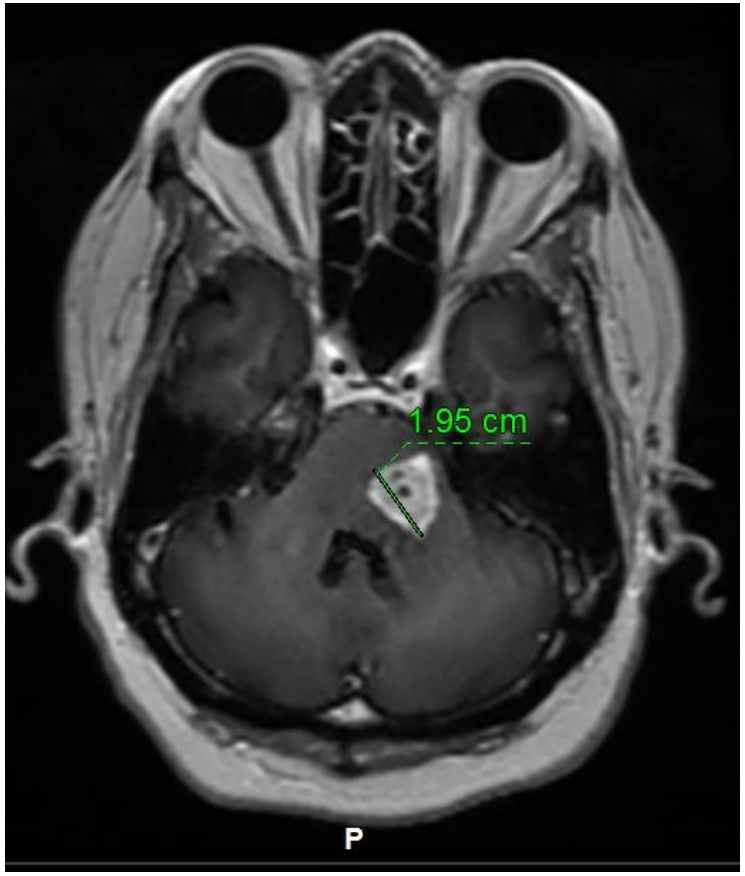
Management of Brain Metastasis

Outline

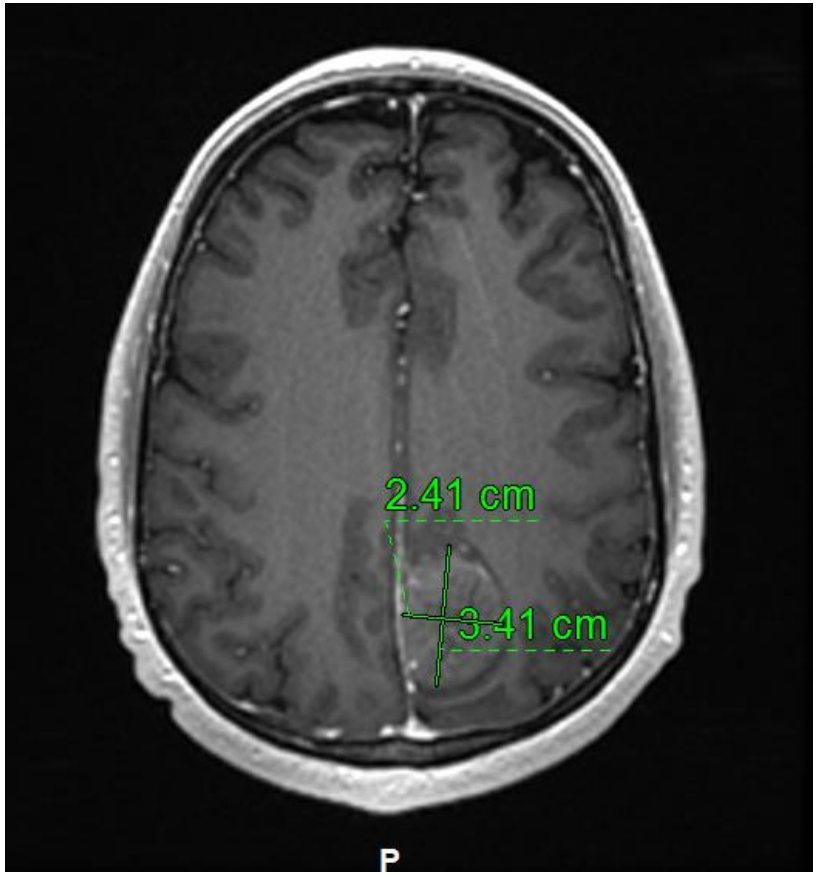
- Case presentation
- Background
- Treatment options
- Whole brain radiation therapy
  - Patchell I: WBRT +/- Surgery for one met
  - Patchell II: Surgery +/- WBRT for one met
  - EORTC 22952-26001 (Kocher): Surgery OR SRS +/- WBRT for 1-3 mets
- SRS for intact BM
  - RTOG 9005: SRS dose escalation
  - RTOG 9508: WBRT +/- SRS for 1-3 mets
  - JROSG 99-1 (Aoyama): SRS +/- WBRT for 1-4 brain mets
  - JLGK0901 (Yamamoto): SRS alone for 5-10 versus 2-4 mets
- Management of post op cases
  - Reminder on classic studies
  - MDACC study
  - NCCTG N107C/CEC·3
  - Consensus guidelines
- Management of BM in the era of Precision Oncology

Case Presentation

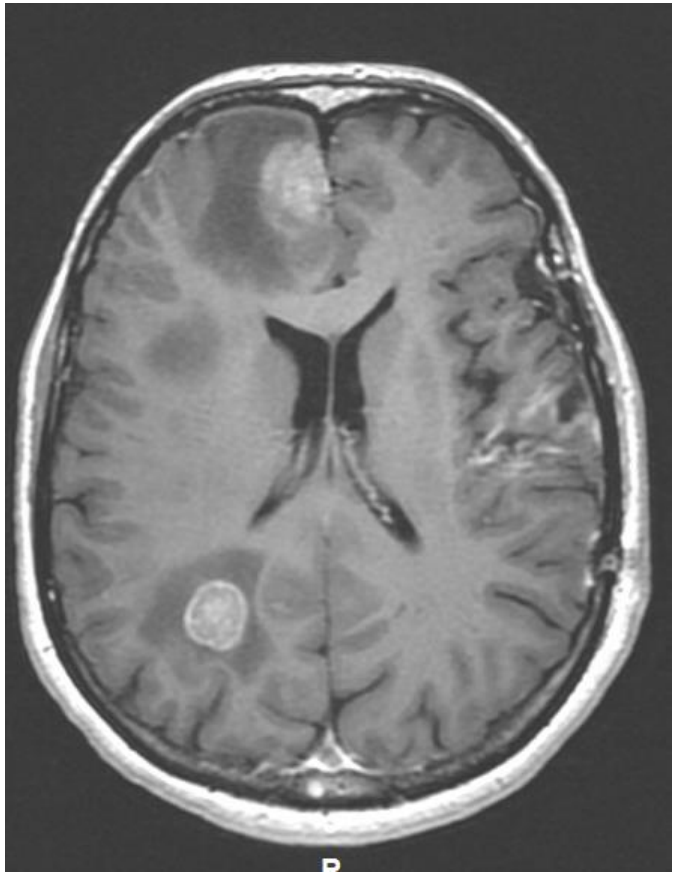
Case presentation



60F w/ EGFRm NSCLC on Osimertinib now pw new L facial numbness



33M w/ testicular NSGCT s/p neoadjuvant BEP pw R foot numbness



46F nonsmoker w/NSCLC found >20 new BM enhancing lesions on staging MRI brain

Background

Background: Pathophysiology

- Hematogenous spread from a site of systemic disease
- Predominantly located at grey/white matter junction and watershed areas
  - Decrease in vessel diameter leads to tumor cell trapping

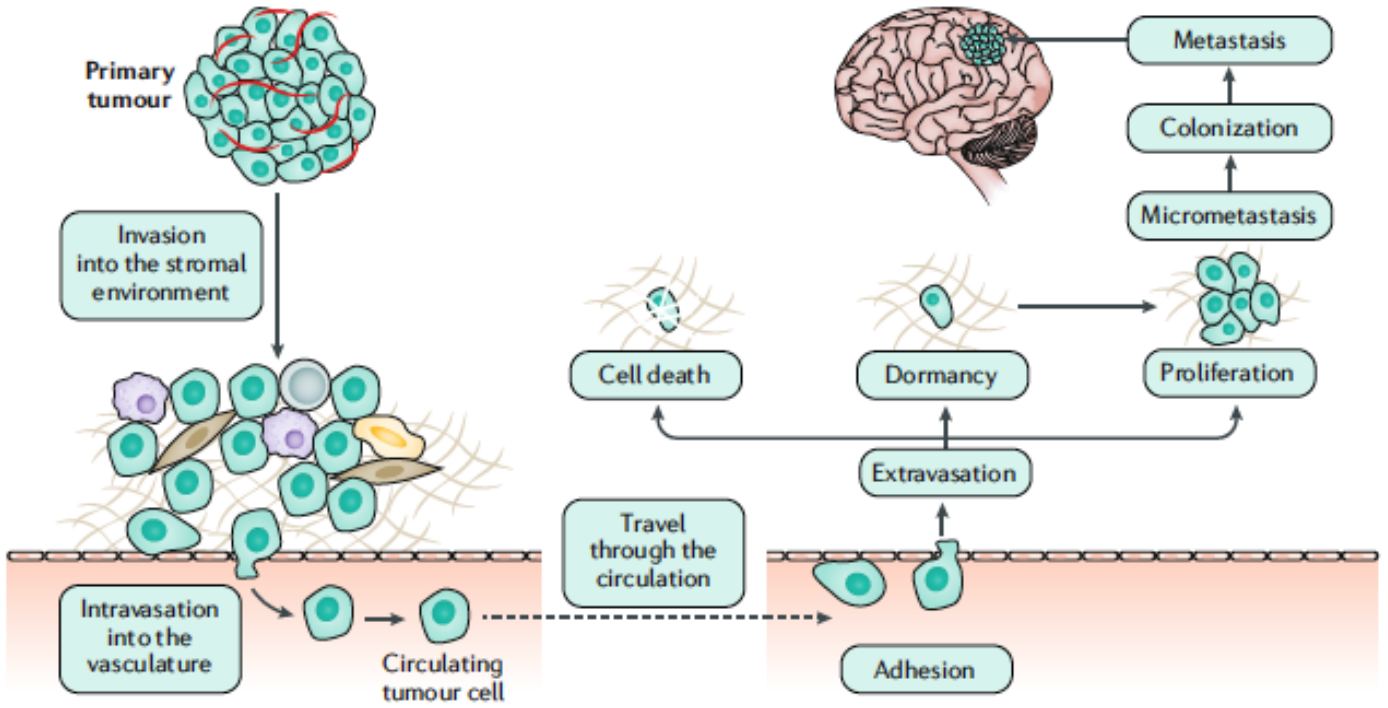


Fig. 1 | **Cancer cell metastatic dissemination.** Brain metastases develop following the haematogenous (that is, through the blood) spread of cells from a primary tumour to the brain microvasculature, with subsequent tumour growth involving microenvironmental niche–tumour interactions, neuroinflammatory cascades and neovascularization. Initially, tumour cells break away from the primary bulk tumour and invade the surrounding tissues, venules, capillaries and lymphatic system (intravasation). Tumour cell interactions with immune cells promote cell motility via clearance of extracellular matrix. Once in the circulation, these circulating tumour cells begin the process of metastatic extravasation from the vasculature, which is facilitated by these cells undergoing adhesive (circulatory) arrest. Brain metastases tend to occur at the junction between grey and white matter and watershed areas between vascular territories where it is postulated that circulating tumour cells benefit from longer relative mean transit times of blood flow, enabling more time for the cells to overcome the blood–brain barrier and successfully egress from the vasculature. After arresting and extravasating, most tumour cells die rather than form metastases whereas others can lie dormant at metastatic sites for extended periods.

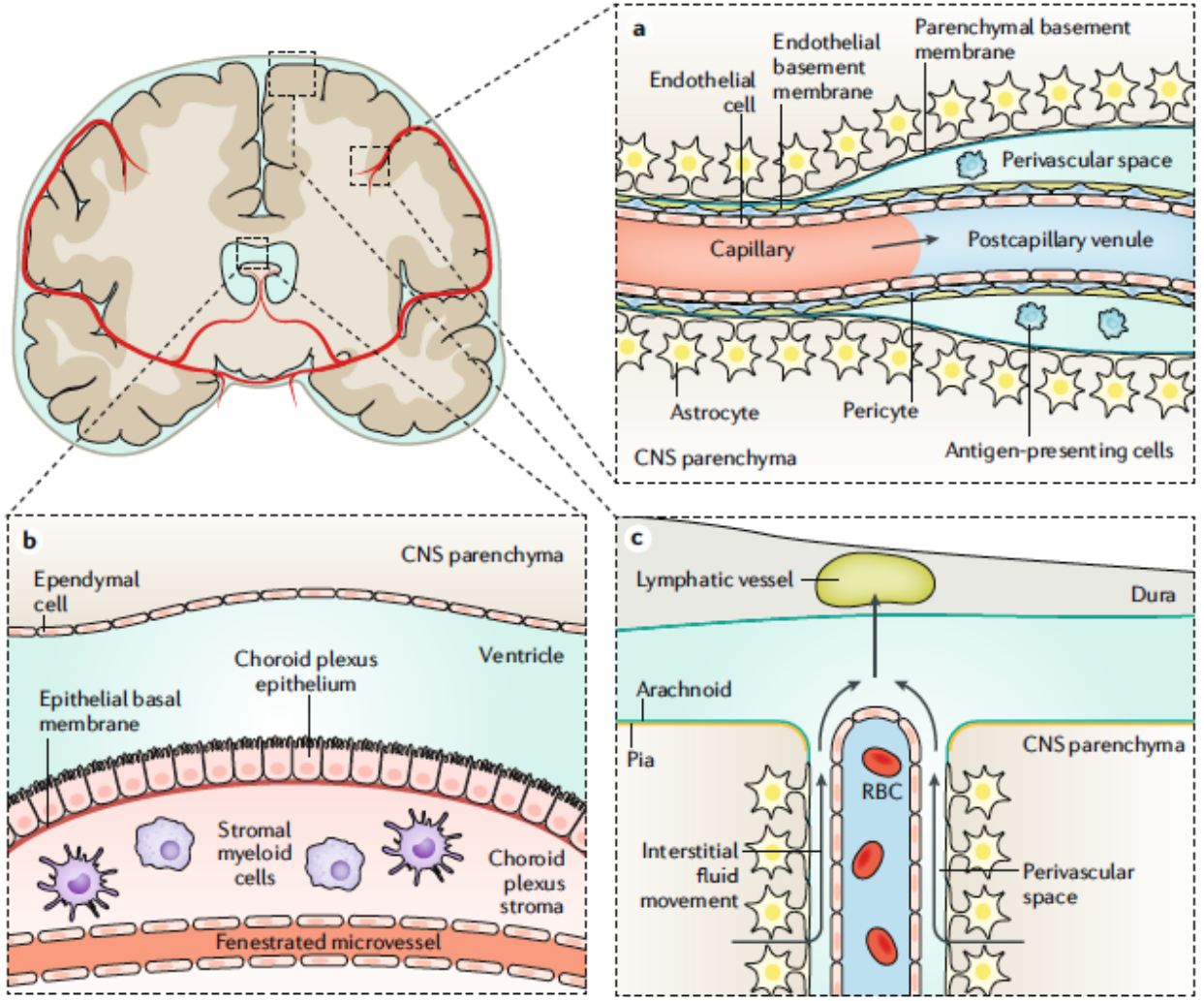


Fig. 2 | **Central nervous system barriers. a** | The blood–brain barrier has evolved as protective insulation for neuronal signalling and comprises endothelial cells characterized by a low transcytosis rate and high expression of efflux pumps that are connected by continuous tight junctions. In addition, two basement membranes (endothelial and astrocytic (parenchymal)), embedded pericytes and the endfeet of astrocytes all further contribute to its barrier functions. At the level of postcapillary venules, there is a potential space between the basement membranes containing sparse antigen-presenting cells. **b** | The blood–cerebrospinal fluid (CSF) junction is formed by choroid plexus epithelial cells that are connected via tight junctions; the choroid plexus capillaries have fenestrations and intercellular gaps that enable the movement of molecules. Circulating leukocytes rarely enter the brain parenchyma under homeostatic conditions, although endogenous parenchymal immune cells are present. **c** | The brain lymphatic system provides a route for immune cells and proteins from the CSF to drain through lymphatic channels in the meninges to deep cervical lymph nodes. CNS, central nervous system; RBC, red blood cell.

Background: Pathophysiology

- Location of lesions mirrors blood flow
  - 80% cerebral hemispheres
  - 15% cerebellum
  - 5% brainstem

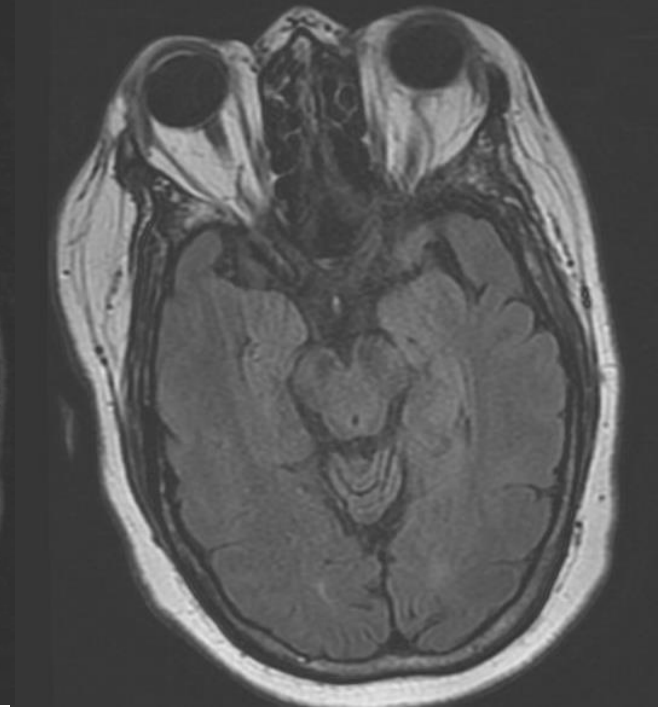
- Predilection of some tumor types for posterior fossa
  - Prostate, uterine, GI
  - Protein expression in endothelium?

