Radiosurgery in the Multidisciplinary Management of Brain Metastases

Emi Yoshida, MD
UCSF Radiation Oncology
UCSF-Washington Radiation Oncology Center

February 10, 2024

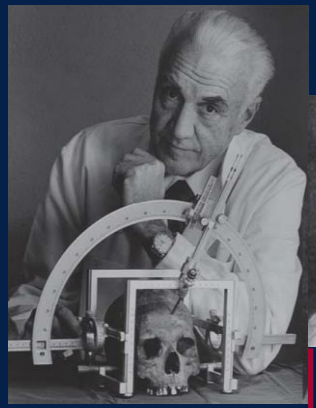
Brain Metastases

Statistics

- Most common type of intracranial tumor
- 20-40% of patients with cancer will have brain metastases
- ~ 300,000 new cases of brain metastases in the United States each year
- With more effective systemic therapies leading to improved survival, the durable control of intracranial disease of increasing importance

History of SRS for Brain Metastases

Radiosurgery has changed the goals of treatment to long-term survival and quality of life



1951

1967

1975

1980s

2006

Yamamoto, Progress in Neuro-Oncology 2015; Images curtesy of Elekta AB

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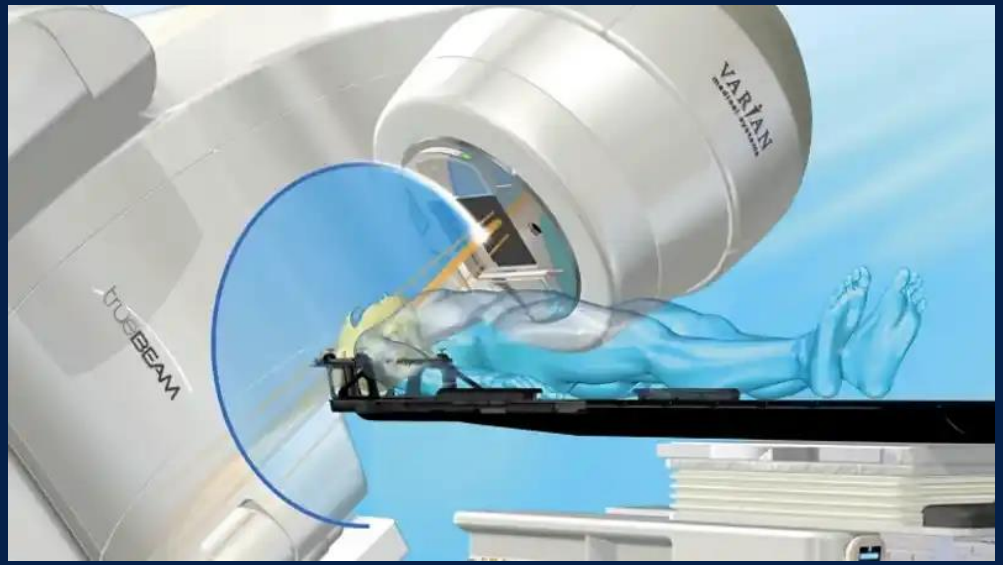
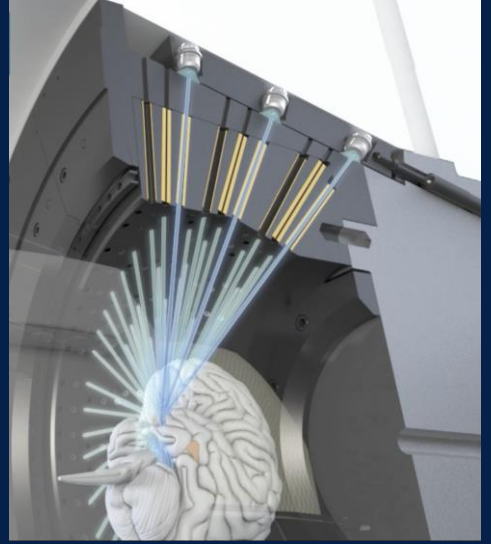
Current SRS



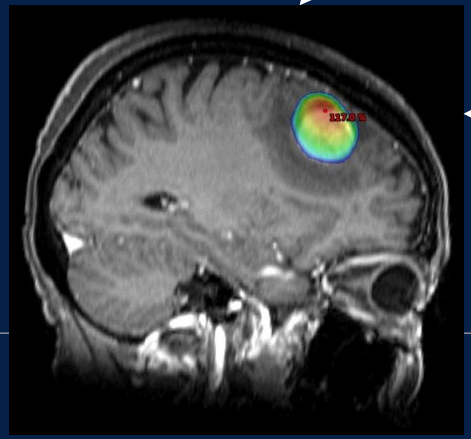


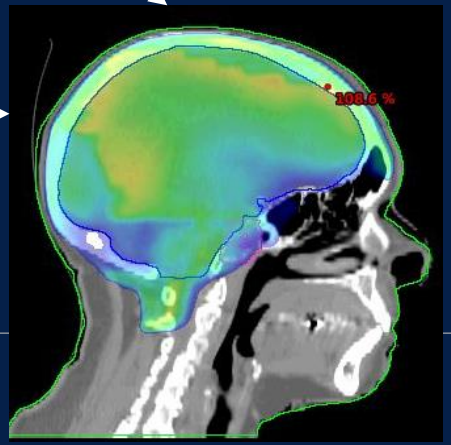
Images curtesy of Varian and Elekta

Treatment Strategies

What is the right treatment for a given patient?

Systemic therapy





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General Agreements

Surgery benefits a select group of patients

Trial	Journal/ Year	Treatment	Patients	Median Survival (weeks)	Functional Independence (wks)	P-value
Patchell	NEJM 1990	WBRT+S	25	40	38	<.01
		WBRT 36 Gy/12 fx	23	15	8	
Noordijk	IJROBP 1994	WBRT+S	32	43	34	.04
		WBRT 40 Gy/20 fx	31	26	21	
Mintz	Cancer 1996	WBRT+S	41	24		NS 0.24
		WBRT 30 Gy/10 fx	43	27		
RTOG/ SWOG*	Am J Clin Oncol 1990	WBRT+S	25	62		<.01
		WBRT 4000 cGy /16 fx + 1000 cGy boost	55	27		

General Agreements

Radiation should be delivered to reduce local recurrence

Phase III surgery +/- WBRT failure patterns and survival (Patchell JAMA 1998)

Failure	Surgery	S + WBRT	P-value
Anywhere in CNS	32/46 (70%)	9/49 (18%)	<.001
Local	21/46 (46%)	5/49 (10%)	<.001
CNS Death	17/39 (44%)	6/43 (14%)	.003
Median Survival	43 weeks	48 weeks	.39

The addition of WBRT lowers all recurrences and CNS deaths, but does not impact on survival

General Agreements…

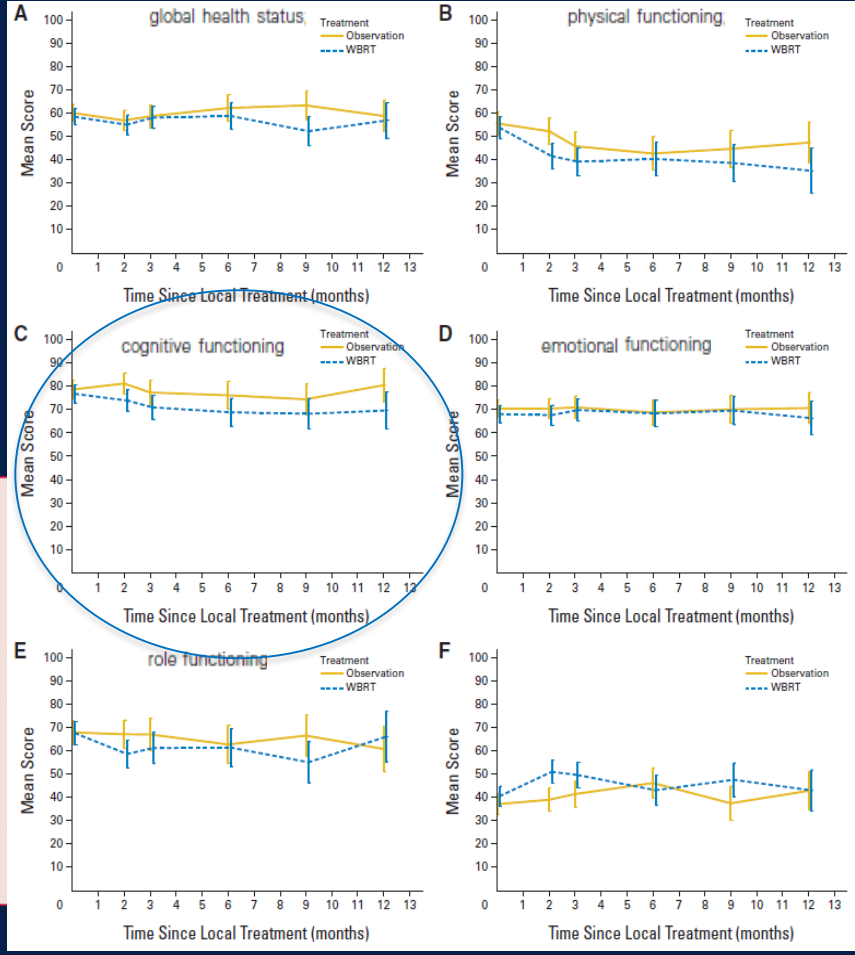
The addition of WBRT to surgery / SRS:

