Stereotactic high-dose per fraction radiation: what, why, and how

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Disclosures: I have none

Glossary

- OAR: Organ at risk
- CFTR: Conventionally-fractionated radiotherapy
- SBRT: Stereotactic Body Radiotherapy
- SABR: Stereotactic Ablative Radiotherapy
- SRS: Stereotactic Radiosurgery (denotes single fraction)
- fSRS: fractionated SRS

Primary Learning Objectives

- Define SBRT /SRS
- Understand the applicability of radiobiology in the clinic (as it pertains to SBRT/SRS)

What's in a name?

- Stereotactic Radiosurgery (SRS): Stereotactic radiation for the brain or spine
- Stereotactic Body Radiation Therapy (SBRT): Stereotactic radiotherapy outside the brain
- Stereotactic Ablative Radiotherapy (SABR): another name for SBRT that some prefer becomes it denotes “ablative” intent
- Stereotactic: uses a 3-Dimensional coordinate system
- Ablate: to destroy (akin to surgery)
- All terms refer to high dose RT per fraction, delivered in a limited number of fractions (~5 or less) with ablative intent (range of dose per fraction is not strictly defined because of situational dependencies, but generally means at least 7 Gy per fraction)

SBRT credo

- There are advantages to high dose per fraction compared to CFRT (beyond patient convenience) that outweigh the potential disadvantages (potential toxicity)

- Higher dose per fraction RT can be delivered safely (based on technology and practitioner skill)

- Therapeutic ratio of SBRT exceeds that of CFRT

    - SBRT achieves outcomes unachievable with CFRT (cure or ablation)

Radiobiology of SBRT (2 challenges)

- 1. We don’t have a validated model for SBRT for estimating tumor killing or normal tissue toxicity
- 2. We don’t really know if there are unique ways that SBRT kills tumors or damages normal tissues compared to CFRT.

The 4 Rs

- Established within the context of CFTR
- Re-oxygenation, re-distribution, re-pair, and re-population don't make sense in the context of single fraction radiation
- Re-oxygenation, re-distribution, re-pair may apply in fractionated SBRT/SRS
- The 5th R (radio-sensitivity) remains applicable and relevant in some SBRT/SRS contexts

Certain tumors appear are more resistant than others (even to SBRT/SRS)

- Sandhu_JNS_2020: 32% rate local failure post spine SBRT for metastatic tumors of gastrointestinal origin (particularly colorectal cancer)
- Zeng_JNO_2021: Local failure after spine SBRT for radio-resistant pathologies (melanoma, sarcoma, GI, thyroid) 22% compared to 8% (prostate)
- Binkley_IJROBP_2015: Local failure after lung metastasis SBRT for colorectal cancer 42% vs. 10% for all other histologic types
- Ahmed_IJROBP_2016: Local failure post-liver SBRT 41% for colorectal cancer vs. 100% for all other subtypes

We have little knowledge of whether, when or how SBRT is “better” than CFRT

Even if higher dose → better tumor killing → better local control, in many clinical scenarios it is hard to predict whether improved local control will be relevant because of the competing risk of death or toxicity

Potential Radiobiologic mechanisms of SBRT/SRS (I)

- Clonogenic assays suggest mechanisms secondary to DNA damage
- Radiation-induced damage to tumor vasculature (e.g. Ceramide-mediated apoptosis of tumor vascular endothelium (Garcia-Barros_Science_2003))
- Defining these mechanisms important because if they could be manipulated so could the therapeutic ratio (for tumors adjacent to sensitive OARs or radio-insensitive tumors)
- Immune activation (abscopal or otherwise)

Potential Indirect mechanisms for SBRT (II)

- Vascular endothelial injury
  - challenged by experiments in which the endothelial cells were rendered resistant or hyper-sensitive to radiation induced apoptosis in mice without affecting tumor killing[1]
- Immune activation
  - Evidence that SBRT reduces the recruitment of immune effectpr cells compared to CFRT[2] vs reports suggest it activates suppression[3]
  - Since the initial excitement about abscopal effects with ipilimumab and SBRT in melanoma[4], trials have failed to detect a consistent signal

1. Moding et al, Sci Tansl Med. 2015
2. Lan et al, IJROBP, 2018
3. Li et al, IJROBP, 2019
4. Postow et al, NEJM, 2012

Nevertheless, with any kind of radiotherapy, more is usually better in terms of tumor killing and thus durable local control

- Rades et al_RO_2018 compared 8 Gy x1 to 4 Gy x 5; re-treatment rates at 6 months were 14 and 3% (p = 0.007).

SBRT “better” than CFRT : stage I non-small cell lung cancer

- Stage I Non-small cell lung cancer is defined as < 4cm in max diameter without nodal or metastatic involvement
- RTOG 0236, a successful SBRT trial: phase II, NSCLC < 5 cm (peripheral) and non-operable. 54 Gy in 3 fx. 7% LF at 5 years = curative treatment
- Ball_LancetOncol_2019: SBRT (54 Gy in 3 fx or **48 Gy in 4 fx**) vs. CFRT (**66 Gy in 33 fx** or 50 Gy in 20 fx). LF rate 14% SBRT vs. 31% CFRT (OS was also improved with SBRT)
  - 66 Gy/33fx BED_{10}=79.2
  - 50 Gy/20fx BED_{10}=62.5 (insufficient dose)
  - 48 Gy/4 fx BED_{10}=105.6
  - SPACE trial[1] (66 Gy/3fx vs 70 Gy/25fx) revealed equivalent LF

1. Nyman_RadiotherOncol_2016

Models

- LQ may overestimate SBRT dose effect or underestimate (because it does not account for secondary mechanisms)
- Those who think it may overestimate can use the LQ-L model, which transitions from the LQ model to a linear tail at high doses (requires definition of when to transition and log kill in the linear portion)
- Some argue (e.g. Song et al. April 2021 HyTec Red journal) that without understanding mechanisms we cannot appropriately model
- In the clinic, modeling normal tissue dose is just as if not more important than tumor killing, since our goal is really to deliver as much dose as is safely possible
- From a clinical perspective, very few trials have applied volume-adapted dosing (Gensheimer_JAMAOnc_2023)

