Precision requirements in stereotactic arrhythmia radioablation for ventricular tachycardia

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Editorial

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The desire for high precision in stereotactic body radiotherapy (SBRT) is ingrained in the radiotherapy community, covering all the usual steps of a course of treatment [1–3]. However, increased precision often comes at the cost of increased complexity and resource consumption. At first glance, clinical outcomes after SBRT appear similar with either passive (internal target volume) or active (gating and tracking) motion management strategies, e.g., for peripheral lung tumours [4]. Upon closer scrutiny, differences in local tumour control and organ-at-risk doses, and thus potential toxicity between active and passive motion management strategies, can be observed for upper abdominal tumours where motion is generally more pronounced [5]. If treatment precision is strongly desired and active motion management such as tracking [6] or gating with breath hold [7,8] is unavailable or impractical, several options can be explored to enhance passive motion management strategies such as abdominal compression (AC) [8,9] and online plan adaptation [10,11]. Recently, lessons from SBRT of solid tumours have been translated into the cardiology realm to tackle another socioeconomic concerning disease, cardiac arrhythmias, by delivering SBRT to the heart in a novel treatment called STereotactic Arrhythmia Radioablation (STAR), also referred to as cardiac radioablation or cardiac SBRT. Given our prior knowledge from conventional SBRT, our current understanding of the radiosensitivity of the heart and the fact that the heart exhibits potentially the most complex motion in the human body, the required treatment precision for STAR is naturally an important consideration for the radiotherapy community.

In this volume of the journal, Mannerberg et al. [12] describe the potential use of AC as a motion management tool for STAR. Using a cohort of 18 lung cancer patients, the authors use 4D computed tomography to assess the utility of abdominal compression for decreasing the breathing component of the heart motion. A reduction of median respiratory heart motion of 1–3 mm in superior-inferior direction was observed with AC. This work contributes to our understanding of the suitability of applying oncology motion management techniques to STAR. In the wider context, this work also highlights questions such as what precision is required for STAR and how much effort we must we put into motion management.

Firstly, one must consider the clinical condition of patients being treated with STAR and their treatment alternatives. Ventricular tachycardia (VT) is a severe life-threatening cardiac arrhythmia condition arising mainly from structural heart disease [13]. Patients are primarily treated with antiarrhythmic drugs and often receive an implantable cardioverter defibrillator to detect and terminate the VT through antitachycardia pacing (ATP) or defibrillation shocks [13,14]. Invasive catheter ablation by means of endo- and/or epicardial localization and disruption of the underlying arrhythmogenic substrate is the standard of care for patients with refractory VT [15]. However, antiarrhythmic drugs and catheter ablation come with significant risks of pharmacological toxicities, procedure complications, and VT recurrences requiring repeat interventional procedures in 20–50 % of the patients [16]. Additionally, catheter ablation may suffer from limitations concerning the depth and accessibility of the targeted arrhythmogenic substrate. STAR has most commonly been used to treat patients with continued refractory VT and limited treatment options [17] and in systematic reviews and meta-analyses promising safety profiles and reductions of more than 85 % of the VT burden have been reported [18,19]. However, to date, STAR treatments have utilized varying technologies and methodologies [17–21], creating heterogeneous cohorts with potentially varying treatment delivery precision, making it difficult to fully understand the risk-safety profile of this new treatment. This highlights the need for a better understanding regarding the choice of optimal technology and methodology for this new and novel treatment and the desire for future technique harmonization and standardization [17].

The technical requirements for STAR treatments are very similar to routine lung SBRT but additional considerations are necessary; electroanatomical mapping and scar imaging are required for target volume definition [20,21], cardiac vital signs may need to be continuously monitored during treatment, and cardiac target motion must be appropriately managed [20,22]. The application of a single fraction radiotherapy dose to the arrhythmogenic substrate, generally following prescriptions of 25 Gy [17], is also very different from treating tumours from a radiobiological standpoint. Two main mechanisms, after high dose radiation in the heart, were identified in preclinical experiments: (1) vacuolization, fibrosis and necrosis after doses exceeding 30 Gy [23,24], and (2) protein changes due to notch activation resulting in increased conduction velocity [25,26]. Clinically, patients may respond to STAR within a few days showing no fibrosis in the treated area [25,27,28] or up to weeks and months later with small pathological lesions [29,30]. Further understanding of these complex interactions and variable treatment effects may eventually lead to different concepts and requirements for target definition, treatment planning and treatment precision. Interestingly, while STAR is showing promising clinical results in VT patients with structural heart damage, dose to the heart is otherwise minimized in thoracic radiotherapy as it is linked to cardiotoxicity and reduced survival in oncological cohorts [31,32].

