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Not for the faint of heart: Functional Radiosurgery

Clinical and Biological Rationale

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63RD ANNUAL MEETING & EXHIBITION

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I have no disclosures

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Learning Objectives

- To enumerate the clinical rationale for functional radiosurgery
- To discuss the radiobiologic principles of functional radiosurgery
- To describe the application of functional radiosurgery for specific disorders
- To recognize the outcomes and toxicities of functional radiosurgery

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Clinical Rationale

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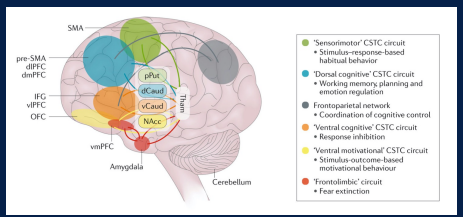
Neurologic disorders have a "functional" basis

Arising from disruptions in intact complex neurologic circuitry



Stein et al. *Nat Rev Dis Primers* 2020

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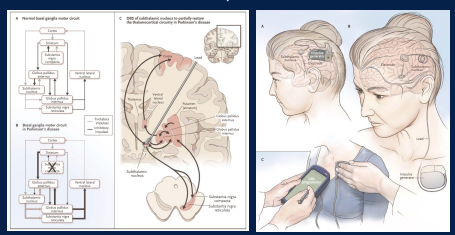
Neurologic disorders have a "functional" basis

Movement disorders stem from disruption in neural networks



Okun *NEJM* 2012

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Functional Neurosurgery

Targeting neural pathways with modulatory or ablative interventions

Role for stereotactic ablative or radiomodulatory interventions?

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Radiobiology

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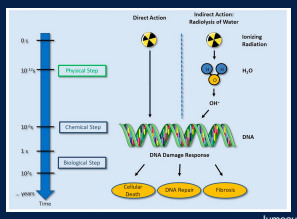
Biological Mechanisms of Radiotherapy

DNA-damage driven response



Jumeau et al. *Frontiers Card Med* 2020

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Biological Mechanisms of Radiotherapy

Augmented response with high-dose per fraction

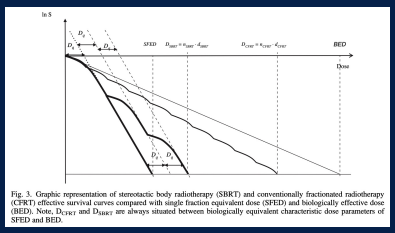

Fig. 3. Graphic representation of stereotactic body radiotherapy (SBRT) and conventionally fractionated radiotherapy (CFRT) effective survival curves compared with single fraction equivalent dose (SFED) and biologically effective dose (BED). Note, D_{CFRT} and D_{SBRT} are always situated between biologically equivalent characteristic dose parameters of SFED and BED.

Park et al. *IJROBP* 2007

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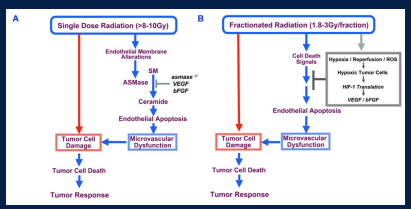
Mechanisms of Stereotactic Radiotherapy

Unique radiobiology and response?

- Targets:
  - DNA
  - Lipids
  - Proteins
- Ablative effect
- Immunostimulation
- Vascular sclerosis
- Radiomodulation



Fuks and Kolesnick et al. *Cancer Cell* 2005; Brown et al. *IJROBP* 2014

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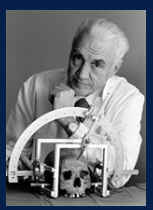
Radiosurgery for Functional Neurosurgery

Dr. Lars Leksell developed radiosurgery (1960s) as an alternative to potentially morbid surgical procedures for functional disorders including:

- Movement disorders
- Psychiatric conditions
- Chronic Pain syndromes



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Clinical Applications

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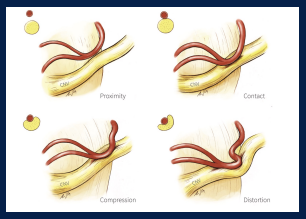
Trigeminal Neuralgia

A "simple" functional disorder

- Severe, unilateral electric-like pain
- Medical therapy 90% effective
- Neurovascular compression at REZ
- Surgery for refractory patients
- High potential morbidity from surgery
- Treated with "radiosurgery" in 1951