- Reduces rate of intracranial progression
- Does not improve overall survival
- Increases rate of neurocognitive decline

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)	p (A>B)
Total recall	52%	24%	96%
Delayed recall	22%	6%	86%
Delayed recognition	11%	0%	86%

p (A>B)=Bayesian probability that the proportion with a significant neurocognitive worsening is higher in stereotactic radiosurgery plus whole-brain radiotherapy than stereotactic radiosurgery alone.

Table 3: **Bayesian posterior mean probability of significant neurocognitive decline at 4 months by treatment group, by HopkinsVerbal Learning Test—Revised**



Chang, Lancet Oncol 2009. Aoyama, JAMA 2006. Kocher, J Clin Oncol 2010.

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General Agreements

Despite worse surgical bed control, post-op SRS associated with equivalent survival, better QOL, and less toxicity, compared to post-op WBRT

Phase III Postoperative SRS vs. WBRT (Brown, et al. Lancet Oncol 2017)

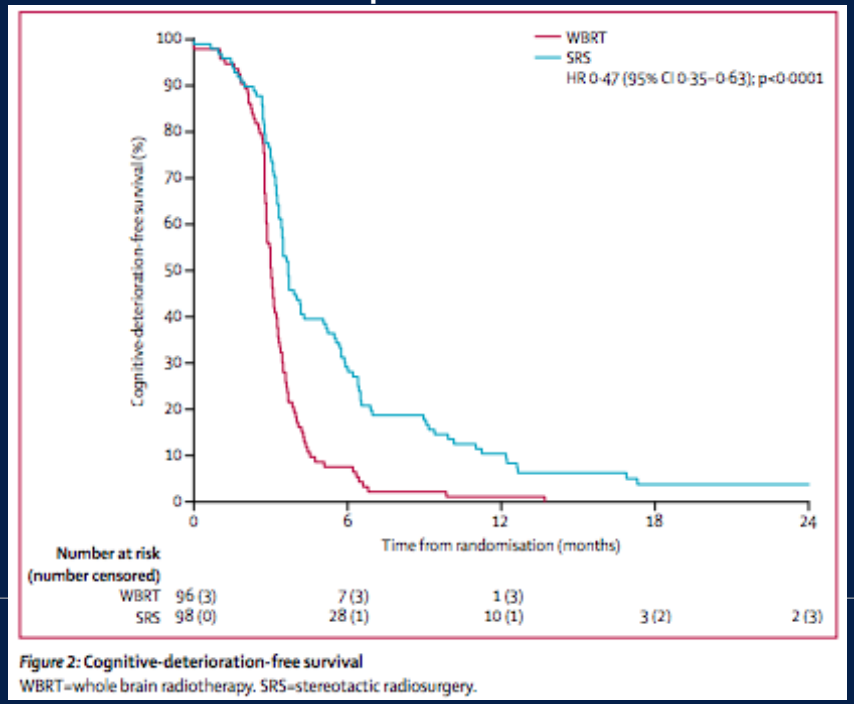

Figure 2: **Cognitive-deterioration-free survival**
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

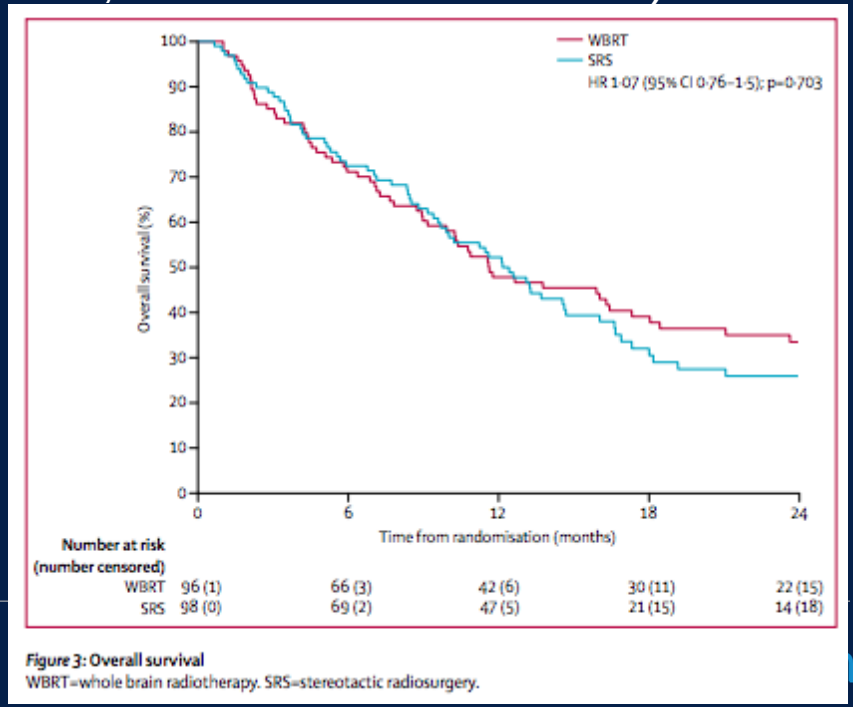

Figure 3: **Overall survival**
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

General Agreements

Post-op SRS for patients with resected brain metastases is a standard of care

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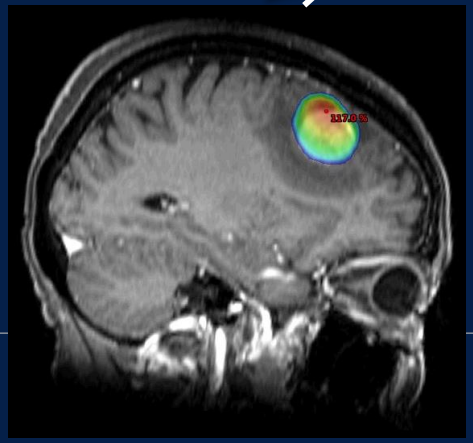

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General Agreements

Pre-operative SRS is safe and effective with excellent local control

A New Treatment Paradigm: Neoadjuvant Radiosurgery Before Surgical Resection of Brain Metastases With Analysis of Local Tumor Recurrence

Anthony L. Asher, MD,[*,§] Stuart H. Burri, MD,[†] Walter F. Wiggins, PhD,[¶] Renee P. Kelly [illegible] BSN,[§] H. James Nort[illegible]

	Six months	Twelve months	Twenty four months
Actuarial Overall Survival	77.8%	60.0%	26.9%
Actuarial Local Control	97.8%	85.6%	71.8%

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Pre-op versus Post-op SRS

- 180 patients with surgical resection of 189 brain metastases.
  - 66 pre-SRS (36.7%)
  - 114 post-SRS (63.3%)
- MVA suggested no difference in:
  - Overall survival (HR 0.74, P=0.10)
  - Local recurrence (HR 1.55, P=0.24)
  - Distant brain recurrence (HR 1.8, P=0.75)