Differential Diagnosis for an Enhancing Hemispheric Lesion

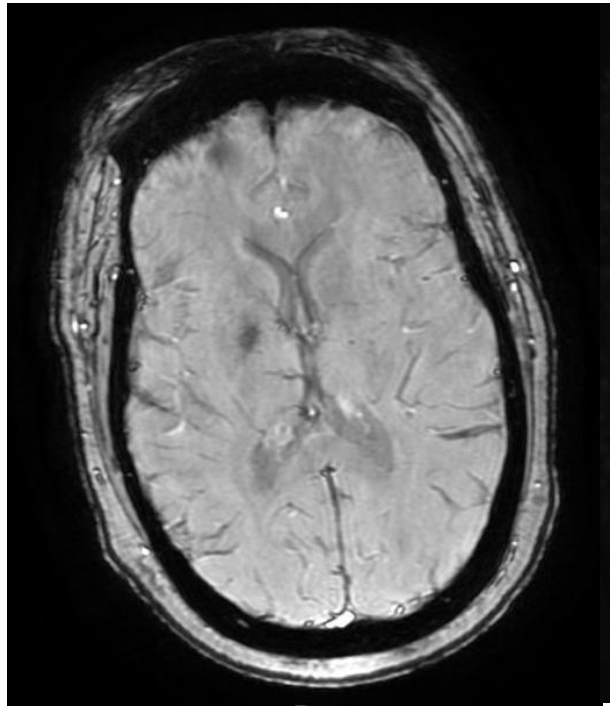
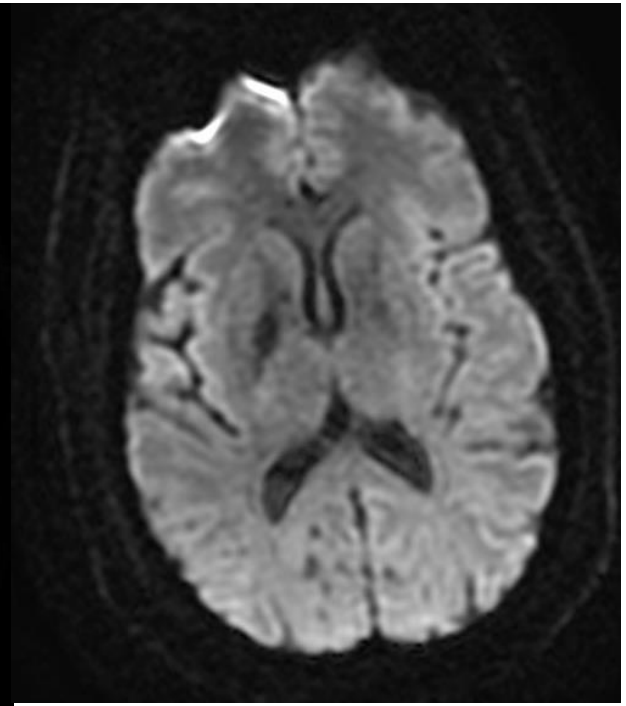
- Brain metastases
  - Often multifocal
  - Commonly at grey-white matter interface
- Malignant Glioma
  - Anaplastic astrocytoma
  - GBM
- CNS lymphoma
- Abscess
- Demyelination
- Stroke





Name the sequence

Differential diagnosis for a ring enhancing lesion

- Gadolinium-enhanced MRI
  - Factors suggestive of metastases:
    - Multiple lesions, associated edema, well-circumscribed, predilection for gray-white interface (watershed regions)
  - T1 pre-gadolinium: may show hemorrhage (melanoma, renal, thyroid, choriocarcinoma, NSCLC)
  - T1 post-gadolinium: enhancement
  - T2/FLAIR: edema
  - Per NCCN: brain MRI in asymptomatic patients only recommended for: SCLC, stage IB-IV NSCLC, stage IV melanoma

Background: Epidemiology

- Most common intracranial tumor
  - 10-30% of adults with systemic malignancies
  - 6-10% of children with systemic malignancies
- ~180,000 cases annually
- Incidence is increasing as systemic therapy improves, with increasing use of MRI and increase in the prevalence of cancer in general
- Up to 20% of pts with solid tumors develop brain metastases.

Background: Epidemiology

- Incidence differs by type of primary
  - Lung: 16-20%
  - Renal Cell: 7-10%
  - Melanoma: 7%
  - Breast: 5%
  - Colorectal: 2%
- Most common primary diseases
  - Lung > Breast > Melanoma

Background: Presentation

- Headaches (40-50%)
  - More likely with multiple lesions or posterior fossa location
- Focal Neurologic Dysfunction (20-40%)
- Cognitive Dysfunction (30-35%)
  - Memory problems, mood/personality change
- Seizure (10-20%)
- Hemorrhagic Stroke (5-10%)
  - More common in melanoma

Goals of treatment

Local & global brain control with the aim of:

- Addressing functional neurologic deficits/dangers (QOL)
- Preventing neurologic death

Treatment options

- Supportive care
- Whole brain radiation therapy
- Surgery
- Partial brain radiation therapy
- Stereotactic radiosurgery
- Systemic therapy

Treatment options

Modality	Pro	Con
Best supportive care	No added tox	Not addressing disease
WBRT	Global brain control	Detrimental to neurocognition
Surgery	Urgent decompression and relief of neuro sx	Surgical morbidity and recovery
SRS	Focal therapy with high local control	RN & fails to address global brain disease
Partial brain RT	Focal therapy for larger volume	Higher fx #, likely worse local control
Systemic therapy	Avoid RT toxicity and addresses systemic disease	Poorly studied long term outcomes and generally lower efficacy than SRS

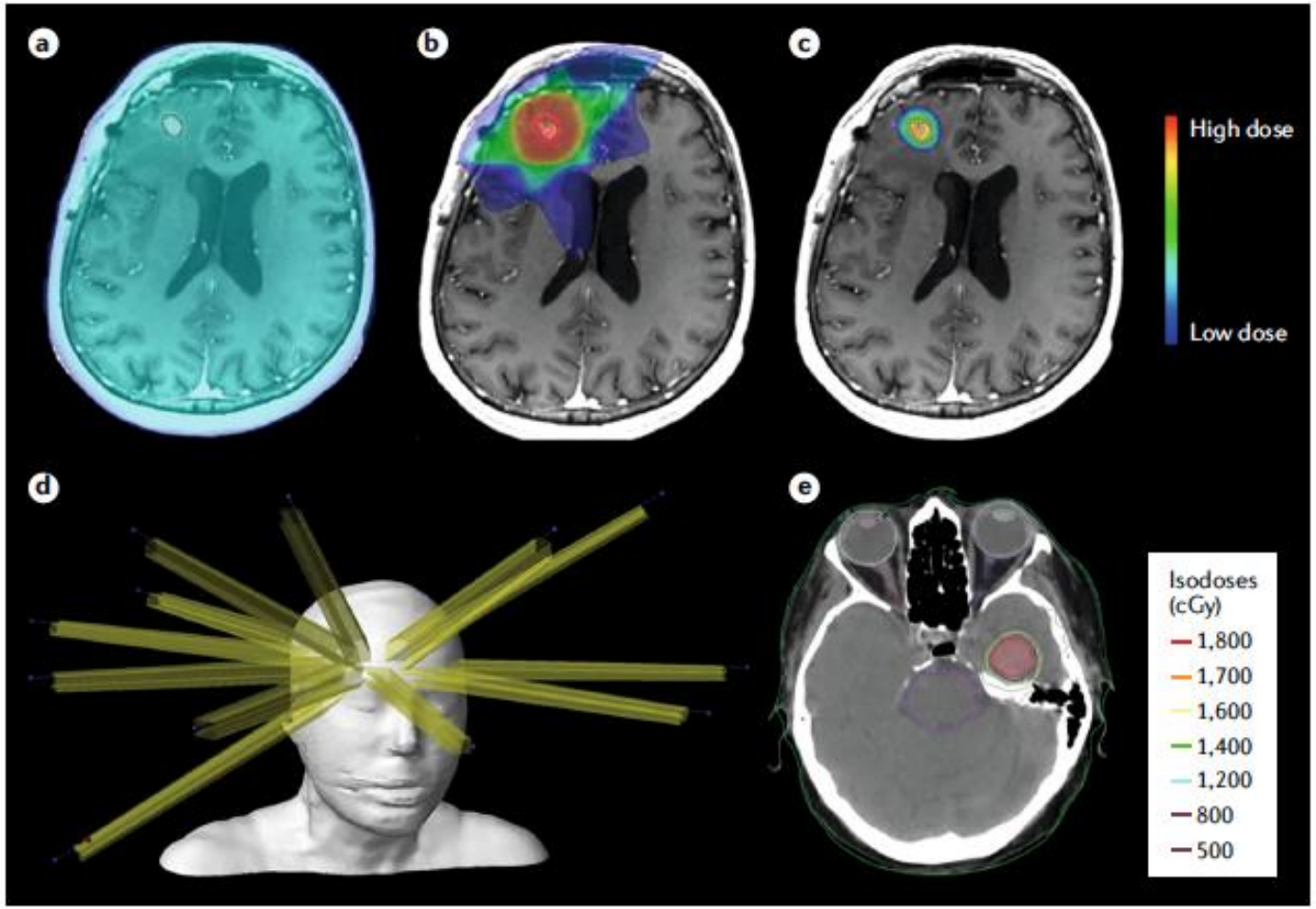
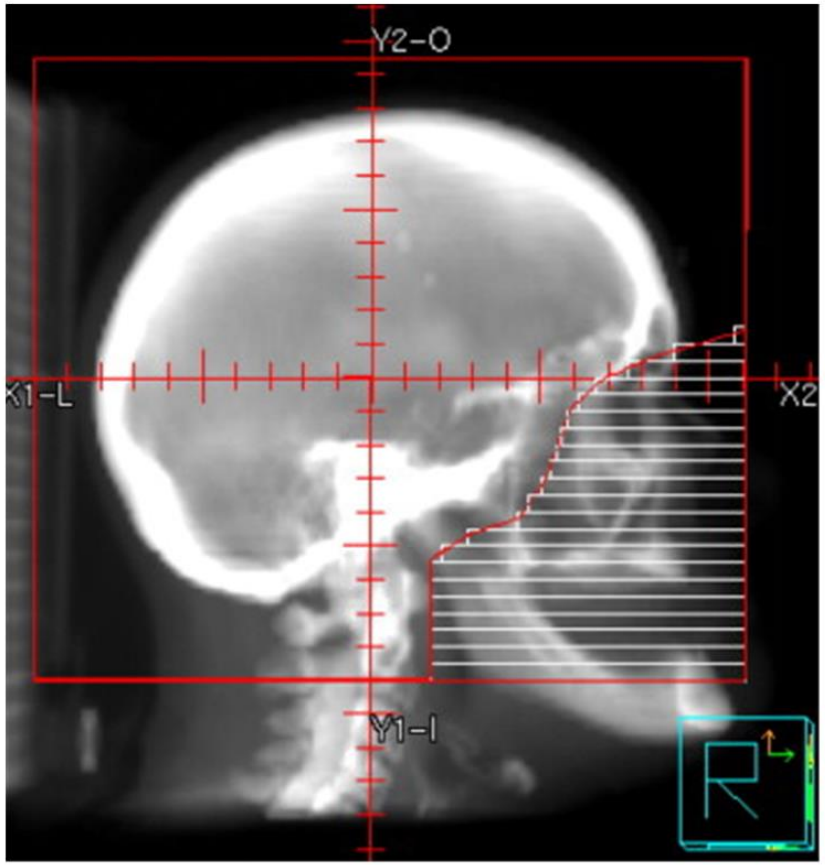


Fig. 5 | **Evolution of radiation-based treatments of brain metastases.** Advances in treatment delivery platforms from whole-brain radiotherapy (panel **a**) and 3D conformal radiotherapy (in which the radiation beams are delivered to match the shape of the tumour; panel **b**) to stereotactic radiosurgery (SRS; panels **c**–**e**) have made treatment for high numbers of brain metastases more technically feasible. SRS involves the precise focusing of radiation around the lesion from different angles to avoid healthy tissues and provides a more confined area of irradiation than 3D conformal radiotherapy. Panel **d** highlights the sample beam arrangement, whereas panels **c** and **e** demonstrate the resulting focal, high-dose radiation delivered with SRS. Hypofractionated SRS, which typically entails 3–5 treatments, is increasingly being used for brain metastases near tissues more sensitive to radiotherapy, such as the optic nerves and chiasm and the brainstem. Early evidence suggests that this approach provides good tumour control with a favourable toxicity profile.

WBRT

Treatment Options: WBRT

- Goal
  - Treatment of visible and micrometastatic disease
- Efficacy
  - Response rate of 50-85%
    - 74% with improvement in HA, 40% improvement in CN deficits
    - 59% radiographic (CT) response (24% complete, 35% partial) after 30 Gy in 10 fractions**



*Caincross JG et al. Ann Neurol 1980;7:529
** Nieder C et al. IJROBP 1997;39:25

Key studies

- Patchell I: WBRT +/- surgery for a single met
- Patchell II: surgery +/- WBRT for a single met
- EORTC 22952: surgery/SRS +/- WBRT for 1-3 mets

Patchell I: What is the added benefit of surgery with whole brain radiation therapy in the treatment of a single brain metastasis?

- Patients:
  - 48 patients that were ≥ 18 yo, KPS ≥ 70, CT and MRI evidence of a resectable single brain metastasis; no leptomeningeal involvement
  - Median KPS 90, primarily NSLC patients, median age ~60yo
  - Excluded SCLC, germ cell tumors, lymphoma, leukemia and multiple myeloma
- Treatments:
    - Arm 1) Biopsy → WBRT (n=23)
    - Arm 2) Surgery → WBRT (n=25)
    - WBRT 36 Gy in 13 fractions, within 14 days of surgery or 48 hours of biopsy
    - Follow up: q3 month neuro exam & imaging

Patchell et al, NEJM 1990

Patchell I: WBRT +/- Surgery for one met

- Results

	Surgery + WBRT	WBRT	p
Local recurrence	20%	52%	0.02
In brain recurrence	20%	13%	0.52
KPS ≥70	38 wk	8 wk	0.005
Neurologic survival	62 wk	26 wk	0.0009
Median survival	40 wk	15 wk	0.01

- Conclusion
  - The addition of surgery to whole brain radiation improved local control and survival in patients with a single brain metastasis and good performance status
- Limitations: Small numbers, all surgical referrals

Patchell et al, NEJM 1990

Patchell II: What is benefit of WBRT added to surgery for a single brain metastasis?

- Patients:
  - 95 patients with a completely resected single brain metastasis (verified by post-op MRI), KPS ≥ 70
  - Median KPS 90, median age 58 & 60, majority were NSCLC
- Treatment:
  - Arm 1) Surgery alone (n=46)
  - Arm 2) Surgery → WBRT (n=49)
  - WBRT **50.4 Gy** in 28 fractions (1.8 Gy/fraction)
  - Follow-up: MRI q3 months for first year, then q6 months, or with symptoms suggesting progression or recurrence

Patchell et al, JAMA 1998

Patchell II: Surgery +/- WBRT for one met

	Surgery	Surgery + WBRT	p
In-brain recurrence	70%	18%	<0.001
Local recurrence	46%	10%	<0.001
KPS ≥70	35 wk	37 wk	0.61
Neurologic survival	81 wk	>115 wk	0.03
Median survival	43 wk	48 wk	0.39

Death due to neurologic causes: Relative risk of death: 2.62 (1.04 -6.64)

- Conclusions
  - The addition of WBRT to surgery improves local and in-brain recurrence and reduces the risk of neurologic death
- Limitations
  - 60% of the surgery alone patients received WBRT eventually
  - Small numbers
  - Unconventional RT dose

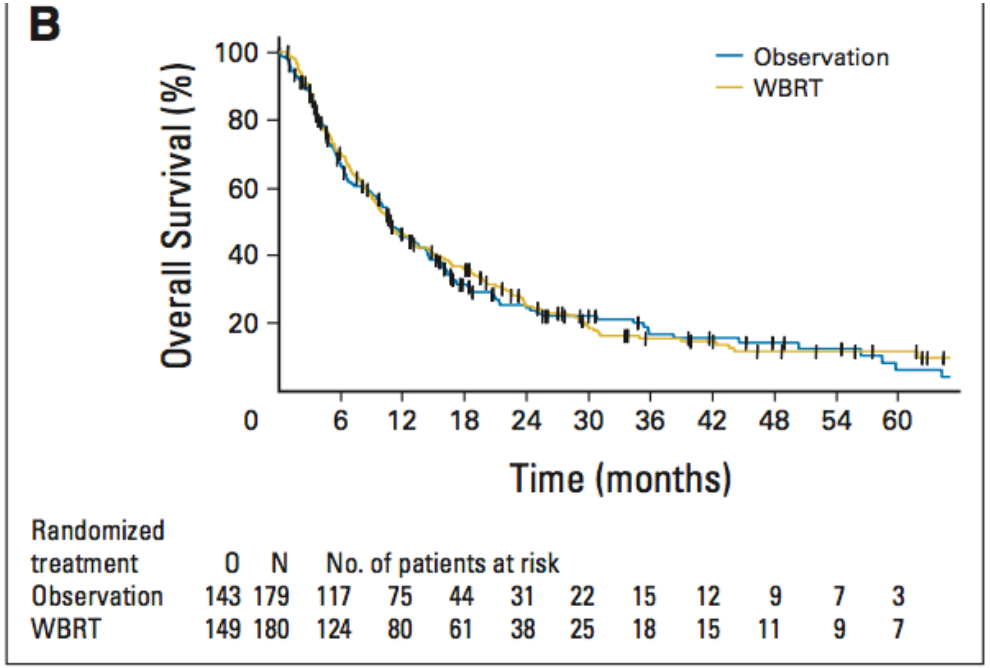
Patchell et al, JAMA 1998

EORTC 22952-26001 (Kocher): What is the benefit of WBRT after surgery or SRS for 1 to 3 brain metastases?

