Advances in Modern Radiosurgery for Brain metastases: From the Gamma Knife to the LINAC

The Next Paradigm in Intracranial Radiosurgery

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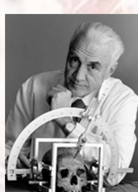
What is stereotactic radiosurgery?

- Stereotactic, from the:
  - Greek στερεός (stereos), meaning *solid*
  - New Latin suffix –taxis, meaning *arrangement*
  - Application of a systematic coordinate system (Cartesian, polar, et al) onto an anatomical structure
- Radiosurgery
  - Term possibly first used in a lecture by Dr Francis Hernaman-Johnson to the Royal Society of Medicine in 1920, "On the value of combined treatment, with special reference to surgery, electricity and X rays"

What is stereotactic radiosurgery? (cont'd)

- Application of the term as we know it, first published in 1951

Leksell, Lars. "The stereotactic method and radiosurgery of the brain." *Acta Chir Scand* 102 (1951): 316-319.



Evolution of early stereotactic apparatuses (left to right): Horsley-Clark frame, first stereotactic apparatus, conceived to study monkey cerebellar function, circa 1908; Spiegel-Wycis Model I, adaptation of the Horsley-Clarke frame for human use, circa 1945; First version of the Leksell stereotactic frame.

What does "radiosurgery" actually mean?

- Stereotactic radiosurgery (SRS)
  - Term preferred by neurosurgeons to describe the ablative delivery of *single* high dose of radiation in lieu of other techniques such as RF ablation or direct EtOH injection
- Fractionated stereotactic radiosurgery (fSRS)
  - Neurosurgeon preferred term when treatment was divided into multiple fractions (or hypofractionated SRS – (hfSRS))
- Fractionated stereotactic radiotherapy (fSRT)
  - Radiation oncologist preferred term for division of procedure into multiple fractions (or hfSRT for shorter division of treatments)

So which term do I use?

- Per ASTRO now, you can use SRS to refer to radiation treatment of any intracranial tumor/target or select base of skull tumors in 1 – 5 fractions at an approximate 1mm accuracy
  - For additional documentation precision, presenter's preference is to refer to anything between 2 and 5 fractions as hfSRT

What constitutes SRS treatment?

Table 44.1 Mandatory components of SRS treatment per ASTRO Model Policy

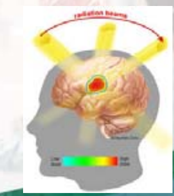
1	Position stabilization (attachment of a frame or frameless)
2	Imaging for localization (CT, MRI, angiography, PET, etc.)
3	Computer-assisted tumor localization (i.e., "image guidance")
4	Treatment planning – Number of isocenters; number, placement, and length of arcs or angles; number of beams, beam size and weight, etc.
5	Isodose distributions, dosage prescription, and calculation
6	Setup and accuracy verification testing
7	Simulation of prescribed arcs or fixed portals
8	Radiation treatment delivery

Table 44.2 Indications and limitations of coverage and/or medical necessity

Primary and secondary tumors involving the brain parenchyma, meninges/dura, or immediately adjacent bony structures
Benign brain tumors such as meningiomas, acoustic neuromas, other schwannomas, pituitary adenomas, pineocytomas, craniopharyngiomas, glomus tumors, or hemangioblastomas
As a boost treatment for larger cranial or spinal lesions that have been treated initially with external beam radiation therapy or surgery (e.g., sarcomas, chondrosarcomas, chordomas, and nasopharyngeal or paranasal sinus malignancies)
Metastatic brain, independent of the number of lesions if other positive clinical indications exist, with stable systemic disease, Karnofsky performance status 40 or greater (and expected to return to 70 or greater with treatment), and otherwise reasonable survival expectations, *or* ECOG performance status of 3 or less (or expected to return to 2 or less with treatment)
Relapse in a previously irradiated cranial where the additional stereotactic precision is required to avoid unacceptable vital tissue radiation

First experiences with SRS

- In a 1981 lecture to the Society of British Neurological Surgeons, Leksell remarked:
- “The first attempt to supplant the electrodes with ionizing radiation was made in the early fifties, with X-rays. It was tempting to try and reduce the hazards of open surgery and by the administration of a single heavy dose of radiation it appeared possible to destroy any deep brain structure, without risk of bleeding or infection.”