- Post-SRS was associated with higher rates of:
  - Leptomeningeal disease (2 years: 16.6% vs. 3.2%, P=0.01)
  - Symptomatic radiation necrosis (2 years: 16.4% vs. 4.9%, P=0.01)

Patel J Neurosurg 2016

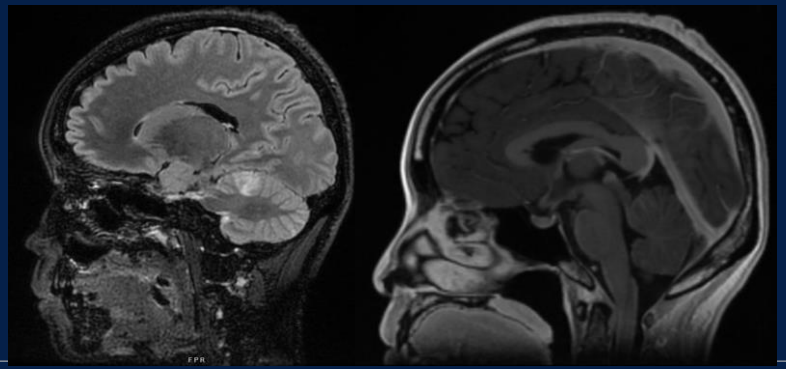
Leptomeningeal Disease

Poor prognosis

- Patients who develop post-resection (nodular) LMD have a median survival of 5.4 months.
- Patients with classical LMD have a median survival of 3.3 months.

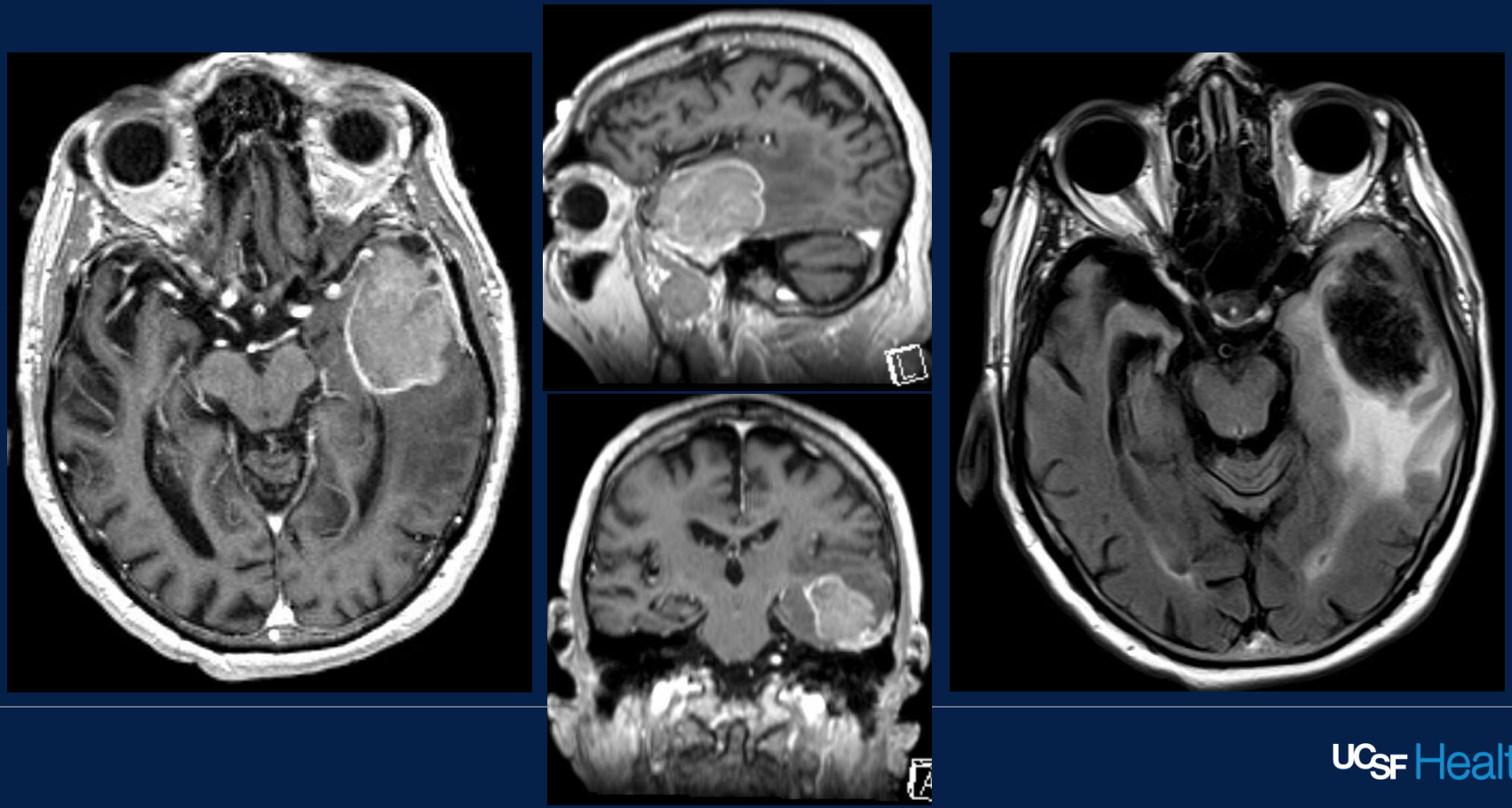
Impact

- The risk of LMD is as high as 30% in patients with breast cancer who normally have the longest expected survival with brain metastases.



