Stereotactic high-dose per fraction radiation (SBRT/SRS): what is it, why do we use it, and how is it different than conventionally fractionated radiotherapy (with brain metastases as a model)

David Shultz, MD, PhD

Clinical Investigator Radiation Medicine Program, Princess Margaret Hospital

Assistant Professor, University of Toronto

April 2023

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 SRS)

What's in a name? That which we call a rose By any other name would smell as sweet[1]

- 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 is preferred by some becomes it denotes “ablative” intent
- Stereotactic: using a 3-Dimensional coordinate system
- Ablate: to destroy (akin to surgery)
- These all denote high dose RT per fraction RT, delivered in a limited number of fractions (~5 or less), and ablative intent (range of dose per fraction is not strictly defined because of situational dependencies)

1. Shakespeare_R&J_1595

SBRT credo

- There are advantages to high dose per fraction compared to CFRT (beyond patient convenience) that outweigh the potential disadvantages (e.g. smaller CTV and potential toxicity)
- Higher dose per fraction radiation can be delivered safely (based on technology and the practitioner's knowledge, skill, and judgement)
- Therapeutic ratio of SBRT exceeds that of CFRT
  - the more situations and the extent to which you believe this determines where you sit on the ideological spectrum
  - Based on improved image guidance, dosimetry, and increased dose (BED) safely deliverable with SBRT vs. CFRT
  - Based on radbiologic properties, SBRT achieves outcomes unachievable with CFRT (cure or ablation)- SBRT adherents also espouse the oligometastatic credo

Radiobiology of SBRT (2 challenges)

- 1. We don't have a validated model that equates one SBRT dose (high dose per fraction [BED]) to another SBRT dose or to CFRT in terms of tumor killing or normal tissue toxicity.
- 2. We don't know if there are unique ways that SBRT kills tumors or damages normal tissues compared to CFRT.
  - However, knowing that those exist and knowing what those are is less important (from a clinical standpoint) than having a model.

The 4 Rs

- Established within the context of CFTR
- Re-oxygenation, re-distribution, re-pair, and re-population don't make sense in a single fraction schema
- Oxygenation, distribution, and repair might make sense for hypofractionated SRS
- The 5th R (radio-sensitivity) seems to apply to SBRT

Certain tumors appear to be relatively resistant to SRS/SBRT

- 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 very little knowledge of whether, when or how SBRT is “better” than CFRT

In order to even have the conversation one must accept that higher dose → better tumor killing → better local control

Even if one accepts that basic tenet, in many clinical scenarios it is hard to predict when better local control will be relevant because of the competing risk of death and because of the balance between toxicity and benefit

Potential Unique Radiobiological mechanisms of SBRT/SRS (I)

- Some experimental assays (e.g. clonogenic) suggest secondary mechanisms to direct cell-death (i.e. from DNA damage)
  - Radiation-induced injury to tumor vasculature (e.g. Ceramide-mediated apoptosis of tumor vascular endothelium (Garcia-Barros_Science_2003))
- Defining these mechanisms is important because if they could be manipulated then so could 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
  - >10 Gy/fx causes vascular injury → cell - theory 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
  - Some evidence that SBRT reduces the recruitment of immunosuppressive cells compared to CFRT[2] though other reports suggest it activates suppression[3]
  - Since the initial excitement from an NEJM article citing a potential abscopal effect with ipilimumab and SBRT in melanoma[4], many trials have attempted 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

Simple truth: With radiotherapy, more is usually better in terms of 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).

Example: Is SBRT "better" than CFRT as a curative therapy for stage I non-small cell lung cancer

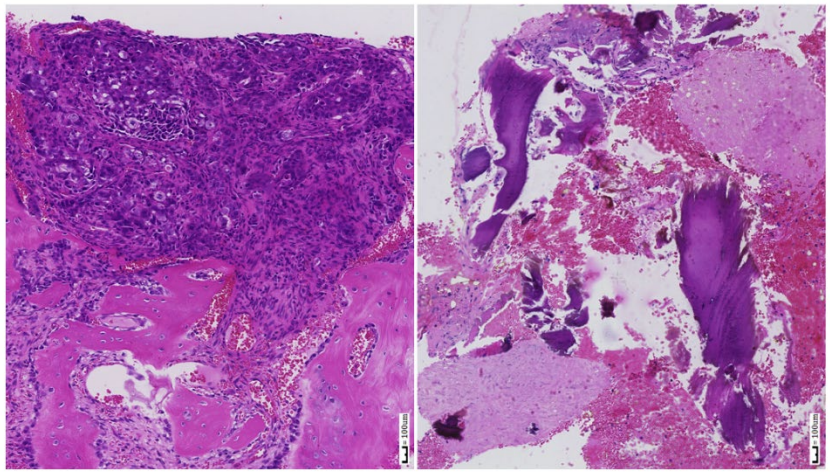
- Stage I Non-small cell lung cancer is defined (currently) as < 4cm in max diameter without nodal or metastatic involvement
- RTOG 0236 is perhaps the most successful SBRT trial: phase II, NSCLC < 5 cm (peripheral) and non-operable. 54 Gy in 3 fx. 7% LF at 5 years. This is potentially curative treatment.
- 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 (66 Gy/3fx vs 70 Gy/25fx) revealed equivalent (very low) LF rates

Modeling

- LQ may overestimate SBRT dose effect (hence LQ-L) or underestimate (does not account for secondary mechanisms) or be reasonably accurate
- Some argue (e.g. Song et al. April 2021 HyTec Red journal) that without understanding mechanisms, we cannot appropriately model
- In the clinic, modeling is just as if not more important for OARs since we often want to deliver as much dose as is safely possible
- From a clinical perspective, very few trials have applied volume-adapted dosing (Gensheimer_IJROBP s89-90_2021)
- Ultimately in a clinical setting, empiricism rules the day

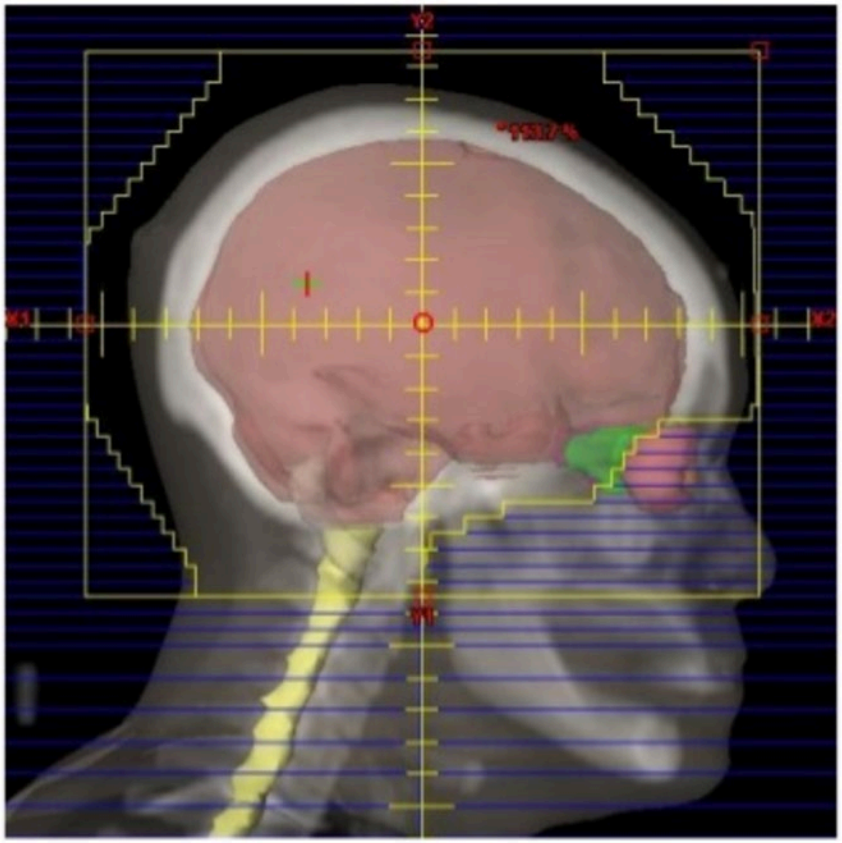
What does SBRT/SRS “do” to tumors and normal tissues?

