



Re-irradiation techniques: Gamma Knife  
A technical and clinical overview

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### Conflicts of Interest

None

(but a presentation about anything Gamma Knife® is almost by definition vendor-specific)

### What is Gamma Knife radiosurgery?

Gamma Knife re-irradiation scenarios

What makes re-irradiation difficult?

Evolution of Gamma Knife for re-irradiation

### 1951: "The Stereotactic Method and Radiosurgery of the Brain"



Lars Leksell with arc-centered stereotactic frame (image courtesy of Elekta, AB)



Leksell at the 185 MeV Uppsala cyclotron facility circa 1958

Leksell, L. 1951. The stereotactic method and radiosurgery of the brain. *Acta Chir. Scand.* 102:316-9.

1967: The first "Gamma Knife"



Lars Leksell and Ladislav Steiner at the Karolinska Institute

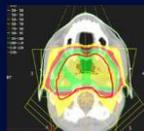


Tony DeSalles and Catherine Gilmore (past president of Elekta) with the original Gamma Knife after it moved to UCLA (1982, picture circa 1993)

Leksell, L. 1971. Stereotaxis and Radiosurgery: An Operative System. Springfield: Thomas Publishing.

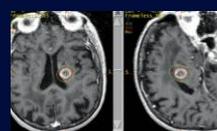
What makes radiosurgery different?

6-field 3D conformal plan



Relies on differential biology

Intracranial SRS treatment plan



Relies on differential targeting

Spreading out energy is the key to SRS



Technical requirement to create many individual small beams led directly to the use of <sup>60</sup>Co

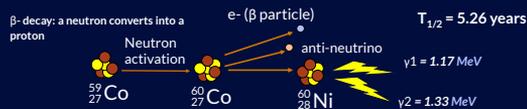
Spreading the energy out generates steep dose gradients that concentrates dose on the target

Model C: 201 beams / isocenter

Perfixion: 192 beams / isocenter

Image courtesy of Elekta, AB

Gamma Knife: powered by nature



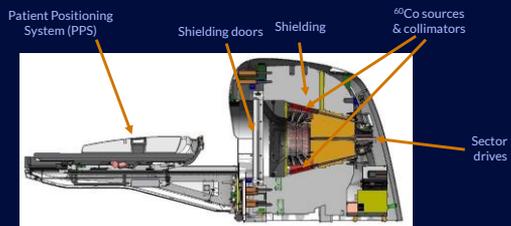
<sup>60</sup>Co decay is a very stable photon source

Sources are usually in pellet-form, triple-encapsulated in steel, then placed in an aluminum source bushing.

A single 36 Ci source yields a dose rate of ~480 mSv/hr at 1 meter!

Source: Georgia registry of radioactive sealed sources and devices, 2001. Decay figure originally by Håkan Nordström, Elekta AB

### Gamma Knife Perfexion/Icon: internal view

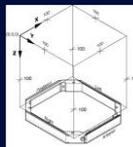


~20 metric tons to protect you from 20 grams of <sup>60</sup>Co  
 Note: Image of a Perfexion. Icon has the same internal configuration

Images: Elekta Instrument, AB

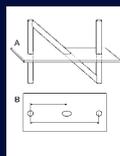
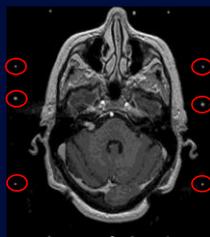
### How do you know where you are aiming?

The traditional method!



The frame defines a targeting coordinate system.  
 Coordinate system origin is to the right, superior, posterior of the patient's head.  
 All coordinates are positive – no sign mistakes.  
 Center of the system is considered to be (100, 100, 100) (mm).

### Stereotactic fiducials



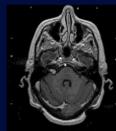
Brown R.A., et al. (2013) The Origin of the N-Localizer for Stereotactic Neurosurgery. Cereus 5(9)