Prabhu 2019, Sperduto 2012, Atalar 2013, Ojerholm 2014

Patient with newly diagnosed brain metastasis



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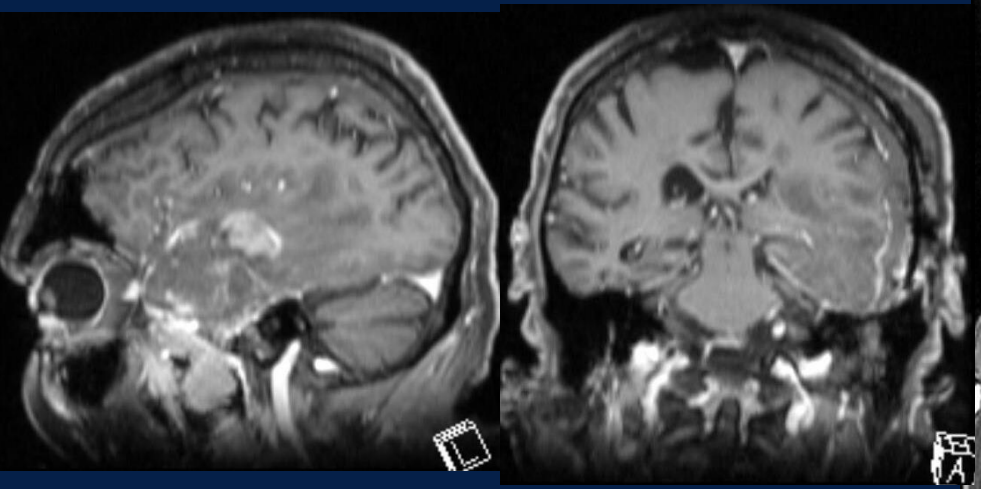
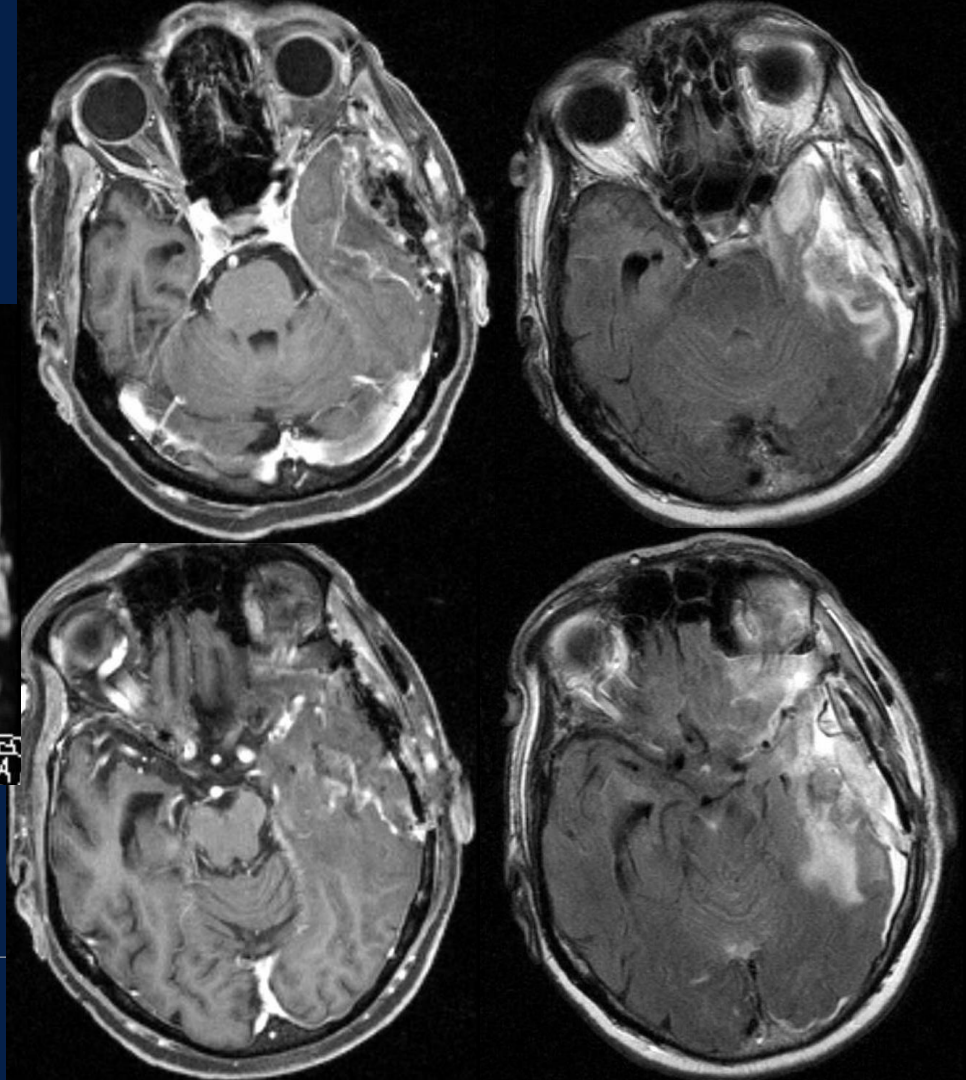
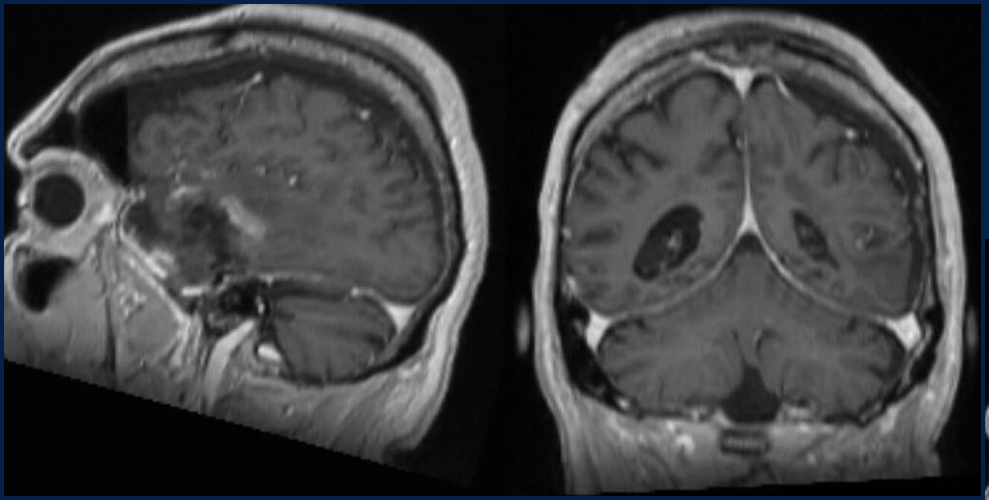
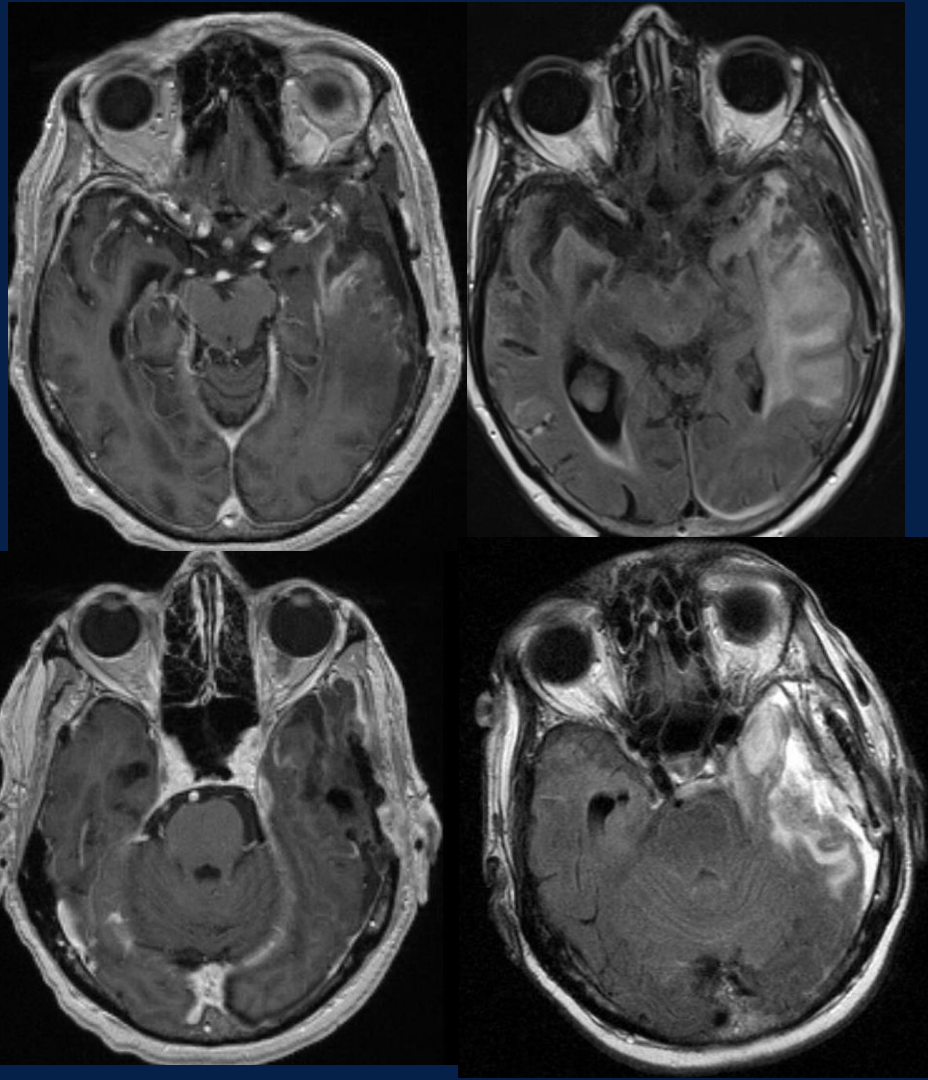
Immediately Post-Op