- 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)



Steverink pre- and post-SBRT H&E

Brain metastases as a model for the use of SRS



Whole Brain Radiation Therapy (WBRT): the antithesis of SBRT/SRS

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

* I made-up that phrase

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

Brown_JAMA_2016

RESULTS There were 213 randomized participants (SRS alone, n = 111; SRS plus WBRT, n = 102) with a mean age of 60.6 years (SD, 10.5 years); 103 (48%) were women. There was less cognitive deterioration at 3 months after SRS alone (40/63 patients [63.5%]) than when combined with WBRT (44/48 patients [91.7%]; difference, −28.2%; 90% CI, −41.9% to −14.4%; *P* < .001). Quality of life was higher at 3 months with SRS alone, including overall

Cognitive Function	Test	Sample Size		Mean Change from Baseline (95% CI)		Mean Difference (95% CI)	p value
		SRS Alone	SRS+ WBRT	SRS Alone	SRS + WBRT		
Immediate Memory	HLVT-R Immediate Recall	61	46	0.3 (0.1, 0.6)	−0.5 (0.9, -0.1)	0.8 (0.3, 1.3)	<0.001
Delayed Memory	HVLT-R Delayed Recall	61	47	0.2 (-0.2, 0.6)	−1.0 (-1.4, 0.5)	1.2 (0.6, 1.8)	<0.001
Executive Function	TMT-B	58	43	0.4 (-0.5, 1.3)	−0.6 (-2.1, 0.9)	1.0 (-0.7, 2.7)	0.048
Verbal Fluency	COWAT	53	43	0.1 (-0.1, 0.4)	−0.2 (-0.5, 0.03)	0.3 (0, 0.6)	0.025

Function	Sample Sizes*		Mean Change from Baseline (95% CI)		Mean Difference (95% CI)	p value
	SRS Alone	SRS+ WBRT	SRS Alone	SRS + WBRT		
Physical Well-being	65	49	−4.4 (-12.4, 3.6)	−18.1 (-30.9, -5.4)	13.7 (-1, 28.4)	0.0071
Functional Well-being	63	48	0.4 (-13.6, 12.8)	−21.9 (-33.1, -10.7)	21.5 (4.6, 38.4)	0.0286
Brain Specific Concerns	64	49	−1.0 (-5.2, 3.3)	−8.8 (-14.0, -3.6)	7.8 (1.2, 14.4)	0.0035
Overall QOL	61	48	−1.3 (-5.4, 2.7)	−10.9 (-15.6, -6.3)	9.6 (3.6, 15.6)	0.0024

* 71 and 53 patients in the SRS and SRS+WBRT groups respectively had at least one post baseline QOL evaluation. Of these 124 patients, 66 and 50 patients in the SRS and SRS+WBRT groups respectively had at least one 3-month QOL score.

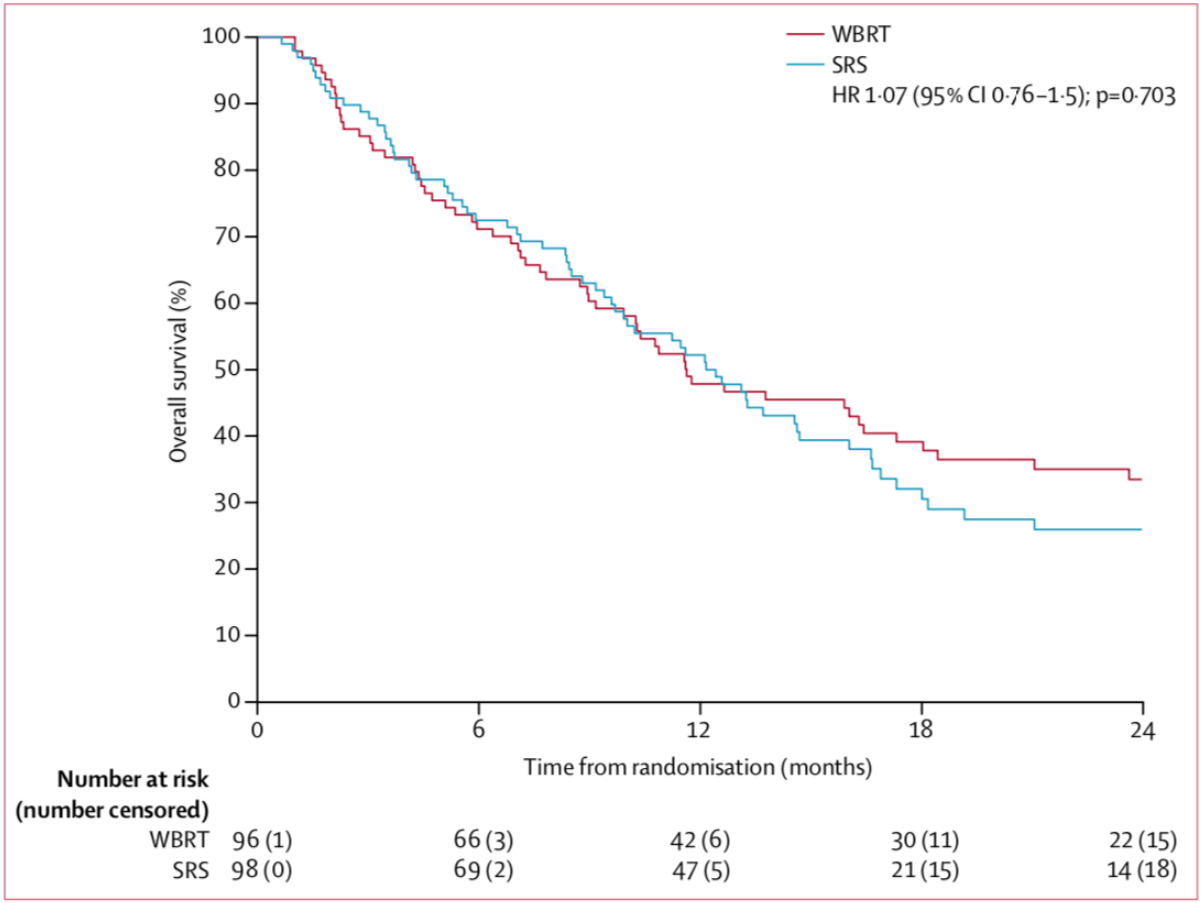
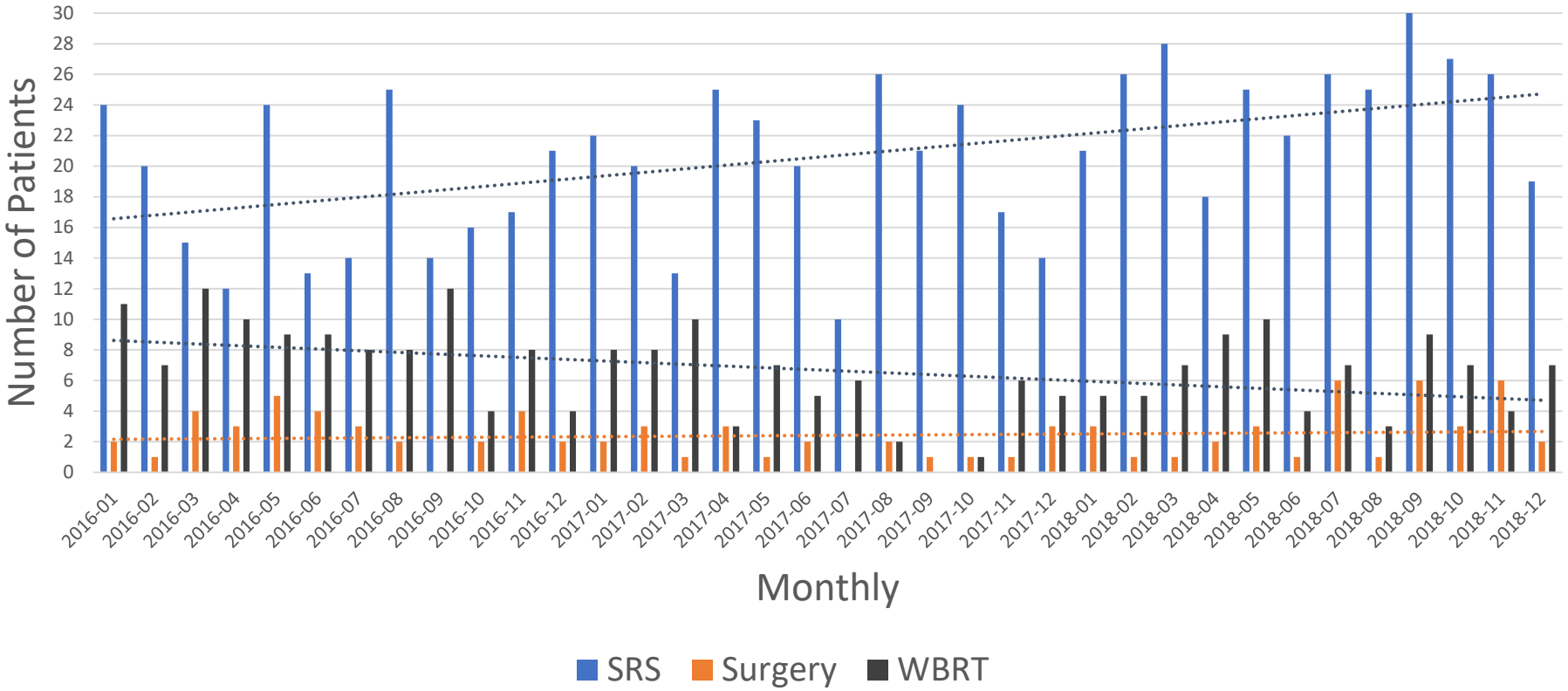