DeSouza et al. *Frontiers in Neuro Anat* 2016

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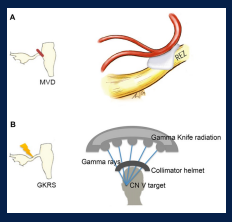
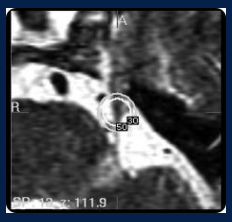
Trigeminal Neuralgia

Targeting root entry zone (REZ), 80Gy@100% IDL, 4mm shot





DeSouza et al. *Frontiers in Neuro Anat* 2016;Tuleasca et al. *JNS* 2018

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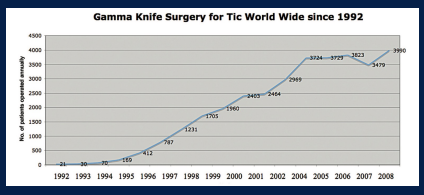
Trigeminal Neuralgia

GK SRS widely adapted for TN



Regis and Tuleasca et al. *JNS* 2011

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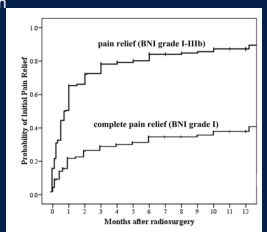
Trigeminal Neuralgia

Clinical Outcomes, University of Pittsburgh

- N=503 patients TN
- 4mm, 80 Gy max dose
- 80% patients had pain relief
- 41% durable relief at 5 yrs
- 10.5% new/incr facial nerve sxs



Kondziolka et al. *JJNS* 2010

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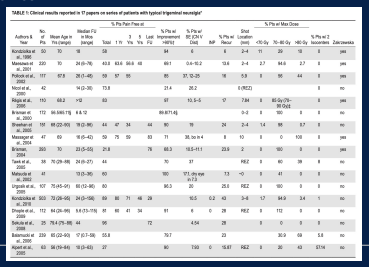
Trigeminal Neuralgia

Clinical Outcomes



Regis and Tuleasca *JNS* 2011

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Trigeminal Neuralgia

Clinical Outcomes, ISRS Guidelines

TABLE 5. Final recommendations

Evidence Level	Recommendation
II	Single-fraction RS is better than hypofractionated RS
II	Previous surgery is a negative predictor for pain relief after RS; this factor does not, however, contraindicate RS
II	A neurovascular conflict is not a negative predictor for RS
II	The minimal effective dose is 70 Gy
I & II	Do not increase the length of the treated nerve; use only one 4-mm isocenter; using 2 isocenters (either continuously or concentrically) yields similar rates of initial efficacy but w/ increased toxicity (so-called Flickinger effect); do not use beam channel blocking at 90 Gy
II	An anterior target & a posterior target have similar initial efficacy
II	An anterior target has lower hypesthesia & bothersome hypesthesia rates than the posterior target
II & III	Additional complications, including dry eye syndrome, are seen only w/ a posterior target
II & III	An anterior target, as compared to the posterior one, has higher pain relief rates on a long-term basis (7 & 10 yrs' FU)
III	SRS is recommended as an alternative to the reference technique, which is MVD for classical trigeminal neuralgia
III	SRS yields a better initial freedom from pain response if performed in the first 3 years after pain onset
III	The maximal effective dose is 90 Gy
III	Beyond 90 Gy, the efficacy rate remains similar but w/ a higher complication rate
III	LINAC & CKR result in higher bothersome hypesthesia rates

Anterior target = placement of a unique 4-mm shot on the cisternal portion of the trigeminal nerve, at approximately 7–8 mm from its emergence from the brainstem; FU = follow-up; posterior target = placement of a unique 4-mm shot at the emergence of the nerve.

Tuleasca et al. *JNS* 2018

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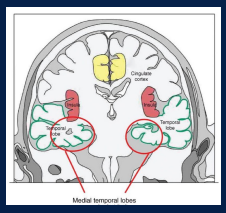
Movement Disorders: MTLE

Mesial Temporal Lobe Epilespy

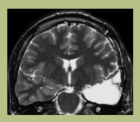
- Chronic, recurrent seizure activity
- Focally orginates in the temporal lobe
- Primary treatment is medical therapy
- Surgery is reserved for salvage



Anterior temporal lobectomy

(1990-2010)

n=209, 53.7%



Spencer et al., 1984

Mathon et al. *Epilepsia* 2017;Shahan E.