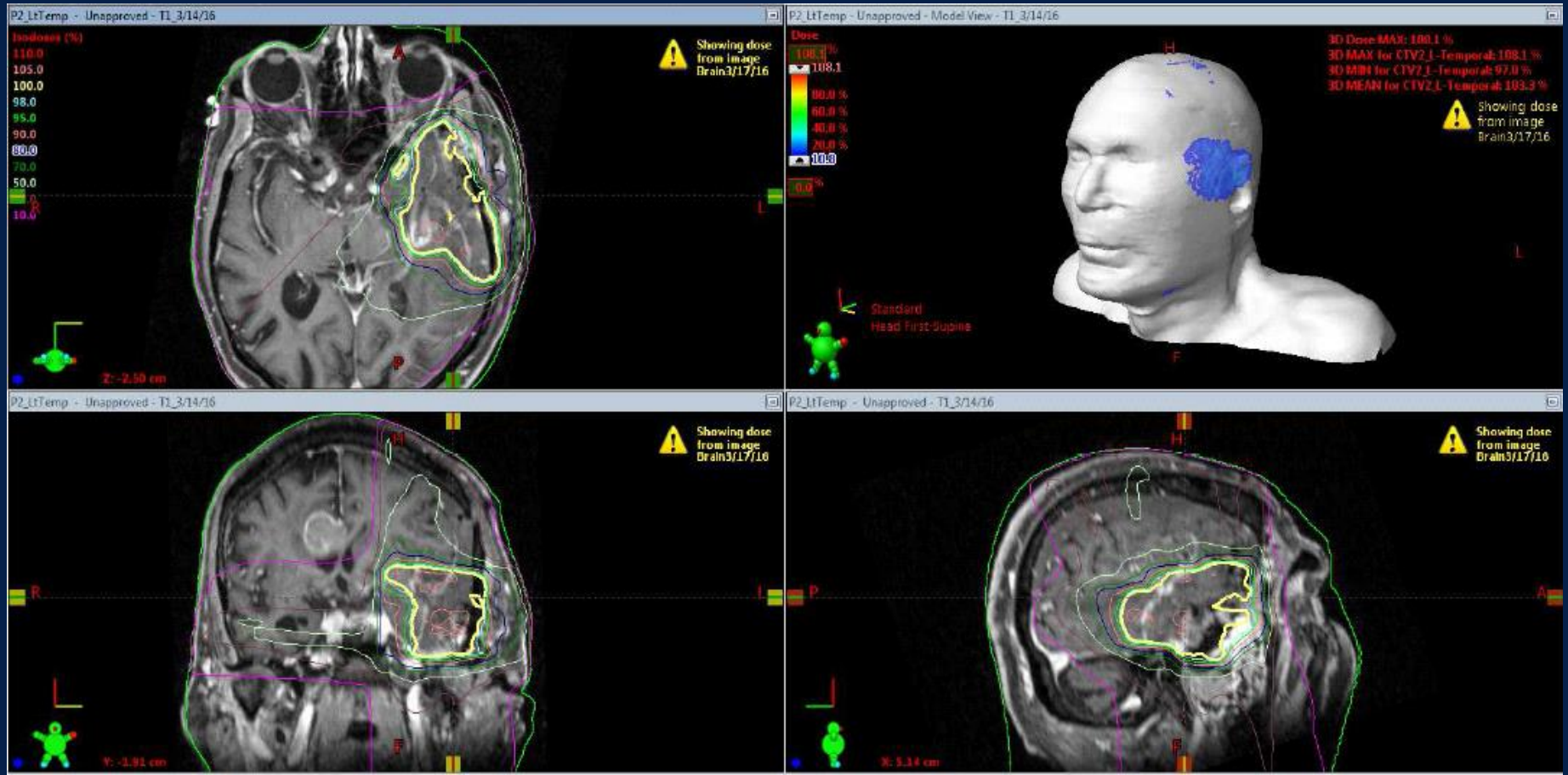


Post-op Day 8





Radiation Treatment Plan



A Phase 1 Dose Escalation Trial of Neoadjuvant Radiosurgery for the Treatment of Metastatic Brain Tumors

Primary Objective:

- To determine the maximum tolerated dose (MTD) of radiation given prior to neurosurgery in subjects with brain metastases.

Hypothesis:

- The MTD will be dependent upon target size and will be similar to those established on RTOG 90-05.

Tumor Diameter	Maximum Tolerated Dose
≤ 2 cm	Stopped at 24 Gy
2-3 cm	18 Gy
3-4 cm	15 Gy

Study Design

SRS was performed prior to resection of the indexed brain metastasis. The dose of radiation administered to the indexed lesion was established as a function of tumor size:

Greatest Dimension	Initial Dose
≤ 2 cm	20 Gy
2-3 cm	14 Gy
3- cm	13 Gy

Prescription dose will be per Escalation With Over Dose Control (EWOC) statistical determination:

- Tumors ≤2.0 cm: 20 Gy to 24 Gy
- Tumors 2.1-3.0 cm: 14 Gy to 18 Gy
- Tumors 3.1-4.0 mm: 13 Gy to 15 Gy

A Phase 1 Dose Escalation Trial of Neoadjuvant Radiosurgery for the Treatment of Metastatic Brain Tumors

Secondary Objective

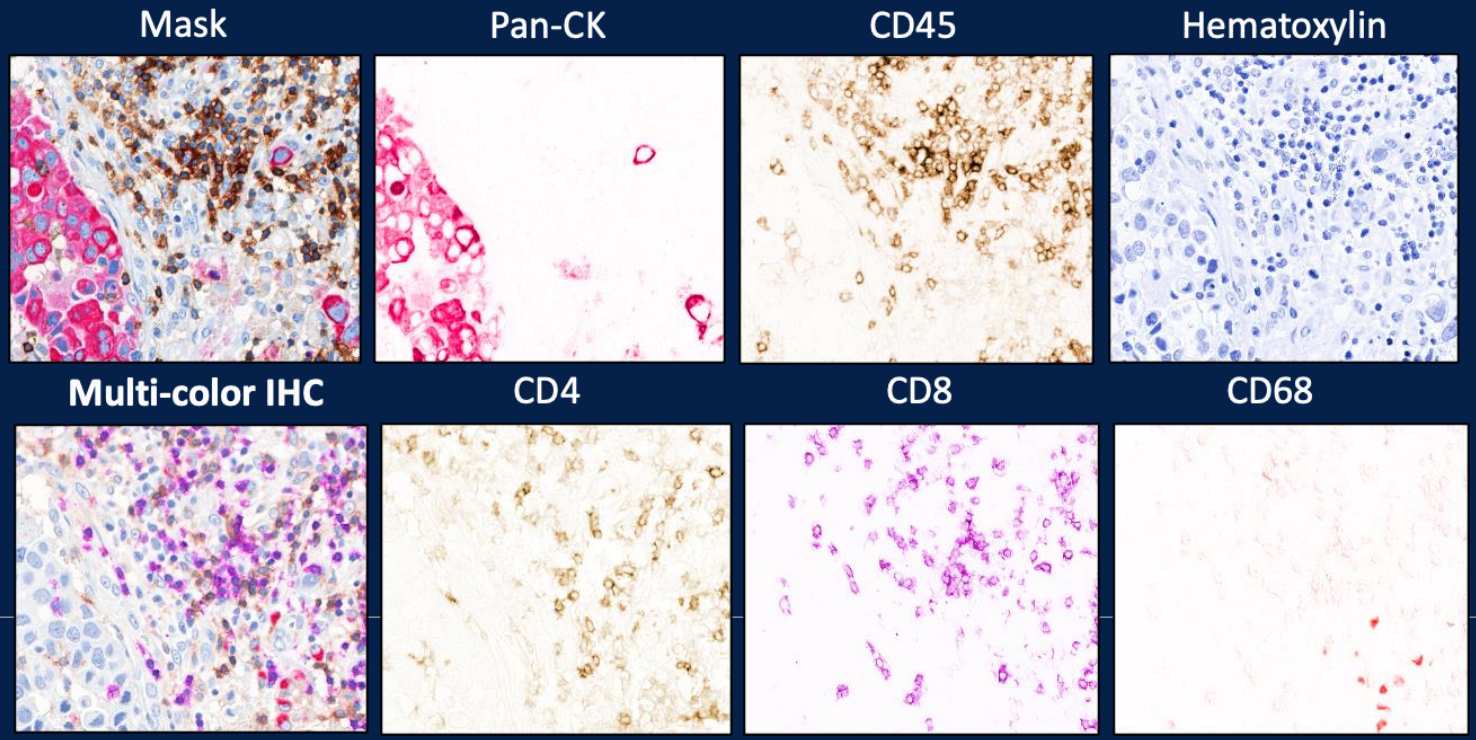
- To describe preliminary rates of image-complete resection, local tumor control, intracranial control, progression-free survival, leptomeningeal spread, and radiation necrosis.

Hypothesis

- Pre-operative SRS will have similar rates of image-complete resection, local tumor control, intracranial control, and PFS as historical controls, with lower rates of leptomeningeal spread and radiation necrosis.

