Clinical Outcomes after Noninvasive Cardiac Radioablation for Ventricular Tachycardia (VT)

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Disclosures

• **Employer**: Washington University
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• **Consulting**: Varian, AstraZeneca, EMD Serono
• **Speaking**: Varian, ViewRay

• Results discussed here involve off-label use of linear accelerators outside of their current 510(k) intended use
Background

TOP TWO KILLERS
By AMERICAN HEART ASSOCIATION NEWS
The total number of Americans dying from heart disease rose in recent years following decades in decline. Cancer deaths have nearly tripled since 1950 and continue to climb.

Heart disease
Cancer

200,000
400,000
600,000
800,000
1,000,000
1,200,000

Source: Centers for Disease Control and Prevention. Published Aug. 24, 2016

Implantable Cardiac Defibrillator (ICD)
Medications (Amiodarone)

Overall Survival, CA for VT (LVEF, prior CA, type of CM)

Catheter Ablation

*Low risk
Medium risk
High risk

**Recurrent VT, NYHA IV

Needs Assessment – Can We “See It & Treat It” Noninvasively?

- **Noninvasive targeting**
  - Renaissance in cardiac and EP imaging

- **Noninvasive treatment**
  - SBRT/SAbR

5 patients with refractory VT treated off-label for clinical need in 2015

Single SBRT treatment, 25 Gy

3 month pre treatment = 6577
6 week blanking = 680
Next 10.5 months = 4
Phase I/II Trial of Electrophysiology-Guided Noninvasive Cardiac Radioablation for Ventricular Tachycardia

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Washington University School of Medicine
Radiation Oncology, Internal Medicine (Cardiovascular Division), Pathology, Radiology
Washington University School of Engineering
Biomedical Engineering

ClinicalTrials.gov NCT02919618
Inclusion and Exclusion

**Inclusion**

- Monomorphic VT or PVC-cardiomyopathy (w/EF<50%)
- Failed at least one antiarrhythmic drug
- Failed (or contraindicated) at least one catheter ablation
- ≥3 VT episodes over 6 months or >20% PVC burden

**Exclusion**

- Prior RT to anticipated field
- NYHA Class IVB (inotrope/LVAD)
- <12 month expected survival in absence of VT
- Polymorphic VT, >3 distinct VT morphologies (or >5 during testing)
Endpoints

Safety (≤ 90 days)

• Serious Adverse Events (SAEs)
• Any CTCAE v4.0 grade 5, any grade 4, any grade 3 requiring hospitalization within 90 days.

Efficacy (6 months)

• Reduction in VT/PVC burden comparing the period six months before ENCORE treatment to the six months after treatment.

• Six-week "blanking period" after therapy

19 patients
Balance between safety (up to 20% SAE) and efficacy (as low as 40%)
Demographics and Treatment Data

Population
- Median Age = 66 y/o (49-81)
- 89.5% Male, 89.5% Caucasian
- Ischemic (57.9%)
- Median LVEF = 25% (15-58)
- Median Prior catheter ablations = 1 (0-4)

Targeting/Treatment
- Median induced VT = 2 (1-5)
- Median GTV = 25.4 cc (6.4-88.6)
  - PTV = 98.9 cc (60.9-298.8)
- Median beam-on 15.3 min (5.4-32.3)
Patients Tolerate Cardiac Radioablation

Cardiac Radioablation

Conventional Ablation
Phase I – Safety Endpoint

• Median 23.5 mo (27.1 mo living pts, 22.3-36.0)

FIRST 90 DAYS—
1 patient with P/D grade 3-4 toxicities (1/19=5%)

Grade 3
• Pericarditis (day 80)
  • Resolved with prednisone

BEYOND 90 DAYS—
3 patients with P/D grade 3-4 toxicities (3/18=16.7%)

Grade 3
• Pericardial effusion (2.2y)
• Pericardial effusion (2.4y)

Grade 4
• 1 gastropericardial fistula (2.4y)
Phase I – Survival

Kaplan-Meier survival estimate

Age | Attribution | Mo
--- | ----------- | ----
CARDIAC DEATH
66 | Possible    | 8.3
60 | Unlikely    | 5.5
77 | Possible    | 23.6
80 | Possible    | 15
56 | Possible    | 14.5
64 | Possible    | 19.4
NON-CARDIAC DEATH
81 | Unlikely    | 0.6
50 | Unlikely    | 7
65 | Unrelated   | 7.8
Phase II – Primary Efficacy Endpoint (n=18)

- 94% of patients met primary endpoint

VT episodes vs. Time:

