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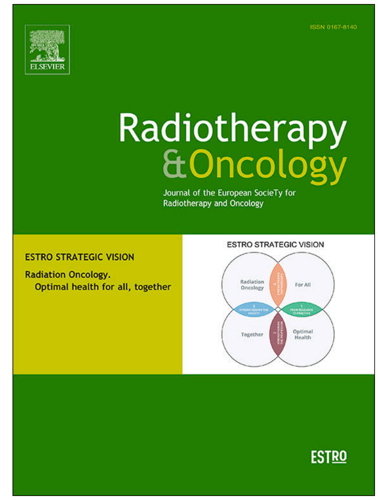

Refining Critical Structure Contouring in STereotactic Arrhythmia Radioablation (STAR): Benchmark Results and Consensus Guidelines from the STOPSTORM.eu Consortium

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Refining Critical Structure Contouring in STereotactic Arrhythmia Radioablation (STAR): Benchmark Results and Consensus Guidelines from the STOPSTORM.eu Consortium.

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Highlights

- STOPSTORM aims to standardise contouring of organs at risk (OAR) for STereotactic Arrhythmia Radioablation (STAR).
- 20 centres were accredited after delineating 31 OAR in 3 STAR cases and receiving expert feedback.
- Delineations for common radiotherapy OAR were similar, but deviations occurred for cardiac substructures.
- Guidelines for STAR OAR contouring were issued to harmonise treatment planning and dosimetry evaluation.
- Harmonisation is important as deviations in contouring can significantly impact STAR treatment.

Abstract

Background and purpose

In patients with recurrent ventricular tachycardia (VT), STereotactic Arrhythmia Radioablation (STAR) shows promising results. The STOPSTORM consortium was established to investigate and harmonise STAR treatment in Europe. The primary goals of this benchmark study were to standardise contouring of organs at risk (OAR) for STAR, including detailed substructures of the heart, and accredit each participating centre.

Materials and Methods

Centres within the STOPSTORM consortium were asked to delineate 31 OAR in three STAR cases. Delineation was reviewed by the consortium expert panel and after a dedicated workshop feedback and accreditation was provided to all participants. Further quantitative analysis was performed by calculating DICE similarity coefficients (DSC), median distance to agreement (MDA), and 95th percentile distance to agreement (HD95).

Results

Twenty centres participated in this study. Based on DSC, MDA and HD95, the delineations of well-known OAR in radiotherapy were similar, such as lungs (median DSC=0.96, median MDA=0.1mm and median HD95=1.1mm) and aorta (median DSC=0.90, median MDA=0.1mm and median HD95=1.5mm). Some centres did not include the gastro-oesophageal junction, leading to differences in stomach and oesophagus delineations. For cardiac substructures, such as chambers (median DSC=0.83, median MDA=0.2mm and median HD95=0.5mm), valves (median DSC=0.16, median MDA=4.6mm and median HD95=16.0mm), coronary arteries (median DSC=0.4, median MDA=0.7mm and median HD95=8.3mm) and the sinoatrial and atrioventricular nodes (median DSC=0.29, median MDA=4.4mm and median HD95=11.4mm), deviations between centres occurred more frequently. After the dedicated workshop all centres were accredited and contouring consensus guidelines for STAR were established.

Conclusion

This STOPSTORM multi-centre critical structure contouring benchmark study showed high agreement for standard radiotherapy OAR. However, for cardiac substructures larger disagreement in contouring occurred, which may have significant impact on STAR treatment planning and dosimetry evaluation.

To standardize OAR contouring, consensus guidelines for critical structure contouring in STAR were established.

Keywords: STOPSTORM consortium, STereotactic Arrhythmia Radioablation (STAR), Stereotactic Body Radiotherapy (SBRT), ventricular tachycardia (VT), contouring benchmark, organs at risk (OAR), cardiac substructures

Introduction

Ventricular tachycardia (VT), which can lead to sudden death, is a malignant cardiac arrhythmia arising mostly from structural heart disease.(1, 2) Patients at high risk for (recurrent) VT receive an implantable cardioverter defibrillator (ICD) which can detect arrhythmias and terminate VT by means of anti-tachycardia pacing (ATP) or defibrillation shocks.(3, 4) However, this does not prevent VT occurrence, for which antiarrhythmic and cardio-protective drugs are prescribed, and catheter ablation may be performed to localise the pro-arrhythmic regions and disrupt the underlying arrhythmogenic substrate. While antiarrhythmic drugs and catheter ablation can result in long-term control of VT episodes, they may be associated with a significant risk of complications and unsatisfactory VT control in 20-50% of the patients requiring repeat procedures, while some patients continue to have recurrent VTs despite all treatments.(2, 3)