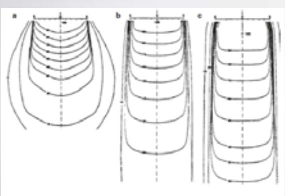


First experiences with SRS (cont’d)

- Contrary to common notion, the first radiosurgeries were not done with Gamma Knife
- First done with 200kV orthovoltage x-ray tubes
- Single fraction doses of 150 – 250Gy

First trial of stereotactic radiosurgery used a 200 kVp X-ray tube mounted on a stereotactic frame

First experiences with SRS (cont’d)



Isodose distributions of 10 cm × 10 cm fields for (a) 200 kVp, SSD = 50 cm, HVL = 1 mm Cu; (b) cobalt-60, SSD, 80 cm; (c) 10 MV X-rays, SSD = 100 cm

- Was very quickly obvious to Leksell that orthovoltage was not ideal for deep-lying targets

“At present X-rays and gamma rays would seem to be the most promising and the easiest to apply**. It is clear, however, that the radiation in the 200 kilovolt range used here should be replaced by radiation of higher energy**. This would give a better depth dose, especially with the extremely small fields used here, and also a better definition of the beam”

Evolution of stereotactic radiosurgery - particles

- After the inadequacy of orthovoltage kV was realized, Leksell turned to particle therapy, which US surgeons and scientists had recently begun exploring

Lars Leksell and his physicist colleague, Borje Larsson, preparing a patient for SRS with a particle beam accelerator in 1958

(left) view from the Divinity school overlying the Harvard Cyclotron Facility, (right) cyclotron during construction in 1948

Evolution of stereotactic radiosurgery - particles

Raymond Kjellberg with a frame for proton beam
therapy of a patient with an AVM.

Leksell preparing a radiosurgery with a proton beam generated by the Uppsala synchrocyclotron in 1960

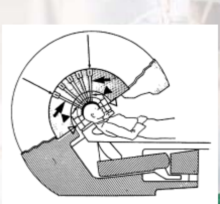
Evolution of stereotactic radiosurgery – Gamma Knife

- Having had enough of dealing with the cumbersomeness of cross-fired proton beams, and poor dosimetry of orthovoltage x-rays, Leksell and his physicist Larrson selected Co-60 as ideal photon source
- 179 bb-sized Co-60 sources in hemi-spherical array
- First GK produced discoid shaped lesions

Leksell with patient affixed within the first Gamma unit (deployed in 1968)

Evolution of stereotactic radiosurgery – Gamma Knife

- Demand for this radiosurgical technique was immediate
- Leksell founded Elekta in 1972
- Second prototype gamma unit, Karolinska University Hospital, installed in 1974
  - Produced more spherical lesions
- First commercial Gamma Knife installed in 1982



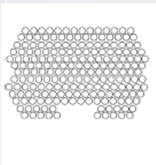
Evolution of stereotactic radiosurgery – Gamma Knife

- The superficial ends of the collimators are the round visible in this picture. Note that the opening is rectangular. This shape was optimal for the thalamotomies which a major indication forwhich the Gamma Unit was designed.
- Indication became greatly reduced following the introduction of L-Dopa at about the same time.