Given the current uncertain radiobiology underpinning STAR treatments, the required treatment precision probably depends on the individual patient. Clinically, it is important to consider the treatment urgency (cardiac storm for an intubated patient vs. infrequent VT for an ambulatory patient), the patients' general condition (age, underlying

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heart disease, ejection fraction, lung function, comorbidities, etc.) and the size and location of the arrhythmogenic substrate especially with respect to serial risk organs like oesophagus and stomach, among other factors. Technically, this translates into varying precision requirements for target volume definition, motion management and treatment delivery. For target definition, the question arises what to specifically treat (e.g., the whole scar or only the precisely defined VT substrate) and what biological mechanism of STAR should be targeted. Inter-observer targeting agreement is consequently poor [33,34] and requirements for the necessary precision of TV contouring are therefore challenging to define. Nevertheless, our technical methods of transporting target concepts from the electrophysiology domain into the radiation oncology domain should be strictly within SBRT precision requirements [21,35,36].

For motion management and treatment delivery, several possibilities have been explored for STAR. To date, the most used motion management technique is the passive combined cardio-respiratory internal target volume approach [17,20]. Target motion is often smaller in VT patients than that observed in abdominothoracic SBRT due to their cardiac impairment and the often-fragile conditions that typically manifest through a low left-ventricular ejection fraction [22]. Simple and easily implemented motion mitigation techniques are therefore applicable in the patient population to whom STAR is currently most commonly being offered. AC can be considered to reduce respiratory motion, however patient compliance is often challenging, and extra cardiac critical structures might be pushed closer to the heart [37]. Furthermore, reductions in respiratory motion amplitudes through AC were generally small in VT patients [38] or surrogate cohorts [12] and assessment of AC suitability for individual patients is strongly advised. Again, it should be emphasised that surrogate cohorts that do not contain patients with an ischemic heart disease situation are prone to overestimating the impact of cardiorespiratory motion relative to currently treated VT patients. If STAR targets are close to critical structures and/or exhibit large motion, active respiratory motion management techniques such as gating, deep-inspiration breath-holds or tracking [20,29] may be necessary to achieve higher treatment delivery precision and targeting. Feasibility of respiratory gating based on cine MR imaging on a low field MR linear accelerator was tested on a single patient [39]. A reduction of the treated volume by more than a factor of two could be achieved. High-field MR-linac systems have shown their potential for enhanced STAR targeting utilizing cardiac MRI [40] as well as active cardiorespiratory motion mitigation through combinations of respiratory tracking and cardiac gating [41].

Treatment precision requirements and the need for more complex active motion management are thought to be higher in STAR treatments for atrial fibrillation (AF) than VT, likely contributing to the relatively lower clinical uptake and success of STAR for AF [42,43]. Reasons for this include the combination of target motion complexity, target motion magnitude and target proximity to critical structures [43], as well as differing antiarrhythmic radiobiology mechanisms and requirements, and the favourable life expectancy and health of the AF patient cohort [42]. The risk–benefit profile for treating benign AF with STAR therefore leans towards ensuring safety, particularly considering current knowledge gaps regarding treatment toxicities.

Currently there does not seem to be a simple answer regarding how precise STAR treatments must be. Required treatment precision and safety margins for STAR depend on many different variables including clinical goals and target characteristics and there are also many unknowns and knowledge gaps, substantiating important future research opportunities in this field. Whilst high precision is desired in STAR, the patient's clinical condition, prognosis and alternative treatment options is perhaps currently a more important factor when making treatment protocol and motion management choices for this new treatment technique.

Declaration of Competing Interest

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References

[1] Guckenberger M, Andratschke N, Dieckmann K, Hoogeman MS, Hoyer M, Hurkmans C, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol 2017;124:11–7. https://doi.org/10.1016/j.radonc.2017.05.012.

[2] Guckenberger M, Baus WW, Blanck O, Combs SE, Debus J, Engenhart-Cabillic R, et al. Definition and quality requirements for stereotactic radiotherapy: consensus statement from the DEGRO/DGMP Working Group Stereotactic Radiotherapy and Radiosurgery. Strahlenther Onkol 2020;196:417–20. https://doi.org/10.1007/s00066-020-01603-1.