### Imaging for treatment planning

Typical imaging protocols

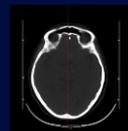
#### Solid tumors

T1-weighted MR + contrast



#### AVMs

Biplane DSA  
 T1-weighted MR + contrast  
 MRA



#### Skull-base and pituitary

T1-weighted MR + contrast  
 T2 CISS or SPACE  
 T1-weighted + fat saturation



### Non-stereotactic imaging

Co-registration allows use of PET, advanced MRI sequences

### Treatment planning today....

Doses are traditionally prescribed to 50% isodose line

### Basic treatment building-blocks

**Base configurations**

**Composites and blocking**

**Weighting**

### But in the end a plan is simple to describe

Run-Step	Shot	Beam	X [mm]	Y [mm]	Z [mm]	Collimator	Isocenter I-J	Time [min]	Notes
1-1	A1	1	78.45	78.45	218.5	0	0 0	2.157	
1-2	A1	2	78.45	78.45	218.5	0	0 0	2.157	
1-3	A1	3	78.45	78.45	218.5	0	0 0	2.157	
1-4	A1	4	78.45	78.45	218.5	0	0 0	2.157	
1-5	A1	5	78.45	78.45	218.5	0	0 0	2.157	
1-6	A1	6	78.45	78.45	218.5	0	0 0	2.157	
1-7	A1	7	78.45	78.45	218.5	0	0 0	2.157	
1-8	A1	8	78.45	78.45	218.5	0	0 0	2.157	
1-9	A1	9	78.45	78.45	218.5	0	0 0	2.157	
1-10	A1	10	78.45	78.45	218.5	0	0 0	2.157	
1-11	A1	11	78.45	78.45	218.5	0	0 0	2.157	
1-12	A1	12	78.45	78.45	218.5	0	0 0	2.157	
1-13	A1	13	78.45	78.45	218.5	0	0 0	2.157	
1-14	A1	14	78.45	78.45	218.5	0	0 0	2.157	
1-15	A1	15	78.45	78.45	218.5	0	0 0	2.157	
1-16	A1	16	78.45	78.45	218.5	0	0 0	2.157	
1-17	A1	17	78.45	78.45	218.5	0	0 0	2.157	
1-18	A1	18	78.45	78.45	218.5	0	0 0	2.157	
1-19	A1	19	78.45	78.45	218.5	0	0 0	2.157	
1-20	A1	20	78.45	78.45	218.5	0	0 0	2.157	

A plan is a list of locations, collimator configurations, and dwell times.  
 Very similar to HDR brachytherapy treatment planning.  
 Each location is a coordinate to position that location at radiation isocenter.  
 Total # beams = 192 x number of locations (unless sectors are blocked).

What is Gamma Knife radiosurgery?

Gamma Knife re-irradiation scenarios

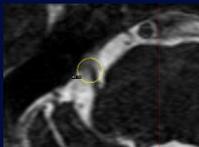
What makes re-irradiation difficult?

Evolution of Gamma Knife for re-irradiation

Re-irradiation of same site

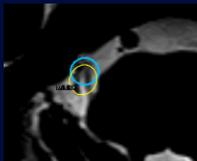
Repeat treatment for trigeminal neuralgia

SRS session 1: 2/2012



40 Gy -> 50%

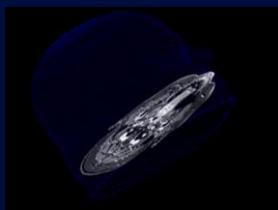
SRS session 2: 9/2017



37.5 Gy -> 50%  
(shielded to protect brainstem)

Re-irradiation for new tumors

## One brain, multiple radiosurgeries



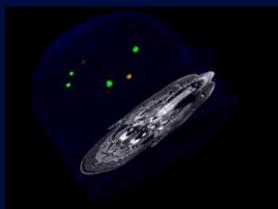
Date	# tumors	Vol 12Gy (cc)	Skull mean dose (Gy)

## One brain, multiple radiosurgeries



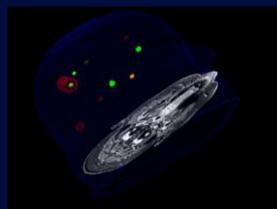
Date	# tumors	Vol 12Gy (cc)	Skull mean dose (Gy)
7/2013	1	0.6	0.1

## One brain, multiple radiosurgeries



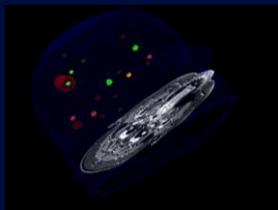
Date	# tumors	Vol 12Gy (cc)	Skull mean dose (Gy)
7/2013	1	0.6	0.1 (0.3)
10/13	5	3.4	0.4 (0.8)

## One brain, multiple radiosurgeries



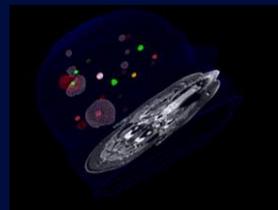
Date	# tumors	Vol 12Gy (cc)	Skull mean dose (Gy)
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## One brain, multiple radiosurgeries