Recently STereotactic Arrhythmia Radioablation (STAR) showed promising results for patients with refractory VT with limited treatment options.(5-10) A single radiotherapy fraction of 25 Gy was administered to the pro-arrhythmic ventricular region with the use of current stereotactic body radiotherapy (SBRT) techniques as routinely performed for different types of cancer.(11, 12) A systematic review for STAR showed a reduction of >85% in VT episodes with a simultaneously promising safety profile in more than 40 patients (13) and many more patients have been treated until now.(14-16) Since most patients treated by STAR do not have any other treatment options these impressive results appear clinically relevant with respect to quality of life, morbidity and mortality.(1, 2)

Reported outcomes after STAR are based on heterogeneous patient cohorts and each clinical study has different inclusion criteria and treatment procedures with various imaging and/or target definition techniques.(17) The complexity of STAR with regard to VT substrate identification by electroanatomic mapping (EAM) during ablation procedure, target volume delineation, cardiac and respiratory motion management, and the application of a high dose single fraction irradiation require high-quality standards for optimal safety and efficacy of this novel treatment.(17, 18)

Since STAR is still performed infrequently in each institution, the EU-funded Standardised Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary (STOPSTORM) consortium was established (EU-Horizon-2020 GA No. 945119).(18) The aim of the consortium is to establish a pooled database within Europe to evaluate the efficacy and safety of this novel treatment and to eventually optimise and harmonise STAR. The STOPSTORM consortium is made of 24 electrophysiology and 22 radiotherapy departments from 31 clinical and research institutes in Europe and is accompanied by several work packages within the scope of its project.(18)

To optimise, harmonise and standardise STAR within the STOPSTORM consortium, a comprehensive quality assurance (QA) programme including benchmark studies was developed. Herein, we report on the results of the critical structure contouring benchmark study which was part of the accreditation process for the consortium member institutions. Besides accreditation, the primary goal of this benchmark was to harmonise contouring of organs at risk (OAR) relevant for STAR which includes commonly used OAR in thoracic SBRT but also several cardiac substructures. Furthermore, the benchmark results were used to provide a critical structure contouring consensus guideline for STAR to refine and standardise future clinical (trial) protocols.

Materials and Methods

Detailed background and project descriptions of the STOPSTORM consortium have been published previously.(18) As part of STOPSTORM and covered by the approval of the institutional ethics committee of the lead institution for the quality assurance work package (UKSH Kiel, D483/21), benchmark establishment of critical structure contouring and treatment planning was intended per project protocol. For the contouring benchmark, an interdisciplinary expert panel (5 from radiation oncology, 1 from cardiology and 1 from cardiac radiology) within the STOPSTORM consortium was formed based on clinical experience on STAR and on cardiac substructure contouring.

Benchmark Data

Three STAR benchmark cases previously used for a national multi-centre trial were selected for the STOPSTORM contouring benchmark after expert panel database review for suitable cases. The patients had sustained VT and were treated off-label with STAR as previously described in greater detail.(19-23) All patients were treated in supine position with no specific diet prior to treatment. For STAR treatment, national guidelines on SBRT were followed (11, 12) and thin-slice planning CTs (1.5–2.0 mm) were deformably co-registered with contrast-enhanced, ECG-triggered cardiac CTs in end diastole (18), which were provided to all participants after data anonymization in the treating centre.

OAR Contouring

Between June and September 2021, each STOPSTORM consortium radiation oncology centre had to delineate 31 different OAR according to literature-based guidelines for all three benchmark cases.(24-29) This set of OAR consisted of well-known structures for radiation oncology departments (e.g., lungs, stomach, oesophagus, proximal bronchial tree, great vessels and spinal canal), but also less familiar cardiac substructures (e.g., chambers and valves, sub-segments of the left ventricle, coronary arteries and sinoatrial and atrioventricular nodes). While radiation oncologists primarily conducted delineation, participants were encouraged to collaborate with internal cardiologists and cardio-radiologists.