[3] Chao ST, Dad LK, Dawson LA, Desai NB, Pacella M, Rengan R, et al. ACR-ASTRO practice parameter for the performance of stereotactic body radiation therapy. Am J Clin Oncol 2020;43:545–52. https://doi.org/10.1097/COC.0000000000000706.

[4] Rieber J, Abbassi-Senger N, Adebahr S, Andratschke N, Blanck O, Duma M, et al. Influence of institutional experience and technological advances on outcome of stereotactic body radiation therapy for oligometastatic lung disease. Int J Radiat Oncol Biol Phys 2017;98:511–20. https://doi.org/10.1016/j.ijrobp.2016.09.026.

[5] Andratschke N, Alheid H, Allgäuer M, Becker G, Blanck O, Boda-Heggemann J, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer 2018;18:283. https://doi.org/10.1186/s12885-018-4191-2.

[6] Keall PJ, Sawant A, Berbeco RI, Booth JT, Cho B, Cerviño LI, et al. AAPM Task Group 264: The safe clinical implementation of MLC tracking in radiotherapy. Med Phys 2021;48:e44–64. https://doi.org/10.1002/mp.14625.

[7] Aznar MC, Carrasco de Fez P, Corradini S, Mast M, McNair H, Meattini I, et al. ESTRO-ACROP guideline: Recommendations on implementation of breath-hold techniques in radiotherapy. Radiother Oncol 2023;185:109734. https://doi.org/10.1016/j.radonc.2023.109734.

[8] Hardcastle N, Gaudreault M, Yeo AU, Ungureanu E, Markham C, Barnes R, et al. Selection of motion management in liver stereotactic body radiotherapy and its impact on treatment time. Phys Imaging Radiat Oncol 2023;25:100407. https://doi.org/10.1016/j.phro.2022.12.004.

[9] Tyagi N, Liang J, Burleson S, Subashi E, Godoy Scripes P, Tringale KR, et al. Feasibility of ablative stereotactic body radiation therapy of pancreas cancer patients on a 1.5 Tesla magnetic resonance-linac system using abdominal compression. Phys Imaging. Radiat Oncol 2021;19:53–9. https://doi.org/10.1016/j.phro.2021.07.006.

[10] Milder MTW, Magallon-Baro A, den Toom W, de Klerck E, Luthart L, Nuyttens JJ, et al. Technical feasibility of online adaptive stereotactic treatments in the abdomen on a robotic radiosurgery system. Phys Imaging Radiat Oncol 2022;23:103–8. https://doi.org/10.1016/j.phro.2022.07.005.

[11] Winkel D, Bol GH, Kroon PS, van Asselen B, Hackett SS, Werensteijn-Honingh AM, et al. Adaptive radiotherapy: The Elekta Unity MR-linac concept. Clin Transl Radiat Oncol 2019;18:54–9. https://doi.org/10.1016/j.ctro.2019.04.001.

[12] Mannerberg A, Nilsson MP, Edvardsson A, Karlsson K, Ceberg S. Abdominal compression as motion management for stereotactic radiotherapy of ventricular tachycardia. Phys Imaging Radiat Oncol 2023;28:100499. https://doi.org/10.1016/j.phro.2023.100499.

[13] Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022;43:3997–4126. https://doi.org/10.1093/eurheartj/ehac262.

[14] Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. J Am Coll Cardiol 2018;72:e91–220. https://doi.org/10.1016/j.jacc.2017.10.054.