Short of a good model, I prefer LQ

- Many tumors are assumed to have a high alpha/beta ratio (lung cancer). These tumors require a relatively high total dose despite hypofractionation to be iso-effective with CFRT

  60 Gy in 2.0 Gy fractions (n=30 fractions) = 60 EQD2 (a/b=10)

  53 Gy in 3.6 Gy fractions (n=15 fractions) = 60 EQD2 (a/b=10)

  40 Gy in 8.0 Gy fractions (n=5 fractions) = 60 EQD2 (a/b=10)

- Tumors with a low alpha/beta (sarcoma) require a lower total dose with hypofractionation

  60 Gy in 2.0 Gy fractions (n=30) = 60 EQD2 (a/b=5)

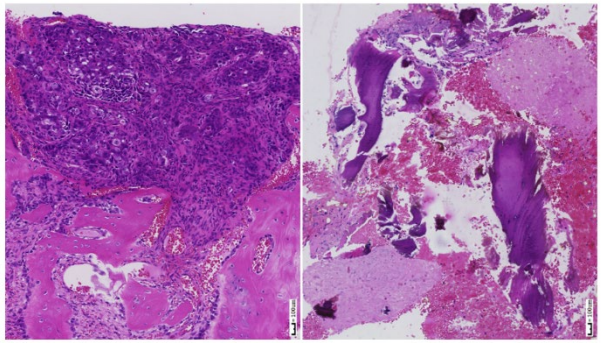
  50 Gy in 3.3 Gy fractions (n=15) = 60 EQD2 (a/b=5)

  35 Gy in 7.0 Gy fractions (n=5) = 60 EQD2 (a/b=5)

- Because normal tissue also has a low alpha/beta (a/b=3), from the standpoint of normal tissue injury, hypofractionation has a higher therapeutic ratio (tumor killing to normal tissue injury) for tumors with a lower alpha/beta

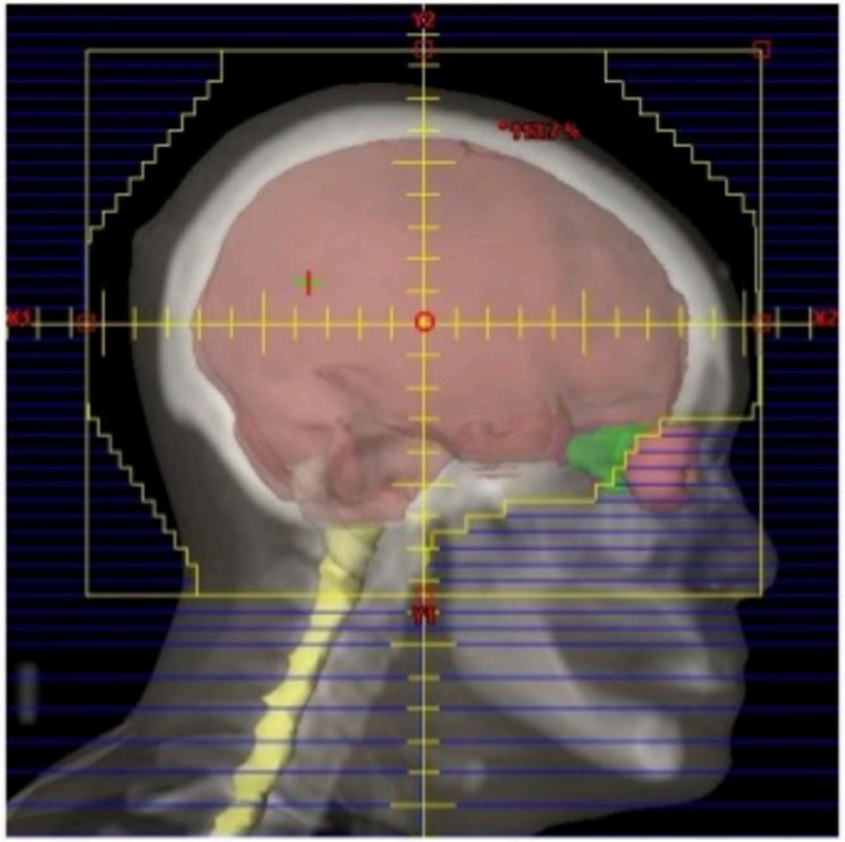
What does SBRT/SRS “do” to tumors and normal tissues?

- Immunohistochemical analysis of 10 vertebral body metastases ~24 h post-SBRT revealed extensive necrosis, tumor cell apoptosis, loss of vasculature (Steverink_IJROBP_2017)
- Immunohistochemical analysis of a vertebral body compression fracture (VCF) 2 years post spine SBRT revealed evidence of necrotic bone, fibrosis, and focal inflammation (Al-Omair_JNS_2013)



pre- and post-SBRT

Brain metastases as a model for the use of SRS



Whole Brain Radiation Therapy (WBRT) for brain metastases: the opposite of SBRT/SRS

- Standard palliative treatment for patients with innumerable brain metastases or leptomeningeal disease
- 5-10 fractions (according to patient factors including Performance Status and control of systemic disease)
- Non-ablative (more of a “cancer sterilizing”* technique in most clinical scenarios)

How do you feel about WBRT ?