***Figure 3*: Overall survival**
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

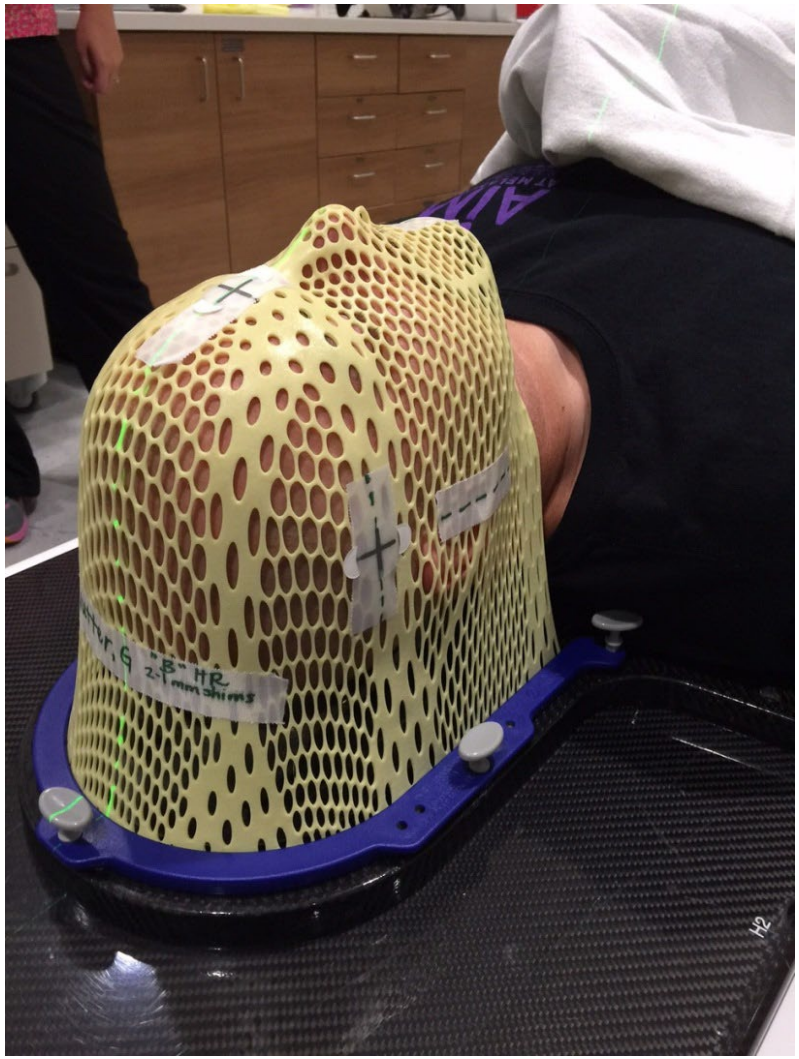
Brown_JAMA_2016

Types of Treatment Over 3 Years within the Brain Mets Clinic at PMH



UHN
Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
COURAGE LIVES HERE

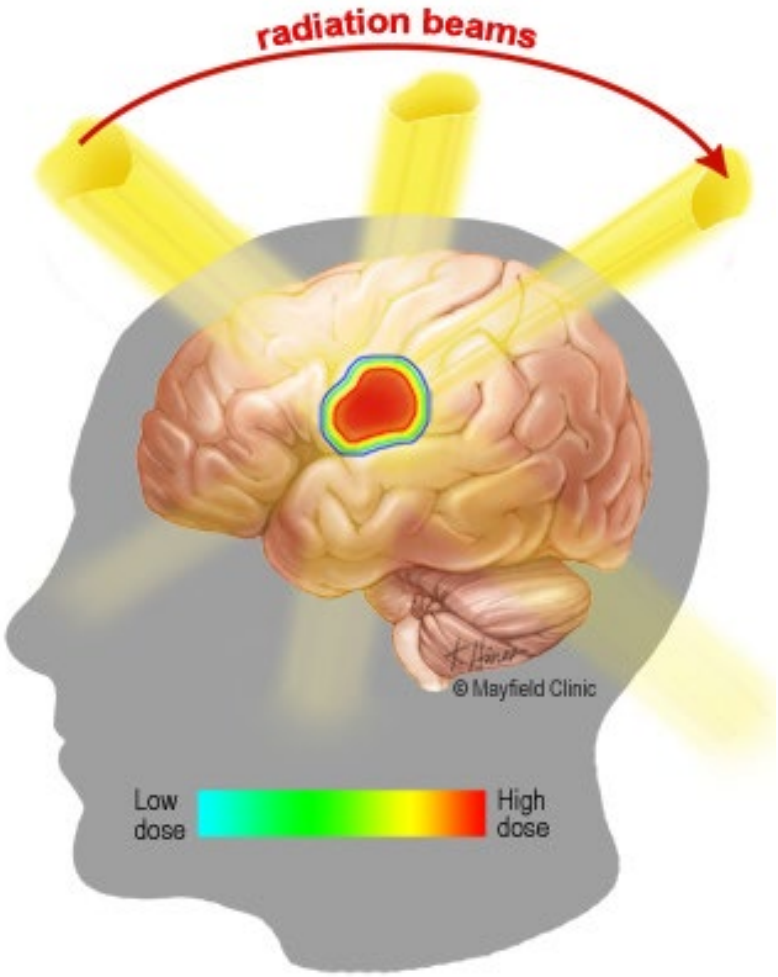
WBRT Treatment



Toxicity: Cognition

- Limited data regarding cognitive changes in adults following cranial radiation (for brain metastases or otherwise)
- Over the past 6 years, 3 major cooperative group studies of brain metastases have used neurocognitive decline as their primary endpoint (not including ongoing CE.7 trial). 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



Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
COURAGE LIVES HERE

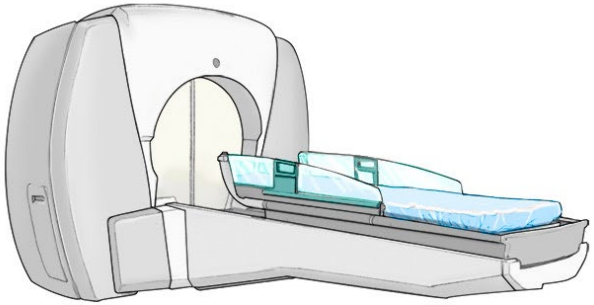
UNIVERSITY OF TORONTO

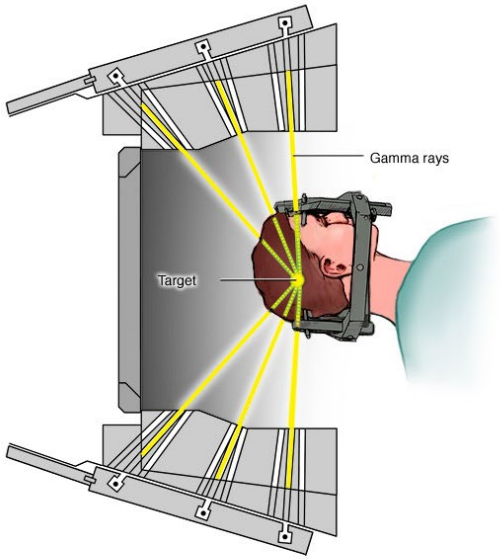
Breneman & Warnick. Mayfield Clinic. 2016.