Date	# tumors	Vol 12Gy (cc)	Skull mean(s) dose (Gy)
7/2013	1	0.6	0.1 (0.3)
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5/14	11	5.1	0.6 (0.9)

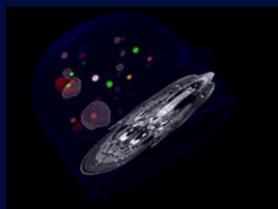
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5/14	11	5.1	0.6 (0.9)
6/15	8	43.8	1.4 (2.3)

9/2014 - WBRT (30 Gy in 10 fractions)

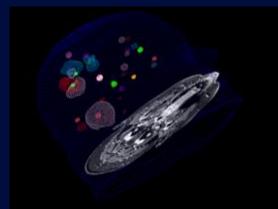
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7/15	4	2.0	0.2 (0.5)

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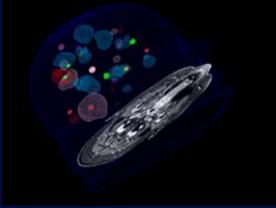
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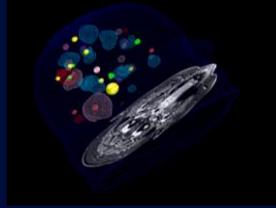
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5/14	11	5.1	0.6 (0.9)
6/15	8	43.8	1.4 (2.3)
7/15	4	2.0	0.2 (0.5)
10/15	6	14.6	0.6 (1.4)
2/16	9	46.2	1.6 (2.3)

9/2014 - WBRT (30 Gy in 10 fractions)

### One brain, multiple radiosurgeries



Date	# tumors	Vol 12Gy (cc)	Skull mean(s) dose (Gy)
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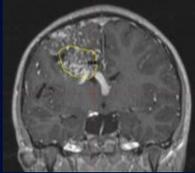
55 tumors, 9 SRS procedures, 3 years  
Still alive as of 8/2018!

9/2014 - WBRT (30 Gy in 10 fractions)

### Geographical fractionation

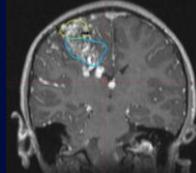
### Staged AVM radiosurgery

Pediatric patient, prior embolization x 2, aborted embolization #3



SRS session 1: 3/2014

13.5 Gy -> 50%  
V<sub>13.5Gy</sub> = 14.6 cc  
V<sub>12Gy</sub> = 17.1cc

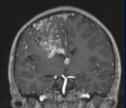


SRS session 2: 4/2014

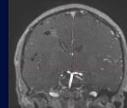
13.5 Gy -> 50%  
V<sub>13.5Gy</sub> = 8.9 cc  
V<sub>12Gy</sub> = 10.8 cc

### Staged AVM radiosurgery

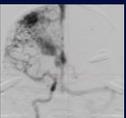
MRI: date of 1<sup>st</sup> GKRS



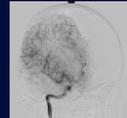
Followup MRI: 6/2017



Angio: date of 1<sup>st</sup> GKRS



Followup Angio: 3/2018



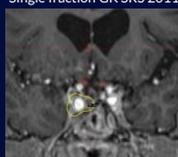
Complete obliteration confirmed via MR (6/2017), angio (3/2018)

### Dose fractionation (sometimes with prior SRS)

### A bit of an extreme case....

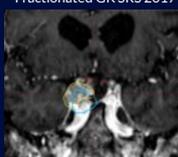
Recurrent pituitary macroadenoma / prolactinoma

Single fraction GK SRS 2011



18 Gy ->50%  
3.3cc Rx volume  
0.01cc OP: 6.3 Gy (RON)

Fractionated GK SRS 2017



20 Gy ->50% in 5 fractions  
5.0cc Rx volume  
0.01cc: 18.7 Gy (RON)

Other therapies:  
post transphenoidal x 4  
post fractionated RT (50.4 Gy, 2010)  
temozolamide 2012, 2015-2016

### Some clinical references (I'll spare the details...)

Year	Author(s)	Journal	Clinical setting
2002	A. Bhatnagar, et al.	IJROBP 53 (3)	Primary and metastatic tumors
2012	K. Park, et al.	Neurosurgery 70 (2)	Repeat trigeminal neuralgia
2015	C. Hellis, et al.	Neurosurgery 77 (5)	Repeat trigeminal neuralgia
2015	S. Lonneville, et al.	Surg Neurol Int 28(6)	Repeat vestibular schwannoma
2017	R. Kotecha et al.	Neurosurgery 80 (6)	Repeat SRS for multiply recurrent brain metastases
2017	A. Ilyas, et al.	J. Clinical Neuroscience 43	Volume-staged AVMs
2018	G. Mehta, et al.	J. Neurooncology	Multicenter repeat SRS Cushing's

Note: This is not (and is not meant) to be complete! This is a physics talk after all!