- **6 mo pre**
- **6 mo post**

Patients

- **6 mo pre**
- **0-6 mo post**
- **6-12 mo post**
- **12-18 mo post**
- **18-24 mo post**
Phase II – Efficacy Over Time

78% of patients continued to meet primary endpoint

**Deceased**

Patients

VT episodes

- 6 mo pre
- 0-6 mo post
- 6-12 mo post
- 12-18 mo post
- 18-24 mo post
- * Deceased
Phase II – Efficacy Over Time

Per-Patient VT Episodes by 6-month time periods

- Median VT burden

<table>
<thead>
<tr>
<th>Time Period</th>
<th>VT Episodes</th>
<th>At risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo PRE</td>
<td>95.5</td>
<td>18</td>
</tr>
<tr>
<td>0-6 mo</td>
<td>3.5</td>
<td>18</td>
</tr>
<tr>
<td>6-12 mo</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>12-18 mo</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>18-24 mo</td>
<td>3.5</td>
<td>12</td>
</tr>
</tbody>
</table>
Pre-Determined 6-month Secondary Endpoints

- **50% VT reduction**: 18 patients, **94%** achieved
- **95% VT reduction**: 16 patients, **67%** achieved
- **Freedom from ICD shock**: 18 patients, **78%** achieved
- **Freedom from VT storm**: 14 patients, **67%** achieved
- **Freedom from death, shock, storm**: 18 patients, **62%** achieved

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Achieved (%)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% VT reduction</td>
<td>94%</td>
<td>18</td>
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Strengths and Limitations

- Rigorous and complete clinical follow up (no drop outs)
- Vigilant and consistent endpoints (lenient ICD-recorded events)
- Broad and thorough evaluation for any adverse event (CTCAE v4.0)
- Small sample size (n=19)
- Inherent difficulty with risk attribution in a population with advanced cardiomyopathy & competing comorbid illnesses
- Survivor bias limits more complete analysis of treatment benefits and risks
The Washington University Experience

5 + 19 + 1 + 15 = 40

Treated n=5
2015
1 year follow up
Published 2017
Reported longer Follow-up 2018

Treated n=19
2017-1/2018
6 month follow up

2+ year follow up ASTRO 2019 and HRS 2020

One patient treated from 1/2018 to 3/2019

Actively treating patients (n=15) off-label with clinical need from 3/2019 – present
Center for Noninvasive Cardiac Radioablation (CNCR)

**Biology**
- How is SBRT antiarrhythmic?
  - Murine (SAARP)
  - Human explant

**Targeting**
- How to determine critical arrhythmia sites?
  - Scar architecture
  - Metabolism
  - Electrical
  - *In silico* modeling
  - Augmented targeting tools

**Clinical**
- How should SBRT be delivered?
  - ENCORE-VT
  - ENCORE-MULTI

**Process**
- How can we improve & standardize the processes?
  - Motion management
  - Automation of feature analysis
  - Augmented decision tools
  - Scalable & Sharable

**Population**
- Can SBRT extend access to care?
  - Global Registry
  - Democratize VT Ablation
Targeting – What people think we do

- **Method 1 - Bring all imaging into TPS**
  - **Pros**
    - All imaging overlaid, look for overlap
  - **Cons**
    - Many “imaging” modalities
    - Different orientations (non-axial), slice thickness, resolution
    - Breath-hold vs. free breathing
    - Different volume status (heart size)
    - EPs don’t “see” in cardinal planes
Targeting – What we actually do

• Method 2 – Use a surrogate, i.e. 17 segment model

• Pro’s
  • Universally used in Cardiology
  • Geometrically stable
  • Allows for “weighting” of data relative to quality and importance
  • Better categorical data for ML applications
  • Allows for a scalable and consistent approach across sites

• Cons
  • May result in larger targets
Target Volume and Survival

• Aim: To identify treatment characteristics associated with all-cause mortality after non-invasive cardiac radioablation

VT circuits localized with noninvasive cardiac imaging (MRI, PET, ECGI)

25 Gy in a single fraction using stereotactic body radiation therapy delivered to the planning target volume (PTV)

Patient and treatment characteristics were analyzed for association with mortality.

Cutpoint analysis was used to identify PTV values associated with increased mortality risk.

There was not a correlation between PTV ≥208 cc and likelihood of mortality event (n=7) being related to radioablation (for 3 patients possibly, 3 unlikely, 1 unrelated to treatment)
Simulation and Motion Management

• Respiratory 4D-CT
  • “Slow” 1 cc/sec contrast

• Cardiac 4D-CT
  • Used as a “gut check”

• Free breathing ITV
  • Compression

• Combine respiratory and cardiac 4DCT
  • ‘by eye’

• Cone Beam CT Alignment
  • ‘average to average’

• Free breathing Treatment
Simulation and Motion Management

Eleven patients underwent respiratory and cardiac 4DCT in preparation for treatment.