Stereotactic Radiosurgery (SRS)

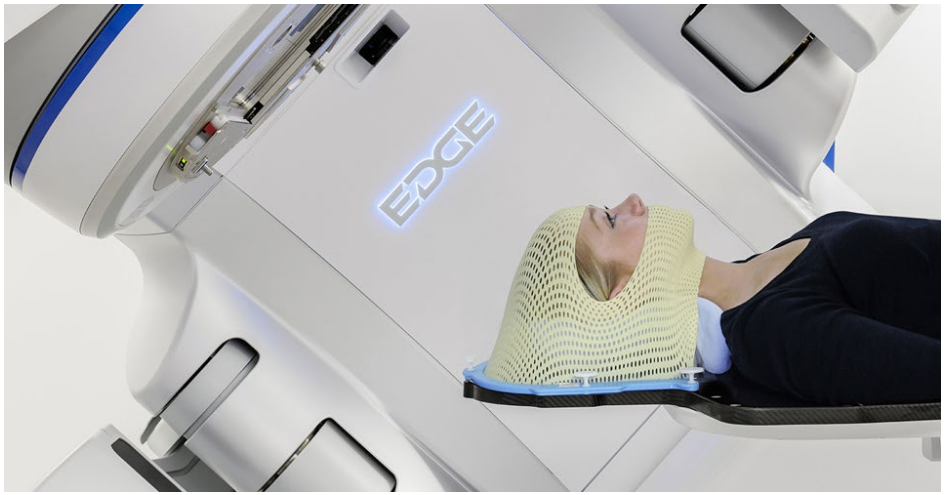
- Highly precise (sub-mm) delivery of ablative radiation
- Rigid Immobilization, precise positioning, image guided delivery
- Technologies: Gamma Knife®; traditional linear accelerator; CyberKnife®

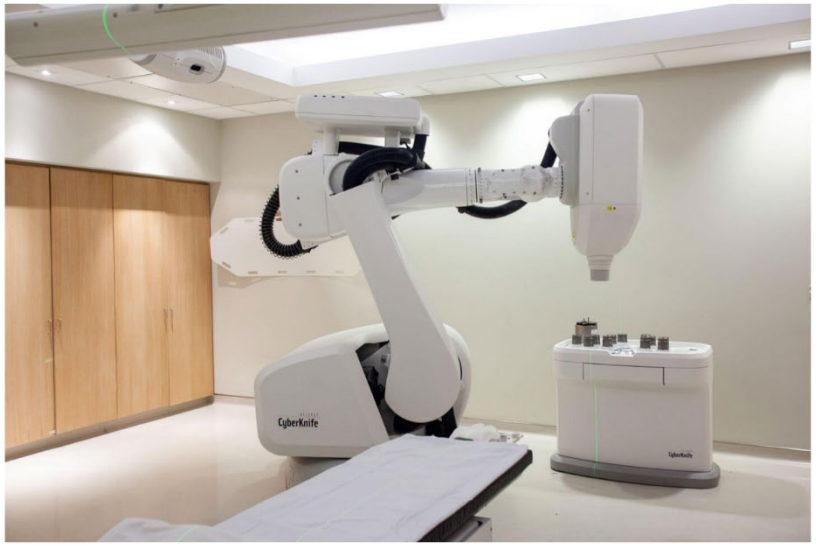
Current technology





Gamma Knife unit and radiation delivery





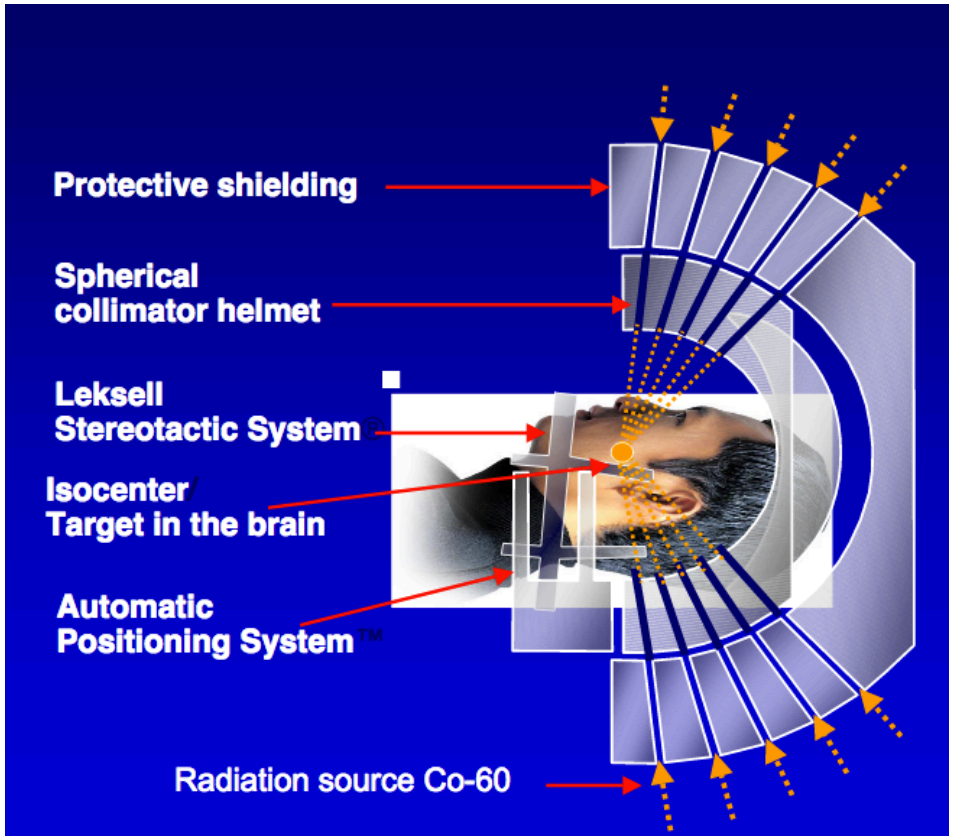
UHN Toronto General Toronto Western Princess Margaret Toronto Rehab
COURAGE LIVES HERE