What is Gamma Knife radiosurgery?

Gamma Knife re-irradiation scenarios

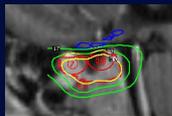
What makes re-irradiation difficult?

Evolution of Gamma Knife for re-irradiation

Radiosurgery is hard.

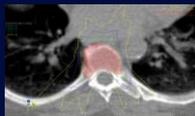
Uncertainty makes it harder.

SRS/SBRT often has difficult constraints



Brain SRS: Pituitary adenoma  
(optic pathways within few mm)

High doses per fraction, small # fractions  
Fields that must conform to anatomy  
Inhomogeneous dose within tumor



Spine SRS: (spinal cord within few mm)

Sharp dose gradients outside target:  
10%-25%/mm (Gamma Knife)  
>10%/mm (linac)

Extremely high requirements for accuracy and precision!

What happens if you really mess up

*The New York Times*

THE RADIATION BOOM  
By WALT BOGDANICH

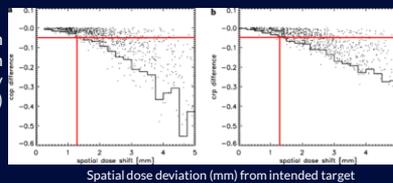
A Pinpoint Beam Strays Invisibly, Harming Instead of Healing  
Published: December 28, 2010

Radiation Offers New Cures, and Ways to Do Harm  
Published: January 23, 2010

More likely...this sort of thing can happen:

You can miss your target...

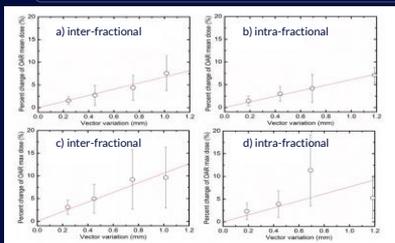
Change in obliteration probability (AVMs)



Change in remission probability (mets)

Treuer H, Kocher M, Hoelsch M, et al., Radiother Oncol., 2006 Oct;81(1):25-32.

...and you can hit an OAR instead.



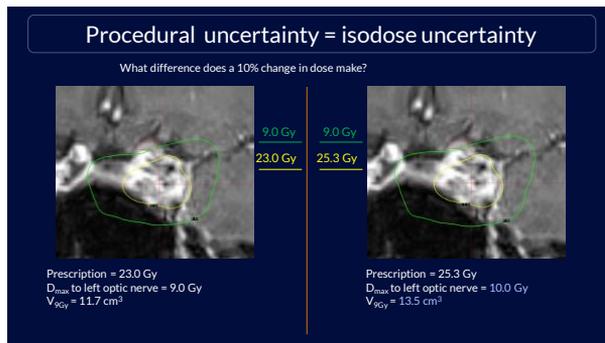
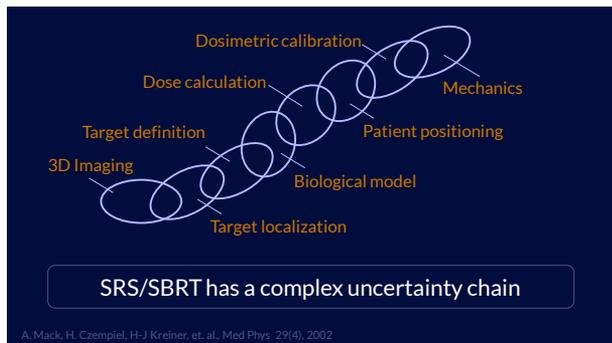
Change in mean OAR dose vs positioning deviation

Change in max OAR dose vs positioning deviation

Kim et al., Inter- and intrafractional dose uncertainty in hypofractionated Gamma Knife radiosurgery, JACMP, 17(2), 2016.

Radiosurgery is hard.

Uncertainty makes it harder.



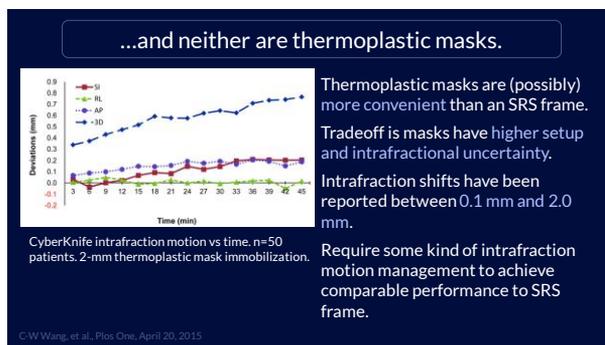
### Stereotactic frames/fiducials are not perfect...