Data Analysis

Contoured OAR were sent to the lead benchmark centre and imported into Velocity (Version 4.1, Varian Medical Systems, Palo Alto, USA) for further analysis. Some serial OAR (e.g., oesophagus, aorta) had to be trimmed down to 4 cm below the diaphragm and cranially up to the aortic arch in some cases to enable a harmonised analysis. The expert panel reviewed all delineations of the participating centres and detailed feedback was provided to decrease the contouring variability for future STAR treatments within the STOPMSTORM consortium. (30)

Further quantitative analysis was performed by calculating the DICE similarity coefficients (DSC) of every combination of two contours for each OAR. A DSC of 0 indicates no overlap in volumes, whilst a value of 1 indicates complete overlap. For the calculation of the Dice Similarity Coefficient (DSC), structure sets were imported in RayStation 9A (RaySearch). A built-in method in the scripting interface was used to calculate the DSC of two structures.

Since DSC only provides data on overlap, small structures are more prone to have a smaller DSC compared to larger volumes. Therefore, the median distance to agreement (MDA) between structures was also calculated. As a measure for the maximum distance to agreement, the 95th percentile distance to agreement (HD95) was calculated, instead of the Hausdorff distance (HD), which is the true maximum distance to agreement. The HD95, which can be thought of as the near-maximum distance to agreement between two structures, is less sensitive to outliers than the HD, because the 5% outliers are not considered.(31) For both HD95 and MDA lower values indicate a higher correspondence between two structures. For the calculation of the Distance to Agreement (DTA) of two structures the python library “trimesh” (version 3.10.7, https://trimsh.org) was used. The points in space that describe the delineated contours of a structure were converted to a mesh. The distances of all points of structure A to the surface of the mesh of structure B, and the other way around, were collected in an array and sorted. The symmetric Median Distance to Agreement (MDA) and the 95th percentile symmetric distance to agreement (HD95) were extracted from the sorted array.

Statistical Analysis

For each structure and each similarity measure (i.e., DSC, MDA, and HD95) the median mean, standard deviation (SD), lower quartile (Q1, 25% percentile) and upper quartile (Q3, 75% percentile) were calculated for all combinations of each two contours using R.(32)

Results

Twenty radiation oncology centres participating in STOPSTORM delineated all 31 structures for the provided three benchmark cases. Seven centres with no prior STAR cases, 7 with 1-3 STAR cases, and 6 with >3 STAR cases. Most centres had extensive SBRT experience (>10 years), with 11 treating >200 cases/year and the rest 50-200 cases/year. Detailed results of the median DSC, MDA and HD95 for several OAR are provided in Table 1 and 2. For each OAR the median, mean, SD, Q1 and Q3 for DSC, MDA and HD95 are provided in Supplementary File 1.

For thoracic and abdominal OAR, the spinal canal (median DSC 0.82, median MDA 0.1 mm and median HD95 1.9 mm), aorta (median DSC 0.90, median MDA 0.1 mm and median HD95 1.5 mm) and lungs (median DSC 0.96, median MDA 0.1 mm and median HD95 1.1 mm) were delineated with small variety between centres. Delineation of the proximal bronchial tree (median DSC 0.58, median MDA 0.3 mm and median HD95 16.5 mm), oesophagus (median DSC 0.75, median MDA 0.1 mm and median HD95 3.3 mm) and stomach (median DSC 0.78, median MDA 0.3 mm and median HD95 17.0 mm) showed some deviation. For the proximal bronchial tree differences in endpoint were seen between centres (first or second bifurcation) Differences in delineations of the stomach and oesophagus were observed, which mainly concerned the gastro-oesophageal junction (GEJ). Some centres delineated this as part of the oesophagus according to the guidelines, whereas others delineated it as part of the stomach. A few centres did not include the GEJ at all (Figure 1).

The whole heart was delineated by all centres with a median DSC of 0.93, median MDA of 0.3 mm and median HD95 of 4.4 mm. The four different chambers (right/left atrium and right/left ventricle) showed large overlap between the different centres with a median DSC of 0.87, a median MDA of 0.2 mm and a median HD95 of 3.7 mm. Some differences for the left atrium were noticed because some centres left out the left auricle.

All centres delineated approximately 5 cm of the right coronary artery (RCA), left main coronary artery (LM), left anterior descending artery (LAD) and the left circumflex artery (LCX) starting from their origin. Although a contrast-enhanced CT was provided, a lot of differences in delineations were seen between the different centres (Figure 2). This resulted in a low median DSC of 0.40 for all arteries combined. Although the median MDA was low (0.7 mm), the HD95 appeared larger (8.3 mm).