Superficial view of second gamma unit collimator

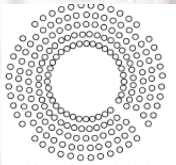
Evolution of stereotactic radiosurgery – Gamma Knife

U Model



Viewed from on top

B model



Viewed from on behind

In the U model the patient slides into the machine and then upwards. The sources and hence collimators are asymmetrically arranged in respect of the head in an upper quadrant of the machine as shown in the figure. The B model had the sources arranged symmetrically in circles around the top of the patients head. In view of the treatment positions in the two machines the views in the figure are from the top on the left and from behind in the patient. However, this is the same direction as in both instances the collimators are viewed looking at the top of the patient’s head. Another consequence of this arrangement was that in the U model the asymmetry meant it was sometimes preferable to treat a patient prone, whereas in the B model the symmetry made this unnecessary

Evolution of stereotactic radiosurgery – Gamma Knife

Shows the B model helmet filled with 8 mm collimators and also shows the 4 collimator sizes. Shows the trunnions (lower left) and attachments (lower right) used to fasten the frame to the helmet. As can be seen there is limited space within the helmet, so correct frame placement is a priority with this Gamma Knife model

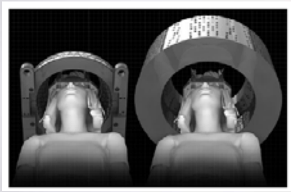
Evolution of stereotactic radiosurgery – Gamma Knife

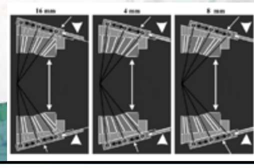
- Four most commonly utilized collimator helmet sizes
- (4mm, 8mm, 14mm, 18mm)

Evolution of stereotactic radiosurgery – Gamma Knife

First gamma unit	1967
Second gamma unit	1974
Gamma Knife Model U/A	1980s
Gamma Knife Model B	1980s – 1990s
Gamma Knife Model C	2000 (U Pitt)
Gamma Knife Model 4C	2005 (U Pitt)
Gamma Knife Perfexion	2006 (Marseilles)
Gamma Knife Icon	2015

Evolution of stereotactic radiosurgery – Gamma Knife Perfexion





- Automated collimator selection without helmets
  - Faster treatments
  - Easier utilization of multiple collimator sizes

Evolution of stereotactic radiosurgery – Gamma Knife Icon

- Availability of thermoplastic mask
  - Easier fractionation
- Onboard CBCT
- Real-time motion monitoring
  - Beacons on nose/mask horns
  - Thermal imaging?

Gamma Knife Workflow

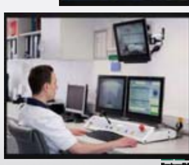
Gamma Knife Workflow (cont'd)

Step 3: A treatment plan is developed

Step 4: The patient lies on the treatment table of the Gamma Knife while the frame is affixed to the appropriate collimator.

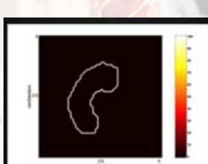
Gamma Knife Workflow (cont'd)

STEP 5: THE DOOR TO THE TREATMENT UNIT OPENS. THE PATIENT IS ADVANCED INTO THE SHIELDED TREATMENT VAULT. THE AREA WHERE ALL OF THE BEAMS INTERSECT IS TREATED WITH A HIGH DOSE OF RADIATION.