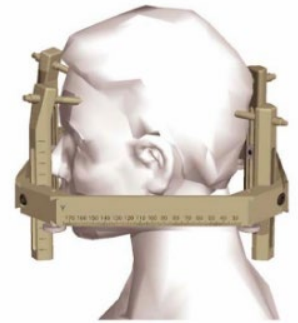
UNIVERSITY OF TORONTO

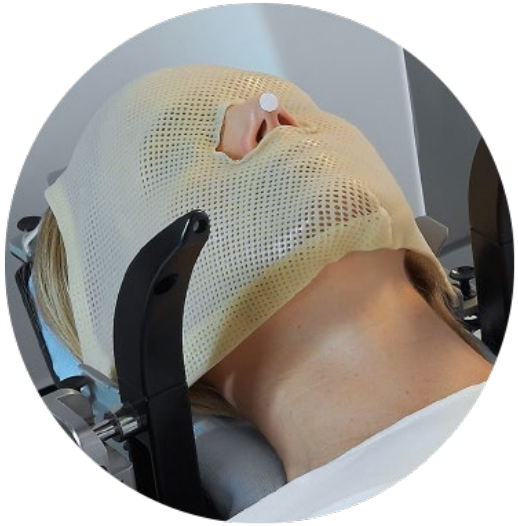
Gamma Knife SRS

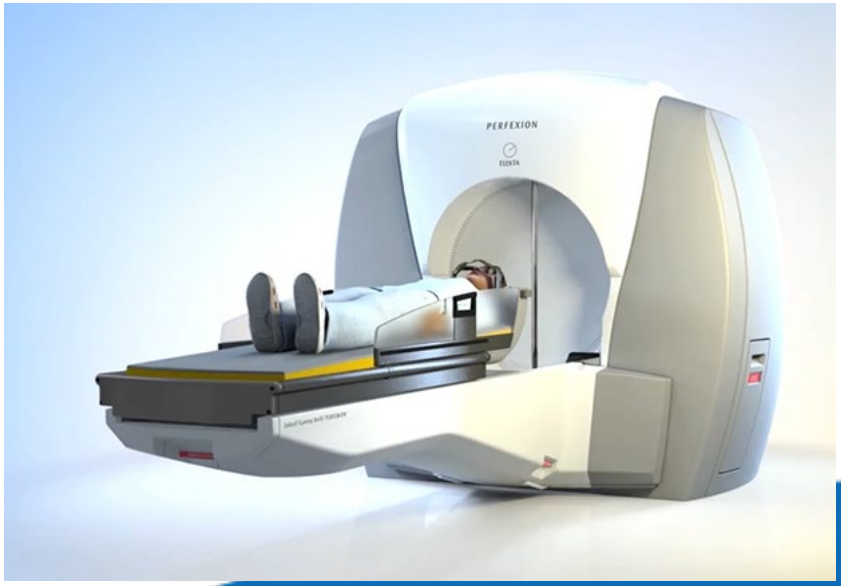
- At UHN, we use a Gamma Knife® (brand name) to deliver SRS. The Gamma Knife can only be used to treat intracranial targets
- Gamma Knife SRS can be delivered using a metal frame that is attached to the patient using metal pins that are tightened until contact the skull bone (to immobilize and establish 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





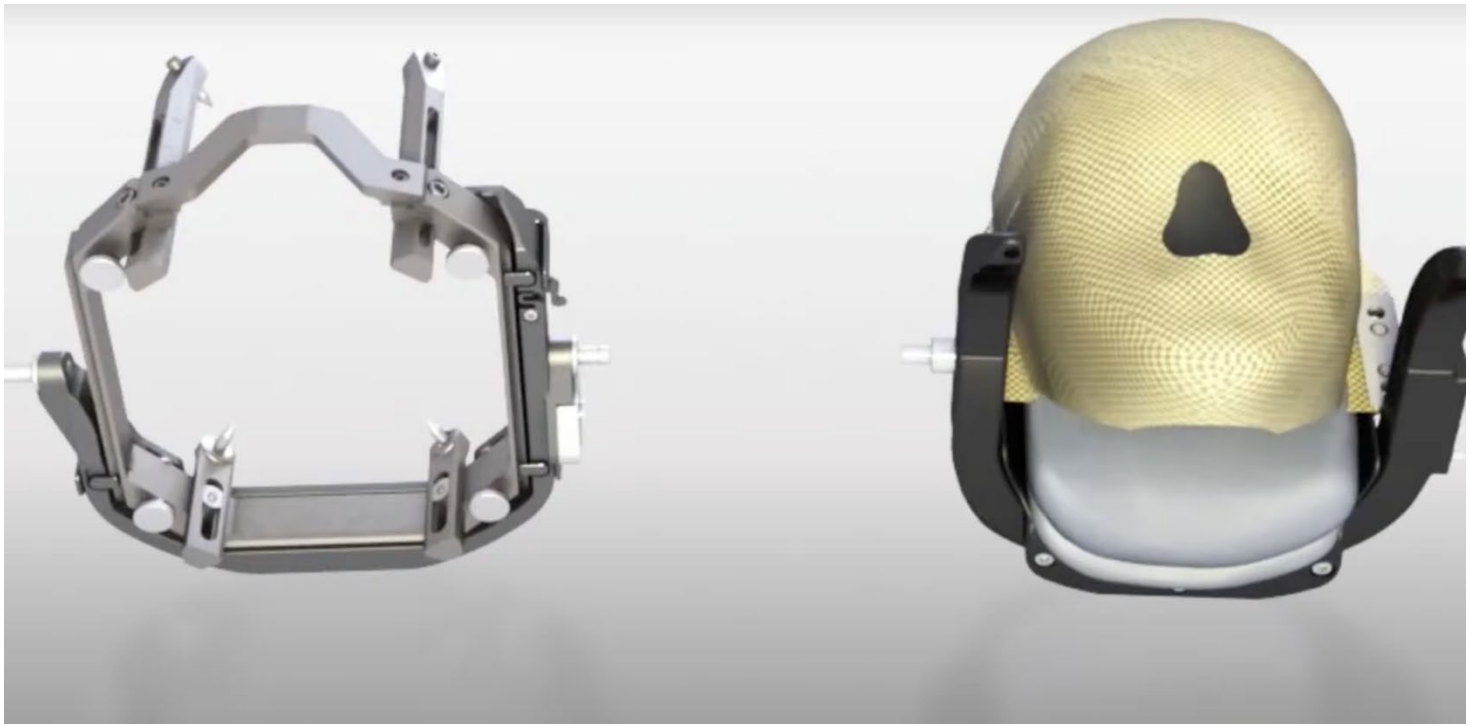




UHN Toronto General Toronto Western Princess Margaret Toronto Rehab
COURAGE LIVES HERE