Delineation of the four different valves of the heart (pulmonic valve, aortic valve, mitral valve, and tricuspid valve) showed large deviations between centres (Figure 3) resulting in a low median DSC of 0.16 and a large median MDA and HD95 of respectively 4.6 mm and 16.5 mm. The results for the area of the sinoatrial node (SAN) and for the area of the atrioventricular node (AVN) as described by Loap et al(28) showed only small overlap between centres (Figure 4). These nodes had a median DSC of 0.29, median MDA of 4.4 mm and a median HD95 of 11.4 mm. For the left ventricle, septal, inferior, lateral, and anterior walls had to be contoured separately. These substructures showed larger deviations between centres with a median DSC of 0.43, a median MDA of 0.5 mm and a median HD95 of 12.5 mm.

After a dedicated workshop in November 2021 for STAR OAR contouring and detailed feedback and discussion (with re-delineation training on a one-on-one basis), accreditation was granted to these centres. Additionally, the STOPSTORM credentialing and audit committee consisting of 2 radiation oncologists, 2 cardiologist, 2 medical physicist and 1 cardiac radiologist monitored this process. Based on the results obtained critical structure contouring consensus guidelines for STAR were formulated, which can be found in Supplementary File 2 in greater detail.

Discussion

The STOPSTORM consortium has established an accreditation program for STAR treatment in Europe. As part of this program, the consortium conducted the first multicentre benchmark study on OAR contouring for STAR, which demonstrated high agreement among experienced centres for standard radiotherapy OAR. However, the study also revealed disagreement in contouring for cardiac substructures, highlighting the need for standardisation in this area. To address this, the consortium established consensus guidelines for critical structure contouring in STAR based on the results of the presented benchmark study. These guidelines represent a significant step towards harmonising OAR contouring and improving the quality and consistency of STAR treatment.

Without harmonised delineation of cardiac substructures and ventricular segments, intra-cardiac vessels, valves, nodes, and OAR in the vicinity, the future evaluation of dose effects on critical structures will be impossible for STAR. As a first step of the STOPSTORM project, we harmonised the delineation of OAR. Overall, 20 centres delineated 31 different OAR for three STAR cases for this benchmark study, the first study of its kind.

Contouring of extra-cardiac OAR is a clinical routine for most radiation oncologists and their teams. Several guidelines and benchmarks exist for thoracic and abdominal organs (26, 27) and hence it is not surprising that we also found large consensus on contouring between the various centres. However, the gastro-oesophageal-junction was not delineated completely by some centres which can be critical for STAR as the oesophagus and stomach are highly radiosensitive and are situated near the heart. One of the provided cases had large artefacts within this area due to the presence of a left ventricle assist device (LVAD), which does make delineation complicated, but missing delineations were also found in the other cases. Most STAR protocols use strict dose constraints of 14 Gy or lower for oesophagus and stomach (16, 19, 33), since severe toxicity including life-threatening fistulas has already been reported in rare cases with target locations in close proximity.(34, 35)

Also, for cardiac substructures, several contouring guidelines have been published and several smaller inter-observer studies have been performed. (24, 25, 28, 29, 36-38) The dose to cardiac substructures becomes more important for conventional and hypo-fractionated thoracic and breast radiotherapy, since previous studies already demonstrated dose-effect relationships on the heart for long term cardiac toxicity.(39-44) However, most data originated from conventional fractionated schedules and in combination with chemotherapy with toxicity arising 10-20 years later. The precise effects of high fraction dose on cardiac substructures like ventricular and atrial walls, arteries, valves, and conduction systems are not well understood. Although patients eligible for STAR cannot be compared to long term survivors after radiotherapy for lymphomas, breast, early-stage lung and childhood cancer, because of their low life expectancy due to underlying heart failure, contouring different cardiac substructures will nevertheless be essential to study long-term effects of high single fraction doses to the heart.

Although we found larger consensus for the delineation of heart and its chambers in our benchmark study, the delineation of the substructures (e.g., arteries, valves, and nodes) revealed larger disagreement between different centres. There are several important limitations to consider when interpreting these findings. Our study highlights the potential impact of variability in contouring expertise across different centres on the accuracy and reproducibility of the delineations for STAR. Additionally, the small sample size and limited variability in organ shape and image quality may further limit the generalizability of the findings to broader patient populations. Nonetheless, our study underscores the importance of standardizing contouring protocols, providing adequate training and carefully monitoring the contouring process to ensure accuracy and consistency across all centres. Also optimizing CT-protocols for visualization of cardiac substructures should be further explored.(45) For those centres in the STOPSTORM consortium with limited STAR experience, we provided detailed feedback and training within our quality assurance and accreditation program to enhance the quality of the treatment and the analysis of the pooled database. For new centres seeking to start a clinical STAR program we are providing a critical structure contouring consensus guideline to enhance a safe and effective start with the novel treatment, provided in Supplementary File 2.