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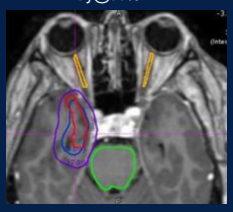
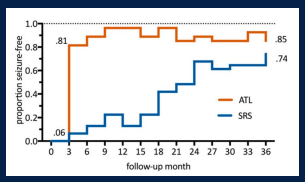
Movement Disorders: Rose Trial

SRS vs Anterior Temporal Lobectomy for refractory unilateral MTLE, n=58 pts

24 Gy@50% IDL





Seizure remission: 58% SRS vs 78% ATL

Barbaro et al. *Epilespsia* 2018; Narayanasamy et al. *JACM* 2018

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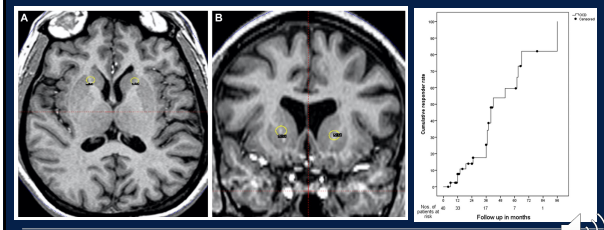
SRS for Obsessive Compulsive Disorder

Gamma Ventral Capsulotomy (IRRF study, n=40), 120-180 Gy @100% IDL



Gupta et al. *Neurosurgery* 2019

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Emerging Applications

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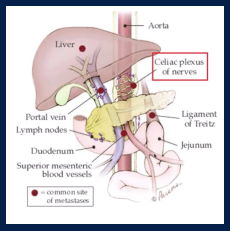
Radiosurgery for Celiac Plexus Neuralgia

Pancreatic cancer pain disorder

- 70-80% patients with pain
- Treatments:
  - Analgesic medical therapy
  - Chemotherapy
  - Celiac plexus nerve block
- Role for radiosurgery?



Lawrence et al. ASCO 2013

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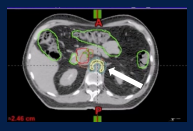
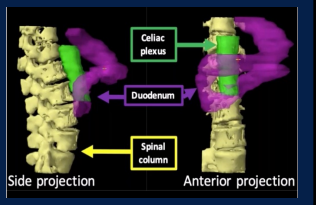
Radiosurgery for Celiac Plexus Neuralgia

Pancreatic cancer pain disorder

- Pilot Trial Sheba Med Center
- 25 Gy in one fraction
- T12-L2 aorta plus prox tumor
- Primary obj: 3 wk pain response





Lawrence et al. ASCO (2013)

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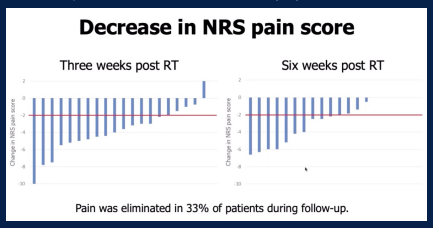
Radiosurgery for Celiac Plexus Neuralgia

Pancreatic cancer pain disorder: Pilot trial n=34 (21)



Lawrence et al. ASCO (2013)

Ongoing international Phase II trial (n=100)

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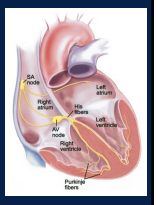
Cardiac Radioablation for Arrhythmias

Morbidity of Ventricular Tachycardia (VT) and Atrial Fibrillation (AF)

Ventricular tachycardia		More than three consecutive QRS complexes originating in the ventricles at a rate of >100 bpm. Regular QRS complex shape missing; subtypes include sustained (>30 s), unsustained (more than three beats, terminating spontaneously), monomorphic (symmetrical QRS morphology from beat to beat) and polymorphic (unstable and multiform QRS morphology from beat to beat)
Atrial fibrillation		Absent P wave combined with an irregular ventricular rate; the isoelectric line can be characterized by either fibrillatory waves (F waves) or just minute oscillations; subtypes include paroxysmal (terminates spontaneously or with intervention within 7 days of onset), persistent (continuous atrial fibrillation that is sustained for 7 days) and longstanding persistent (continuous atrial fibrillation for >12 months)