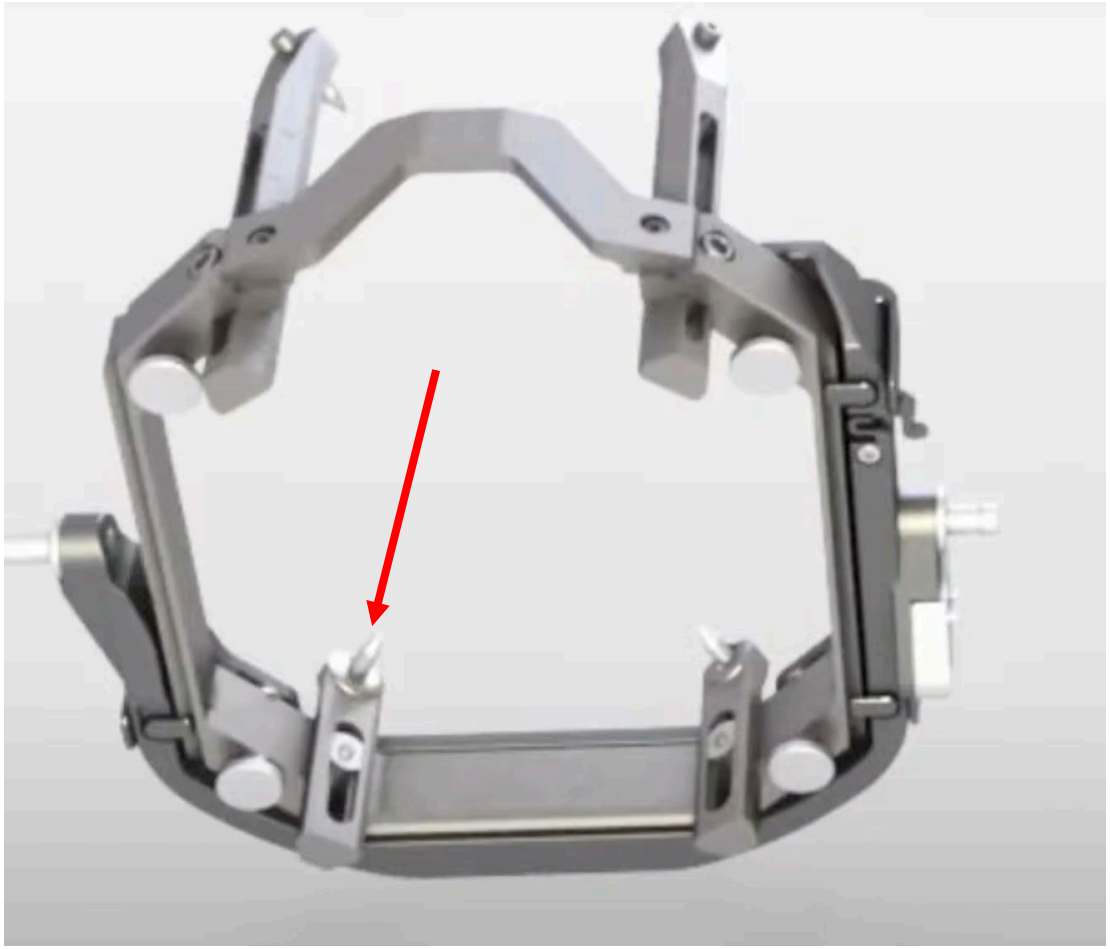
UNIVERSITY OF TORONTO

Frame versus Mask



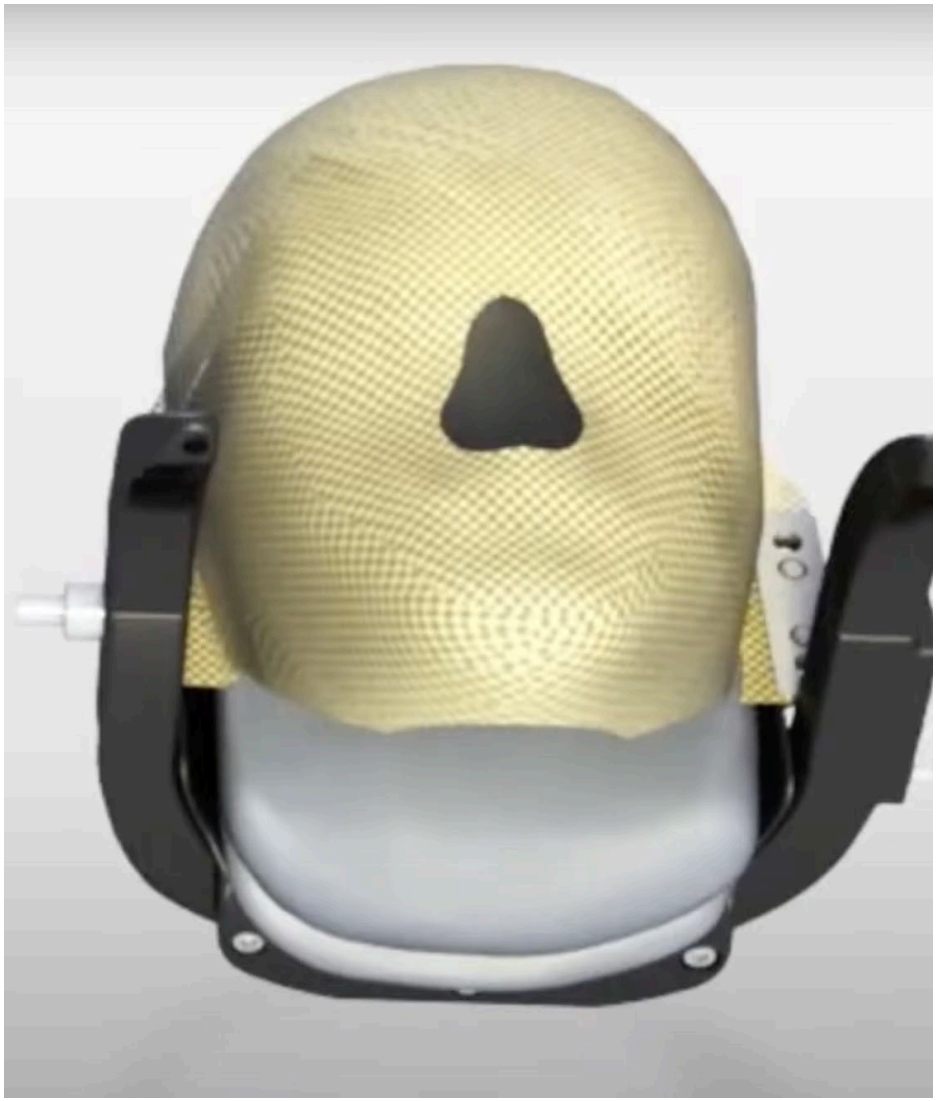
Frame

- 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



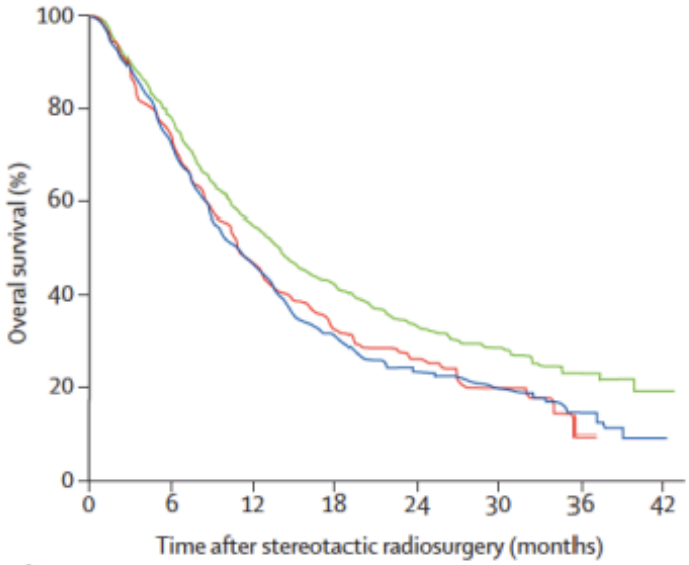
The Big Clinical Unknowns in Brain Metastasis Management (from an RT perspective)

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

SRS 1-10 metastasis: Prospective

- N=1194, prospective observational study
- 1-10 BrM SRS alone
- Survival **non-inferior** for 5-10 mets vs 2-4 mets

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

Figure: Kaplan-Meier curves of overall survival
HR=hazard ratio.

