Functional Neurosurgical Applications of Modern Precision Radiosurgery

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Disclosure

- Honoraria
  - Varian Medical Systems
- Institutional Research Agreement
  - Varian Medical Systems

Outline

- Functional radiosurgery background
- What are some of the clinical indications?
- How has functional radiosurgery traditionally been performed?
- Can functional radiosurgery be performed on my Edge™ radiosurgery system/TrueBeam® STx system?
  - Can it be done without cones?
  - What kind of dosimetry can be expected?
Background

- Functional neurosurgery can be broadly described as a neurosurgical intervention when physiology is altered, but anatomy may or may not be normal.
- Historically, functional neurosurgery required thermal ablation or direction injection of a chemical such as phenol or ethanol.
- Developed in parallel with the practice of stereotaxy.

History of Functional Radiosurgery

- 1951 – Introduction of SRS by Leksell.
- Original intended use was functional conditions (e.g., PD, psych disorder, chronic pain).
- 1958 – First described use of protons for fxnl SRS by Larson, Leksell & Reed (2000y to anterior internal capsule).
- Immediately in use for functional disorders.
- 1988 – First described LINAC fxnl SRS (trigeminal neuralgia) by De Salles et al.
- 2003 – CyberKnife first used for fxnl SRS (trigeminal neuralgia) by Romanelli, Adler, et al.
- 2004 – First non-trigeminal fxnl SRS, Frighetto, De Salles et al.

Clinical Conditions for which Functional Radiosurgery Has Been Used

- Trigeminal neuralgia (70-90Gy TGN)
- Parkinsonian tremor (1300y Gpi)
- Essential tremor (1300y VMA)
- Dystonia (1200y STN)
- Cancer pain (1300y CMN or 1600y Pituitary)
- Thalamic pain (1300y VPM)
- Obsessive compulsive disorder (1300y anterior capsule)
- Epilepsy
  - hypothalamic hamartomas (~15Gy to hamartoma)
  - mesial temporal sclerosis (40-80Gy amygdala)
- Sphenopalatine neuralgia (800Gy to SPG)
- Chronic cluster headaches (800Gy to SPG or TGN)
Current practices in functional radiosurgery
- Nearly all functional SRS cases are currently performed on Gamma Knife® Perfexion™, a linear accelerator with cones,

Functional radiosurgery devices
- Nearly all functional SRS cases are currently performed on Gamma Knife®, a linear accelerator with cones, or CyberKnife®
- Typically treated using a 4-5 mm diameter spherical “shot”

Functional Radiosurgery at UAB
- Completely non-invasive (no head frame)
- Comfortable mask (Qfix® Encompass™ SRS Immobilization System)
- Fast, precise treatment (45-60 min), under conscious sedation
- Real-time patient motion tracking (OSMS®: optical surface monitoring system)
Functional Radiosurgery at UAB

Virtual Cone SRS on the Edge

- Pre-calculated fixed modulation pattern VMAT plan, with static MLC leaves
- Designed to replicate dosimetry of a 4mm Gamma Knife helmet
- No patient specific QA necessary!

VC MLC aperture and arc geometry

- 5-mm x 2.1-mm MLC aperture using High-definition 120 Multileaf Collimator (HD 120™ MLC)
- CW & CCW arcs with collimator ±45 degrees
- 20 (half) arcs at table angles 0, 16, 72, 288, 324 degrees (avoiding vertex arc)
- Dose rate is sin(gantry angle), max 2400 MU/min for 10X FFF
Trigeminal Neuralgia

- One of most frequently seen neuralgias in older adult population
- Incidence increases with age
- SRS used for medically refractory/non-surgical cases
- Rx = 70 to 90 Gy, usually at trigeminal nerve DREZ near brainstem
- Pain relief usually about 70% at one year

UAB Virtual Cone SRS for Trigeminal Neuralgia Trial

- **Stage I** (Pilot at UAB Only, Single Institution)
  - To determine the feasibility of frameless Virtual Cone trigeminal neuralgia radiosurgery at a single institution prior to multi-institutional enrollment.
- **Stage II** (Multi-institutional)
  - To measure pain relief after Virtual Cone radiosurgery utilizing the Barrow Neurologic Institute Pain Intensity Score (BNI).

Comparison of dosimetry for a clinically delivered Gamma Knife Trigeminal Neuralgia treatment, with Virtual Cone technique
Promising trial of VIM Thalamotomy for Essential Tremor has inspired new attention

Radiosurgical Thalamotomy

- Typically performed with Gamma Knife
- 201/192 Cobalt-60 sources arranged for stereotactic targeting
- Lesion is usually placed at the ventral intermediate nucleus of the contralateral thalamus

Other treatments we are exploring

RAD 1601: Edge Radiosurgery for Essential Tremor (medically refractory, non-DBS candidate patients)
Comparison of GK Thalamotomy to Virtual Cone Thalamotomy

Eligibility:
- Patients with medically refractory ET or tremor-dominant PD
- >18 years old, ECOG ≤ 2
- no prior brain RT

Assessments (1 year follow-up)
- Toxicity (CTCAE v4)
- Fahn-Tolosa-Marin Tremor Rating Score (FTMTRS)
- QOL-36/PROMIS
- Patient Satisfaction Questionnaire-VAM

UAB RAD 1601 – SRS thalamotomy

RAD 1601 – Accrual
- ClinicalTrials.gov identifier: NCT03305588
- additional patients treated off trial
- extension phase in preparation