PRO

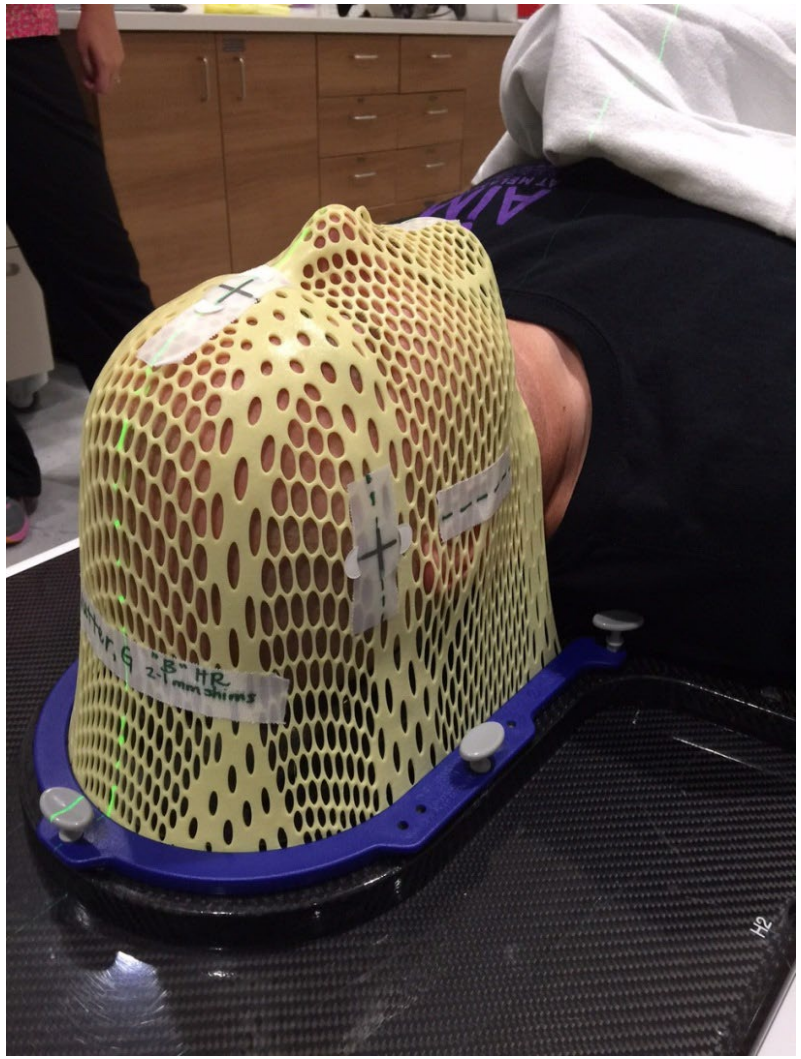
Improved “distant brain control” and so decreases risk of needing additional courses of RT (including SRS)

Sterilizes” the brain so that no seeds of cancer allowed to sprout

CON

Results in worsened cognition 3-6 months following treatment compared to SRS

WBRT Treatment

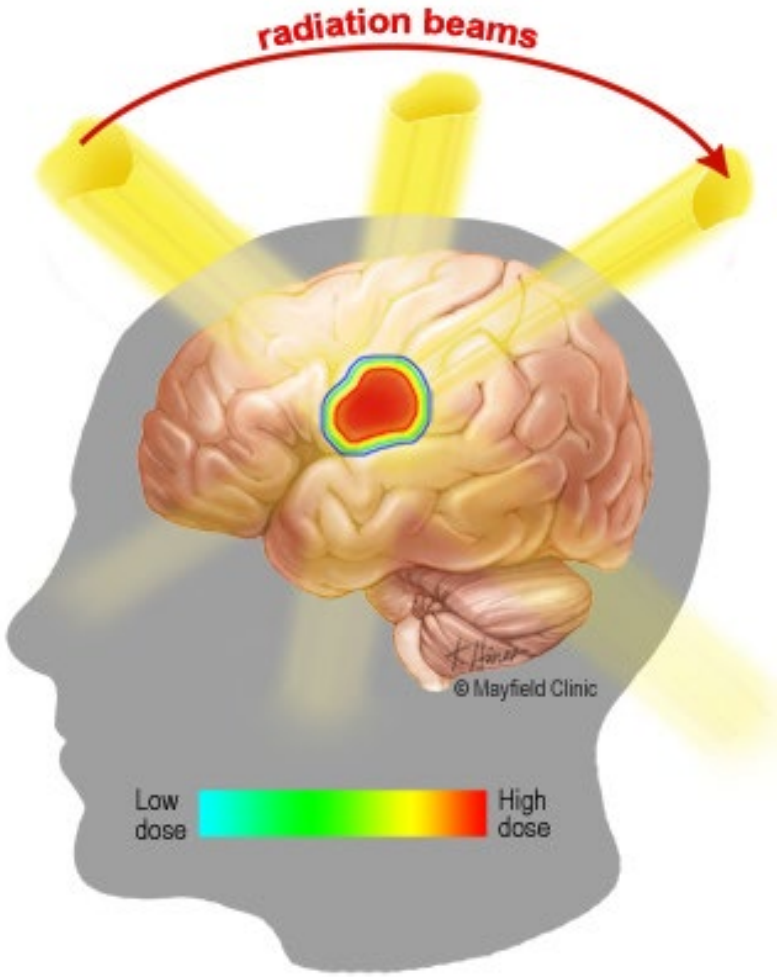


Toxicity: Cognition

- Over the past decade, 3 major cooperative group studies of brain metastases used neurocognitive toxicity as their primary endpoint
- 1 SD from baseline on at least 1 of 7 cognitive tests

  - Brown_JAMA_2016: SRS +/- WBRT; 3 months post RT [66 vs. 92%, p<.001].
  - Brown_LancetOncol_2017: cavity SRS vs. WBRT; 6 months post RT [52 vs. 85%, p<.001].
  - Brown_JCO_2020: HA-WBRT vs WBRT; rate of cognitive-decline greater with WBRT [HR = 0.74]