Exploratory Objective

- To characterize the immune response to radiation within metastatic brain lesions and identify associated biomarkers (analysis of the immune composition and signaling using multiplex flow cytometry, cytokine arrays and immunohistochemistry)



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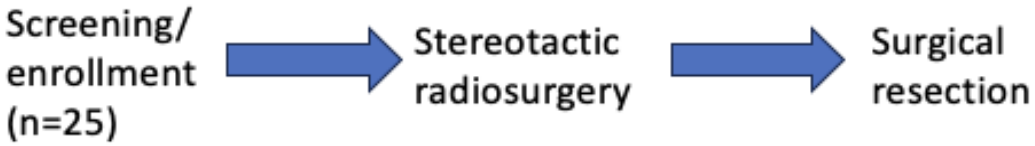


- DLT evaluation: 30-day window post surgery
- Follow up evaluation: physical exam, MRI, labs every 3 months for 1 year

Tumor Diameter	Maximum Tolerated Dose
≤ 2 cm	Stopped at 24 Gy (no MTD)
2-3 cm	Stopped at 18 Gy (no MTD)
3-4 cm	Stopped at 15 Gy (no MTD)

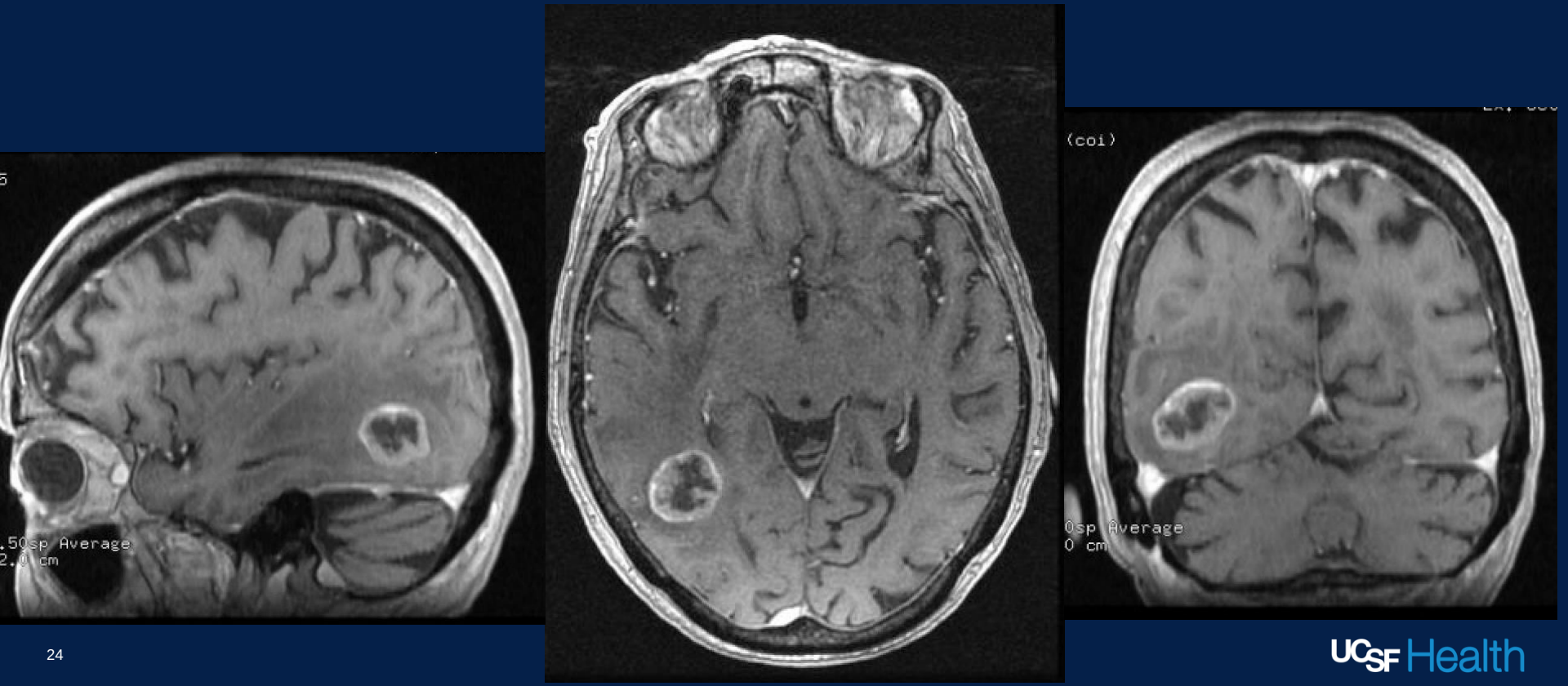
Clinical characteristics (n=25)	
Characteristic	No. (%)
Age, median (range, years)	65 (30-79)
Sex	
Female	15 (60%)
Male	10 (40%)
Karnofsky Performance Status	
100	2 (8%)
90	16 (64%)
80	5 (20%)
70	2 (8%)
Index lesion size, median (range, cm)	2.3 (1.2-4)
Index lesion location	
Frontal	5 (20%)
Parietal	8 (32%)
Temporal	2 (8%)
Occipital	5 (20%)
Cerebellum	5 (20%)
Primary histology	
NSCLC	9 (36%)
Gynecologic	4 (16%)
Breast	3 (12%)
Genitourinary (renal cell, bladder)	3 (12%)
Gastrointestinal (rectum, pancreas)	2 (8%)
Melanoma	2 (8%)
Thyroid	1 (4%)
Other*	1 (4%)
Number of brain metastases	
1	17 (68%)
2	4 (16%)
3	2 (8%)
4	2 (8%)
Extent of surgery	
Radiographic gross total	23 (92%)
Partial	2 (8%)

Outcomes

Tumor size	# of patients	Dose levels
≤2cm	9	20Gy – 4 23Gy - 2 24Gy - 3
2.1-3	12	14Gy - 1 15Gy - 1 16Gy – 1 18Gy – 3 19Gy – 2 20Gy – 1 21Gy – 1 23Gy - 2
3.1-4	4	13Gy – 1 15Gy – 2 17Gy – 1 18Gy - 1

- Median 2 days between SRS and surgery (range 1-8)
- Safety
  - No DLTs
- Crude rates
  - Mortality 15/25
  - Local recurrence of index lesion 2/25
  - Distant brain failure 13/25
  - Leptomeningeal disease 1/25
  - Radiation necrosis 3/25