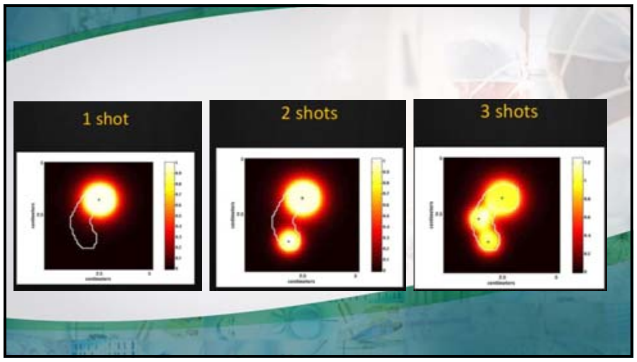


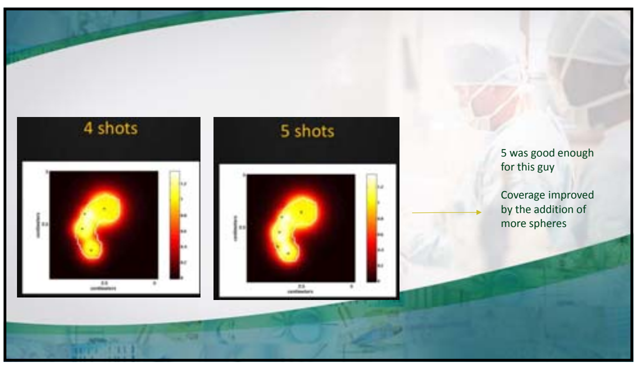
GK Treatment Planning

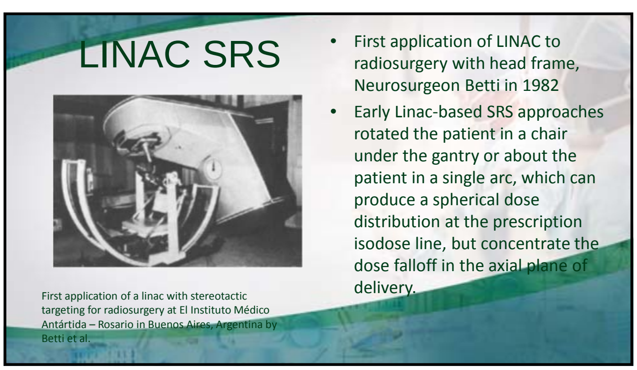
- Through an iterative approach we determine:
  - the number of shots
  - the shot sizes
  - the shot locations
  - the shot weights
- The quality of the plan is dependent upon the patience and experience of the user



Example Target


1 shot
2 shots
3 shots

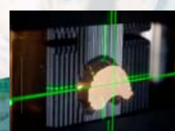

4 shots
5 shots
5 was good enough for this guy
Coverage improved by the addition of more spheres


LINAC SRS
• First application of LINAC to radiosurgery with head frame, Neurosurgeon Betti in 1982
• Early Linac-based SRS approaches rotated the patient in a chair under the gantry or about the patient in a single arc, which can produce a spherical dose distribution at the prescription isodose line, but concentrate the dose falloff in the axial plane of delivery.
First application of a linac with stereotactic targeting for radiosurgery at El Instituto Médico Antártida – Rosario in Buenos Aires, Argentina by Betti et al.

Further LINAC SRS Landmarks

- Late 1980s – Led by William Friedman, Frank Bova, and others, the University of Florida was an early pioneer in linac radiosurgery.
- From the late 1980s onward, they amassed extensive experience treating a variety of pathologies with cone-based SRS.
- Early treatments used a single isocenter, but increased experience led them to utilize sphere packing of multiple isocenters for improved conformality of non-spherical targets

- 1993, Brainlab entered into a partnership with Varian Medical Systems with the intent of creating a linac dedicated to radiosurgery.
- A Varian 600SR was modified with the addition of a micro MLC to create the Novalis radiosurgery platform, and in 1997 the first shaped-beam dedicated radiosurgery platform was installed at UCLA.



- 1995 - Cedric Yu of the University of Maryland proposed simultaneously coupling dynamic MLC leaf movement with gantry movement
  - increase the efficiency and improve upon the general workflow of tomotherapy, which he called intensity-modulated arc therapy (IMAT)
  - Ahead of its time


Physics in Medicine & Biology

Intensity-modulated arc therapy with dynamic multileaf collimation: an alternative to tomotherapy