Stereotactic Radiosurgery

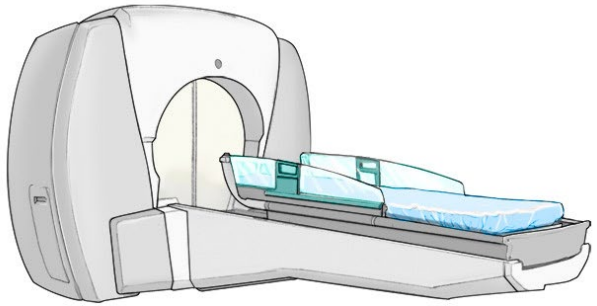


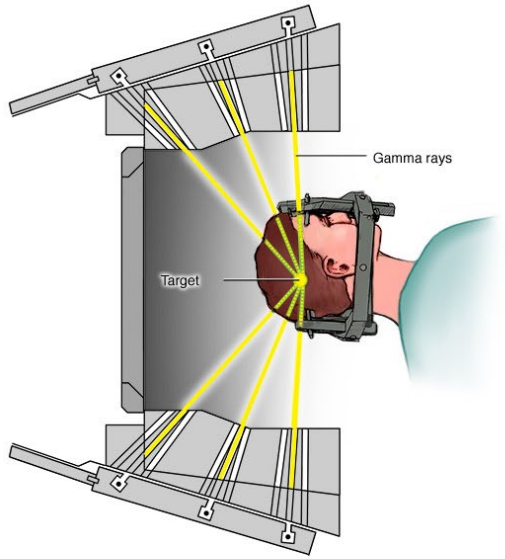
Breneman & Warnick. Mayfield Clinic. 2016.

Stereotactic Radiosurgery (SRS)

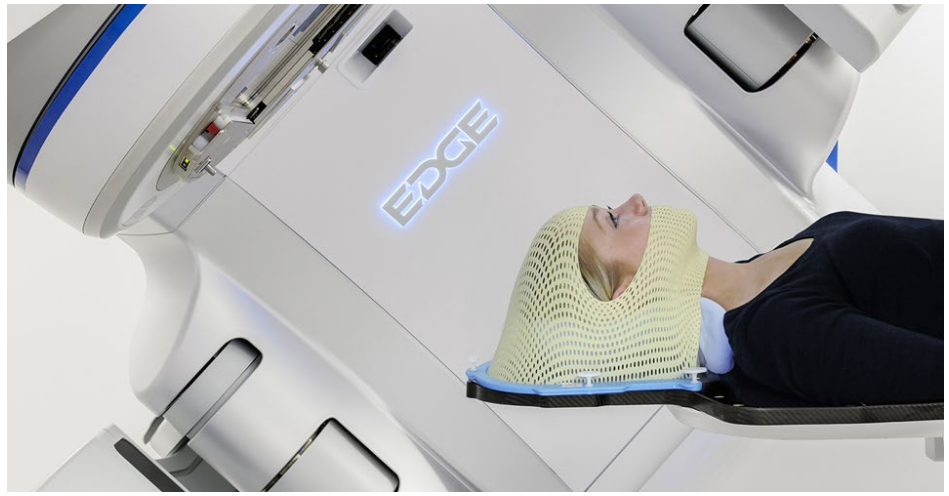
- Highly precise (sub-mm) delivery of ablative radiation
- Rigid Immobilization, precise positioning, image guided delivery
- Technologies: Gamma Knife®; traditional linear accelerator; CyberKnife®