Difference between frame/fiducial and cone-beam CT defined SRS coordinate systems, n=150 frame cases

Shift direction (units)	Absolute Mean Shift	Median Shift	Standard Deviation	Range
Pitch (degrees)	0.14	-0.02	0.19	-0.71 to 0.63
Yaw (degrees)	0.16	0.05	0.21	-0.5 to 0.83
Roll (degrees)	0.12	0.02	0.15	-0.37 to 0.51
Left-right (mm)	0.29	-0.12	0.35	-1.29 to 0.82*
Anterior-posterior (mm)	0.24	-0.21	0.19	-0.59 to 0.33
Superior-inferior (mm)	0.24	0.13	0.27	-0.69 to 0.91

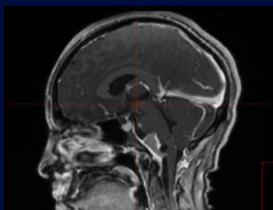
\* 3 cases exceeded 1.0 mm translational difference, all in the left-right direction (-1.05, -1.13, -1.29 mm)

S. Dutta, et al., IJROBP, in press, 2018





...and it can be difficult to localize a target



Does this MR have distortion?

## Sources of MR geometric distortion

### System-level

Caused by hardware imperfections  
 Static-field inhomogeneities  
 Gradient nonlinearities  
 Gradient and RF frequency maladjustments  
 Eddy currents due to gradient switching

Worse on periphery of image  
 Mostly correctable with vendor-supplied algorithms (gradient coil modeling)

**Both tend to be worse at higher field strengths and better with higher bandwidth!**

J. Weygand, et al., IJROBP 95(4), 2016; A. Fransson et al., Strahlenther. Onkol, 2001.

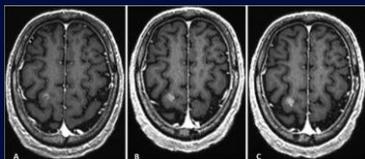
### Patient-specific

Caused by magnetic properties of individual patients

Magnetic susceptibility  
 Chemical shift

More difficult to correct, but usually smaller in magnitude

Even subtle timing differences can matter



Scan 1: time of injection  
 Scan 2: ~10 min delay  
 Scan 3: ~15 min delay

Scans compared (n=53 studies)	% studies w $\geq 1$ new lesion	95% CI	Range of # new lesions
Scan 1:2	35.3%	22.4%-49.9%	1-10
Scan 2:3	21.6%	11.3%-35.3%	1-9
Scan 1:3	43.1%	29.3%-57.8%	1-14

M. Kuzhmirsky et al., JNS 124, 2016.

Re-irradiation makes uncertainties more critical.

What is Gamma Knife radiosurgery?

Gamma Knife re-irradiation scenarios

What makes re-irradiation difficult?

Evolution of Gamma Knife for re-irradiation

Gamma Knife accuracy and precision

Support for multiple fractions

Workflow flexibility

Quantitative imaging

### Mechanical accuracy and precision

**Linear encoders**  
Resolution: 0.01  $\mu\text{m}$   
Accuracy over entire length of scale:  $\pm 5 \mu\text{m}$



System gets target coordinate and calculates # encoder rotations

↓

Rotational encoder tracks motion

↓

System compares linear encoder to desired position. Must be within tolerance.