C X Yu

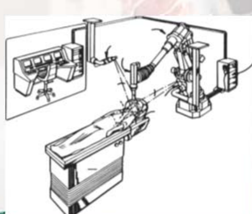
- 2005 – Karl Otto
  - Honed IMAT approach into VMAT algorithm
    - armed with a decade of improvements not only in MLC engineering but also the >25 factor increase in CPU clock speed
    - allowed complete treatment in one arc in the minimum gantry rotation period of 1 min
  - Three factors optimized/varied throughout treatment
    - MLC shaping, intensity, gantry speed


MEDICAL PHYSICS

Volumetric modulated arc therapy: IMRT in a single gantry arc

CyberKnife

- Conceptualized by Dr John Adler
  - Brigham trained neurosurgeon who fellowed under Dr Leksell
- Designed to bring radiosurgery outside of the brain
- Compact 6MV linear accelerator powered by an X-band RF source to a Japanese industrial Fanuc robotic arm


Original art from US Patent and Trade Office application for the CyberKnife robotic radiosurgery system

CyberKnife (cont'd)

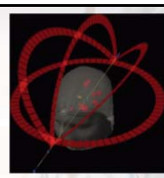
- Similar treatment planning approach to GK (sphere packing)
- Delivered in shots at various linac arm positions(called nodes)
  - Can be >200
- Can be outfitted with MLC or cones
- Typically uses continuous floor mounted kV images for image guidance

Radiosurgery @UAB

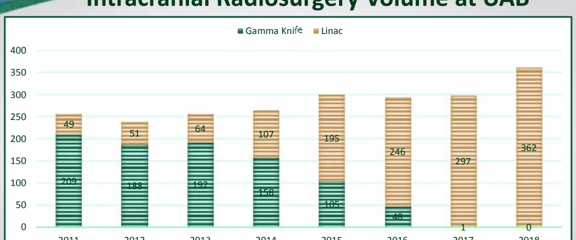
- Linac radiosurgery (1991)
- Gamma Knife™ (1995)
- Intensity Modulated Radiation Therapy (1999)
- CBCT image guidance (2004)
- RapidArc™ (2008)
- TrueBeam™ (2010)
  - High-intensity mode (FFF)
  - Gated RapidArc™
  - Triggered Imaging – (2011, 1st in world)
- Edge™ (2015)
- HyperArc (2017) – 1st in N/S America

Radiosurgery at UAB

- MLC-Linac based
- VMAT
- 10MV, w/ HDMLC, FFF (2400 MU/min)
- 6DOF couch
- Optical surface monitoring for intrafraction motion assessment



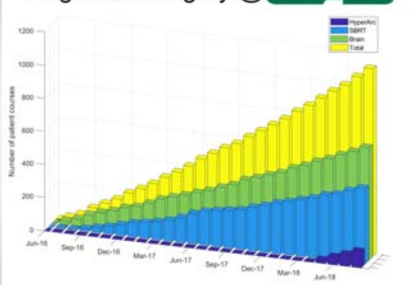
Intracranial Radiosurgery Volume at UAB



TrueBeam 2010, Edge 2016, Gamma Knife decommissioned June 2017

One Gamma Knife Case in 2017

Edge radiosurgery @UAB

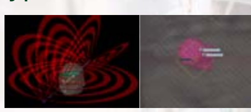


HyperArc – What exactly is it?

- Technology to **automate** and **simplify** sophisticated intracranial radiosurgery
- Treatment planning
  - pre-specified beam templates
  - one-click SRS designed normal tissue optimizer
- Treatment delivery
  - Templated delivery and modeling of couch allow seamless automation of the couch movements for non-coplanar arcs
- **Plug and play radiosurgery**

Who is Not Getting HyperArc at UAB?