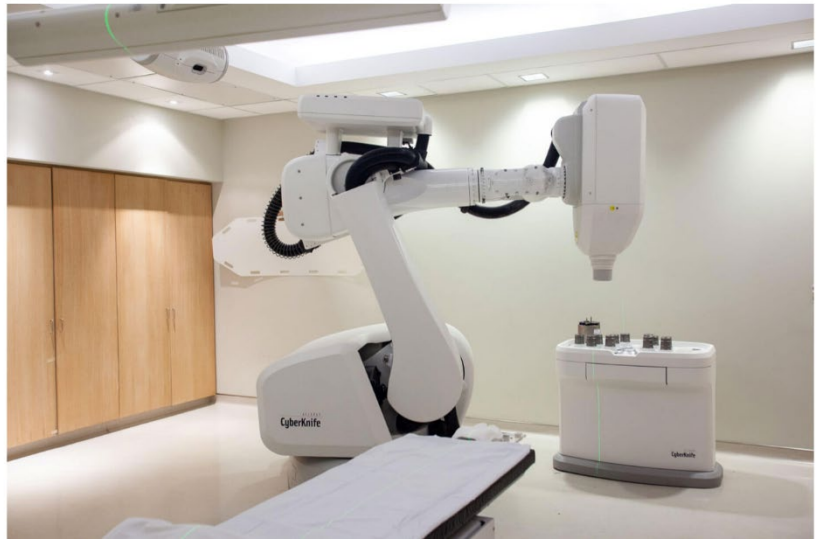
Current technology





Gamma Knife unit and radiation delivery

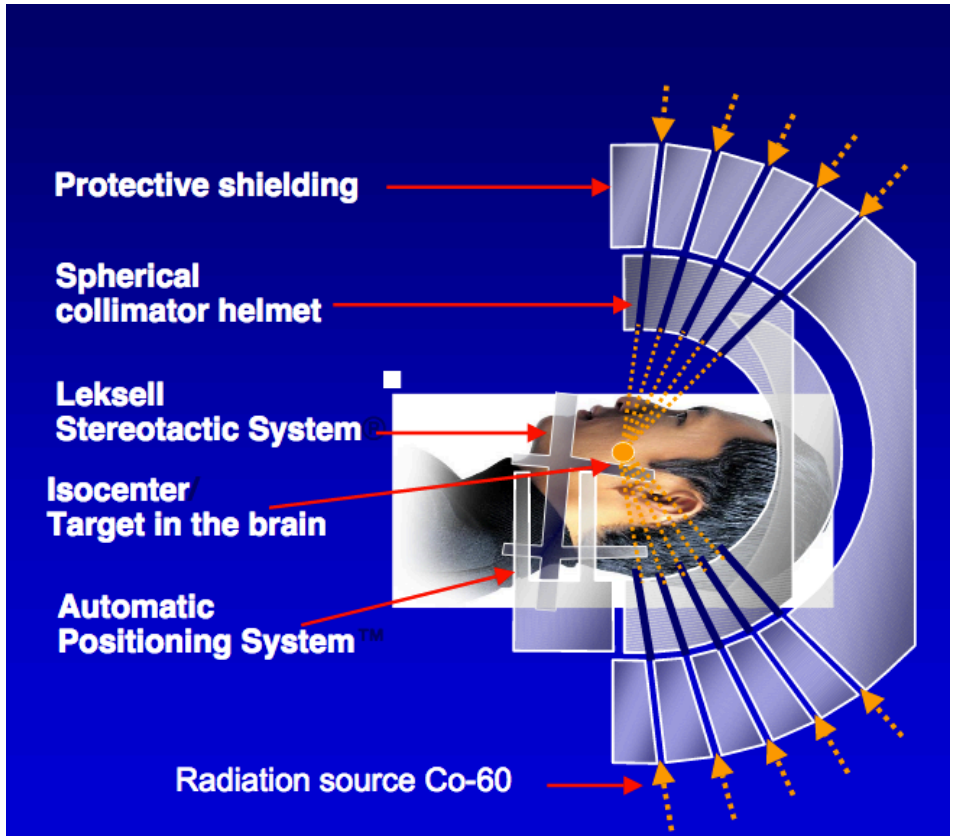


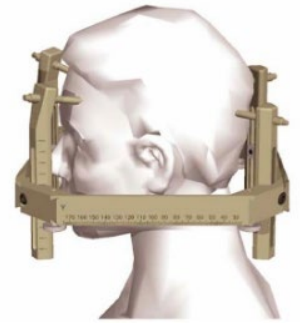


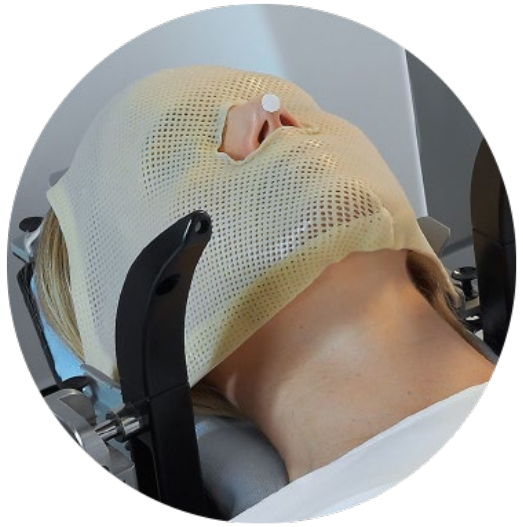
Gamma Knife SRS

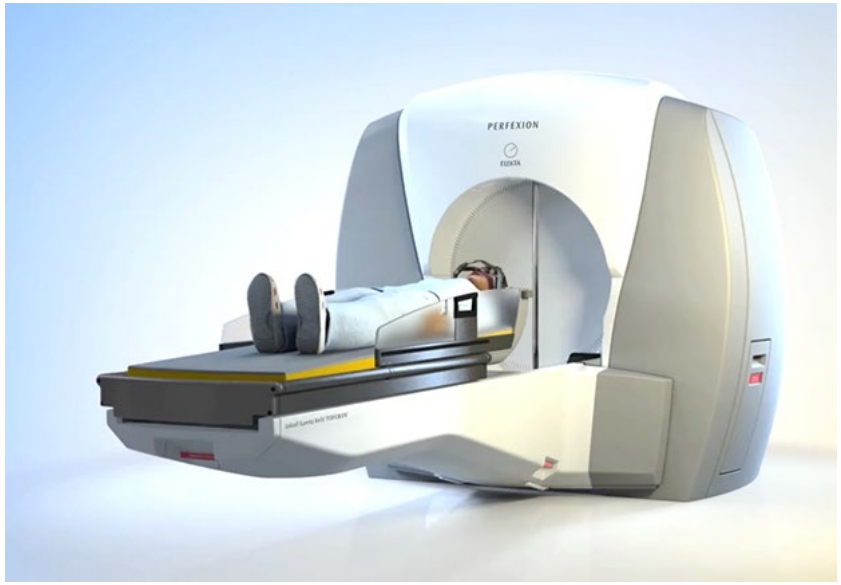
- At UHN, we use a Gamma Knife® (brand name) to deliver SRS. The Gamma Knife can only be used to treat intracranial targets
- Gamma Knife SRS can be delivered using a metal frame that is attached to the patient using metal pins that are tightened until contact the skull bone (to immobilize and establish a 3-D coordinate system, aka stereoactic space) or a plastic mask (in which case the stereotactic space is established on the basis of CT scans taken prior to and at the time of treatment (the skull bones define stereotactic space).