Each phase (0%-100%, 10% increments) of the r4DCT and c4DCT was rigidly registered back to the reference (0%)

Displacements were measured (mm) in the left-right (LR), anterior-posterior (AP), and superior-inferior (SI) directions to calculate “motion

Range of motion due to cardiac and respiratory motion compared. Gated and full ITVs estimated assuming maximum motion from respiration and heartbeat from exhale or all phases

<table>
<thead>
<tr>
<th>Scan</th>
<th>LR / mm</th>
<th>AP / mm</th>
<th>SI / mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>3.8 (2.8-6.9)</td>
<td>3.9 (2.2-5.4)</td>
<td>4.8 (2.3-7.9)</td>
</tr>
<tr>
<td>Respiratory (Exh)</td>
<td>3.9 (1.7-6.9)</td>
<td>4.1 (2.2-5.4)</td>
<td>4.7 (2.2-7.9)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3.4 (1.0-4.8)</td>
<td>4.3 (2.6-6.5)</td>
<td>4.1 (1.4-8.0)</td>
</tr>
<tr>
<td>Max Ex resp/card</td>
<td>3.6 (1.1-4.8)</td>
<td>4.3 (2.6-6.5)</td>
<td>4.2 (2.2-8.0)</td>
</tr>
<tr>
<td>Max resp/card</td>
<td>4.5 (3.1-6.9)</td>
<td>4.8 (3.0-6.5)</td>
<td>5.5 (2.3-8.0)</td>
</tr>
</tbody>
</table>

Table 2: Mean and range of motion for the respiratory 4D, respiratory exhale 4D phases, cardiac 4D scans and full and gated ITV estimations
Workflow Improvement

• Aim: To identify treatment characteristics associated with all-cause mortality after non-invasive cardiac radioablation

• A series of process control charts over the course of ENCORE-VT demonstrated:

  • **Significant** decreases in:
    • PTV volume, but not GTV or ITV volume
    • Mean doses to the non-target heart (Heart-PTV volume)

  • **Subjective** decreases in:
    • R50
    • Gradient measure
    • Treatment time
Possible role of protons

- **Pros:**
  - Lower *intermediate and low doses* to OARs

- **Cons:**
  - Sensitive to motion
  - Neutrons / ICD damage
  - Poor understanding of RBE for cardiac tissue
  - Limited availability

NIH 1 R01 HL148210-01

“Novel imaging and treatment technologies for image-guided noninvasive stereotactic cardiac radiosurgery.”

(PI: Yang/Gach)
Known Clinical Treatments Worldwide

- >100 patients treated
- >35 centers worldwide
- >10 different countries

EU: Zurich, Heidelberg, Kiehl, Barcelona
UK: Newcastle, Sheffield, Middlesborough
CAN: Montreal, Toronto,
Asia: Seoul, Tokyo

Palo Alto (CK)
Ostrava, Monterrey
St. Louis (C-arm linac)
St. Louis (MR-linac)
Lausanne, Boston, Austin, Atlanta, Beijing

Number of patients treated

Multicenter Clinical Trial

Co-Primary Endpoints

- **Safety**
  - Cumulate rate serious AE (SAEs) of significant interest (SAESI) at 6 months

- **Efficacy**
  - ≥75% reduction in VT (anti-tachycardia pacing, ICD shock), comparing the 6 months before and after ENCORE or CA

Study Infrastructure

![Diagram showing various components of the study infrastructure including Steering Committee, PI, Data Safety and Monitoring Board, Multicenter Clinical Trial Support Center, Targeting Core, Credentialing and Planning Core, Imaging Core, Event Adjudication Core, OncoInformatix, and REDCap.](image)
VT Suppression Happens in Days to Weeks

Initial Interrogation: Quick Look II
Cardiac Compass Trends (Jul-2016 to Sep-2017)

- Treated VT/VF (#/day)
- AT/AF (min/day)
- Patient Activity (hr/day)

- Off mex
- Off amio
Fibrosis Alone Can Not Account for the Magnitude of the Clinical Effect

Unpublished:
U Goldsztejn, A Lang, C Robinson, P Cuculich, S Rentschler

Scale bars: 500um
Cardiac radioablation—A systematic review

Published: March 20, 2020 • DOI: https://doi.org/10.1016/j.hrthm.2020.03.013
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