- Functional SRS
  - trigeminal rhizotomy
  - tremor thalamotomy
  - OCD capsulotomy (soon)
- Single target with isocenter outside protection zone
- Very infrequent tumor that represents a predominant organ avoidance treatment planning problem



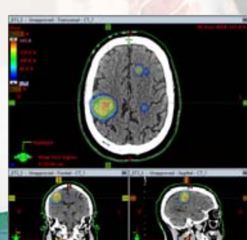
(left) 20-arc treatment geometry, and (right) beam's-eye view of fixed 2.1mm x 5mm MLC aperture for each arc

HyperArc improves RapidArc Dosimetry

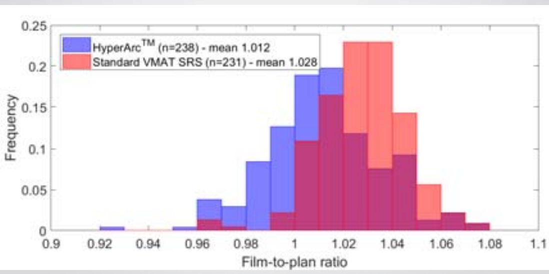
- n = 6,
- GTV_{total} = 17.75cc
- Rx = 30Gy, Fx = 5

UAB Clinical (RapidArc – UAB Recipe)

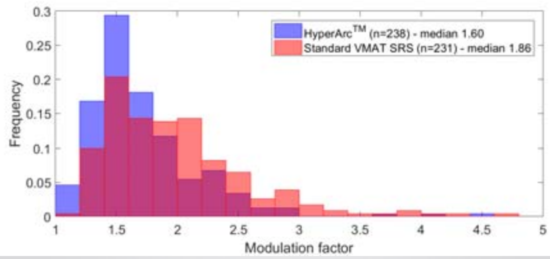
HyperArc Re-Plan



Film to plan ratio - HyperArc™

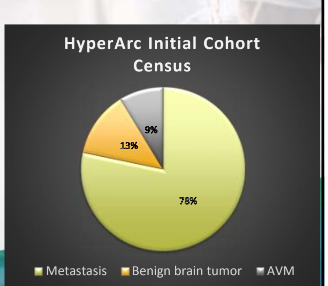


Modulation factor



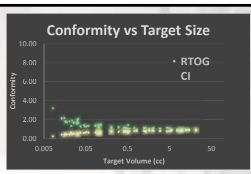
HyperArc Initial Cohort Outcomes

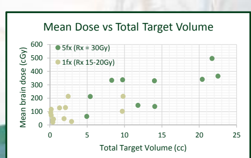
- 23 patients
  - 19 alive
    - Deaths (2 hepatic failure, 1 acute metabolic encephalopathy [age 91], 1 pneumonia)
  - Median f/u = 14.0 months
- 62 treated lesions
  - 57 metastases (18 patients)
    - 41 lesions (15 patients) had avail imaging f/u
      - 2 patients passed from fulminant hepatic failure 2/2 rapid liver progression prior to first scan
      - 1 patient elected for all f/u in hometown
  - LC 39/41 (95.1%)
    - Failures:
      - Rectal ca x1 (1.9cc, rx = 20Gy)
      - Melanoma (BRAFmut, 0.05cc, rx = 20)



HyperArc Initial Cohort Plan Quality

- 62 targets (n = 1 -13 /plan)
  - Volume
    - Range: 0.0081cc – 20.5cc
    - Mean 2.65cc, Median 0.2cc
  - Conformity
    - RTOG CI
      - Range: 0.98 – 3.24
      - Mean 1.37, median 1.23





HyperArc Delivery times – very short!