Gamma Knife SRS

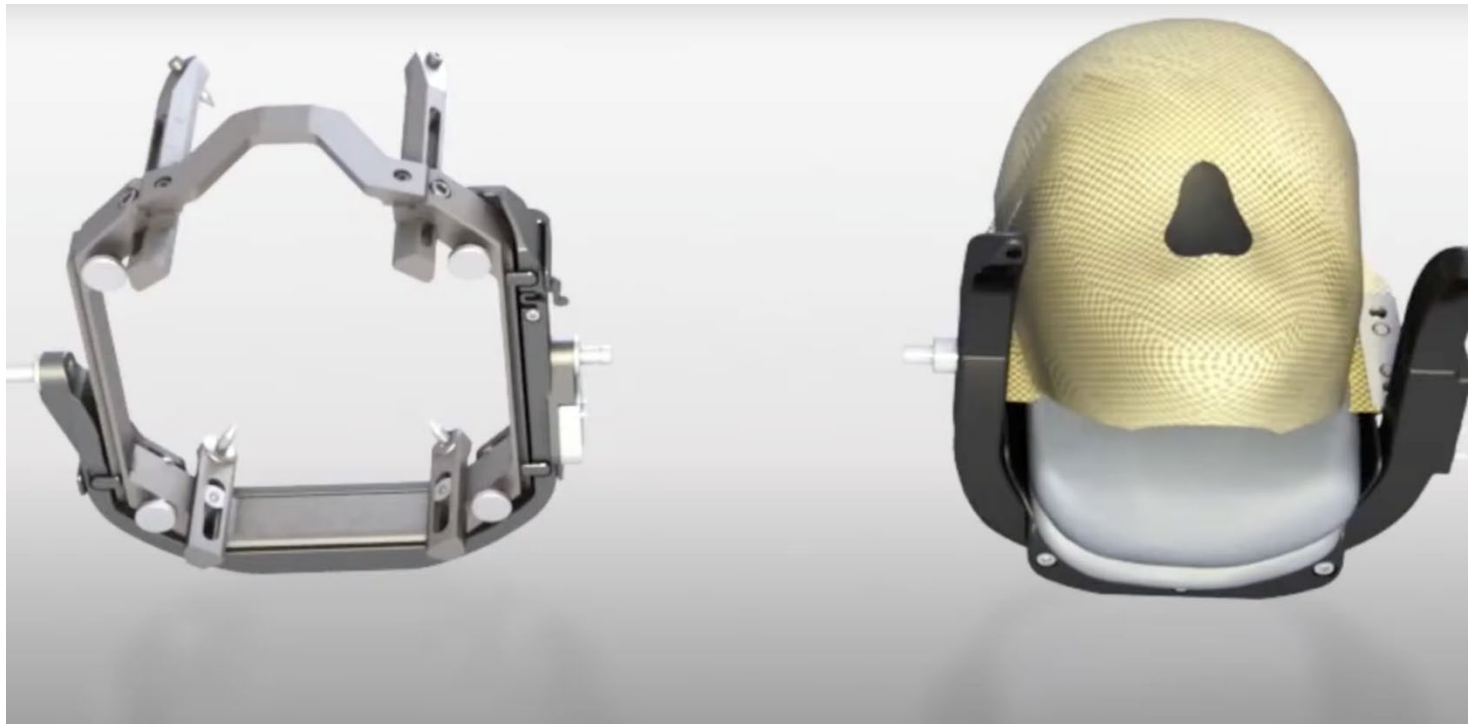








Frame versus Mask

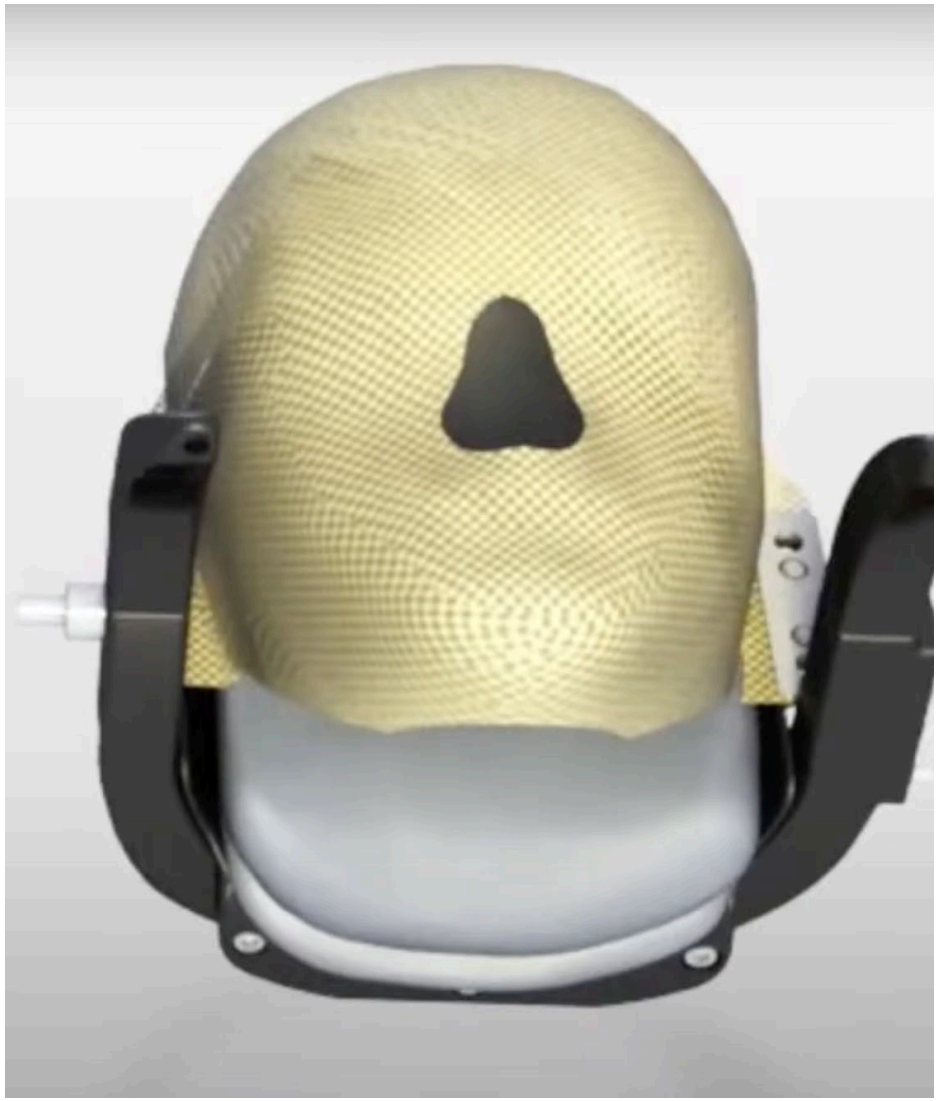


Frame

- Traditional means of immobilization
- Attached to skull using metal pins that pierce the skin and exert pressure on the skull (to immobilize and establish a 3-D coordinate system, aka stereotactic space)