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab
COURAGE LIVES HERE

UNIVERSITY OF TORONTO

Yamamoto Lancet Oncol 2015

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

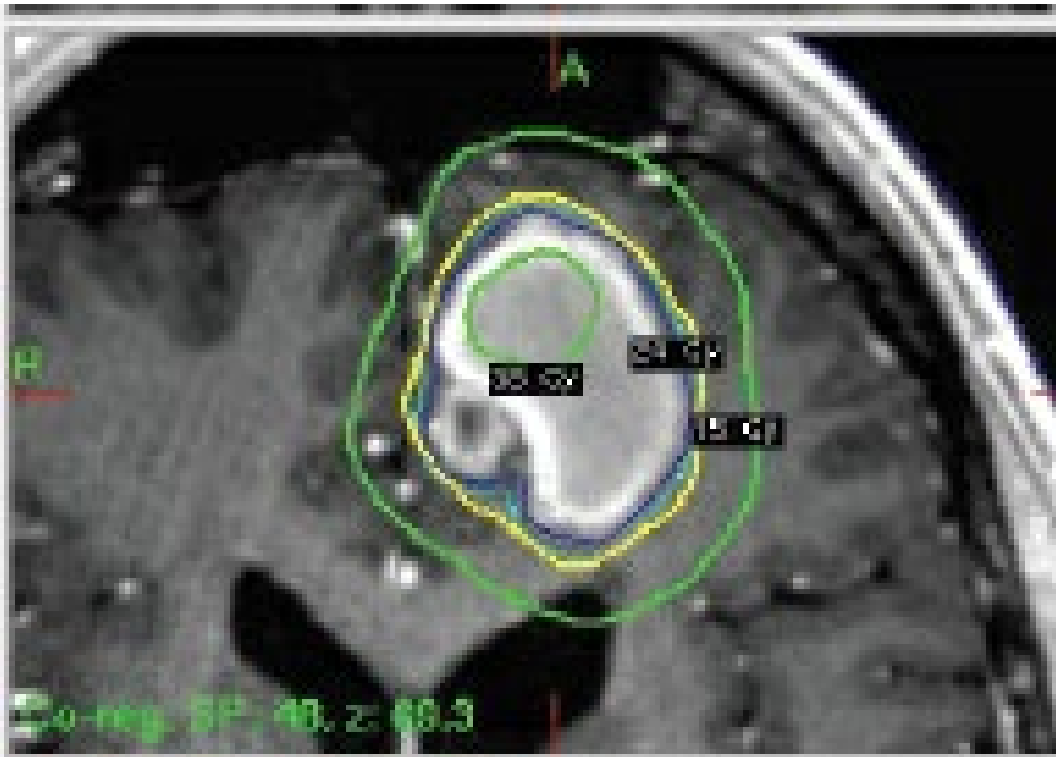
SRS

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

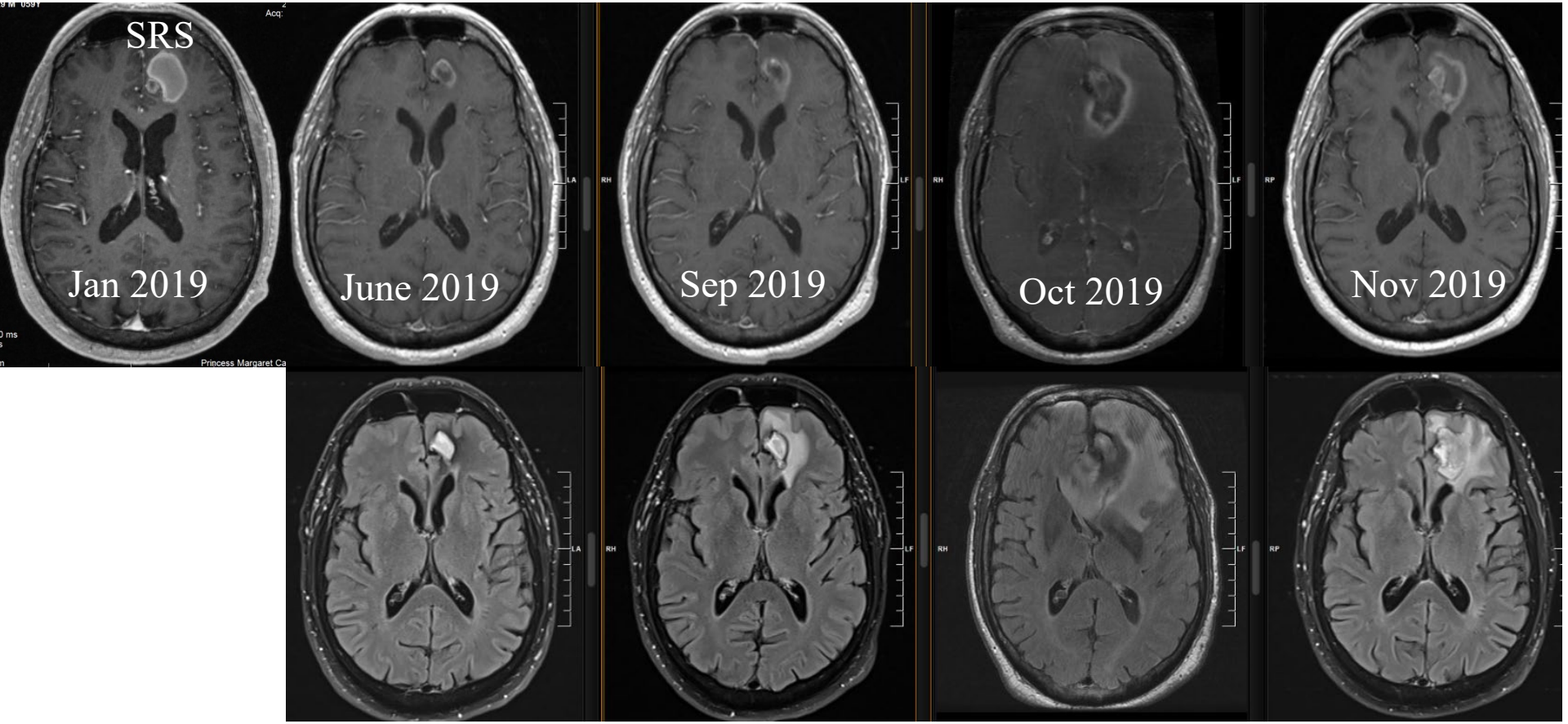
Toxicity: Radionecrosis

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

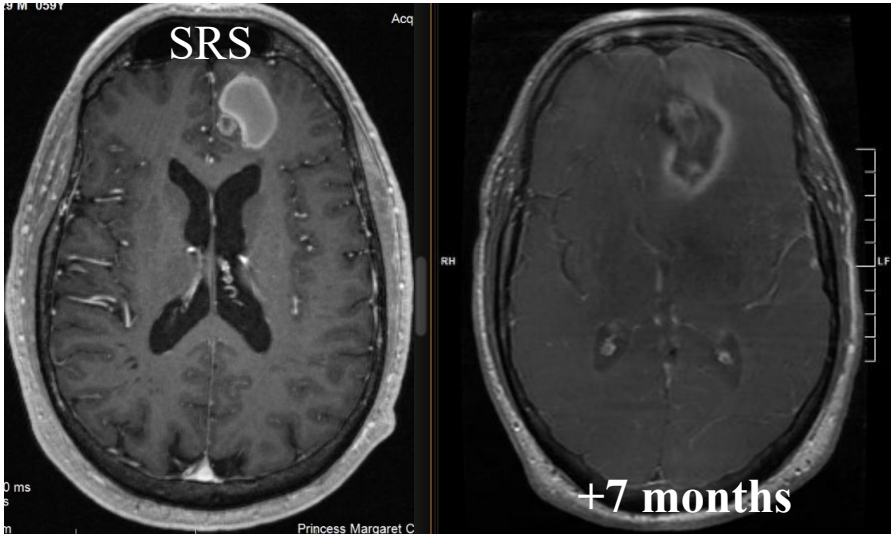


December 2019 left frontal craniotomy showed extensive necrosis without viable tumor
February 2020: patient died

UHN
Toronto General
Toronto Western
Princess Margaret
Toronto Rehab
COURAGE LIVES HERE

Radionecrosis: 6-24 months following SRS

- Risk factors: tumor size, SRS dose, concomitant meds (immunotherapy)
- Treatment: Dexamethasone, Bevacizumab, Surgery
- Questions: How differentiate on imaging from tumor progression, how decrease risk while ensuring tumor control, what is it?