- Patients:
  - 359 patients with 1-3 brain metastases, WHO PS 0-2 with stable systemic disease for at least 3 months, cerebral mets only, no leptomeningeal disease
- Treatment:
  - Arm 1) Surgery or SRS → WBRT (n=180)
  - Arm 2) Surgery or SRS → Observation (n=179)
  - Surgery: complete resection obtained
  - SRS: 25Gy to center, 20Gy minimum to 1-2mm margin (single met ≤ 3.5cm or up to 3 mets ≤ 2.5cm)
  - WBRT: 30 in 10 within 6 weeks of surgery/SRS
  - Follow up MRI q3mos
- Primary endpoint: Functional independence
- Others: PFS, overall survival, QOL, failure within brain, late toxicities

Kocher et al, JCO 2011

EORTC 22952-26001 (Kocher): Surgery OR SRS +/- WBRT for 1-3 mets



	WBRT	Obs	p
Intracranial progression	48%	78%	<0.001
Initial site relapse $_{24mo}$			
Surgery	27%	59%	<0.001
SRS	19%	31%	0.04
Elsewhere brain progression $_{24mo}$			
Surgery	23%	42%	0.008
SRS	33%	48%	0.023
Use of salvage	16%	51%	
Median time to WHO PS > 2 (functional independence)	9.5 mo	10 mo	0.71
Median PFS	4.6 mo	3.4 mo	0.02
Median OS	10.7 mo	10.9 mo	0.89
Neurologic death	28%	44%	<0.002

Kocher et al, JCO 2011

EORTC 22952-26001 (Kocher): Surgery OR SRS +/- WBRT for 1-3 mets

- Conclusions:
  - No difference in overall survival
  - Neurologic death was more common in the observation arm: 44% vs 28% ($p < 0.002$)
  - Intracranial relapses less common with WBRT than observation (48% vs 78%)

Kocher et al, JCO 2011

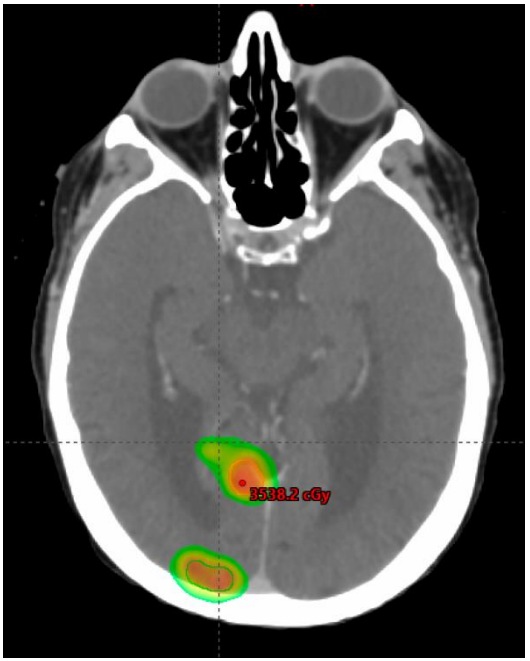
Secondary analysis of Kocher

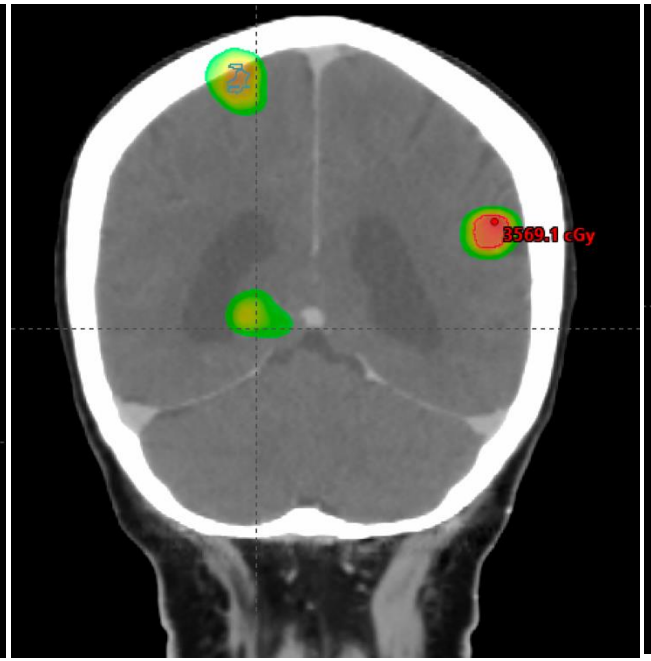
- https://pubmed.ncbi.nlm.nih.gov/30419088/

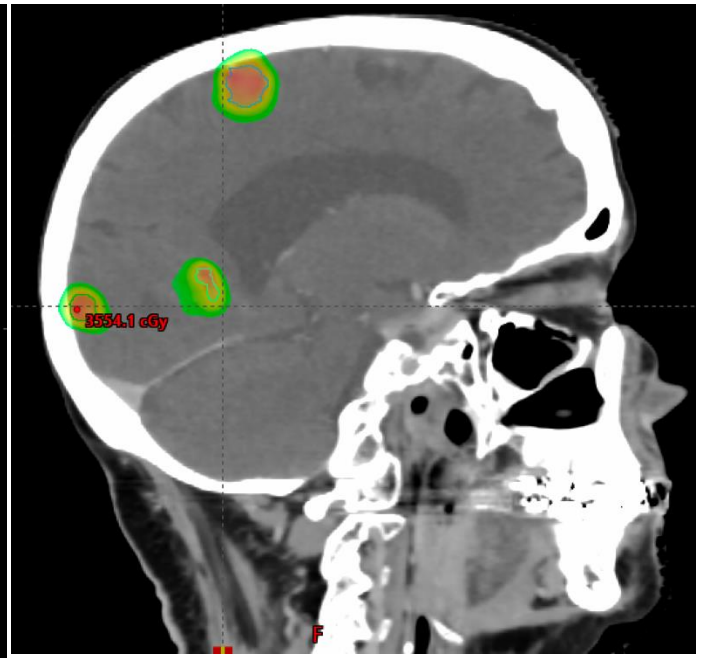
WBRT dosing

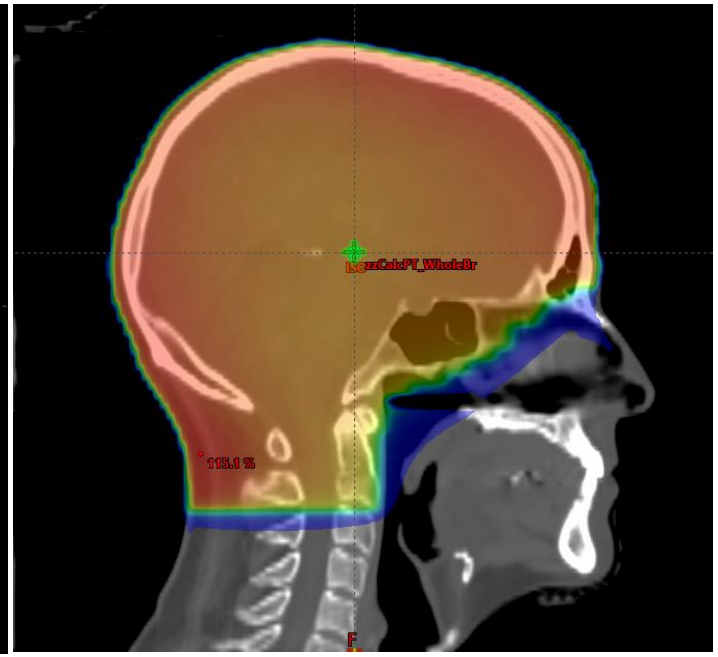
- RTOG 6901, 7361, 7916→ no difference between 20/5, 30/6, 30/10, 30/15, 40/15, 40/20
- More protracted courses not superior for better prognosis patients (RTOG 7606)
- No benefit to accelerated hyperfractionation (54.4/1.6 bid; RTOG 9104)
- RCT regimens: 50.4/28 (Patchell 2), 36/12 (Patchell 1), 37.5/15 (RTOG 9508), 30/12 (Chang)
- In practice:
  - 30/10 is the most common
  - 35/14 is as well tolerated
  - 20/5 can be utilized if shorter anticipated survival

Treatment options: SRS for intact BM









76-year-old woman with EGFR mutant lung adenocarcinoma, who presented with new onset left arm weakness who received SRS

62-year-old man with small cell lung cancer and multiple brain metastases who received WBRT

Goal: attain high degree of local control without neurotoxicity

RTOG 9005: Single fraction SRS dose escalation

- Design: dose escalation study; goal 10 patients on a given treatment arm which was then closed for toxicity assessment; if no unacceptable acute toxicity, then the dose for that tumor size was escalated; hard stop for 3/10 or 4/15 patients suffered unacceptable acute toxicity (gr3-5 CNS toxicity < 3 months of SRS)
- Patients:
  - ≥18yo status post partial/whole brain RT ≥ 3 months prior to enrollment, now with CT/MRI evidence of a solitary intracranial recurrence measuring ≤ 40mm
  - KPS ≥ 60, life expectancy ≥ 3 months
  - Multiple lesions allowed as long as only one dominant
  - 168 patients from 1990-1994, >10-15 patients entered onto each arm before it was closed due to rapid accrual
- Methods: LINAC-based (80%) or GammaKnife permitted

RTOG 9005:Single fraction SRS dose escalation

Table 3. Accrual by treatment arm and dose

Tumor diameter	Treatment arm/dose/accrual			
≤ 20 mm	Arm 1—>	Arm 4—>	Arm 7	
	18 Gy	21 Gy	24 Gy	
	$n = 12$	$n = 18$	$n = 10$	
21–30 mm	Arm 2 —>	Arm 5 —>	Arm 8 —>	Arm II
	15 Gy	18 Gy	21 Gy	24 Gy
	$n = 15$	$n = 15$	$n = 13$	$n = 12$
31–40 mm	Arm 3 —>	Arm 6—>	Arm 9	
	12 Gy	15 Gy	18 Gy	
	$n = 21$	$n = 22$	$n = 18$	

RTOG 9005:Single fraction SRS dose escalation

- Results
  - MTDs: 24Gy, 18Gy and 15Gy for ≤20mm, 21-30mm, and 31-40mm
  - MTD for ≤20mm set due to reluctance of investigators to exceed 24Gy
- Maximum tumor diameter was significantly associated with toxicity:
  - Tumors 21-40mm were 7.3-16x more likely to develop grade 3-5 toxicity compared to ≤20mm
  - 11% radionecrosis at 24 months

Table 5. Incidence of Grade 3, 4, and 5 CNS toxicity by tumor size and treatment arm

Incidence of Grade 3, 4, and 5 CNS Toxicity						
				% of Patients With Toxicity		
Tumor size*	Arm	Dose	No. of patients	Acute	Chronic	Total
≤ 20 mm						
	1	18 Gy	12	0	8	8
	4	21 Gy	18	0	11	11
	7	24 Gy	10	0	10	10
21–30 mm						
	2	15 Gy	15	7	7	13
	5	18 Gy	15	0	20	20
	8	21 Gy	13	8	31	38
	11	24 Gy	12	33	25	58
31–40 mm						
	3	12 Gy	21	5	5	10
	6	15 Gy	22	0	14	14
	9	18 Gy	18	17	33	50

* Maximum tumor diameter.

SRS dosing – MSK approach

- Dosing based on tumor size:
  - <2cm, 21 Gy x1 (~90% 1 yr local control)
  - 2-~3cm, 9Gy x 3
  - >~3cm, surgery or 6Gy x 5
- Postop radiation
  - SBRT/SRS ~~9Gy x 3~~ or 6Gy x 5

SRS dosing – MGH approach

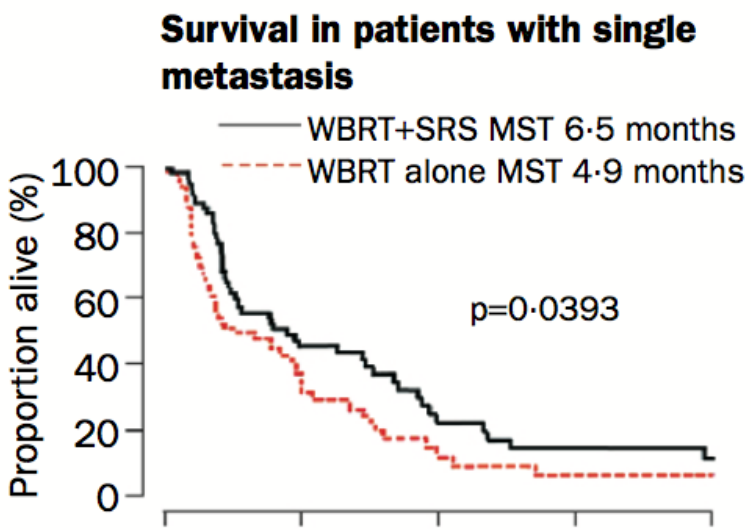
- Dosing based on tumor size:
  - <1.5cm, 18 Gy x1
  - 1.5-3cm, 17 Gy x1 or 11 Gy x2
  - >3cm, surgery or fractionate in 3 Gy/fx to 39-42 Gy
- Postop radiation
  - Prefer fractionated RT 3 Gy/fx to 30-36 Gy
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7156661/pdf/41598_2020_Article_63158.pdf

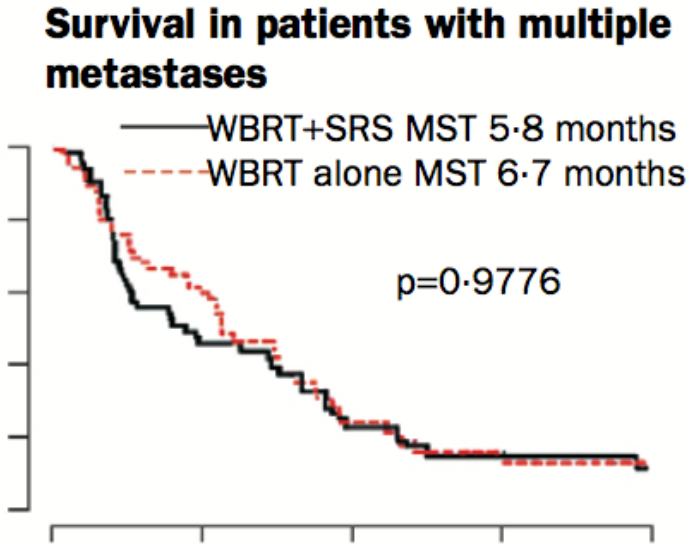
RTOG 9508: Does the addition of SRS to standard WBRT improve outcomes in patients with 1-3 brain metastases?

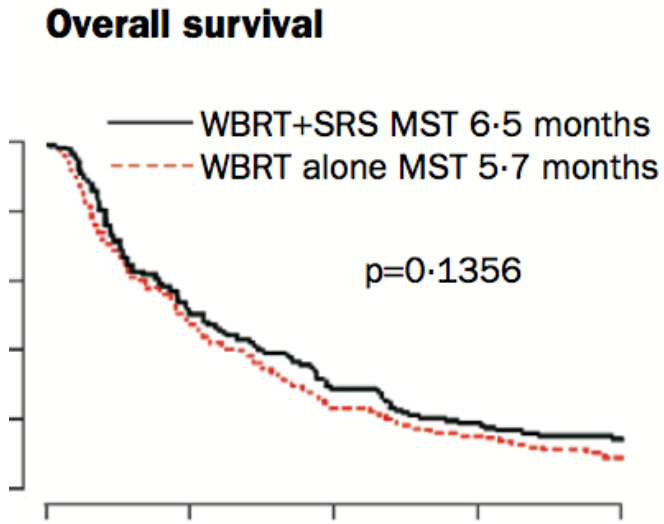
- Patients:
  - 331 patients with 1-3 brain metastases (maximum 4cm for largest, 3cm for others), KPS<70 excluded, active extracranial disease excluded
  - Predominantly lung metastases
  - 75% RPA class II
- Treatments:
  - Arm 1) WBRT → obs
  - Arm 2) WBRT → SRS
  - WBRT 37.5Gy in 15
  - SRS boost within one week with doses per RTOG 9005 (24 Gy for ≤ 2 cm, 18 Gy for ≤ 3 cm, and 15 Gy ≤ 4 cm)
- Stratification:
  - Number of brain metastases (single vs 2–3)
  - Extent of extracranial disease (none vs present)
- Primary outcome: overall survival

Andrews et al, Lancet 2004

RTOG 9508: WBRT +/- SRS for 1-3 mets







Andrews et al, Lancet 2004

RTOG 9508: WBRT +/- SRS for 1-3 mets

- Conclusions
  - Significant survival benefit in patients with a single unresectable brain metastasis
  - No survival benefit for 2-3 metastases
    - Local control benefit
    - Improved KPS (small numbers)
    - Decreased steroids
  - A non-significant doubling in toxicity with addition of SRS
    - 0->3% acute grade 3 or 4
    - 3->6% late grade 3 or 4 (radiation necrosis)

Andrews et al, Lancet 2004

Brown et al, JAMA 2016: SRS+/-WBRT (N0574)

Original Investigation

Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases

A Randomized Clinical Trial

Paul D. Brown, MD; Kurt Jaeckle, MD; Karla V. Ballman, PhD; Elana Farace, PhD; Jane H. Cerhan, PhD; S. Keith Anderson, MS; Xiomara W. Carrero, BS; Fred G. Barker II, MD; Richard Deming, MD; Stuart H. Burri, MD; Cynthia Ménard, MD; Caroline Chung, MD; Volker W. Stieber, MD; Bruce E. Pollock, MD; Evanthia Galanis, MD; Jan C. Buckner, MD; Anthony L. Asher, MD

Brown

IMPORTANCE Whole brain radiotherapy (WBRT) significantly improves tumor control in the brain after stereotactic radiosurgery (SRS), yet because of its association with cognitive decline, its role in the treatment of patients with brain metastases remains controversial.