91 yo F with h/o recurrent melanoma and new lesion found on MRI brain



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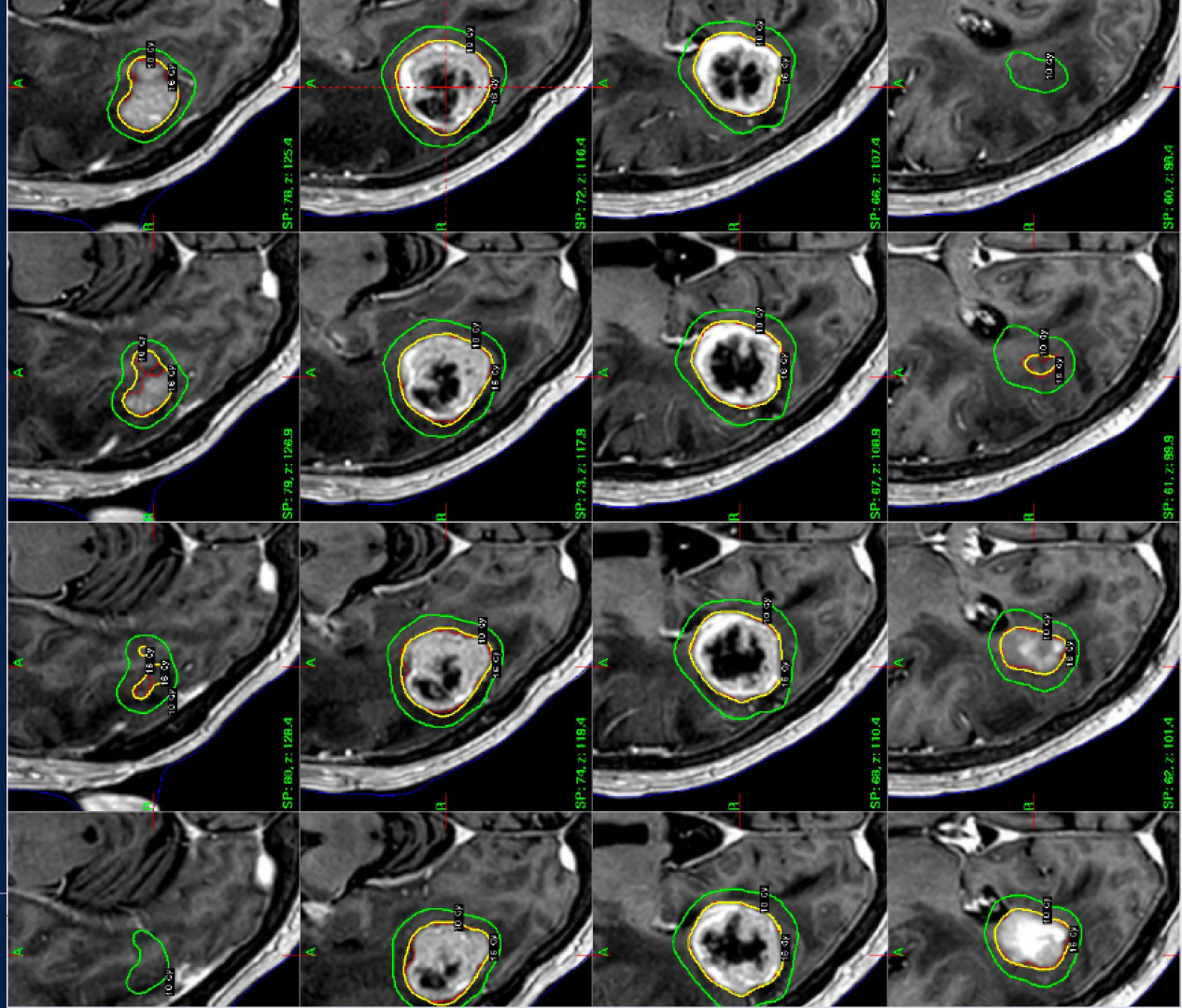
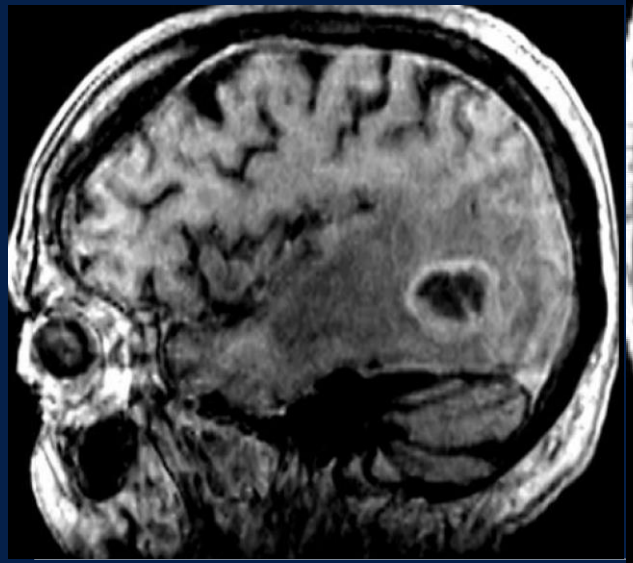
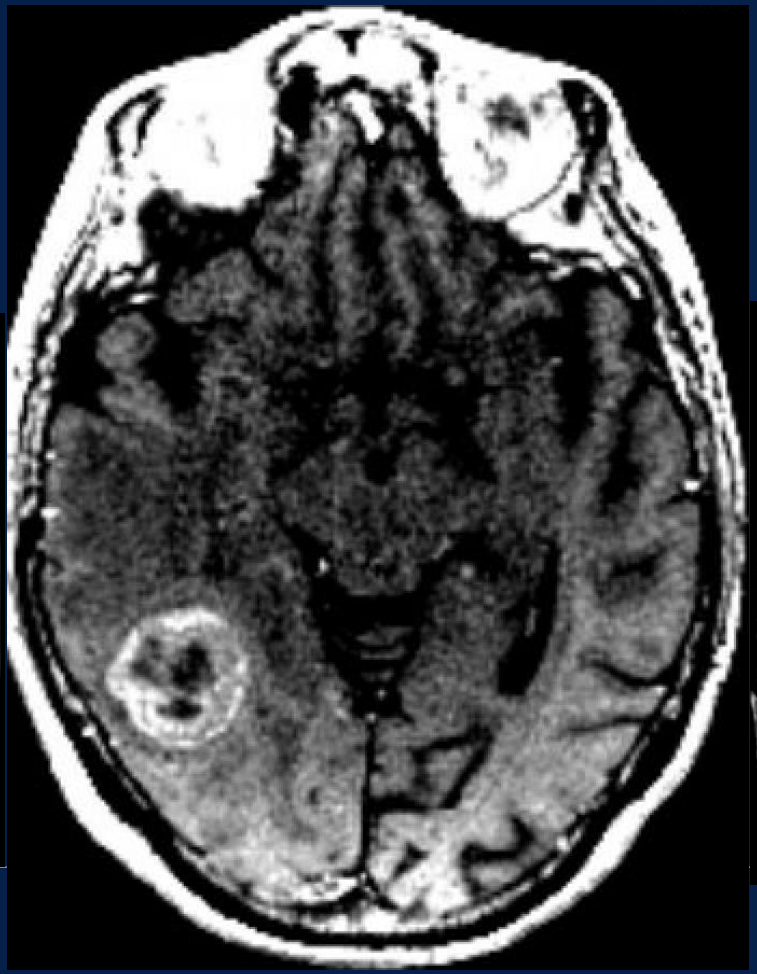
Radiosurgery plan