Mask

- Thermoplastic mask (customized)
- Stereotactic space established via CT scans
- Motion during treatment evaluated with an infrared sensor placed on the patient's nose that is tracked with a camera. If the sensor moves >1.5mm then treatment is stopped, a new CT is obtained, and treatment begins again based on the newly established target location



Big Unknowns

- How many is “too many” for stereotactic radiosurgery (SRS)?
- Can we avoid/delay radiation in some patients?
- What is the best strategy for larger (> 3 cm) brain metastases?
- How to best mitigate toxicity?

Ongoing: CE.7 (CCTG, ALLIANCE, NRG)

- Phase III trial of stereotactic radiosurgery (SRS) vs. WBRT for **5-15** brain metastases (400 patients)
- There are 2 primary outcomes: OS and neurocognitive progression-free survival (1.5 SD on 2 of 6 tests), reduce the 6-month event rate of 50% to around 34%. Median survival 9 vs. 7.5 months.

Potential Side Effects and Risks of WBRT

- Fatigue
- Alopecia
- Dermatitis
- Headaches
- Nausea
- Short-term memory/cognitive deficits

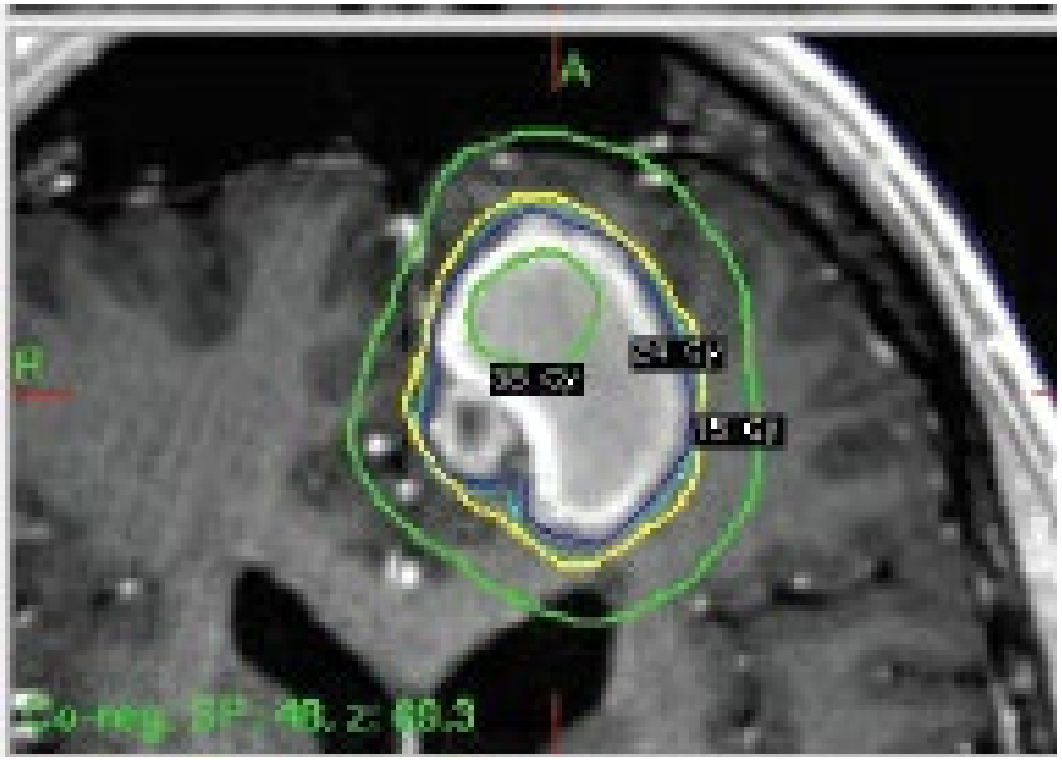
SRS

- Fatigue
- Headache (from Frame)
- Benign inflammation
- **Radionecrosis**

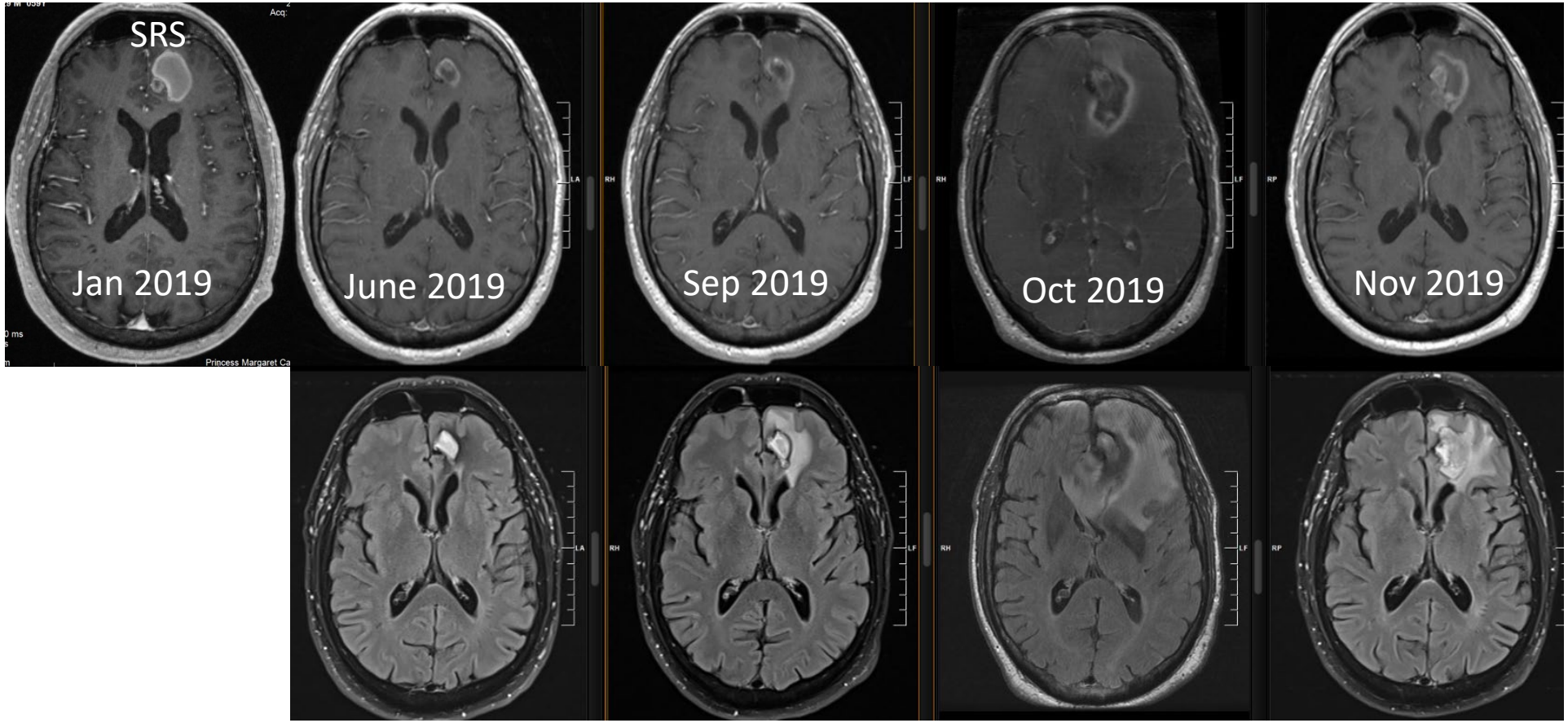
Toxicity: Radionecrosis

59 yo man diagnosed with melanoma 1997

- Metastatic disease late 2018 to brain and lung (BRAF +)
- Ipilumumab and Nivolumab started December 31, 2018-March 2019
- Stereotactic radiosurgery (SRS) 24 Gy in 3 fractions January 2-4, 2019
- Nivolumab March 2019-December 2019
- Immuno-mediated side effects (pancreatitis and hypophysitis)
- No evidence of new metastatic disease, partial response to lung nodule



+Dexamethasone



December 2019 left frontal craniotomy showed extensive necrosis without viable tumor
February 2020: patient died

The rationale for hypofractionated SRS (fSRS)

- The rationale for fSRS is improving local control while decreasing toxicity –these benefits are most relevant for *larger* lesions (>2 cm or >4 cc) because larger tumors have more surface area contact with normal brain (even though the surface area/volume ratio decreases with larger tumors)
- RTOG 90-05 was a protocol that defined the maximum safe dose for brain tumors treated with single SRS based on maximum tumor dimension (0-2 cm, 2-3 cm, 3-4 cm).
- RTOG 90-05 defined those as 15Gy, 18Gy, and 24 Gy respectively

Local control of large brain metastases treated with single fraction SRS alone isn't very good

*Estimated percentage of patients in whom time to local failure exceeded 3, 6, 9, and 12 months**