OBJECTIVE To determine whether there is less cognitive deterioration at 3 months after SRS alone vs SRS plus WBRT.

DESIGN, SETTING, AND PARTICIPANTS At 34 institutions in North America, patients with 1 to 3 brain metastases were randomized to receive SRS or SRS plus WBRT between February 2002 and December 2013.

INTERVENTIONS The WBRT dose schedule was 30 Gy in 12 fractions; the SRS dose was 18 to 22 Gy in the SRS plus WBRT group and 20 to 24 Gy for SRS alone.

MAIN OUTCOMES AND MEASURES The primary end point was cognitive deterioration (decline >1 SD from baseline on at least 1 cognitive test at 3 months) in participants who completed the baseline and 3-month assessments. Secondary end points included time to intracranial failure, quality of life, functional independence, long-term cognitive status, and overall survival.

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 quality of life (mean change from baseline, −1.3 vs −10.9 points; mean difference, 9.6; 95% CI, 3.6-15.6 points; $P = .002$). Time to intracranial failure was significantly shorter for SRS alone compared with SRS plus WBRT (hazard ratio, 3.6; 95% CI, 2.2-5.9; $P < .001$). There was no significant difference in functional independence at 3 months between the treatment groups (mean change from baseline, −1.5 points for SRS alone vs −4.2 points for SRS plus WBRT; mean difference, 2.7 points; 95% CI, −2.0 to 7.4 points; $P = .26$). Median overall survival was 10.4 months for SRS alone and 7.4 months for SRS plus WBRT (hazard ratio, 1.02; 95% CI, 0.75-1.38; $P = .92$). For long-term survivors, the incidence of cognitive deterioration was less after SRS alone at 3 months (5/11 [45.5%] vs 16/17 [94.1%]; difference, −48.7%; 95% CI, −87.6% to −9.7%; $P = .007$) and at 12 months (6/10 [60%] vs 17/18 [94.4%]; difference, −34.4%; 95% CI, −74.4% to 5.5%; $P = .04$).

CONCLUSIONS AND RELEVANCE Among patients with 1 to 3 brain metastases, the use of SRS alone, compared with SRS combined with WBRT, resulted in less cognitive deterioration at 3 months. In the absence of a difference in overall survival, these findings suggest that for patients with 1 to 3 brain metastases amenable to radiosurgery, SRS alone may be a preferred strategy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00377156

JAMA. 2016;316(4):401-409. doi:10.1001/jama.2016.9839
Corrected on August 7, 2018.

Editorial page 393

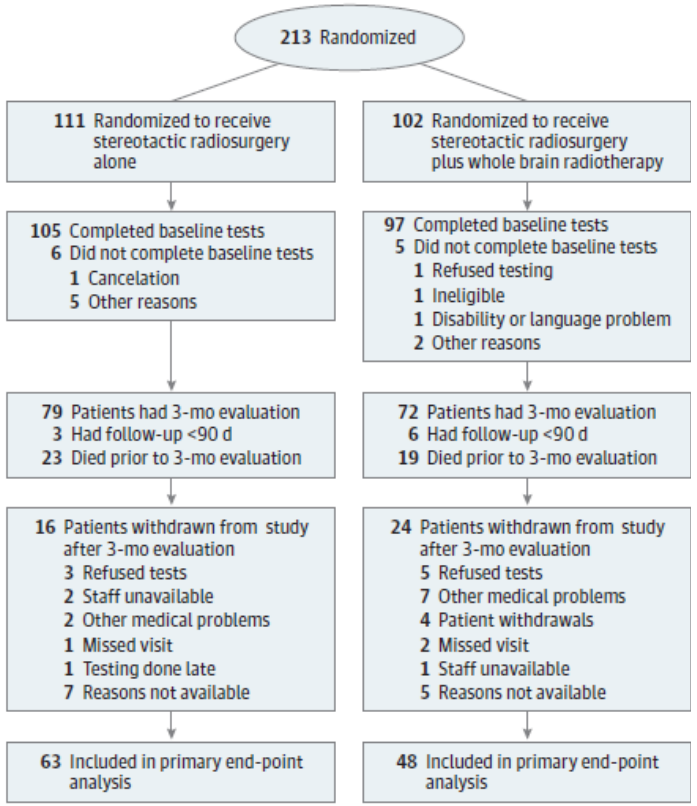
Supplemental content at jama.com

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Brown et al, JAMA 2016: SRS+/-WBRT

Figure 1. Participant Flow in the NO574 Trial



The number of patients screened for eligibility and the number excluded are not available.

Table 1. Baseline Characteristics in the NO574 Trial

Characteristics	SRS Alone (n = 111)	SRS Plus WBRT (n = 102)
Age, mean (SD), y	59.8 (10.4)	61.4 (10.6)
Age group, y, No. (%)		
18 to 59	53 (47.7)	44 (43.1)
≥60	58 (52.3)	58 (56.9)
Sex, No. (%)		
Female	57 (51.4)	46 (45.5)
Male	54 (48.6)	55 (54.5)
Race, No. (%)		
White	95 (86.4)	85 (83.3)
Nonwhite	15 (13.6)	17 (16.7)
Months of systemic disease control, No. (%)		
≤3	81 (73.0)	75 (73.5)
>3	30 (27.0)	27 (26.5)
No. of brain metastases, No. (%)		
1	55 (49.5)	56 (54.9)
2	39 (35.1)	36 (35.3)
3	17 (15.3)	10 (9.8)
ECOG performance score, No. (%)[a]		
0	49 (44.5)	49 (48.0)
1	50 (45.5)	45 (44.1)
2	11 (10.0)	8 (7.8)
Primary tumor site, No. (%)		
Breast	11 (9.9)	7 (6.9)
Colorectal	7 (6.3)	4 (4.0)
Lung	80 (72.1)	66 (65.3)
Skin/melanoma	3 (2.7)	9 (8.9)
Bladder	1 (0.9)	1 (1.0)
Kidney	1 (0.9)	4 (4.0)
Gynecologic	2 (1.8)	3 (3.0)
Other	6 (5.4)	7 (6.9)
Cranial nerves, No. (%)		
Normal	102 (91.9)	92 (91.1)
Abnormal	9 (8.1)	9 (8.9)
Sensation, No. (%)		
Normal	105 (94.6)	96 (96.0)
Abnormal	6 (5.4)	4 (4.0)
Motor, No. (%)		
Normal	97 (87.4)	89 (88.1)
Abnormal	14 (12.6)	12 (11.9)
Cerebellar, No. (%)		
Normal	92 (82.9)	85 (84.2)
Abnormal	19 (17.1)	16 (15.8)

(continued)

Table 1. Baseline Characteristics in the NO574 Trial (continued)

Characteristics	SRS Alone (n = 111)	SRS Plus WBRT (n = 102)
FACT-Br total score, mean (SD)[b]	146.6 (24.0)	141.7 (27.7)
Cognitive test scores, mean (SD)[c]		
HVLT-R		
Immediate recall	−1.4 (1.4)	−1.7 (1.3)
Delayed recall	−1.3 (1.8)	−1.6 (1.7)
Recognition	−0.8 (1.9)	−0.9 (1.8)
TMT-A time to complete	−1.7 (3.6)	−1.9 (3.1)
TMT-B time to complete	−2.8 (4.3)	−3.2 (4.3)
COWAT total	−1.0 (1.2)	−1.1 (1.2)
GPS total, mean (SD), s	−6.2 (8.6)	−5.4 (6.0)

Abbreviations: COWAT, Controlled Oral Word Association Test; ECOG, Eastern Cooperative Oncology Group; FACT-Br, Functional Assessment of Cancer Therapy–Brain; GPS, Grooved Pegboard Test; HVLT-R, Hopkins Verbal Learning Test–Revised; SRS, stereotactic radiosurgery; TMT, Trail Making Test; WBRT, whole brain radiotherapy.

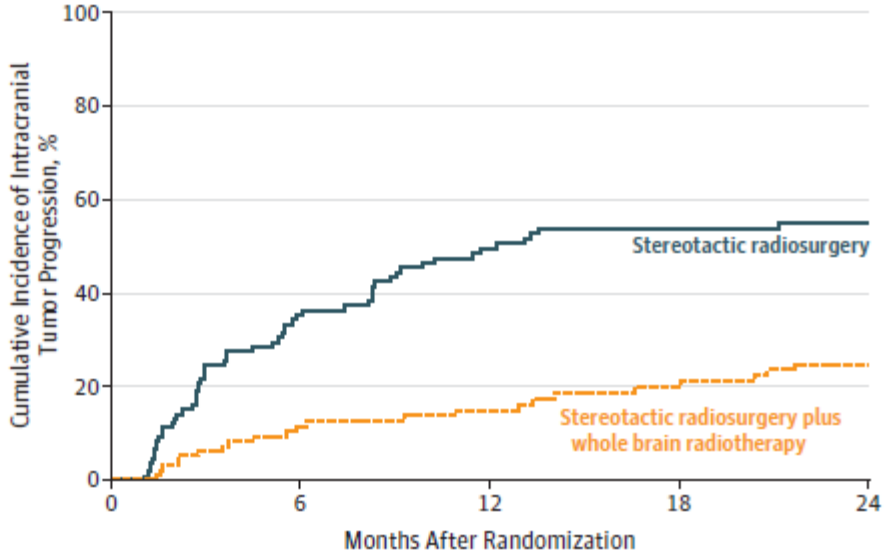
[a] ECOG performance status scores range from 0 to 5, with higher numbers indicating greater disability; a score of 0 indicates no symptoms; 1, mild symptoms; and 2, symptomatic (<50% in bed during the day).

[b] FACT-Br scores range from 0 to 200; higher scores indicate better quality of life.

[c] Cognitive tests are reported as standardized scores (*z* scores, transformed so that higher scores indicate better cognitive performance): (patient value − published-norm mean value)/published-norm standard deviation value.

Brown et al, JAMA 2016: SRS+/-WBRT

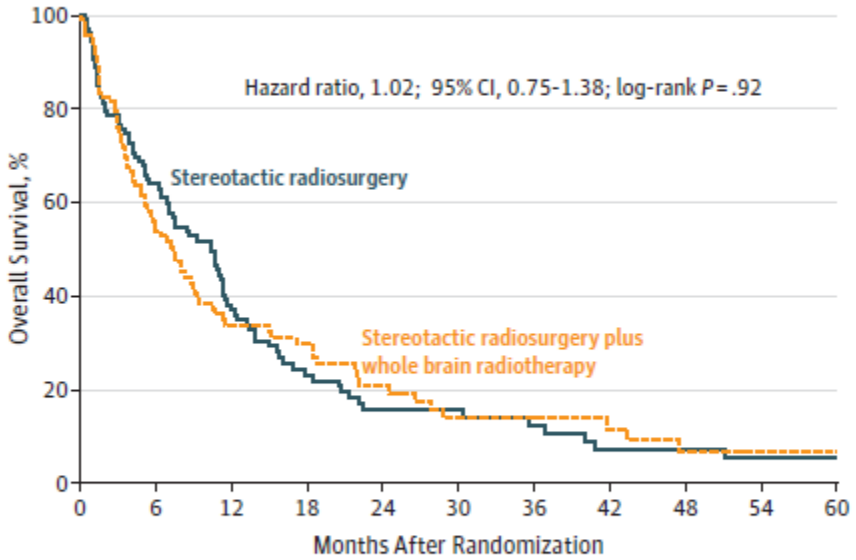
Figure 2. Cumulative Incidence of Brain Tumor Progression (Local and/or Distant) After Correcting for the Competing Risk of Survival According to Treatment Group



No. at risk					
Stereotactic radiosurgery	111	35	12	5	1
Stereotactic radiosurgery plus whole brain radiotherapy	102	43	24	16	9

Brown et al, JAMA 2016: SRS+/-WBRT

Figure 3. Kaplan-Meier Estimates of Overall Survival According to Treatment Group



No. at risk											
Stereotactic radiosurgery	111	64	35	19	13	10	7	4	4	2	2
Stereotactic radiosurgery plus whole brain radiotherapy	102	50	28	22	13	8	8	5	3	1	1

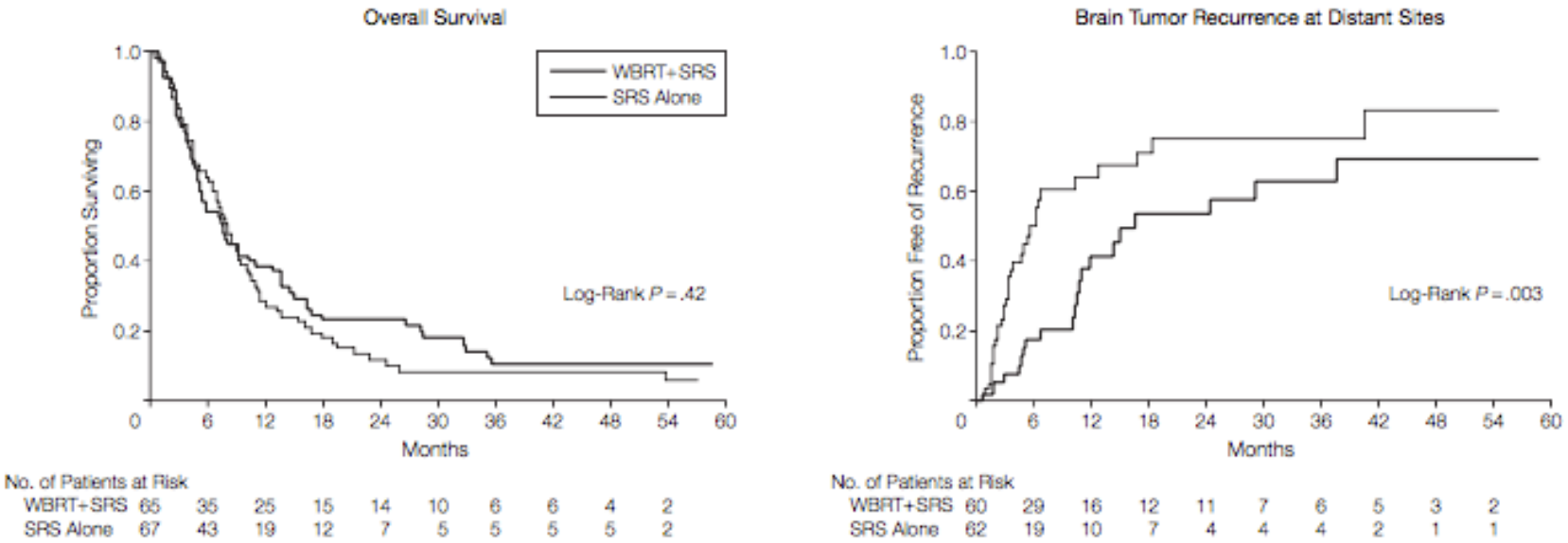
Aoyama (JROSG 99-1): What is the benefit of adding WBRT to SRS for 1-4 BM?

- Patients
  - 132 patients with 1-4 brain metastases measuring <3cm (1999-2003 at 11 centers)
  - KPS 70 or higher
  - Stratification based on # mets (1 vs 2-4)
- Treatment:
  - Arm 1) SRS alone
  - Arm 2) SRS + WBRT
  - SRS:
    - 0-2cm – 22-25Gy
    - 2-3cm – 18-20Gy
    - 30% dose reduction with combined WBRT+SRS
  - WBRT: 30 in 10
- Primary endpoint: overall survival

Aoyama et al, JAMA 2006

Aoyama (JROSG 99-1): SRS +/- WBRT for 1-4 brain mets

- Results



  - MVA HR for OS: Age (1.48), stable primary (1.62), stable extracranial mets (2.35), KPS (1.69)
  - Hazard ratio OS for # brain mets (1 vs 2-4) was 1.36 (p=0.10);
  - In-brain recurrence (46% vs 76%) and local control (89% vs 73%) improved in favor of WBRT+SRS (p<0.001, p=0.002)
- Conclusion: Addition of WBRT to SRS does not improve OS, but improves local and all-brain control; survival for 1 met vs 2-4 similar

Aoyama et al, JAMA 2006

Secondary analysis – WBRT improved OS in good PS patients

- https://jamanetwork.com/journals/jamaoncology/article-abstract/2293217

Yamamoto (JLGK0901): is SRS alone appropriate for 5-10 BM?