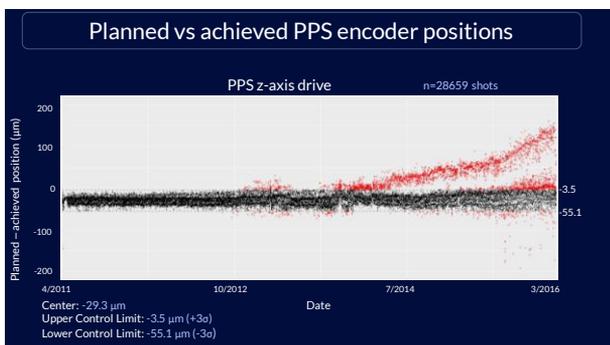
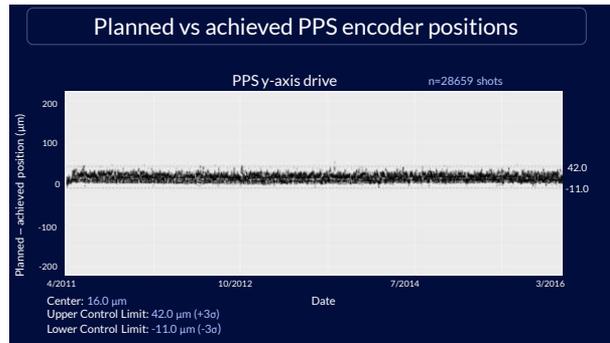
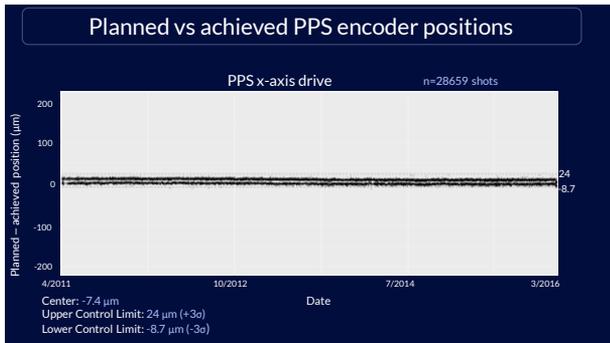
**Rotational encoders**  
2000 pulses per rotation  
Pitch on sector screws is 1mm  
Resolution: 0.5  $\mu\text{m}$



### Mechanical specifications

Specification	Tolerance	Source
RFP vs PPS (master diode, center target, 4mm isocenter)	<0.15mm (0.08 at installation)	Preventive maintenance procedures
RFP vs PPS (master diode, center target, 8/16 mm isocenter)	<0.2mm	Preventive maintenance procedures
RFP vs PPS (master diode, off-center target, 4mm isocenter)	<0.4mm	Preventive maintenance procedures
RFP vs PPS (site diode)	<0.5mm	Perflexion user's manual
Film RFP vs PPS	<0.3mm per axis, <0.4mm radial, at 50% line	Acceptance procedures
Sector positions	<0.1mm, all sectors/sector positions	Preventive maintenance procedures

RFP = radiation focus point PPS = patient positioning system (treatment bed)



### Gamma Knife technical fault – 3/2016

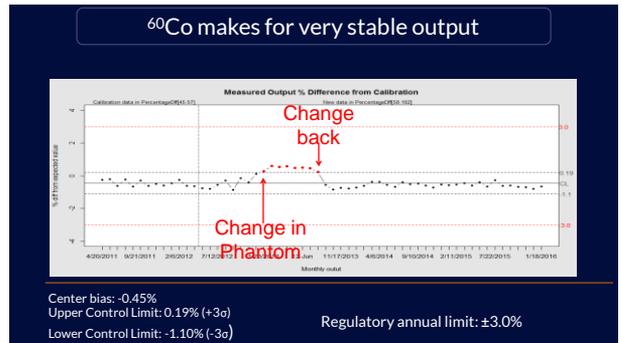
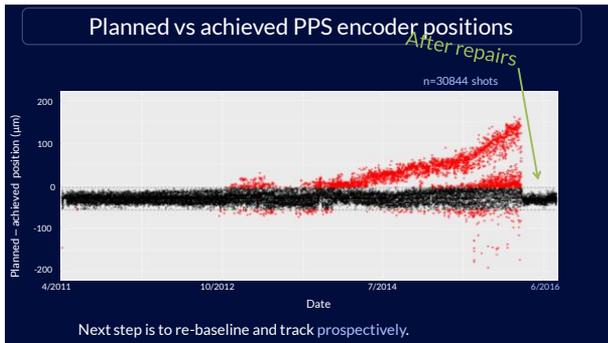


Gamma Knife Z drive  
(looking up at PPS)



Faulty gearbox spacers

Decayed spacers allowed increase torque on Z-drive gearbox with increasing PPS travel in into the unit.  
 Torque released tension on drive belt, so bed would stop moving while drive was still moving.  
 Control system would eventually time out and cause a system fault.