- **Total setup and delivery time is 10 – 15 minutes**
  - Includes initial kV/kV match
  - CBCT
    - CBCT / CT sim match
    - Manually verified by RO & NS
    - No 2nd CBCT if shift magnitude is very small (~0.1mm)
  - Delivery of 2 to 4 arcs
    - 360° arc = ~1 min
    - 180 ° arc = ~ 36 sec
    - Auto sequencing eliminates room entries

HyperArc

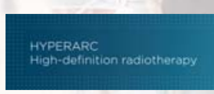
Without HyperArc

- Generating high quality plans for traditional RapidArc can be somewhat onerous for plans with many targets, or multiple prescriptions
  - Ring structures, Boolean operations, manual individual dose level manipulation

With Hyperarc

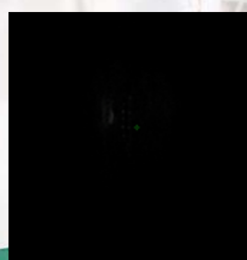
- Seamless, integrated automation of ring structure based optimization into an easy to use radically revised SRS specific NTO
- Simplified workflow
- Pre-ordained geometry template that designed to meet planning goals for nearly all cases

- Massive reduction in SRS treatment planning time
- Systematic SRS treatment planning results



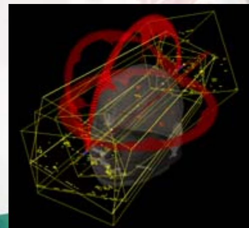
Clinical Case

- 68yoCM w/ hx of metastatic ocular melanoma
  - DecisionDx-UM assay, Class 2 (high metastasis risk)
  - 10/2015 – L eye plaque brachytherapy
  - 02/2016 – Liver metastases discovered
  - 06/2016 – initiated Keytruda via clinical trial
  - 09/2017 – dc'd Keytruda 2/2 pneumonitis
  - 06/2018 – presented to ED w/ 2wk hx of worsening L hemibody weakness, ataxia
    - 8 small, 2 large hemorrhagic (R frontal) metastases
    - 06/25/2018 - Resection of large metastases
  - 07/2018 - 20Gy/1fx to 8 small mets,
  - 08/2018 - Sequential 30Gy/5fx to 2 resection cavities

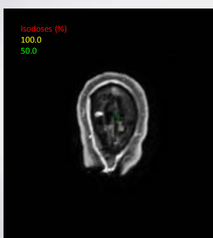


20Gy/1fx to 8 metastases

GTV	Volume (cc)
1	0.127463
2	0.372552
3	0.026953
4	0.126932
5	0.177291
6	0.355489
7	0.303539
8	0.0543596



HyperArc (Plan 1) Quality
20Gy/1fx, GTV 1-8



GTV	Volume (cc)	RTOG CI
1	0.13	1.16
2	0.37	1
3	0.03	1.49
4	0.13	1.19
5	0.18	1.19
6	0.36	1.27
7	0.30	1.16
8	0.05	1.55
	V12Gy (cc)	7.19
	Mean brain (cGy)	178.1
	Plan CI	1.24
	Plan GI	6.7

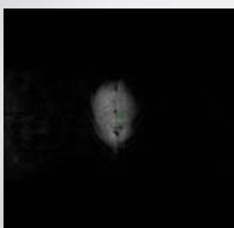
Treatment (Plan 1)
20Gy/1fx, GTV 1-8

- KV setup (AP & Lat)
- CBCT match
- Treatment
  - CW Arc
  - LPO Arc
  - RAO Arc
  - Vertex Arc
- Alignment & Treatment
  - Total treatment time: **13 minutes, 1 second**

30Gy/5fx to 2 resection cavities

GTV	Volume (cc)	RTOG CI
9	7.01	1.08
10	4.56	1.1
	V18Gy (cc)	31.36
	Mean brain (cGy)	210.8
	Plan CI	1.08
	Plan GI	3.37

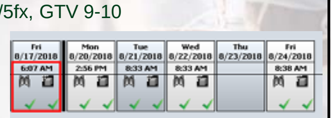
HyperArc (Plan 2) Quality
30Gy/5fx, GTV 9-10

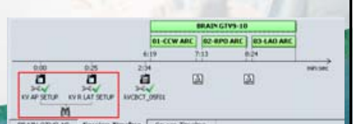


GTV	Volume (cc)	RTOG CI
9	7.01	1.08
10	4.56	1.1
	V18Gy (cc)	31.36
	Mean brain (cGy)	210.8
	Plan CI	1.08
	Plan GI	3.37