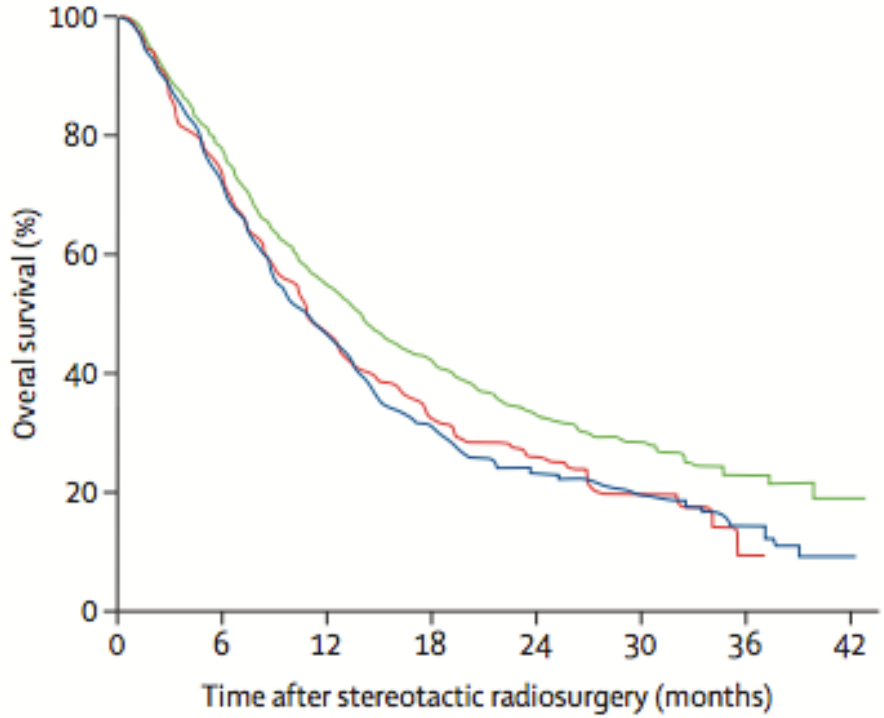
- Design: prospective observational non-inferiority study
  - Threshold for non-inferiority: upper 95% CI for HR<1.3 for OS
- Patients:
  - 1194 patients with 1-10 newly diagnosed brain metastases
  - largest tumor <10mL vol and <3cm diameter with <15mL total BM volume
  - KPS 70 or higher
- Treatments:
  - Gamma Knife units (sponsored study)
  - Doses by lesion volume:
    - <4mL ➔ 22Gy (~1.5cm diameter)
    - 4-10mL ➔ 20Gy
    - Brain stem dose reduced

Yamamoto et al, Lancet Onc 2014

Yamamoto (JLGK0901): SR versus 2-4 mets

- Results:
  - OS for 5-10 mets was non-inferior to 2-4 mets (pNI<0.0001)
  - No difference in local recurrence
  - Patients with 1 met did best (HR=.76)
  - MVA factors for OS included female sex, KPS, 1 met alone, maximum diameter, controlled extracranial disease
    - UVA HR for tumor volume = 1.50 (>1.9mL)
    - UVA HR for diameter = 1.43
- Conclusions: OS using SRS alone for 5-10 mets is non-inferior to 2-4 mets
  - ***Many patients can be spared WBRT***

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.

Yamamoto et al, Lancet Onc 2014

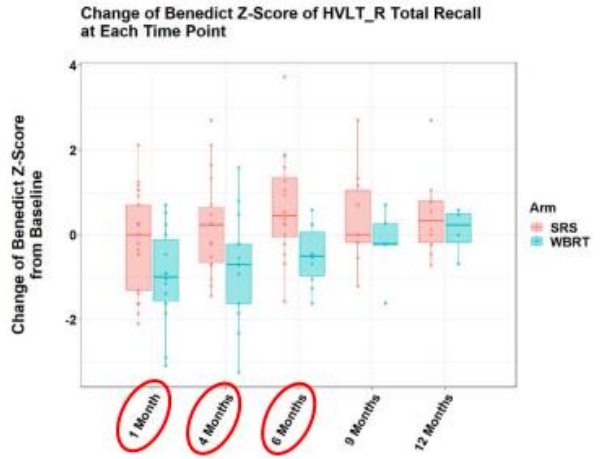
MDACC study: SRS vs. WBRT for 4-15 BM

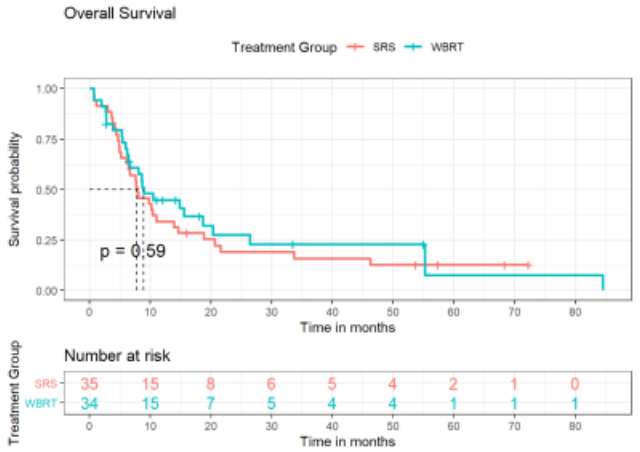
- Design:
  - Phase III RCT
  - Co-primary endpoints of local control at 4 months and memory function at 4 months, stratified for histology, age, # lesions, KPS, extracranial disease status, baseline HVLT, and prior SRS
- Patients:
  - 100 patients with 4-15 untreated BM (and up to 20 allows at time of treatment), KPS 70+, no prior WBRT, excluding SCLC, melanoma, lymphoma, GCT
- Treatments:
  - SRS: 15-24Gy single fraction SRS per RTOG 9005
  - WBRT: 30Gy in 10 fractions, with memantine strongly encouraged

Li et al, ASTRO 2020

MDACC study: SRS vs. WBRT for 4-15 BM

- Results
  - HVLT at 4 months decreased (and at 1 and 6 months)
  - Local control 95% SRS v. 87% WBRT (p=0.79)
  - Overall survival similar (7.8 vs. 8.9 mos p=0.6)
- Conclusions:
  - Preserved cognition and similar OS with use of SRS in 4-15 BM





Li et al, ASTRO 2020

Management of post op cases

Reminder on evidence from classic studies

- Patchell II: surgery +/- WBRT for a single met
  - WBRT decreases local failure from **~50% to ~10%** and improves regional control
- EORTC 22952: surgery/SRS +/- WBRT for 1-3 mets
  - WBRT improves local control after surgery and less so after SRS, improves regional control, and decreases neurologic death

In the absence of RT, local failure after surgery alone ~50% or greater

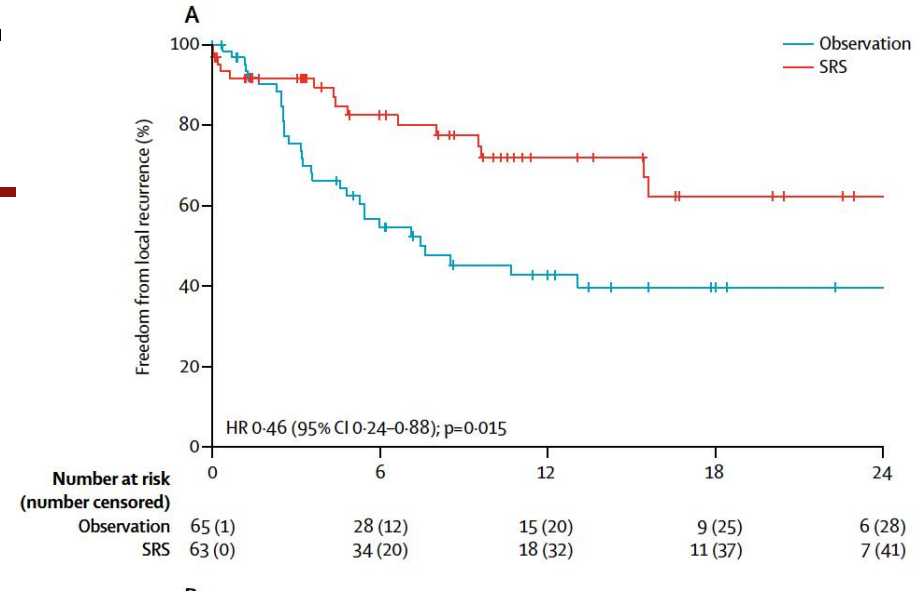
MDACC Prospective Trial: obs vs. SRS after surgical resection

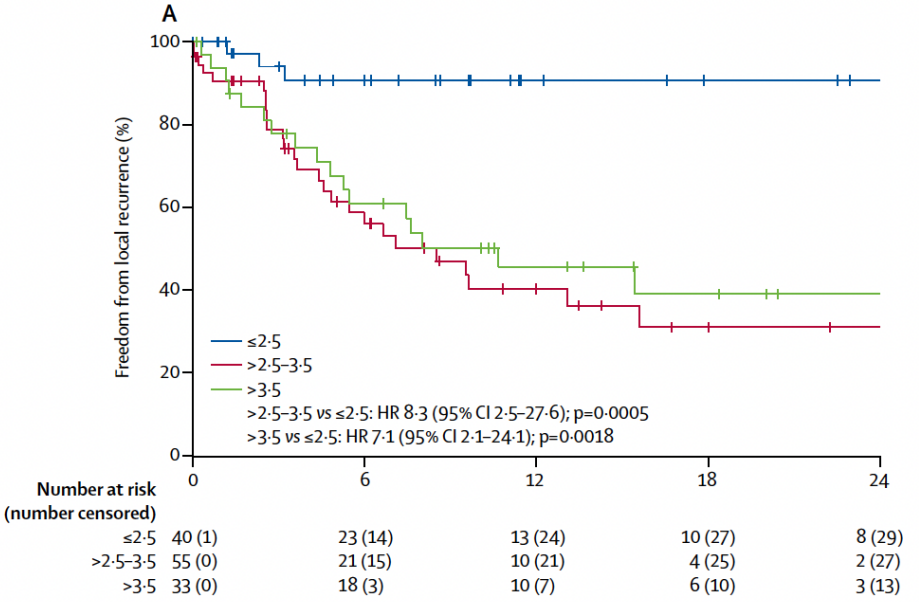
- Design
  - Phase III RCT
  - Primary endpoint was time to local failure in the surgical cavity
  - Stratified by histology, tumor size, and #BM
- Patients
  - 132 patients from a single center
  - KPS 70+
  - Complete resection of 1-3 BM, maximum diameter 4cm
- Treatments
  - Observation
  - SRS
    - 16 Gy (for ≤10 cc), 14 Gy (for 10·1–15 cc), and 12 Gy (for >15 cc)
    - Multi-D review of volumes, with expansion along dura for contact; tract not included
    - PTV = cavity +/- dural margin + 1mm

Mahajan et al, Lancet Onc 2017

MDACC Prospective Trial: obs vs. SRS after surgical resection

- Results
  - Local recurrence in 24% SRS vs. 48% obs of patients
  - 12-month freedom-from-local recurrence was **72% SRS vs. 43% obs** (HR 0.46, p=0.015)
    - In a competing risks model, 6-month local recurrence was 15% SRS vs. 34% obs
  - Failures more common w/ larger BM
  - OS similar ~18 mos
- Conclusions
  - Improved local control with SRS over observation, but significantly higher rates of failure than with adjuvant WBRT (Patchell)





Mahajan et al, Lancet Onc 2017

NCCTG N107C/CEC·3: post-op SRS vs. WBRT for single BM

- Design:
  - Prospective phase III RCT
  - Powered for superiority with primary endpoint of cognitive deterioration-free survival at 6 months, co-primary endpoint of OS; secondary endpoints including time to intracranial progression were included in a competing risks model
- Patients:
  - 194 pts randomized 1:1
  - Single brain metastasis that had undergone surgical resection, up to 5cm in diameter
  - Stratified by age, duration of extracranial disease control, number of brain metastases, histology, maximal resection cavity diameter, and treatment center
- Treatments:
  - WBRT (30Gy in 10 fx or 37.5 in 15 fx)
  - SRS (12-20Gy as a single fraction, depending on cavity volume)
    - 20 Gy if cavity volume was less than 4·2 mL, 18 Gy if 4·2–7·9 mL, 17 Gy if 8·0–14·3 mL, 15 Gy if 14·4–19·9 mL, 14 Gy if 20·0–29·9 mL, and 12 Gy if 30·0 mL or more up to the maximal surgical cavity extent of 5 cm
    - PTV = cavity plus 2mm expansion

Brown et al, Lancet Onc 2017

NCCTG N107C/CEC·3: post-op SRS vs. WBRT for single BM

- Results
  - Met primary endpoint of CDFS (HR 0.47, favoring SRS, p<0.0001)
  - OS was similar (HR 1.07, p=0.703)
  - Time to intracranial failure was shorter for SRS: 6.4 vs. 27.5 mos, HR 2.45, p<0.001)
  - ***6-month cavity control was 80.4 SRS vs. 87.1% WBRT (p=0.0068)***
  - 4% SRS vs 0% WBRT radiation necrosis rate
- Conclusions
  - Improved CDFS with single fraction SRS but concerning local failure rate
  - High failure rates expected to be related to undercoverage of margin (marginal misses)

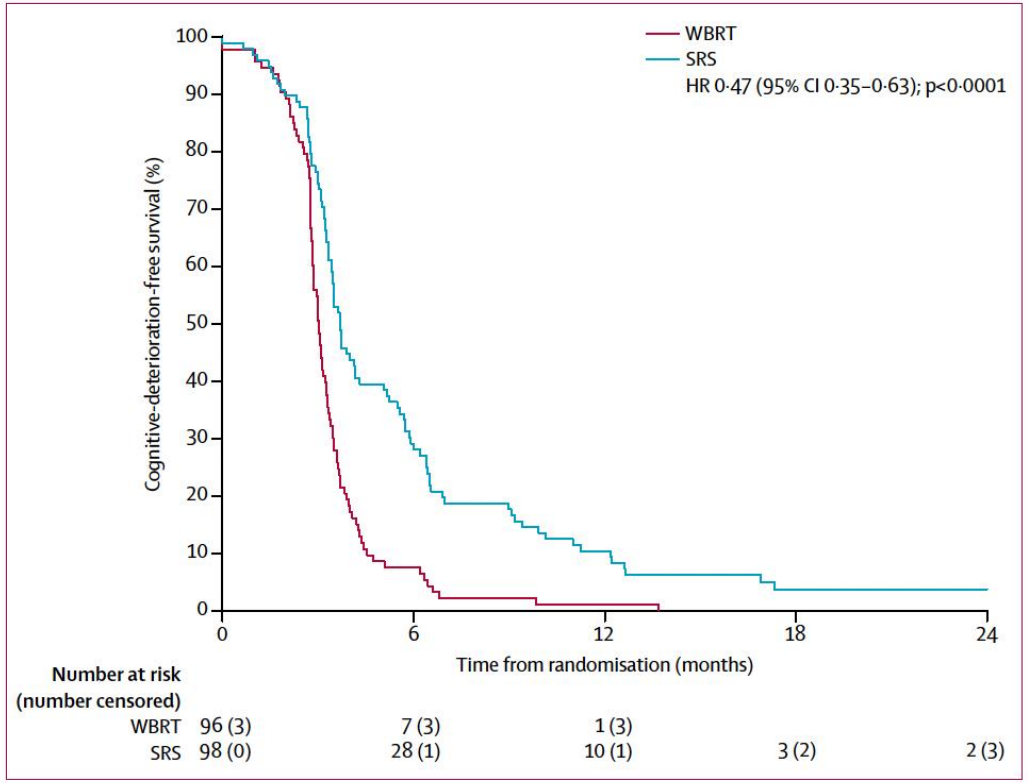


Figure 2: **Cognitive-deterioration-free survival**
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

Brown et al, Lancet Onc 2017

NCCTG N107C/CEC·3: post-op SRS vs. WBRT for single BM

Supplemental Table S3.
Intracranial Brain Control Rates

	Control Estimates (95%CI)		Gray's K-sample p-value
	SRS	WBRT	
Surgical Bed Control			
at 3 months	95·9% (92·0, 99·9)	93·5% (88·7, 98·7)	
at 6 months	80·4% (72·8, 88·7)	87·1% (80·5, 94·2)	p = 0·00068
at 12 months	60·5% (51·3, 71·3)	80·6% (73·0, 89·1)	
Local Control			
at 3 months	84·7% (77·9, 92·1)	96·7% (93·2, 100)	
at 6 months	69·4% (60·8, 79·1)	92·5% (87·3, 98·0)	p = 0·00016
at 12 months	61·8% (52·8, 72·3)	87·1% (80·5, 94·2)	
Distant Brain Control			
at 3 months	88·7% (82·6, 95·2)	96·8% (93·3, 100)	
at 6 months	72·1% (63·7, 81·6)	94·6% (90·1, 99·3)	p = 0·00045
at 12 months	64·7% (55·8, 75·0)	89·2% (83·1, 95·8)	
Leptomeningeal Disease Control			
at 3 months	98·0% (95·2, 100)	97·9% (95·0, 100)	
at 6 months	93·9% (89·2, 98·7)	96·8% (93·3, 100)	p = 0·62
at 12 months	92·8% (87·8, 98·1)	94·6% (90·1, 99·3)	
Total Intracranial Brain Control (based on time to first recurrence of any type)			
at 3 months	79·6% (72·0, 88·0)	90·4% (84·7, 96·6)	
at 6 months	55·1% (46·1, 65·9)	80·8% (73·1, 89·2)	p < 0·0001
at 12 months	36·6% (28·1, 47·8)	72·1% (63·6, 81·8)	

Local control means that tumor did not recur at the unresected metastases treated with SRS ; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; distant brain control means that a new tumor did not appear at a site not treated. Intracranial Brain Control Rates estimated via 1-Cumulative Incidence Rate from Competing Risk survival analysis of time to the specific recurrence type. Deaths without recurrence are censored at time of death.