In any event, to increase the conformity of cardiac substructure contouring, a combined effort of radiation oncologists, cardiac electrophysiologists and cardio-radiologist is strongly mandated. More recently, whole organ OAR auto-contouring with the help of artificial intelligence (AI) has been explored (46-48) which also may further reduce differences in contouring for STAR. Importantly, arrhythmogenic volumes can be displayed using the American Heart Association 17-segment model for the left ventricle and efforts have been made to auto-contour these segments on the radiotherapy planning-CT.(49) Already, first steps into auto-segmentation for the delineation of cardiac substructures have been made (47, 50) and joint efforts will be made within the STOPSTORM consortium to enhance AI auto-segmentation based on the pooled STAR database.

Conclusion

In summary, we conclude that although specific guidelines and contouring atlases were already provided prior to this benchmark study, the delineation of cardiac substructures still show lower conformity between centres as compared to other thoracic organs. This led to further refinement of the STOPSTORM contouring guidelines and the provision of essential feedback to each consortium member as a means for quality assurance during the accreditation process. Further studies within the STOMSTORM project are warranted to validate the promised increased conformity for the delineation of OAR for STAR.

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Author Statement

BB and OB designed and BB, OB and MG coordinated the critical structure contouring benchmark study and drafted the paper. BB, OB, MG, MK, DR and ML developed the critical structure contouring guidelines. MK, DR, ML, PA, JB, SC, JC, ED, OE, NG, RJ, DK, ML, MM, FM, MM, MP, LP, PT, VV contoured all critical structures for their centre. BB and JV analysed the data. MB, PP and EP gave input to the manuscript as non-radiation oncologist. JJV and EP are the PI and Co-PI of the STOPSTORM consortium. All authors read and approved the manuscript.

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Declaration of Interest Statement:

The authors of this article declare no financial or personal interests that could influence the research or interpretation of the results presented in this manuscript. They have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no conflicts of interest to disclose.

Figure 1: Delineation of the gastro-oesophageal junction. In all 3 provided contouring cases (A, B and C) the gastro-oesophageal junction part was occasionally omitted by some centres in the delineation. (Green = oesophagus, Yellow = stomach)

Figure 2: Delineation of the different coronary arteries. Differences in delineation between the participating centres of the left main coronary artery (A), left anterior descending artery (B), the left circumflex artery (C) and the right coronary artery (D).

Figure 3: Delineation of the different valves of the heart. Differences in delineation between the participating centres of the aortic valve (A), pulmonic valve (B), mitral valve (C) and the tricuspid valve(D).

Figure 4: Delineation of the conducting nodes. Differences in delineation between the participating centres of the sinoatrial node (A) and atrioventricular node (B).

Table 1: Median values of DSC, MDA, and HD95 for the pooled substructures of the heart.

Substructures of the heart	DSC	MDA (mm)	HD95 (mm)
Heart	0.90	0.1	1.5
Chambers[a]	0.83	0.2	6.5

Coronary arteries[b]	0.72	0.3	8.0
Left ventricle walls[c]	0.58	0.3	16.5
Valves[d]	0.82	0.1	1.9
Nodes[e]	0.77	0.2	4.0

[a] includes the left ventricle, the right ventricle, the left atrium and right atrium
[b] includes the left main artery, the left circumflex artery. the left anterior descending artery and the right coronary artery
[c] includes the septal, inferior, lateral and anterior wall of the left ventricle
[d] includes the pulmonic, aortic, mitral and tricuspid valve
[e] includes the sinoatrial node and the atrioventricular node area
DSC = Dice similarity coefficient, MDA = Median distance to agreement, HD95 = 95th percentile distance to agreement

Table 2: Median values of DSC, MDA, and HD95 for the remaining organs at risk.

Organs at Risk	**DSC**	**MDA (mm)**	**HD95 (mm)**
Aorta	0.90	0.1	1.5
Pulmonary artery	0.83	0.2	6.5
Vena cava[a]	0.72	0.3	8.0
Proximal Bronchial Tree	0.58	0.3	16.5
Spinal canal	0.82	0.1	1.9
Trachea	0.77	0.2	4.0
Stomach	0.78	0.3	17.0
Oesophagus	0.75	0.1	3.3
Lungs	0.96	0.1	1.1
ICD can/generator	0.83	0.3	4.6

[a]includes the vena cava superior and inferior
DSC = Dice similarity coefficient, MDA = Median distance to agreement, HD95 = 95th percentile distance to agreement