\pm$ 0.08	0.00 $\pm$ 0.00	0.12 $\pm$ 0.12	1.4 $\pm$ 0.5