Brown et al, Lancet Onc 2017

LBA 11

Patterns of Failure afte
Whole Brain Radiother
Central Imaging Reviev
Phase III Clinical Trial

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Purpose/Objective(s): Whole brain radiotherapy (WBRT) has historically been the main instrument to decrease intracranial progression after resection of brain metastases. The previously reported NCCTG N107C/CEC.3 (Alliance) randomized phase III clinical trial of WBRT vs. stereotactic radiosurgery (SRS) demonstrated that overall survival did not significantly differ between arms, while SRS was associated with less cognitive decline than WBRT. However, the initial analysis also showed that local tumor bed control (LC) was significantly worse with SRS than WBRT, with an unexpectedly low 12-month LC rate of 60.5% in patients receiving post-operative SRS. To further investigate LC, a central imaging review was performed.

Materials/Methods: In N107C/CEC.3, 194 patients were randomized to SRS (n=98) or WBRT (n=96). SRS dose was dependent on resection cavity volume and ranged from 12 Gy to 20 Gy all in a single fraction, and WBRT dose was 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. For this analysis, patients with local failure (LF) or leptomeningeal failure that had imaging available were centrally reviewed by two radiation oncologists to verify pattern of failure. Patient and treatment characteristics were assessed for association with updated outcomes after central review using Cox proportional hazards, Pearson's chi-square, or Kruskal-Wallis tests.

Results: Seventy-three patients with LF or leptomeningeal failure determined by their local site were centrally reviewed. After adding patients with no LF or leptomeningeal failure, 185 (95% of total enrolled) patients were included in this analysis as 9 patients with LF did not have imaging available for central review. Of 59 patients initially determined to have LF, 20 were determined on central review to be free of LF. Accordingly, after central review post-operative SRS was no longer associated with significantly lower rates of LC than WBRT (79.2% vs. 86.5% 12-month LC, respectively, p=0.099). After central review, the interrelated variables of tumor diameter, target volume, and prescription dose were associated with risk of LF. Patients with resection cavities > 3 cm had higher rates of LF than those with smaller cavities (23.5% vs. 12.6% 12-month LF rate, respectively; p=0.010). Larger target volume was associated with increased risk of LF (HR: 1.05, 95% CI: 1.01 – 1.09, p=0.008), while higher prescription dose was associated with lower risk of LF (HR: 0.81, 95% CI: 0.67 – 0.96, p=0.018).

Conclusion: In contrast to the initial report, after central review SRS was not associated with significantly higher rates of LF than WBRT. Patients with larger surgical cavities had higher rates of LF, though it is unclear whether this is related to cavity size, biology, or radiation dose. Randomized data comparing single to multifraction SRS in larger surgical cavities is awaited.

Author Disclosure: W. Breen: None. K.E. Dooley: None. E. Twohy: None. P.D. Brown: None. K. Ballman: None. J.H. Cerhan: None. J.J. Urbanic: None. A.C. Whitton: None. J. Greenspoon: None. I.F. Parney: None. N.N. Laack: None. J. Bahary: None. F. Barker: None. D. Khuntia: Independent Contractor; Precision Cancer Specialists. C. Giannini: None. E. Galanis: None. D. Roberge: Independent Contractor; University of Montreal. Research Grant; Elekta. Honoraria; Varian Medical Systems, Siemens Medical Systems, Precirix, Novocure, Kyowa Kirin. Consultant; Recordati. In-kind Donation; Accuray. Cureus CARO Channel. J.B. Ashman: Honoraria; ASTRO.––

Multi-institutional retrospective post op SRS/SBRT study: Eitz et al, JAMA Onc 2020

- Design:
  - Retrospective multi-institutional study
  - Primary endpoint overall survival and local control
- Patients:
  - 558 pts with 581 resected cavities, mainly pts with NSCLC, MM, RCC, BC and GI tumors
  - KPS 70+ in 81% of pts; 64% with 1 BM, 31% with 2-3, and 5% with 4+
  - 50% of pts had extracranial disease
  - Median PTV = 24cc (~3.6 cm diameter)
- Treatments:
  - SBRT median dose 30Gy in 6Gy fx
  - Target volumes per institution but typically cavity expanded to create a CTV and then a symmetric PTV expansion
  - Radiation necrosis determined by a multi-D tumor board

Multi-institutional retrospective post op SRS/SBRT study: Eitz et al, JAMA Onc 2020

- Results
  - Local control was 94% at 5 months, 84% at 1 year, and 75% at 2 years (median not reached)
  - Median OS was 21%
  - Radionecrosis observed in 8.6% of patients; grade 1 in 42 cases (88%) and grade 2-3 in 3 cases (6.3%); confirmed by MRI or biopsy in 39 and 9 cases;
    - Median time to RN was 13 months
- Conclusions
  - Low rates of local failure and RN in resected BM treated with fractionated SBRT

Ongoing Alliance study (A071801): Phase III of post-surgical single fraction radiosurgery compared to fractionated SRS for resected metastatic brain disease

- Inclusion criteria: 1-3 BM s/p GTR measuring 2cm or larger with a resection cavity <5cm, unresected lesions <4cm, KPS 60+, no leptomeningeal disease, no prior WBRT
- Randomization:
  - Single fraction SRS [12-20 in 1]
  - Multi-fraction SRS [27 in 3 or 30 in 5]
- Primary endpoint: time to surgical bed failure
- Secondary endpoints: QOL, OS, post-tx adverse events, lepto, and time to WBRT

Compelling retrospective data

- Choi et al, IJROBP 2011 (Stanford series) – use of a 0mm vs. 2mm margin for single fraction SRS – 12 month LF 16% vs 3%
- Abuodeh et al, World Neurosurg 2016 (Moffitt 5x5 series) – 1y local control 89% with 5Gy x 5

Consensus Contouring Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases

Hany Soliman, MD,* Mark Ruschin, PhD,* Lilyana Angelov, MD,† Paul D. Brown, MD,‡ Veronica L.S. Chiang, MD,§ John P. Kirkpatrick, MD, PhD,‖ Simon S. Lo, MD,¶ Anita Mahajan, MD,‡ Kevin S. Oh, MD,# Jason P. Sheehan, MD, PhD,** Scott G. Soltys, MD,†† and Arjun Sahgal, MD*

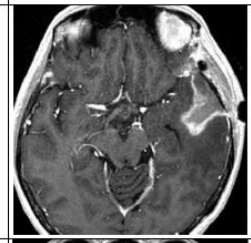
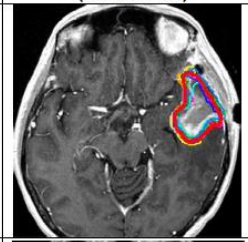
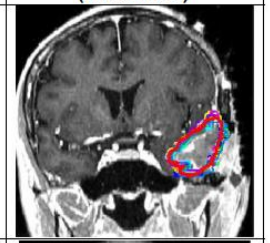
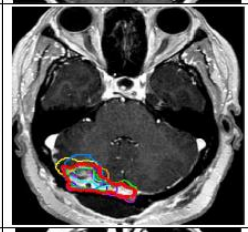
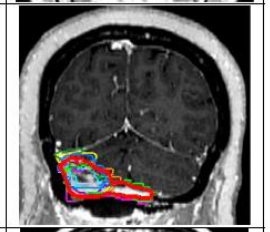
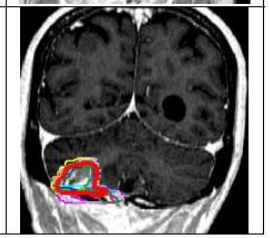
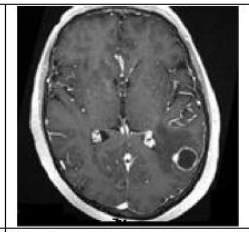
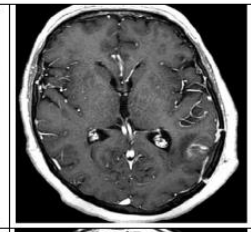
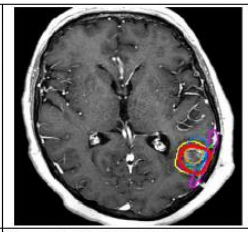
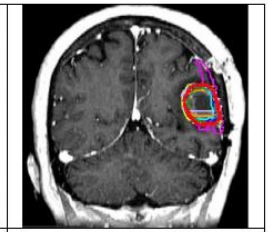
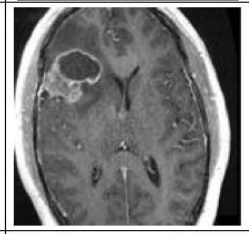
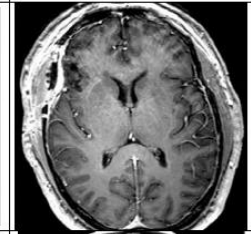
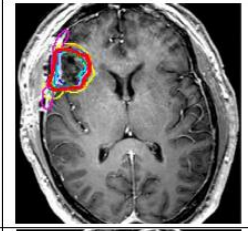
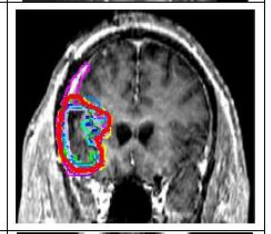
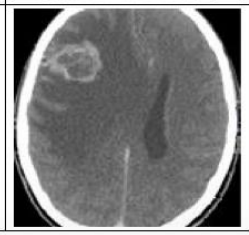
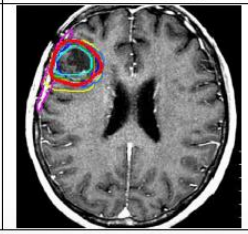
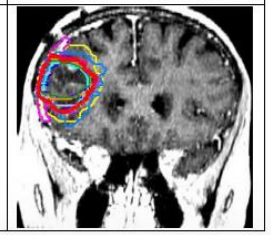
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Soliman et al, IJROBP 2017

Table 2 Recommendations for CTV contouring for post-operative completely resected cavity SRS

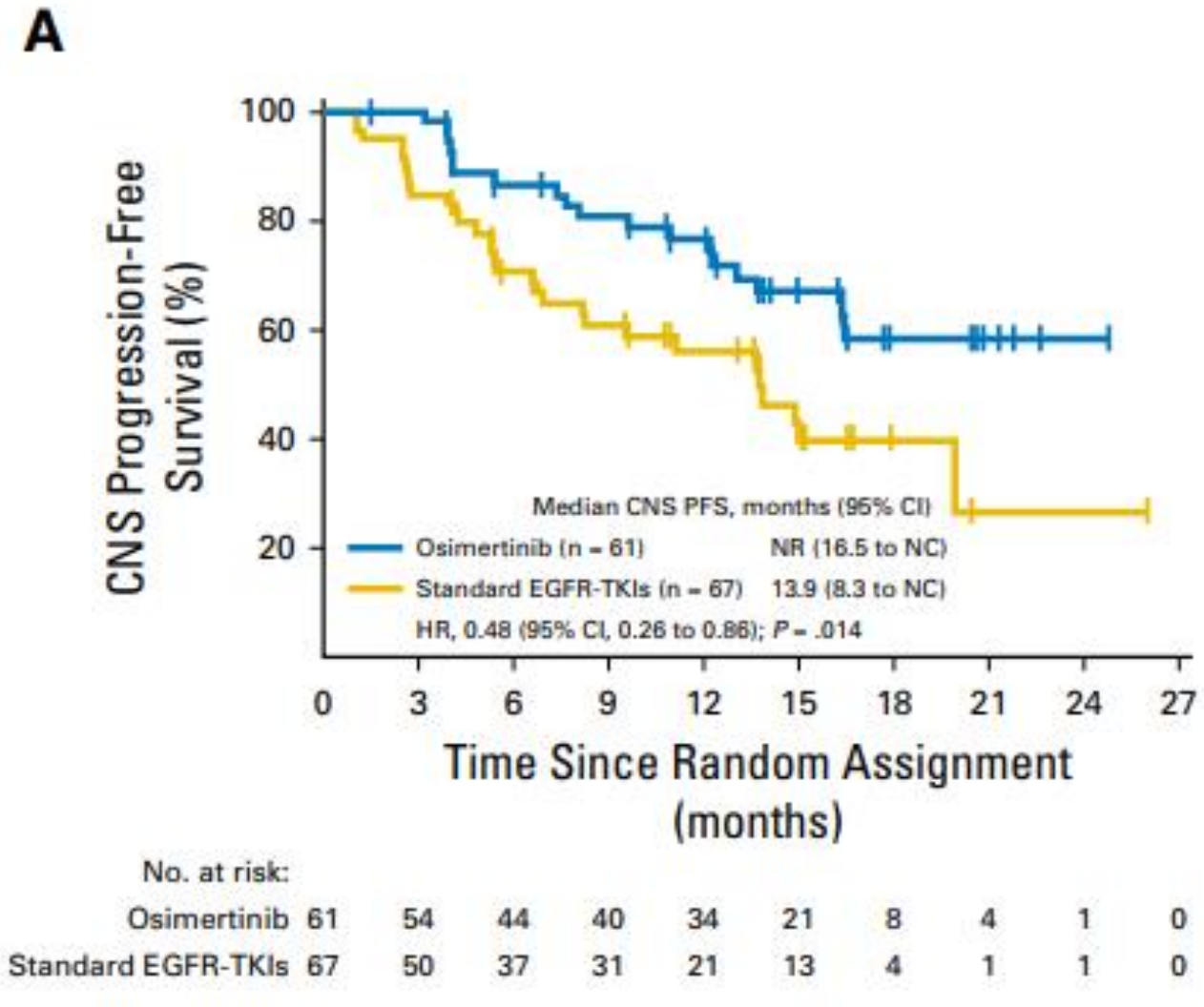
Recommendation
CTV should include the entire contrast-enhancing surgical cavity using the T1-weighted gadolinium-enhanced axial MRI scan, excluding edema determined by MRI
CTV should include entire surgical tract seen on postoperative CT or MRI
If the tumor was in contact with the dura preoperatively, CTV should include a 5- to 10-mm margin along the bone flap beyond the initial region of preoperative tumor contact
If the tumor was not in contact with the dura, CTV should include a margin of 1 to 5 mm along the bone flap
If the tumor was in contact with a venous sinus preoperatively, CTV should include a margin of 1 to 5 mm along the sinus

Abbreviations: CT = computed tomography; CTV = clinical target volume; MRI = magnetic resonance imaging; SRS = stereotactic radiosurgery.

Case #	Preoperative axial CT or MRI	Postoperative axial MRI	Postoperative axial MRI (with contours)	Postoperative coronal MRI (with contours)
Case 1: 3.2 cm left temporal tumor with dural contact metastatic from triple negative ductal carcinoma of the breast				
Case 2: 3.2 cm right cerebellar tumor with dural and venous sinus contact metastatic from adenocarcinoma of the lung				
Case 3: 3 cm right cerebellar tumor without dural or venous sinus contact metastatic from Her-2-neu positive ductal carcinoma of the breast				
Case 4: 2 cm left temporal tumor without dural contact metastatic from adenocarcinoma of the lung				
Case 5: 4.5 cm right frontal tumor with dural contact metastatic from colorectal cancer				
Case 6: 3.5 cm right frontal tumor with dural contact metastatic from melanoma				

Management of brain metastases in the era of Precision Oncology

EGFRm NSCLC: osmertinib vs. standard TKIs (FLAURA post-hoc)



Reungwetwattana et al, JCO 2018

ALK-fusion positive NSCLC: alectinib vs. crizotonib (ALEX post-hoc)

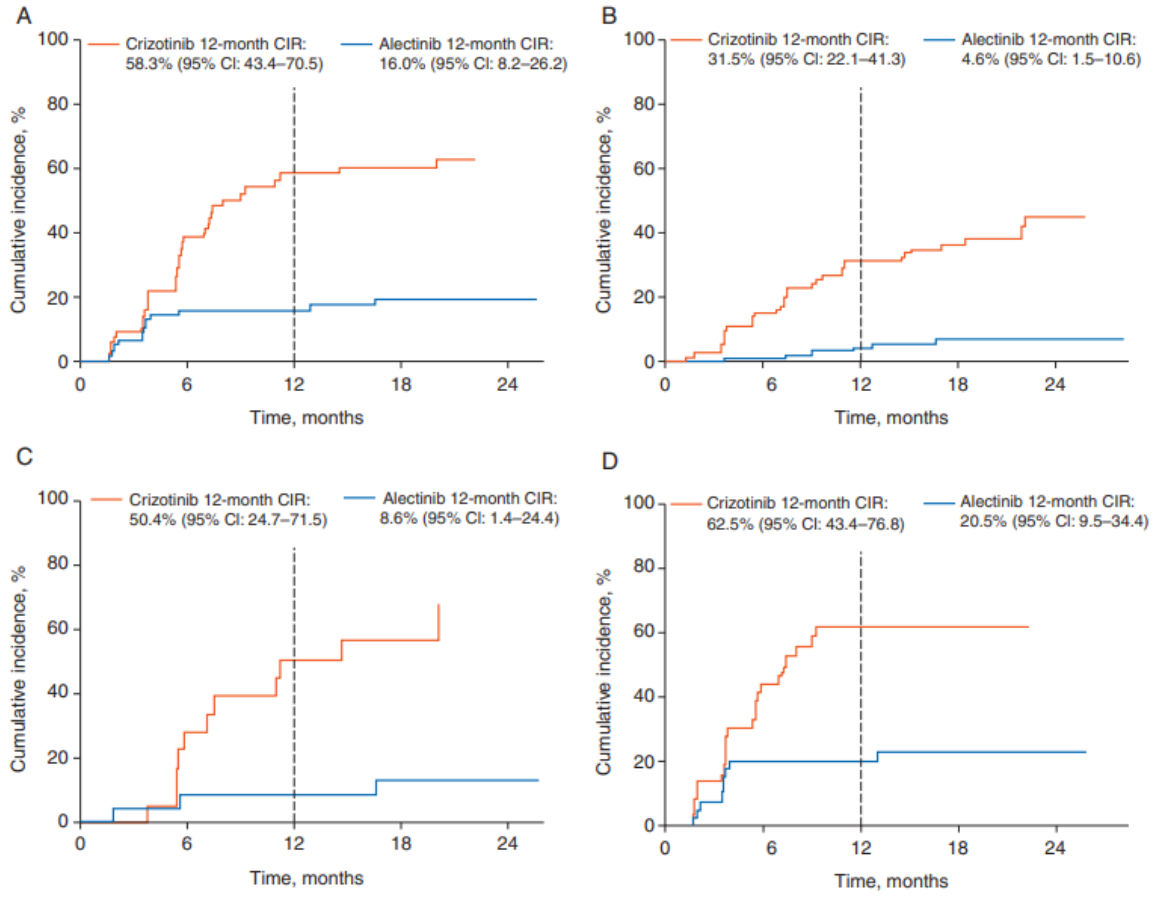


Figure 3. Cumulative incidence rate (CIR) of central nervous system (CNS) progression. For each patient, the first event of CNS or non-CNS progression or death was counted: (A) patients with CNS metastases at baseline, (B) patients without CNS metastases at baseline, (C) patients with CNS metastases at baseline who had received prior radiotherapy, and (D) patients with CNS metastases at baseline who had not received prior radiotherapy. CI, confidence interval.