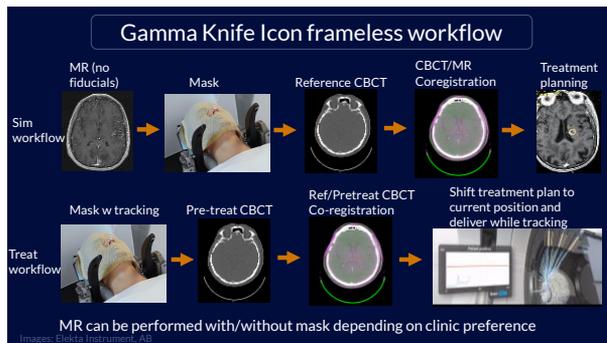
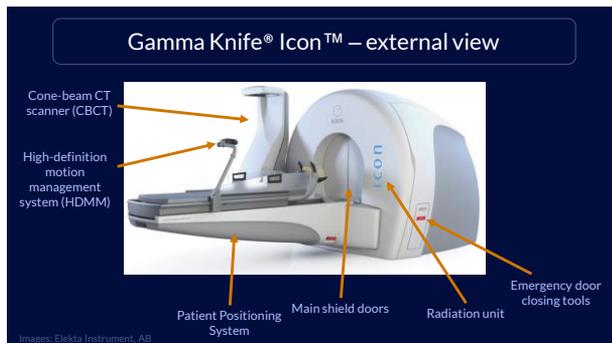
### Stereotactic frames help patients to be still

SRS frames provide for low setup uncertainty and robust immobilization. Practically limits treatment to single fraction. Looks more invasive than it really is.

	Setup Error				Intrafraction Error			
	Translation (mm)			Rotation (°)	Translation (mm)			Rotation (°)
	LR	AP	CC	Vector	LR	AP	CC	Vector
Mean	-0.19	0.08	-0.35	0.40	0.14	-0.03	0.10	0.05
SD	0.32	0.29	0.50	0.66	0.25	0.19	0.20	0.22

Li, et al., IJROBP 2016.

- Gamma Knife accuracy and precision
- Support for multiple fractions
- Workflow flexibility
- Quantitative imaging



### Cone beam CT system

	CTDI 2.5	CTDI 6.3
	2.5 mGy	6.3 mGy
Charge/projection	0.4 mAs	1.0 mAs
Tube current	0.1 mA	0.25 mA
X-ray energy	90 kV	90 kV

### Cone beam CT system

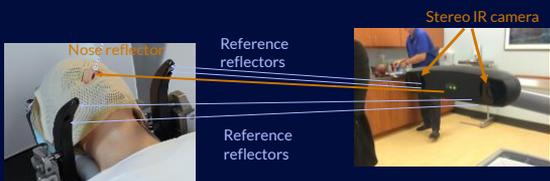
Characteristics	Value
Source to axis distance (SAD)	750mm
Source to detector distance (SDD)	1000mm
Magnification factor	1.27
Reconstructed volume	224 x 224 x 224mm <sup>3</sup>
Cone beam angle	35°
Fan angle	35°
Scan time	30s
Film	< 0.2mm

Components	Properties
Detector	Layers: Cu, Tl <sup>+</sup> (amorphous Si) 760 x 720 pixels (dashed mode), Pixel resolution = 0.368 mm
X-ray tube	Energy range: 70-120 kVp, Spot size: 0.6 mm, Weight: 17kg

Table 1: The geometric characteristics of the CBCT system.

Table 2: Components.

### High-definition motion management (HDMM)



The HDMM system tracks the relative position of a marker placed on the patient's nose vs four reference markers built into the mask adapter (on black posts).

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### Intra-fraction motion management with GK Icon



A clinical threshold is set for nose marker motion

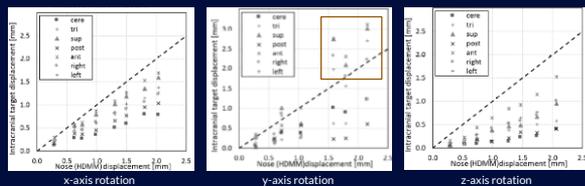
Baseline is established as time-averaged nose marker position during pre-treatment CBCT

System gates on and off if nose marker deviates above line

Re-baseline (CBCT) required if patient remains out of position

UVA Gamma Knife Center

### Nose marker tracking seems mostly conservative



For most cases, tumor anatomy will deviate less than the nose marker



G. Wright, et al., JRSBRT 4, 2017

original image from: netmeister.com

Gamma Knife accuracy and precision

Support for multiple fractions

Workflow flexibility

Quantitative imaging



Dose contributions can be examined in detail

Replan case: Dose contribution from both treatments



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Gamma Knife accuracy and precision

Support for multiple fractions

Workflow flexibility

Quantitative imaging

Not specific to Gamma Knife SRS, but important for re-irradiation

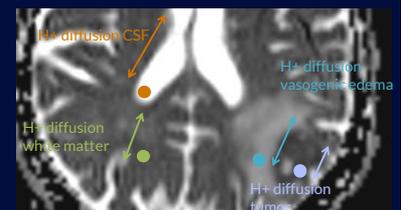
Diffusion-weighted (DWI) imaging

Indirectly measures the "cellularity" of tissue  
CSF has fewer cells, less restrictive to diffusing H+

Actively growing tumors have many cells, more restrictive to diffusion.