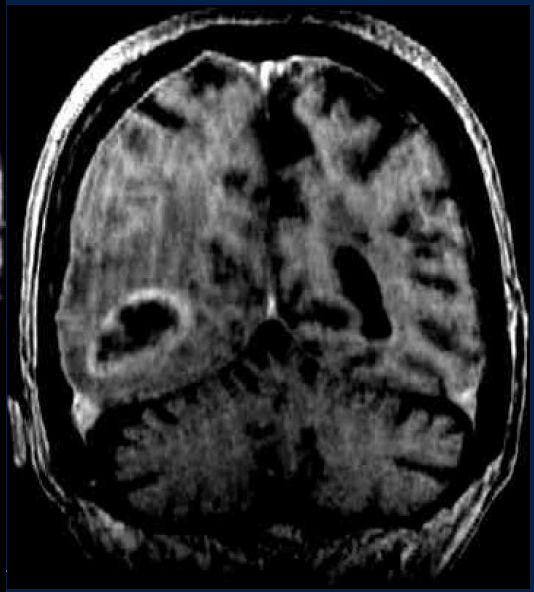
16 Gy x 1



Post SRS







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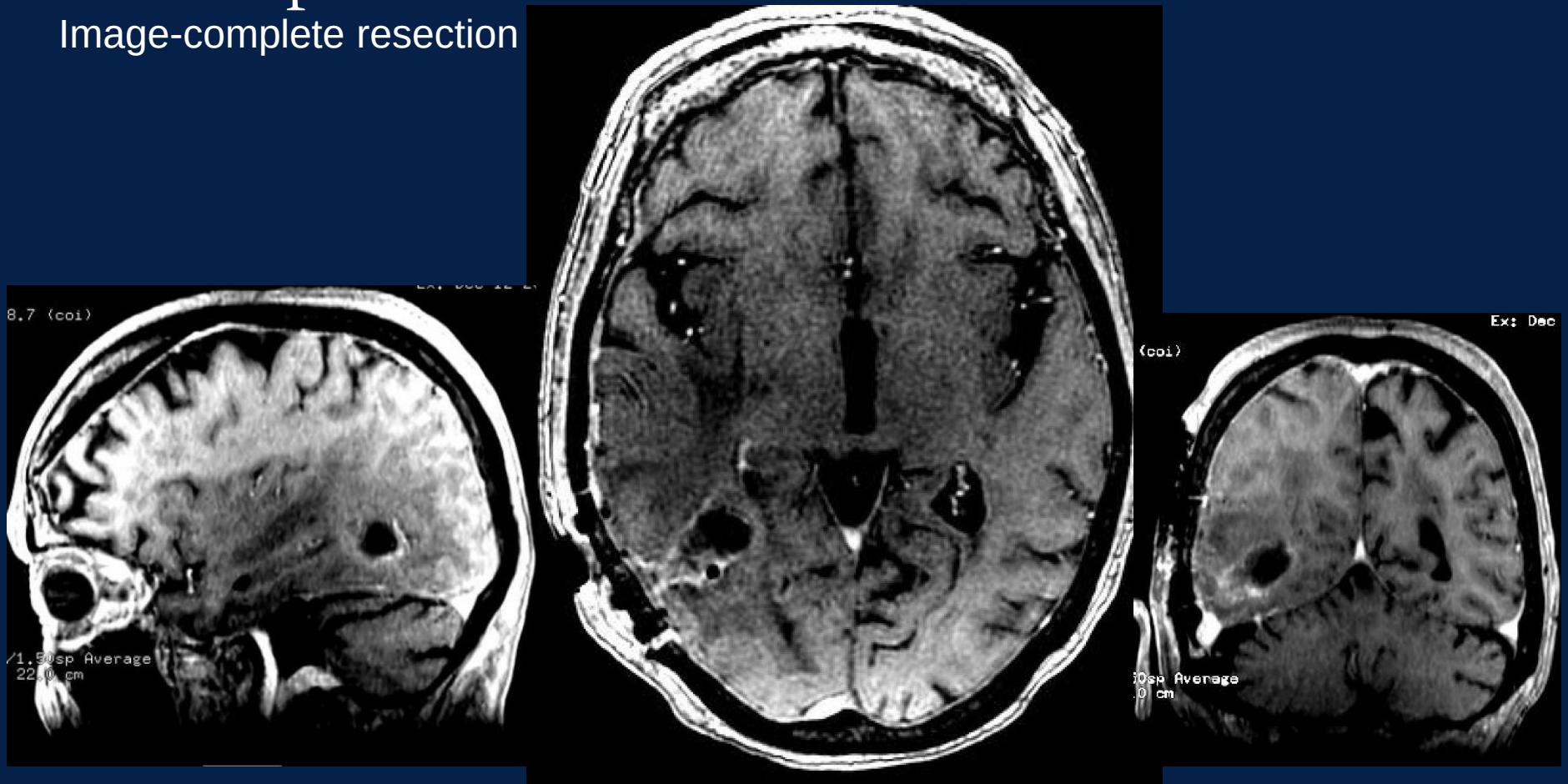
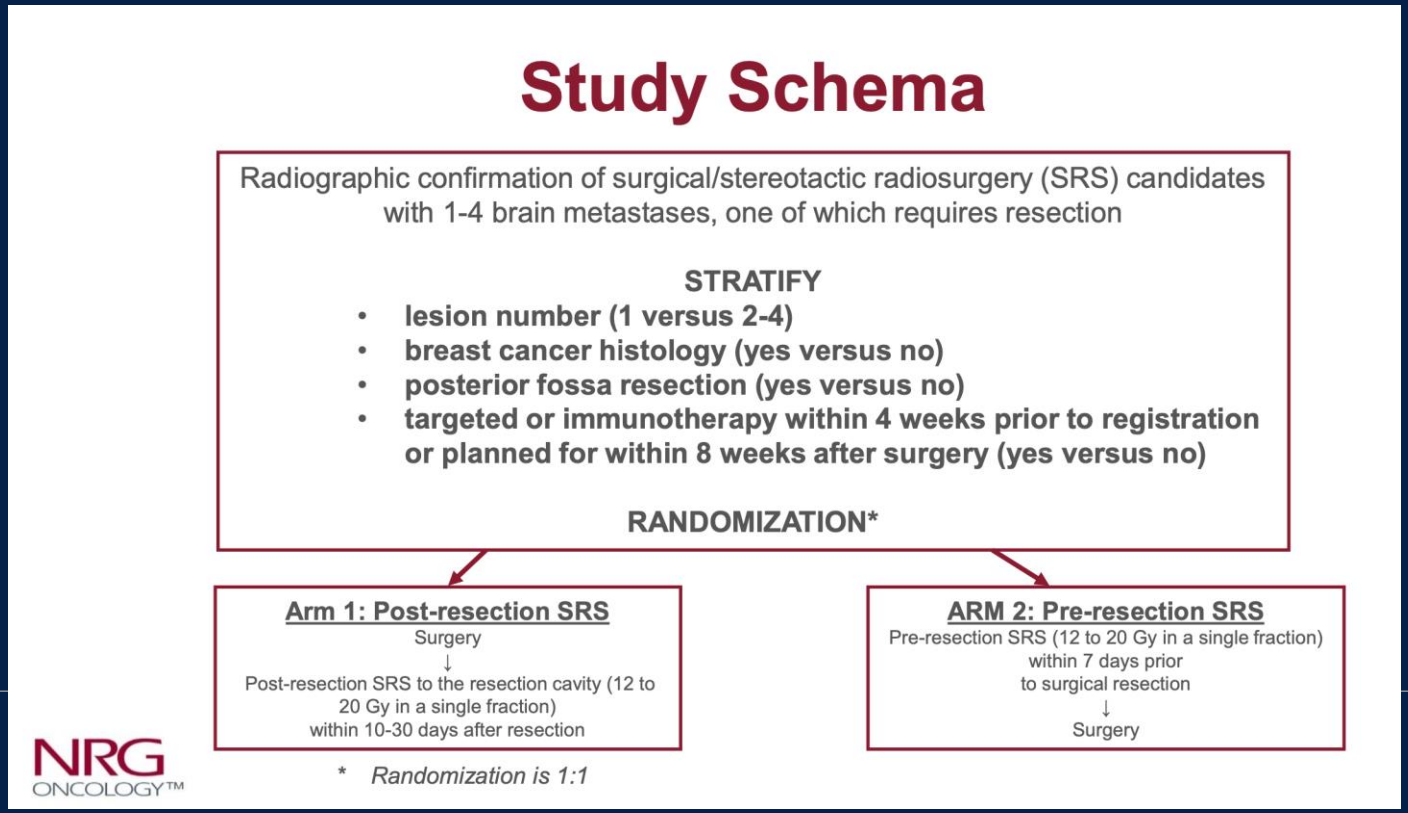
Post-op

Image-complete resection



NRG BN012

A Randomized Phase III Trial of Pre-Operative Compared to Post-Operative Stereotactic Radiosurgery in Patients With Resectable Brain Metastases



Primary Objective(s)

- To determine if the time to composite adverse endpoint (CAE) *[defined as:1) local tumor progression within the surgical bed; and/or 2) adverse radiation effect (ARE), the imaging correlate of post-SRS radiation necrosis; and/or 3) nodular meningeal disease (nMD)]* is improved in patients treated with pre-resection SRS to the intact lesion versus those treated with post-resection SRS.

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Secondary Objective(s)

- To assess the trajectory of symptom burden in patients treated with pre-resection SRS to the intact lesion versus those treated to the post-resection surgical cavity as measured by MD Anderson Symptom Inventory for brain tumor (MDASI-BT).
- To determine whether there is improved overall survival (OS) in patients with resected brain metastases who undergo pre-resection SRS compared to patients who receive post-resection SRS.
- To compare rates of ARE, the imaging correlate of radiation necrosis, in patients who receive pre-resection SRS to patients who receive post-resection SRS.
- To determine whether there is increased time to whole brain radiotherapy (WBRT) in patients who receive pre-resection SRS compared to patients who receive post-resection SRS.
- To assess the trajectory of neuro-cognitive function in patients treated with pre-resection SRS to the intact lesion versus those treated to the post-resection surgical cavity as measured by the Montreal Cognitive Assessment (MoCA).
- To compare rates of nodular meningeal disease in patients who receive pre-resection SRS to patients who receive post-resection SRS.
- To compare rates of local recurrence in the resection cavity for patients who receive pre-resection SRS to patients who receive post-resection SRS.
- To compare rates of local recurrence of intact, non-index metastases treated with SRS.
- To compare rates of distant brain failure in patients who receive pre-resection SRS to patients who receive post-resection SRS.
- To assess toxicity in the two treatment arms.

Thank You

emi.yoshida@ucsf.edu

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