Gadgeel et al, Annals Onc 2019

HER2CLIMB study: capecitabine, trastuzumab +/- tucatinib for HER2+ breast cancer

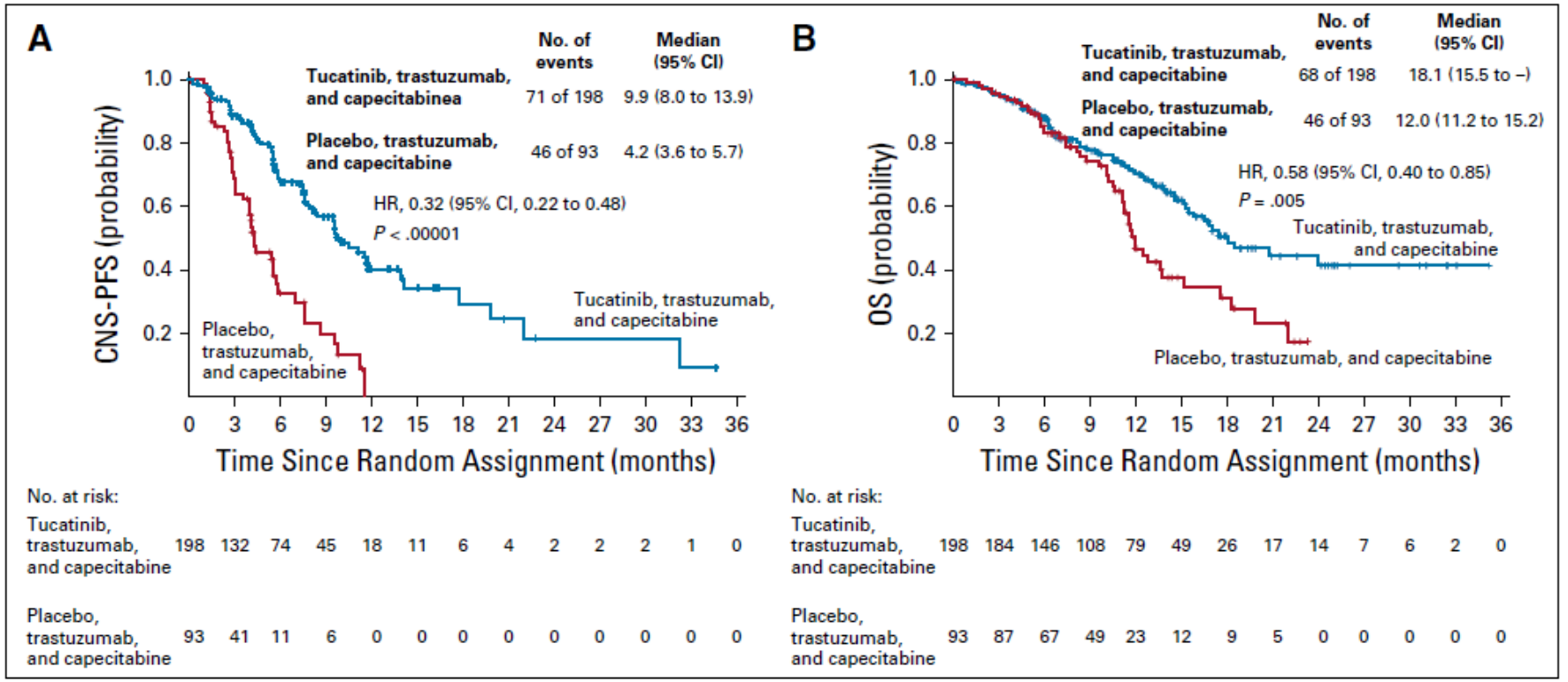


FIG 1. Kaplan-Meier curves for patients with brain metastases. (A) CNS progression-free survival (CNS-PFS) per investigator assessment. (B) Overall survival (OS). Hazard ratio (HR) computed from the Cox proportional hazards model using stratification factors (Eastern Cooperative Oncology Group performance status [0 or 1], region of world [North America or rest of world]) at random assignment. Two-sided *P* value calculated from stratified log-rank test.

Lin et al, JCO 2020

Checkmate 204: Ipi/Nivo for untreated melanoma BM

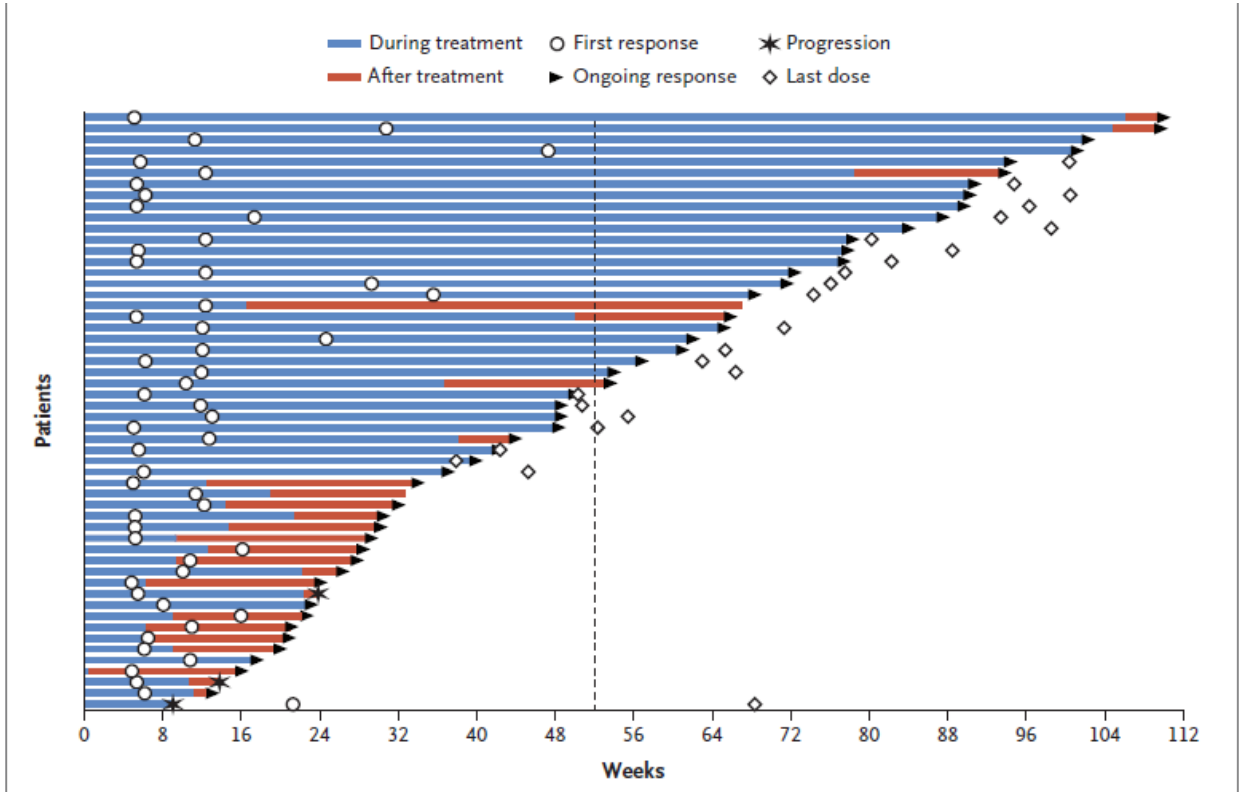


Figure 1. Time to and Duration of Intracranial Response.

The plot shows the onset and durability of intracranial objective responses to the combination of nivolumab and ipilimumab, according to modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, criteria. Open circles indicate the first evidence of objective response (complete or partial response), and arrows indicate an ongoing response; 47 of 52 responses (90%) were ongoing at the time of the analysis. The dashed line indicates 1 year after treatment initiation. The median time to response was 2.3 months (range, 1.1 to 10.8). The median duration of intracranial response has not been reached.

Tawabi et al, NEJM 2018

And much more…

- Targeted therapy and IO approaches to brain metastasis and the molecular features of BM are very active areas of research and merit a stand alone talk!

Not covered in this talk, but important topics

- More detail on targeted therapy/genomics
- Management of leptomeningeal disease
- Utilization of preoperative SRS

WBRT Toxicity and Neurocognition

Neurocognition after WBRT

- Neurocognitive effects from WBRT may not be detected using crude metrics
- Verbal learning, short term memory, executive functioning may be affected in a biphasic manner
- Neurocognitive sequelae from WBRT must be balanced with that caused by recurring brain mets
- Relationship to QOL less clear
- So...how can we balance tumor control and treatment-related neurocognitive toxicity?

NCCTG (Alliance) N0574

- What are the cognitive outcomes for patients treated with WBRT in addition to SRS?

Brown et al, JAMA 2016

NCCTG (Alliance) N0574: SRS +/- WBRT for 1-3 mets

- Patients:
  - 213 patients with 1-3 brain metastases measuring <3cm identified by MRI
  - Median age 60, lung most common (68%)
- Treatments:
  - Arm 1) SRS alone
  - Arm 2) SRS + WBRT
- **Primary outcome: cognitive progression at 3 months**—defined as decline >1SD from baseline in any of 6 cognitive tests

Brown et al, JAMA 2016

NCCTG (Alliance) N0574: SRS +/- WBRT for 1-3 mets

- Results:

Outcome	SRS	SRS+WBRT	p-value
Cognitive progression at 3mos	61.9%	88.0%	0.002
Immediate recall	8%	31%	0.007
Delayed recall	20%	51%	0.002
Verbal fluency	2%	19%	0.02
Intracranial control 6mos	66.1%	88.3%	<0.001
Intracranial control 1yr	50.5%	84.9%	<0.001
Median OS	10.7mos	7.5mos	0.93

- Conclusions:
  - WBRT hastens cognitive decline but does not improve OS in patients treated with SRS for 1-3 brain metastases

Brown et al, JAMA 2016

RTOG0614

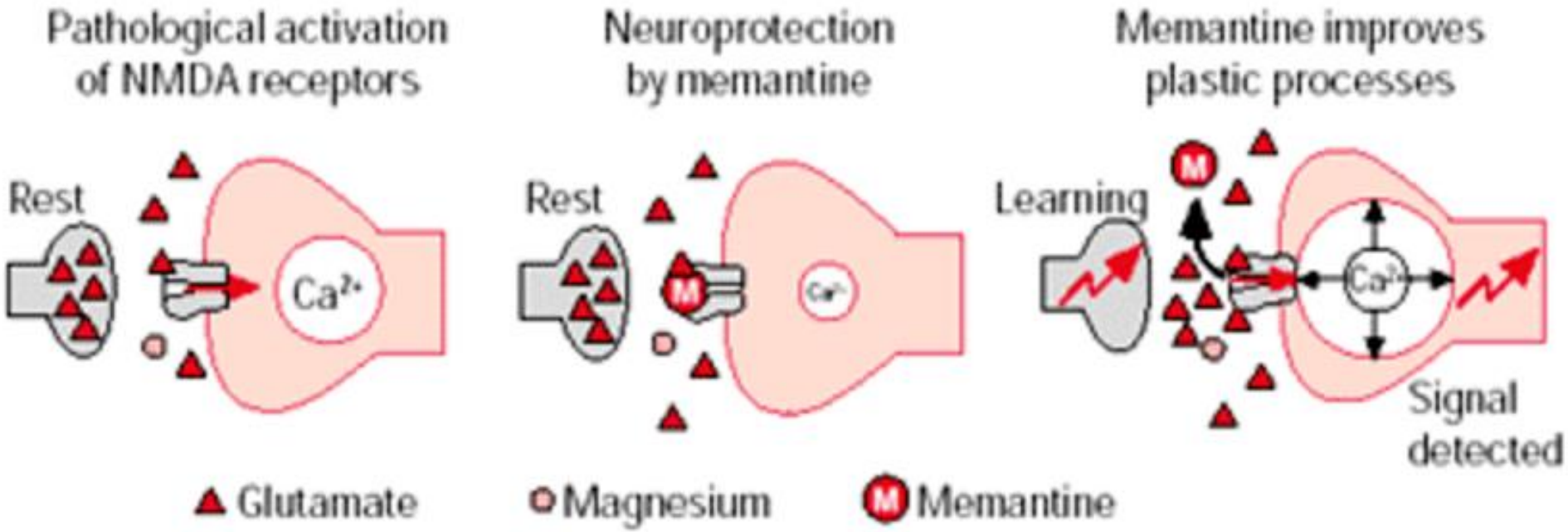
- Does the utilization of memantine improve NCF after WBRT?

RTOG 0614:WBRT +/- Memantine

- Patients:
  - 508 patients with MRI/CT-I+ confirmed brain metastases and known solid malignancy, KPS>70, MMSE>18, stable systemic disease >3mos; prior SRS ok and included in stratification
- Treatment:
  - Arm 1) WBRT + memantine ➔ memantine (24wks total)
  - Arm 2) WBRT + placebo ➔ placebo (24wks total)
  - WBRT 37.5Gy in 15 fractions
  - Memantine given PO in an escalating fashion
    - Week 1 – 5mg qd
    - Week 2 – 5mg bid
    - Week 3 – 10mg qam, 5mg qhs
    - Week 4 through 24 – 10mg bid
    - Serial standardized tests of cognitive function on weeks 0, 8, 16, 24, 52 with HVLT-R, TMT-A, TMT-B, COWA, MMSE

Brown et al, Neuro-Oncology 2013

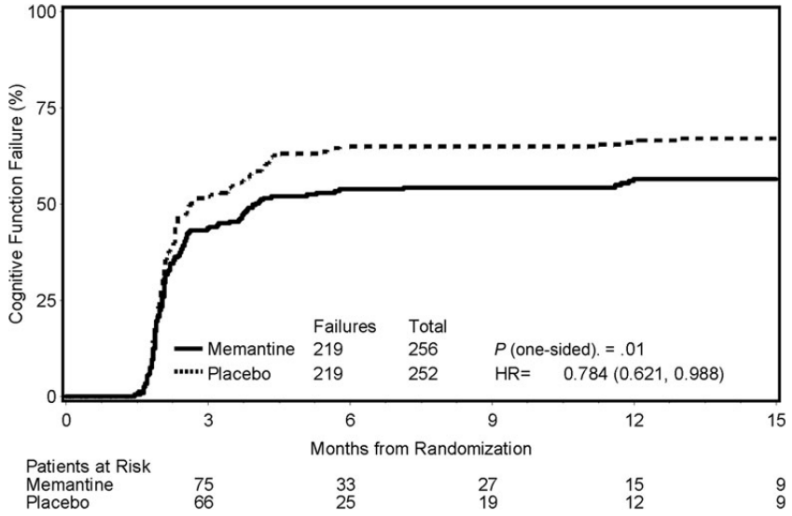
RTOG 0614: WBRT +/- Memantine



Memantine is an NMDA receptor antagonist

RTOG 0614: WBRT +/- Memantine

- Results
  - Memantine arm had significantly longer time to cognitive decline (HR 0.78, [0.62, 0.99]
  - Less decline in delayed recall in memantine arm @24 weeks (p=0.059)
  - Probability of cognitive function failure at 24 weeks was 53.8% in memantine arm and 64.9% in placebo arm
  - Memantine arm had better executive function at 8 weeks (p=0.008) and 16 weeks (p=0.0041) and for processing speed (p=0.0137) and delayed recognition (p=0.0149) at 24 weeks
  - 14% grade 3-4 treatment related toxicity in both arms
- Conclusions: improves cognitive endpoints at 24 weeks



Brown et al, Neuro-Oncology 2013

NRG CC001 (Brown)

Does hippocampal avoidance improve neurocognitive function compared to standard WBRT + memantine?