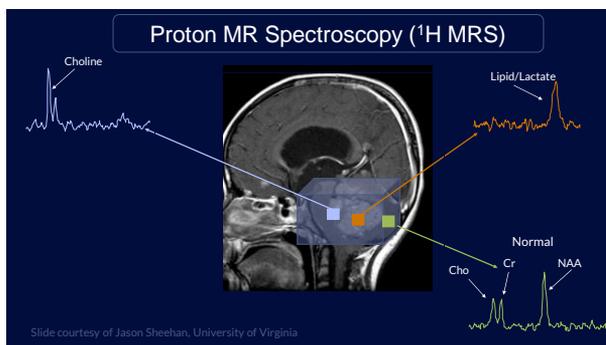
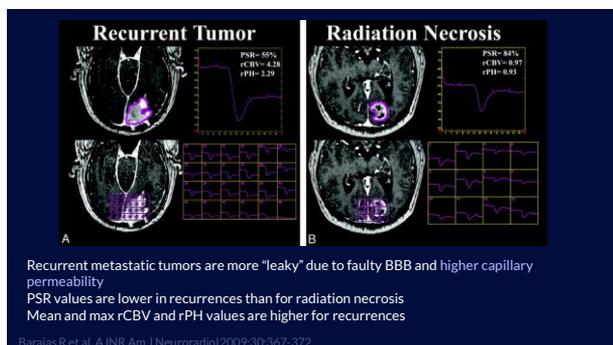
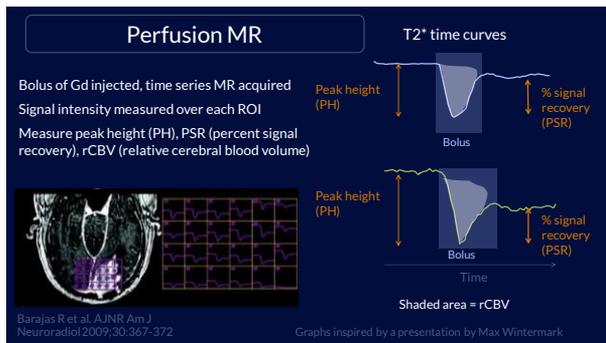
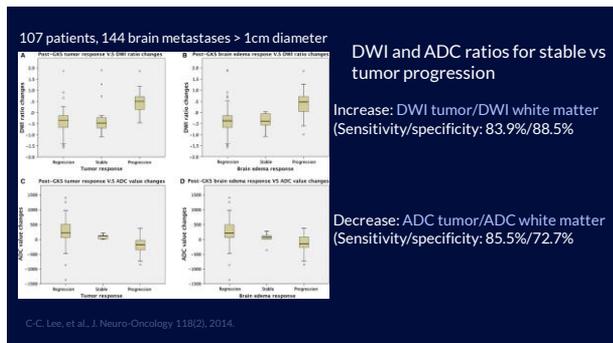
Often expressed in terms of an apparent diffusion coefficient (ADC)

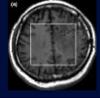
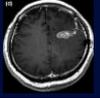
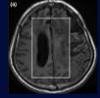
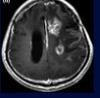
Fractional anisotropy (FA) – measurement of diffusion directionality



ADC map brain with brain metastasis

Slide adapted from a presentation by Max Wintermark. Images courtesy UVA.



Radiation injury vs recurrent glioma				
	T1 MR w ROI	T1+C MR	MR Spect	Ratio differences
Radiation injury				
Recurrent tumor				>Cho/Cr* >Cho/NAA* <NAA/CR* *p<0.01, n=55

Q. Zeng, et al., J Neurooncol 84(1), 2007

## Conclusions

Stereotactic radiosurgery requires careful understanding of procedural uncertainties

Re-irradiation reduces the acceptable uncertainty budget

Gamma Knife radiosurgery assists in re-irradiation scenarios by minimizing the beam-delivery portion of the uncertainty chain

Quantitative imaging can help evaluate when re-irradiation is appropriate

Thank You!

### Acknowledgements

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Elekta Instrument, AB  
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 Jonas Johansson

And of course the organizers – Thank You!



One-way to get re-irradiated. (Hint: don't do this with a loaded Gamma Knife!)