Treatment (Plan 2)
30Gy/5fx, GTV 9-10

- KV setup (AP & Lat)
- CBCT match
- Treatment
  - CCW Arc
  - RPO Arc
  - LAO Arc
- Alignment & Treatment for each fx
  - 10 minutes, 5 seconds
  - 9 minutes, 11 seconds
  - 10 minutes, 49 seconds
  - 10 minutes, 17 seconds
  - 9 minutes, 0 seconds

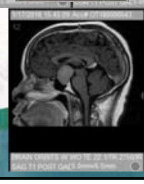




Pituitary Case

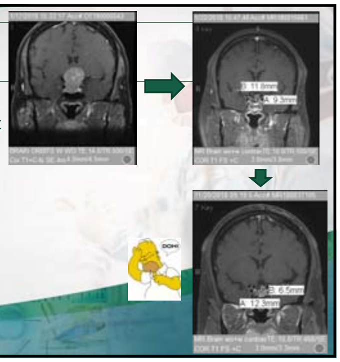
- 41yoAAM Crimson Tide Fan
  - 2y hx of headache, left visual loss
  - Ophtho exam shows OS acuity loss, >1.2log RAPD, poss bitemp hemianopsia
    - Sent for MRI for concern of pituitary tumor
- MR shows 3.6cm x 3.0cm sellar/suprasellar mass extending into the suprasellar cistern with moderate mass effect on optic chiasm
- Lab w/u rules out prolactinoma

Prelim labs:
Prolactin 6.2
Cortisol 3.3
FT4- WNL but low
FT3- WNL
HCT- 36
Na 136
Gluc- 113



Pituitary (cont'd)

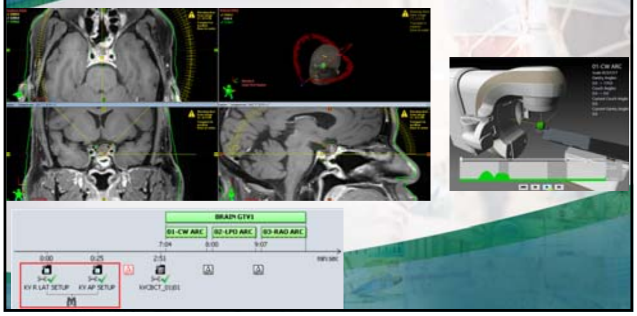
- 02/2018 – undergoes transphenoidal what is thought to be GTR
  - Path c/w null cell adenoma
- 05/2018 – f/u shows residual tumor (STR)
  - Panhypopit -> put on replacement
- 11/2018 – f/u imaging shows growth of resid tumor



Pituitary (cont'd)

- Referred to radiation oncology for salvage tx
- Considerations
  - No OS vision, only OD acuity intact
  - Aggressive sparing of R optic nerve and chiasm
- Decision made to treat 25Gy/5fx to ensure minimal risk of further compromising ability to watch Alabama play in yet another NCAAF National Championship

Pituitary (cont'd)



HyperArc Takeaways

- Faster planning
  - Increased dosimetrist utilization
  - Faster turn around
  - More time scheduling the cases than planning
- More consistent planning
  - Less inter-planner variability
  - Consistently reproducible high quality SRS plans
- Faster delivery
  - Happy patients
  - Happy radiation oncologists
  - Happy neurosurgeons

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John Fiveash
Professor & Vice-chair
Radiation Oncology

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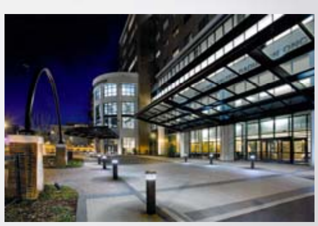


QUESTIONS
ANSWERS