Grune et al. *Nat Rev Cardiology* 2021; Wang and Estes *Circulation* 2003

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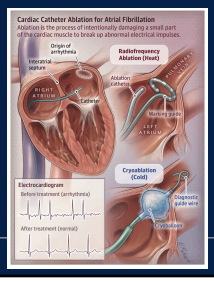
Cardiac Radioablation for Arrhythmias

Management of Ventricular Tachycardia (VT) and Atrial Fibrillation (AF)



- Pharmacologic therapy
- Temporary Pacing
- Permanent Pacemaker/Defibrillator
- Cardiac Catheter Ablation
  - Radiofrequency Ablation
  - Cryoablation

Singh et al . *JAMA* 2019

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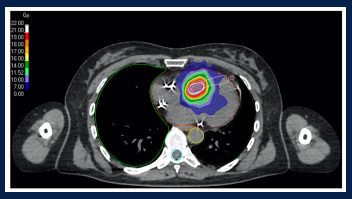
Cardiac Radioablation for Arrhythmias

Radiosurgery for Ventricular Tachycardia (VT) and Atrial Fibrillation (AF)



- Non-invasive high-dose radiation to arrthymogenic target in heart
- Requires precise image-guidance and motion management strategies

Jumeau et al. *Fronteirs Card Med* 2020

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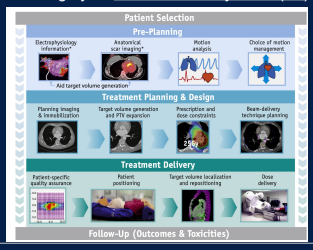
Cardiac Radioablation for Arrhythmias

Radiosurgery for Ventricular Tachycardia (VT) and Atrial Fibrillation (AF)



- Electroanatomical Mapping
- Motion Management
  - Tracking
  - Internal Target Volume
  - External Pacing

Lydiard et al. *IJROBP* 2021

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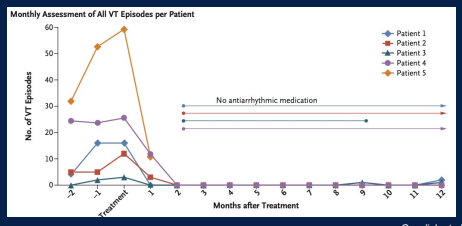
Cardiac Radioablation for Arrhythmias

Radiosurgery for Ventricular Tachycardia (VT) and Atrial Fibrillation (AF)



Cuculich et al. *NEJM* 2011

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Cardiac Radioablation for Arrhythmias

Radiosurgery for Ventricular Tachycardia (VT) and Atrial Fibrillation (AF)

	Washington University, USA	Ostrava University, Czech Republic	Emory University, USA	Lausanne University Hospital, Switzerland
Number of patients	19	10	10	10
Age	66 (49–81)	66 (61–78)	61 (51–78)	66 (47–75)
Cardiopathy: I/NI/INFL	11/6/2	7/2/0	4/6/NA	3/4/2
LVEF (%)	25 (15–58)	26.5 ± 3.2	NA	37 ± 14
RT device	Linac	CyberKnife System	Linac	CyberKnife System
PTV margin (mm)	5	0	1–5	0–3
PTV (ml)	98.9 (80.9–298.8)	22 (14.2–29.6)	81.4 (29–238)	23 (14–35)
Dose (Gy)	25	25	25	22 (20–25)
Toxicity	• 1 case with heart failure exacerbation • 1 case of radiation pericarditis • 2 cases of radiation pneumonitis	• 4 cases with nausea • 1 case of possible mitral regurgitation worsening at 17 months	• 2 cases of radiation pneumonitis	• 1 case of nausea • 1 case of broken rib
VT burden reduction	94% at 13 months	87.6% at 28 months	69% at 5.8 months	99.4% at 4 months

VT, Ventricular Tachycardia; Linac, Linear accelerator; PTV, Planning Target Volume; I, Ischemic; NI, Non-Ischemic; INFL, Inflammatory; NA, Not available.

Lydiard et al. *IJROBP* 2020

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Summary

- Functional radiosurgery is safe and effective for non-invasive management of numerous non-malignant conditions
- High-dose technique requires precise mapping for ablation
- Well-established efficacy and safety for treatment of trigeminal neuralgia
- Additional indications include eplipsy and obsessive compulsive disorder
- Expanding applications including sites of neuralgia, cardiac arrhythmia

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Thank You

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