[15] Natale A, Zeppenfeld K, Della Bella P, Liu X, Sabbag A, Santangeli P, et al. Twenty-five years of catheter ablation of ventricular tachycardia: a look back and a look forward. Europace 2023;25. https://doi.org/10.1093/europace/euad225.
[16] Fernandez-Armenta J, Soto-Iglesias D, Silva E, Penela D, Jáuregui B, Linhart M, et al. Safety and outcomes of ventricular tachycardia substrate ablation during sinus rhythm: A prospective multicenter registry. JACC Clin Electrophysiol 2020;6:1435–48. https://doi.org/10.1016/j.jacep.2020.07.028.
[17] Grehn M, Mandija S, Miszczyk M, Krug D, Tomasik B, Stickney KE, et al. STereotactic Arrhythmia Radioablation (STAR): the Standardized Treatment and Outcome Platform for Stereotactic Therapy Of Re-entrant tachycardia by a Multidisciplinary consortium (STOPSTORM.eu) and review of current patterns of STAR practice in Europe. Europace 2023;25:1284–95. https://doi.org/10.1093/europace/euac238.
[18] van der Ree MH, Blanck O, Limpens J, Lee CH, Balgobind BV, Dieleman EM, et al. Cardiac radioablation—A systematic review. Heart rhythm 2022;17:1381–92. https://doi.org/10.1016/j.hrthm.2020.03.013.
[19] Viani GA, Gouveia AG, Pavoni JF, Louie AV, Detsky J, Spratt DE, et al. A Meta-analysis of the Efficacy and Safety of Stereotactic Arrhythmia Radioablation (STAR) in Patients with Refractory Ventricular Tachycardia. Clin Oncol (R Coll Radiol) 2023;35:611–20. https://doi.org/10.1016/j.clon.2023.04.004.
[20] Lydiard S, Blanck O, Hugo G, O'Brien R, Keall P. A review of cardiac radioablation (CR) for arrhythmias: procedures, technology, and future opportunities. Int J Radiat Oncol Biol Phys 2021;109:783–800. https://doi.org/10.1016/j.ijrobp.2020.10.036.
[21] Mayinger M, Boda-Heggemann J, Mehrhof F, Krug D, Hohmann S, Xie J, et al. Quality assurance process within the RAdiosurgery for VENtricular TAchycardia (RAVENTA) trial for the fusion of electroanatomical mapping and radiotherapy planning imaging data in cardiac radioablation. Phys Imaging Radiat Oncol 2023;25:100406. https://doi.org/10.1016/j.phro.2022.12.003.
[22] Stevens RRF, Hazelaar C, Fast MF, Mandija S, Grehn M, Cvek J, et al. Stereotactic Arrhythmia Radioablation (STAR): Assessment of cardiac and respiratory heart motion in ventricular tachycardia patients - A STOPSTORM.eu consortium review. Radiother Oncol 2023;188:109844. https://doi.org/10.1016/j.radonc.2023.109844.
[23] Blanck O, Bode F, Gebhard M, Hunold P, Brandt S, Bruder R, et al. Dose-escalation study for cardiac radiosurgery in a porcine model. Int J Radiat Oncol Biol Phys 2014;89:590–8. https://doi.org/10.1016/j.ijrobp.2014.02.036.
[24] Kim JS, Choi SW, Park Y-G, Kim SJ, Choi CH, Cha M-J, et al. Impact of high-dose irradiation on human iPSC-derived cardiomyocytes using multi-electrode arrays: implications for the antiarrhythmic effects of cardiac radioablation. Int J Mol Sci 2021;23. https://doi.org/10.3390/ijms23010351.
[25] Zhang DM, Navara R, Yin T, Szymanski J, Goldsztejn U, Kenkel C, et al. Cardiac radiotherapy induces electrical conduction reprogramming in the absence of transmural fibrosis. Nat Commun 2021;12:5558. https://doi.org/10.1038/s41467-021-25730-0.
[26] Blanck O, Boda-Heggemann J, Hohmann S, Mehrhof F, Krug D. Cardiac stereotactic radiotherapy induces electrical conduction reprogramming. Strahlenther Onkol 2022;198:209–11. https://doi.org/10.1007/s00066-021-01891-1.
[27] Knutson NC, Samson PP, Hugo GD, Goddu SM, Reynoso FJ, Kavanaugh JA, et al. Radiation therapy workflow and dosimetric analysis from a phase 1/2 trial of noninvasive cardiac radioablation for ventricular tachycardia. Int J Radiat Oncol Biol Phys 2019;104:1114–23. https://doi.org/10.1016/j.ijrobp.2019.04.005.
[28] Miszczyk M, Sajdok M, Nożyński J, Cybulska M, Bednarek J, Jadczyk T, et al. Histopathological examination of an explanted heart in a long-term responder to cardiac stereotactic body radiotherapy (STereotactic Arrhythmia Radioablation). Front Cardiovasc Med 2022;9:919823. https://doi.org/10.3389/fcvm.2022.919823.
[29] Neuwirth R, Cvek J, Knybel L, Jiravsky O, Molenda L, Kodaj M, et al. Stereotactic radiosurgery for ablation of ventricular tachycardia. Europace 2019;21:1088–95. https://doi.org/10.1093/europace/euz133.