The rationale for hypofractionated SRS (fSRS)

- The rationale for fSRS is improving local control while decreasing toxicity – in the *de novo* setting these benefits are relevant for *larger* lesions (>2 cm or >4 cc)
- 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

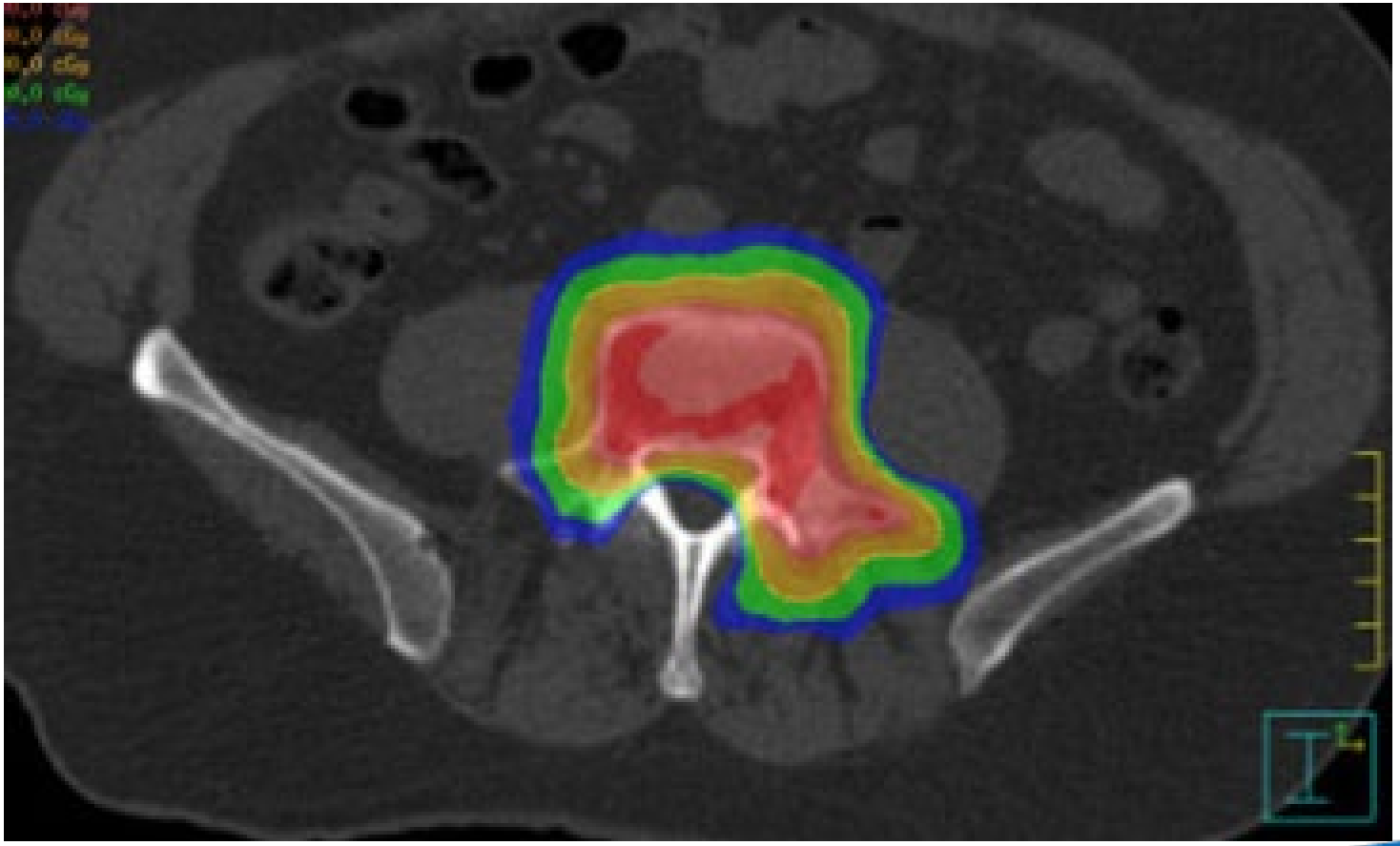
Hypofractionated SRS (fSRS) for brain metastases

- There isn't much high quality data (dose per volume) for fSRS and no trials comparing SRS to fSRS to SRS
- Minniti_IJROBP_2017: For 343 tumors > 2 cm, 1 year LC following SRS (15-18 Gy) vs fSRS (27 Gy/3 fx) was 77 vs 91% and radionecrosis 20 vs 8%.
  - Linac-based treatment
  - fSRS tumors were bigger (median PTV 17.9 cc vs 12.2 cc)
  - RN vs LC determined using F-DOPA PET-CT and perfusion MRI
- From a purely LQ basis 15 Gy x1 (a/b= 10) is 37.5 whereas 9 Gy x 3 = 51.3….but again, in the clinic, empiricism wins, what works better, with less toxicity? And what about histology, precise molecular features, immune activity, concurrent medications….

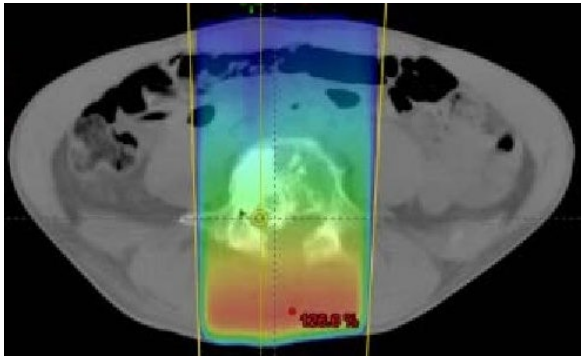
Interpreting the data: important considerations

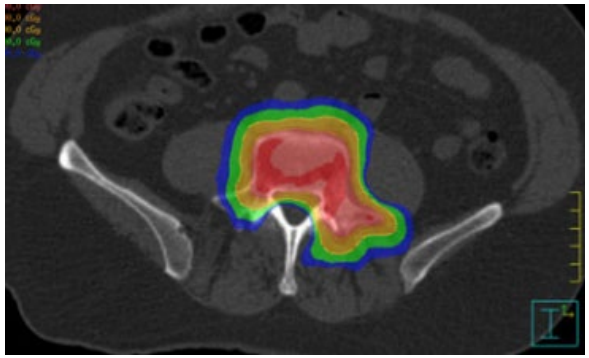
- Dose distributions from CyberKnife, Gamma Knife, and linac-based SRS are very different, meaning pooled studies involving treatment using these devices aimed at determining toxicity are difficult to interpret
- Our ability to differentiate radiation necrosis from local failure radiologically has improved immensely over the past decade but it's still far from perfect
- Most of the time surgical resection reveals an mix of active tumor and necrosis (there is no standard way of defining one vs. the other in this scenario)
- In the best of circumstances additional variables to dose and volume that affect outcome include tumor histology and concurrent medications
- Thus only a carefully controlled prospective trial will likely to define what is "ideal" for larger brain metastases in terms of dose and fractionation and even then the answer is probably technology- and histology- specific

Vertebral body metastases as a model for SBRT



What is paraspinal stereotactic body radiotherapy (SBRT) and how is it different from conventional palliative radiotherapy?





Immobilization (various devices) → Precision (image guidance and 6 degree-of-freedom couch → Increased Dose per fraction

	SBRT	Conventional RT
Minimally Resource intensive		✓
Time to treatment		✓
Likelihood of missing tumor sub-clinical tumor		✓
Ability to treat larger volumes of disease		✓
Risk of serious injury (spinal cord, esophagus)		✓
Local Control	✓	
Pain Control	✓	
Optimal modality for retreatment	✓	

Who benefits from spine SBRT

- Philosophical vs. Medical vs. Technical
- Philosophical: Oligometastatic disease, life expectancy beyond 6 months (Rewards+ Resources+ Risks), performance status, NHx)
- Medical: radio-resistant cancers (melanoma, sarcoma, RCC, HCC)
- Technical: +/- epidural disease, limited field size

Oligometastatic spine : special considerations

- SBRT offers improved local and pain control
- For oligometastatic patients, good PS, expected to live > 6 months, improved local control may significantly improve QOL, PFS, and OS
- Beyond conventional palliative paradigm: treat before symptoms occur (due to significant epidural involvement causing radiculopathy or cord compression)

Why: SRS vs conventionally fractionated radiotherapy (CFRT)?

- For "bulky" paraspinal tumors, 1-yr LC with CFRT ~46%; 1-yr LC with SRS is 70-90%
- Reirradiation
- SRS offers the potential for rapid, durable, and complete pain control

The great challenge of spine SBRT

- The dose required to ensure long term control for most cancer types exceeds spinal cord tolerance, and so the risk of radiation induced myelopathy must be balanced against that of tumor progression resulting from under treatment.

Summary

- SBRT/SRS represents a paradigm shift in radiation oncology on many different 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 – ultimately we must contend with those unknowns in addition to (in many circumstances) not knowing what dose is needed to achieve local control and what the risk is to adjacent normal tissues were we to achieve that
- At the end of the day, I rely on the LQ model and my own and others' experience to determine dose prescription and constraints especially when using SBRT in novel clinical scenarios. Models are interesting but empiricism rules in the clinic.