Factor	Dose & Local Control Rate (95% CI)†		
	15 Gy	18 Gy	24 Gy
total no. of lesions	41	85	249
follow-up interval			
3 mos	100%	99% (96–100%)	100%
no. of lesions at risk	31	56	166
6 mos	71% (54–88%)	87% (77–96%)	92% (87–97%)
no. of lesions at risk	18	37	92
9 mos	63% (44–81%)	64% (49–80%)	85% (78–92%)
no. of lesions at risk	13	18	60
12 mos	45% (23–67%)	49% (30–68%)	85% (78–92%)
no. of lesions at risk	6	8	37

* Metastases are categorized according to prescribed SRS dose. The probability value for all follow-up intervals was less than 0.0001 and was calculated using the log-rank test.

† These values represent the number of lesions that were controlled and were still being followed with MR imaging or computerized tomography studies at each interval (lesions at risk of further spread).

Vogelbaum_JNS_2006

Hypofractionated SRS (fSRS) for brain metastases

- No published trials comparing SRS to fSRS to SRS
- From a purely LQ basis 15 Gy x1 (a/b= 10) is 37.5 whereas 9 Gy x 3 = 51.3
- In the clinic, empiricism wins, what works better, with less toxicity?
- And what about histology, precise molecular features, immune activity, concurrent medications….

Important considerations for data interpretation

- Dose distributions from CyberKnife, Gamma Knife, and linac-based SRS are very different, meaning pooled studies involving treatment using different devices difficult to interpret
- Our ability to differentiate radiation necrosis from local failure radiologically has improved over the past decade but it's still imperfect, regardless, most of the time surgical resection reveals a mix of active tumor and necrosis, so what do you call that (there is no standard way of defining one vs. the other in this scenario)
- Additional variables to dose and volume that affect outcome include histology and concurrent medications
- Only controlled prospective trials can define "ideal" for larger brain metastases in terms of dose and fractionation, even then the answer will be technology and histology specific

Summary

- SBRT/SRS represents a paradigm shift in radiation oncology on many fronts: philosophically, technically, and medically
- We don’t necessarily know how it works or when to use it
- Improved local control may translate to improved survival, improved quality of life, or neither –we must contend with those unknowns in addition to not knowing what minimum dose is needed to achieve local control
- Models are interesting but empiricism rules in the clinic.