[30] Kučera T, Jedličková K, Šramko M, Peichl P, Cvek J, Knybel L, et al. Inflammation and fibrosis characterize different stages of myocardial remodeling in patients after stereotactic body radiotherapy of ventricular myocardium for recurrent ventricular tachycardia. Cardiovasc Pathol 2023;62:107488. https://doi.org/10.1016/j.carpath.2022.107488.
[31] Taylor CW, Kirby AM. Cardiac side-effects from breast cancer radiotherapy. Clin Oncol (R Coll Radiol) 2015;27:621–9. https://doi.org/10.1016/j.clon.2015.06.007.
[32] Banfill K, Giuliani M, Aznar M, Franks K, McWilliam A, Schmitt M, et al. Cardiac toxicity of thoracic radiotherapy: existing evidence and future directions. J Thorac Oncol 2021;16:216–27. https://doi.org/10.1016/j.jtho.2020.11.002.
[33] Boda-Heggemann J, Blanck O, Mehrhof F, Ernst F, Buergy D, Fleckenstein J, et al. Interdisciplinary clinical target volume generation for cardiac radioablation: multicenter benchmarking for the radiosurgery for ventricular tachycardia (RAVENTA) trial. Int J Radiat Oncol Biol Phys 2021;110:745–56. https://doi.org/10.1016/j.ijrobp.2021.01.028.
[34] van der Ree MH, Cuculich PS, van Herk M, Hugo GD, Balt JC, Bates M, et al. Interobserver variability in target definition for stereotactic arrhythmia radioablation. Front Cardiovasc Med 2023;10:1267800. https://doi.org/10.3389/fcvm.2023.1267800.
[35] Abdel-Kafi S, Sramko M, Omara S, de Riva M, Cvek J, Peichl P, et al. Accuracy of electroanatomical mapping-guided cardiac radiotherapy for ventricular tachycardia: pitfalls and solutions. Europace 2021;23:1989–97. https://doi.org/10.1093/europace/euab195.
[36] van der Ree MH, Visser J, Planken RN, Dieleman EMT, Boekholdt SM, Balgobind BV, et al. Standardizing the cardiac radioablation targeting workflow: enabling semi-automated angulation and segmentation of the heart according to the American Heart Association Segmented Model. Adv Radiat Oncol 2022;7:100928. https://doi.org/10.1016/j.adro.2022.100928.
[37] Daly M, McWilliam A, Radhakrishna G, Choudhury A, Eccles CL. Radiotherapy respiratory motion management in hepatobiliary and pancreatic malignancies: a systematic review of patient factors influencing effectiveness of motion reduction with abdominal compression. Acta Oncol 2022;61:833–41. https://doi.org/10.1080/0284186X.2022.2073186.
[38] Prusator MT, Samson P, Cammin J, Robinson C, Cuculich P, Knutson NC, et al. Evaluation of motion compensation methods for noninvasive cardiac radioablation of ventricular tachycardia. Int J Radiat Oncol Biol Phys 2021;111:1023–32. https://doi.org/10.1016/j.ijrobp.2021.06.035.
[39] Mayinger M, Kovacs B, Tanadini-Lang S, Ehrbar S, Wilke L, Chamberlain M, et al. First magnetic resonance imaging-guided cardiac radioablation of sustained ventricular tachycardia. Radiother Oncol 2020;152:203–7. https://doi.org/10.1016/j.radonc.2020.01.008.
[40] Akdag O, Mandija S, van Lier A, Borman PTS, Schakel T, Alberts E, et al. Feasibility of cardiac-synchronized quantitative T1 and T2 mapping on a hybrid 1.5 Tesla magnetic resonance imaging and linear accelerator system. Phys Imaging Radiat Oncol 2022;21:153–9. https://doi.org/10.1016/j.phro.2022.02.017.
[41] Akdag O, Borman PTS, Woodhead P, Uijtewaal P, Mandija S, Van Asselen B, et al. First experimental exploration of real-time cardiorespiratory motion management for future stereotactic arrhythmia radioablation treatments on the MR-linac. Phys Med Biol 2022;67. https://doi.org/10.1088/1361-6560/ac5717.
[42] Franzetti J, Volpe S, Catto V, Conte E, Piccolo C, Pepa M, et al. Stereotactic radiotherapy ablation and atrial fibrillation: technical issues and clinical expectations derived from a systematic review. Front Cardiovasc Med 2022;9. https://doi.org/10.3389/fcvm.2022.849201.
[43] Lydiard S, Pontré B, Lowe BS, Ball H, Sasso G, Keall P. Cardiac radioablation for atrial fibrillation: Target motion characterization and treatment delivery considerations. Med Phys 2021;48:931–41. https://doi.org/10.1002/mp.14661.

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