<table>
<thead>
<tr>
<th>RAD 1601</th>
<th>n = patients</th>
<th>Time assessment</th>
<th>Projected close date</th>
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<tr>
<td>Enrolled</td>
<td>16 of 20 (80%)</td>
<td>Dec 2017</td>
<td>Nov 2021</td>
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<td>Active screening</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>Screened and/or seen in consult</td>
<td>60</td>
<td></td>
<td></td>
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<tr>
<td>Referral source</td>
<td>+ UAB + non-UAB</td>
<td>about 50%</td>
<td>about 50%</td>
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UAB RAD 1601 – Primary Objective

• Primary objective:
  • Determine the efficacy of frameless Virtual Cone SRS thalamotomy in tremor patients who are not candidates for DBS or do not want DBS

• Secondary objectives:
  • Acute and late neurologic toxicity
  • QOL changes and health-related outcomes
  • Patient satisfaction
  • Acquire preliminary data for developing new targeting methods based on structural/functional connectivity (3T/7T MRI)
  • Changes in rs-fMRI

Radiosurgical Thalamotomy

• Lesion is usually placed at the ventral intermediate nucleus (VIM) of the contralateral thalamus

Automated stereotactic targeting

• AP: 1/4 of the AC-PI distance plus 1 mm anterior to the IPC
• Lat: 1/2 the width of the 3rd ventricle plus 11 mm from the AC-PC line
• Sup-Inf: 2.5 mm superior to the AC-PC
• 130 Gy (max 80 Gy to 4.5 mm VC)
• 20% (280 Gy) 5Gy line kept medial to IC
Scripted treatment planning

- 0.8 mm grid size
- 10 framework agent servers
- Calculation time:
  - AAA 13.6 – 23.4 min
  - Acuros XB 13.6 (plan dose) – 16.8 min
  - Acuros XB 13.6 (field by field) – 1.8 min
- Soon: GPU acceleration for massively parallel computation

SRS thalamotomy plan (MPRAGE)

SRS thalamotomy plan (FGATiR)
FGATIR sequence on 3T and 7T

- FGATIR = Fast Gray Matter Acquisition T1 Inversion Recovery
- white-matter nulled sequence
- same acquisition as MPRAGE (different inversion time)
- allows for improved delineation of subcortical structures
  - specifically thalamus, striatum, GPe/GPi, RN, SNr
- enables seeing internal lamina of the GPi, fiber bundles from the IC piercing the stratum, and the boundaries of the STN

First Treated Essential Tremor Patient – 130Gy dmax to Left VIM of thalamus
Pre-tx MRI compared to 3mo post-tx MRI

In vivo dose delivery verification!

Active/Recently Active Trials of Functional Radiosurgery

- Tremor
  - NCT01796152 - Stereotactic Radiosurgery for Essential Tremor and Parkinsonian Tremor (SA)
  - NCT02525984 - Gamma Knife Radiosurgery for Treatment of Essential Tremor
  - NCT02061360 - Deep Brain Stereotactic Radiosurgery for Drug Resistant Unilateral Tardive Dyskinesia: Dose Escalation Pilot Study (CyberKnife)
  - NCT01967746 - Radiosurgery for Drug Resistant Unilateral Tardive Dyskinesia (SA)
  - NCT02061360 - Deep Brain Stereotactic Radiosurgery for Parkinson Disease
- Pain
  - NCT02554685 - Celiac Plexus Radiosurgery for Pain
- Management (Opioids)
  - NCT01620319 - Treatment of Opioid-refractory Pain (WHO Level III) by Pulsed Radiofrequency (PRF)
- Psychiatric
  - NCT01989876 - Radiosurgical Treatment for Obsessive-compulsive Disorder (WHO Level III) (CyberKnife)
  - NCT02500888 - Evaluation of Capsulotomy by Linear Accelerator Radiosurgery in Severe and Refractory Obsessive-Compulsive Disorder (CyberKnife)
- Other
  - NCT01989876 - Radiosurgery or Open Surgery for Epilepsy Trial (WCC/UPMC)
GK vs Virtual Cone Dosimetry comparison for other functional SRS Cases

<table>
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<tr>
<th>Source cone</th>
<th>Mean</th>
<th>Clinical Acceptable</th>
<th>Gradient Measure (cm)</th>
<th>V12 (cc)</th>
<th>Model based</th>
<th>Mean</th>
<th>Clinical Acceptable</th>
<th>Gradient Measure (cm)</th>
<th>V12 (cc)</th>
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<td>130</td>
<td>Yes</td>
<td>0.15</td>
<td>1.10</td>
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<td>Subthalamotomy</td>
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<td>0.14</td>
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<td>0.24</td>
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<td>Ant. capsulotomy</td>
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<td>1.98</td>
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<td>SPG ablation</td>
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<td>Hypophysectomy</td>
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<td>0.38</td>
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<td>1.11</td>
<td>18.2</td>
<td>Yes</td>
<td>0.16</td>
<td>1.80</td>
<td>20.0</td>
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Benefits of Frameless Virtual Cone SRS to patient

- Fast (20-30 minutes vs ~90 minutes on GK)
- More comfortable
- No frame required
  - particularly useful for anti-coagulated patients who bruise easily from screws
- If individual nuclei can be visualized, ability to contour the dose shape to the nucleus in question

Conclusions

- Once principally relegated to Gamma Knife, or cumbersome time-consuming cone treatments
- High-quality functional SRS is now feasible on the Edge/TrueBeam STx platform
  - Cookie cutter plan template can replicate 4mm helmet dosimetry
  - Doesn’t require patient specific QA
  - Template can be re-optimized to mimic other helmet dosimetries
  - Fits into normal clinical workflow without cone mounting!
Acknowledgements

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- John Fiveash
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- Harrison Walker
- Barton Guthrie
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Q&A