Brown et al, JCO 2020

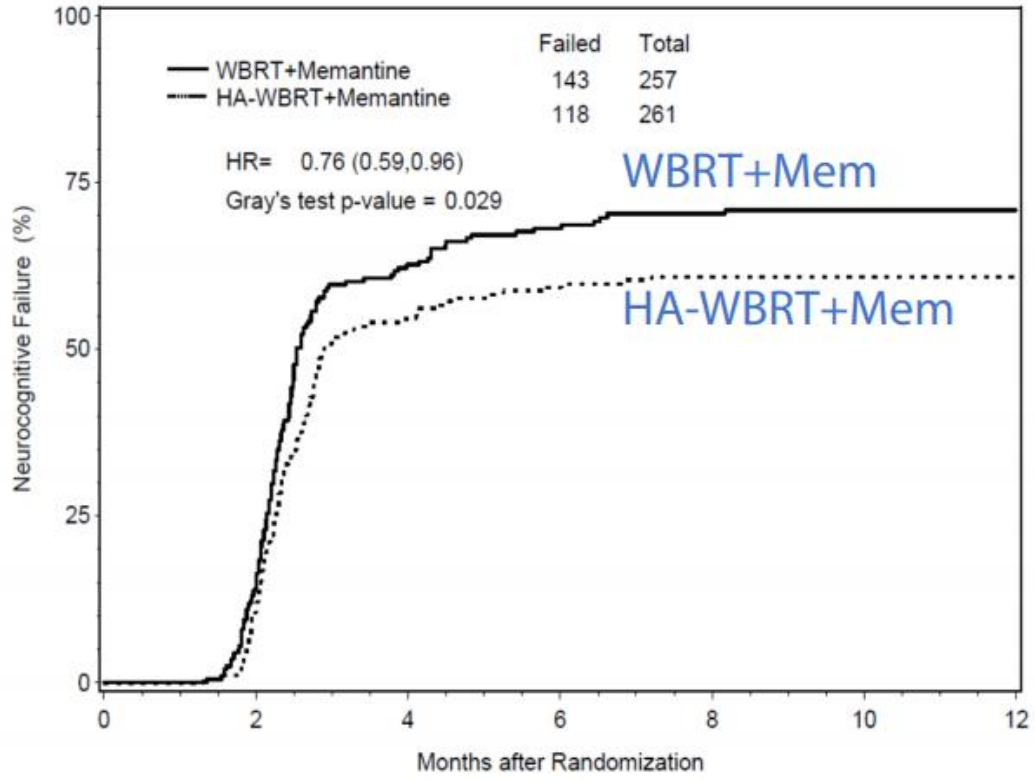
NRG CC001 (Brown): HA-WBRT+ memantine vs WBRT + memantine

- Phase III trial
- Eligibility: brain metastases 5mm outside of hippocampus, KPS>70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing
- 518 patients randomized to:
  - WBRT 30 Gy + memantine
  - HA-WBRT 30 Gy + memantine
- Stratified by RPA and prior therapy

- Primary endpoint was cognitive function failure based on at least one cognitive test
- Secondary endpoints: OS, intracranial PFS, toxicity, patient reported symptom burden

Brown et al, ASTRO 2019, JCO 2020

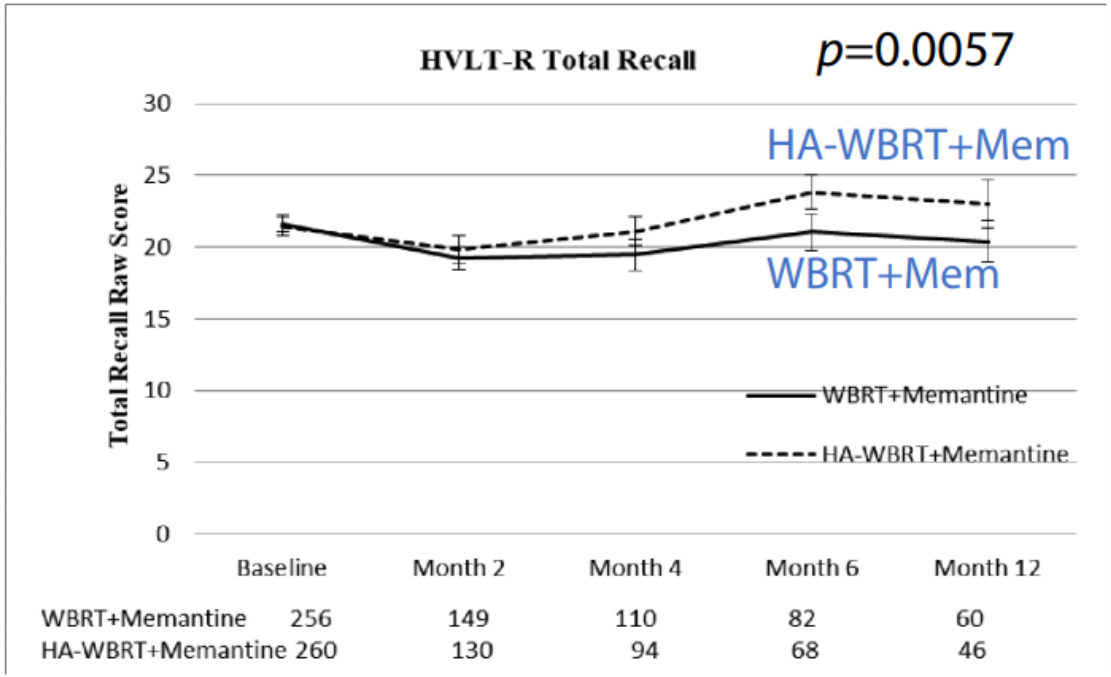
NRG CC001 (Brown): HA-WBRT+ memantine vs WBRT + memantine



Patients at Risk

WBRT+Memantine	257	133	34	19	11	9	5
HA-WBRT+Memantine	261	124	40	27	22	21	14

Mixed effects models using multiple imputation:



WBRT+Memantine	256	149	110	82	60
HA-WBRT+Memantine	260	130	94	68	46

Higher score indicates better performance

Brown et al, ASTRO 2019, JCO 2020

NRG CC001 (Brown): HA-WBRT+ memantine vs WBRT + memantine

- Conclusions
  - HA-WBRT + memantine preserves cognitive function and patient-reported symptoms in brain metastasis patients
    - Improvements in patient-reported cognition over time and 6-month change in neurologic symptom burden, interference of neurologic symptoms with daily activities, and problems remembering things
    - Benefits in executive functioning at 4 mos, recognition at 4 and 6 mos, and all domains of learning and memory over time
  - Similar toxicity, intracranial PFS and overall survival outcomes
  - For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.

Brown et al, ASTRO 2019, JCO 2020

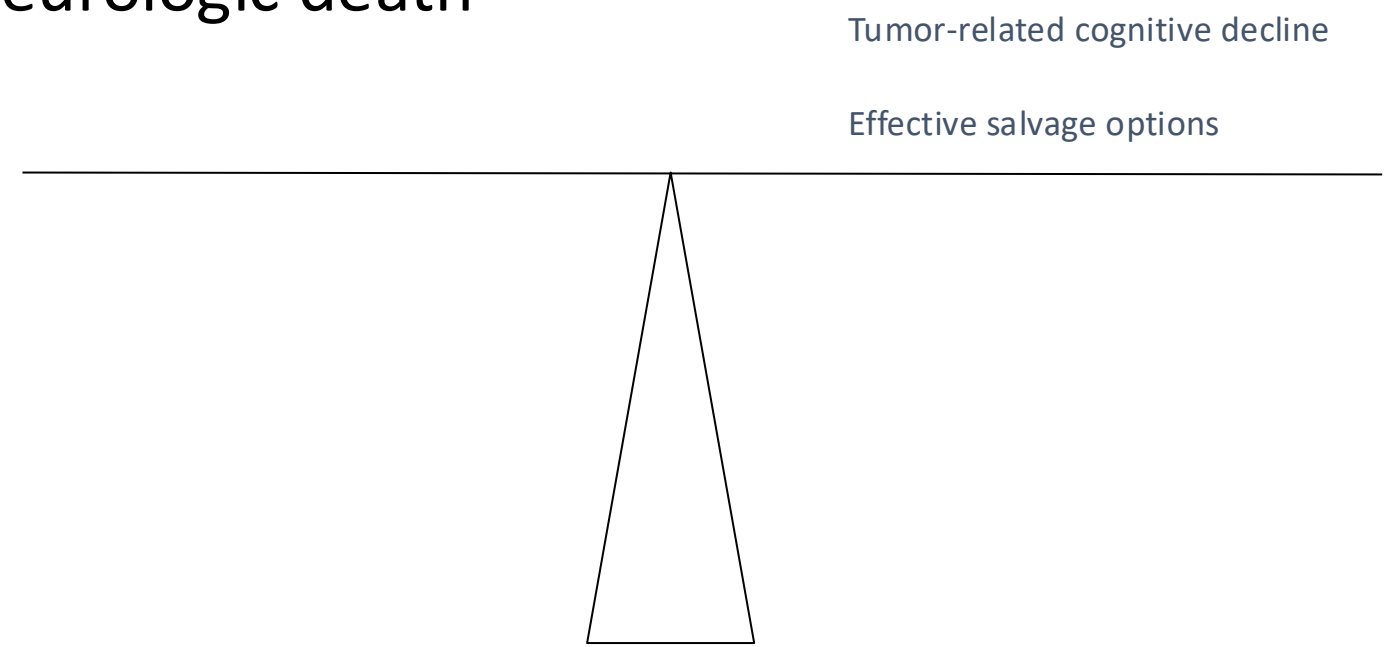
Summary

- WBRT improves distant and local control but does not improve overall survival when added to surgery or radiosurgery
- WBRT has significant neurotoxicity
- SRS is an effective tool for the management of 1-10 brain metastases

Appendix

WBRT now or later?

- Long term neurocognitive decline
- Improved in-brain control
- Decreased neurologic death



Summary

Study	#Mets	Comparison	Outcome
Patchell I	1	WBRT +/- surgery	□Local Recurrence No difference IBR □OS
Patchell II	1	Surgery +/- WBRT	□Local Recurrence ↓IBR ↓Neurologic death No difference in OS
EORTC 22952-6001	1-3	Surgery or SRS +/- WBRT	□Local Recurrence ↓IBR ↓Neurologic death No difference in OS
RTOG9508	1-3	WBRT +/- SRS boost	□Local Recurrence No difference in OS >1 met □OS for 1 met, RPA1, SquamCC
NCCTG N0574	1-3	SRS +/- WBRT	↓IBR ↑↑Neurocognitive decline mOS unchanged
RTOG0614	NS	WBRT +/- memantine	Improved cognitive outcomes at 24 weeks
RTOG0933	NS	WBRT +/- HA	7% cognitive decline at 4 months (versus 30% historical control)

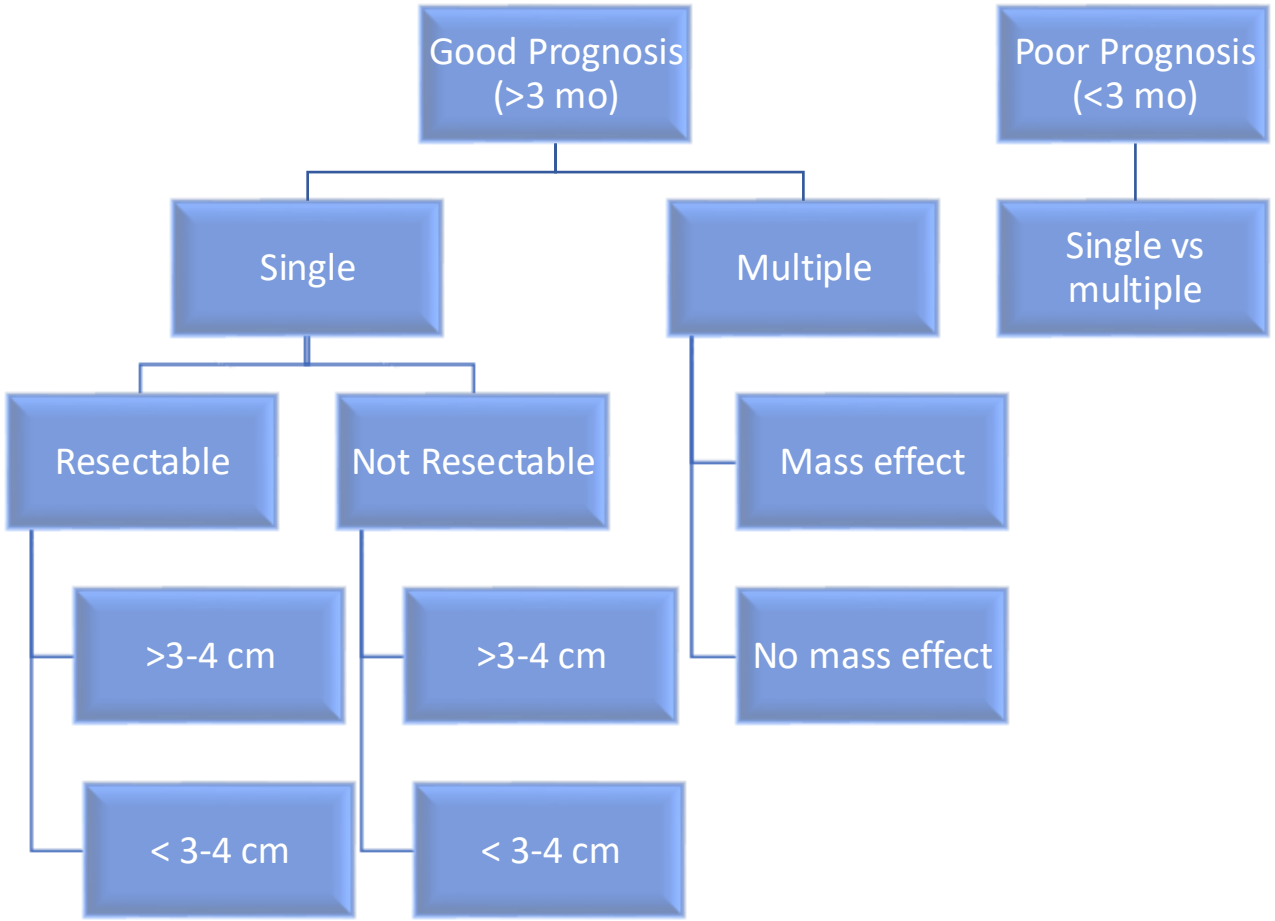
Workup: Chart Biopsy

- Know disease status in rest of body (overarching disease course, therapies, and current systemic disease status)
  - Durability of control versus competing risks
- Current and future systemic treatment

Aims of Treatment

- Survival
- Local lesion control
- Distant brain control
- Preservation of CNS function and quality of life

Management Schema



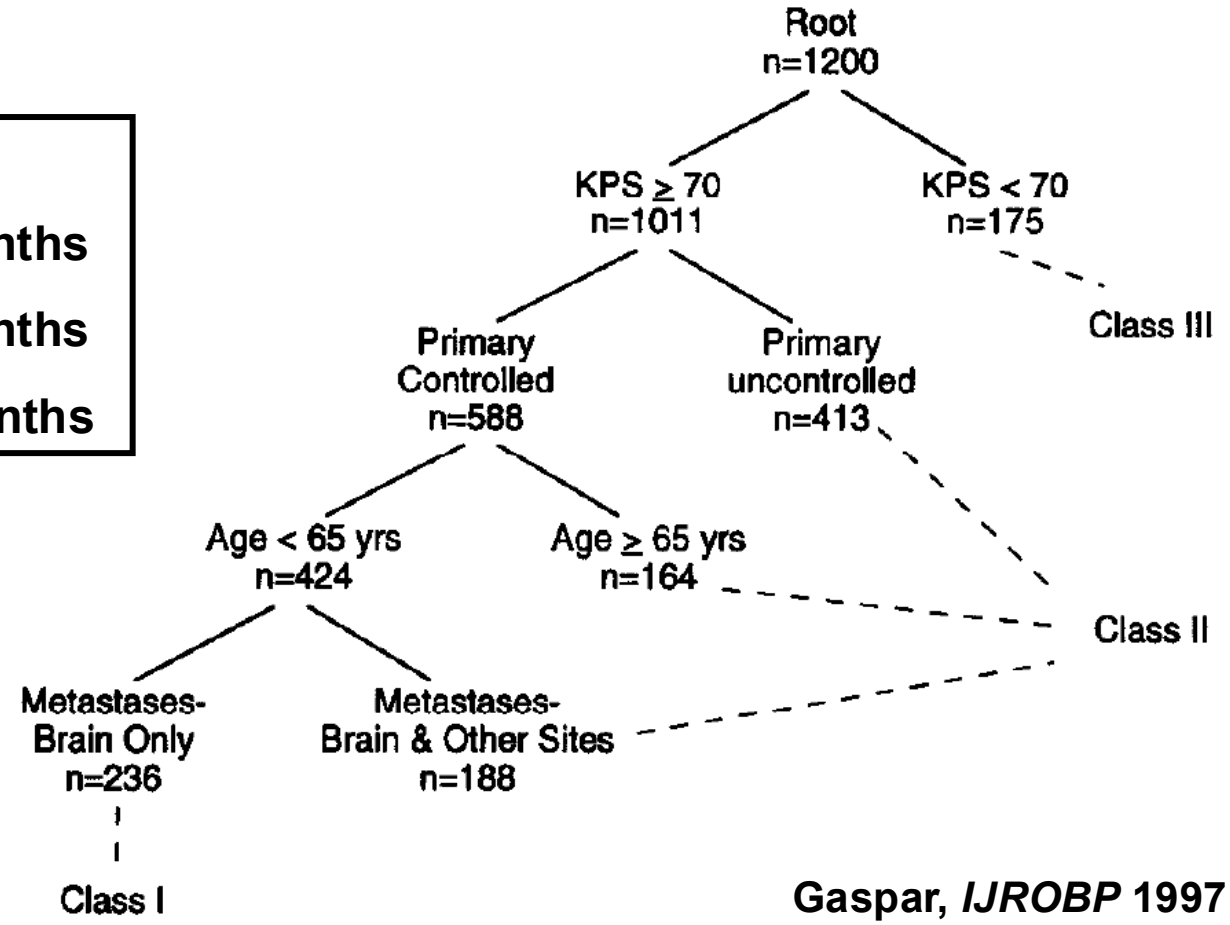
Prognostication: RPA

Median survival

Class I: 7.1 months

Class II: 4.2 months

Class III: 2.3 months



Gaspar, *IJROBP* 1997

Prognostication: Graded Prognostic Assessment (GPA)

- Retrospective review of 3940 patients with newly diagnosed brain metastases
- UVA and MVA to identify disease-specific factors correlating with overall survival
- Validated on an independent database of >4000 patients

Sperduto, J Clin Oncol 2012

Prognostication: Graded Prognostic Assessment (GPA)

Non–small-cell and small-cell lung cancer

Prognostic Factor	0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

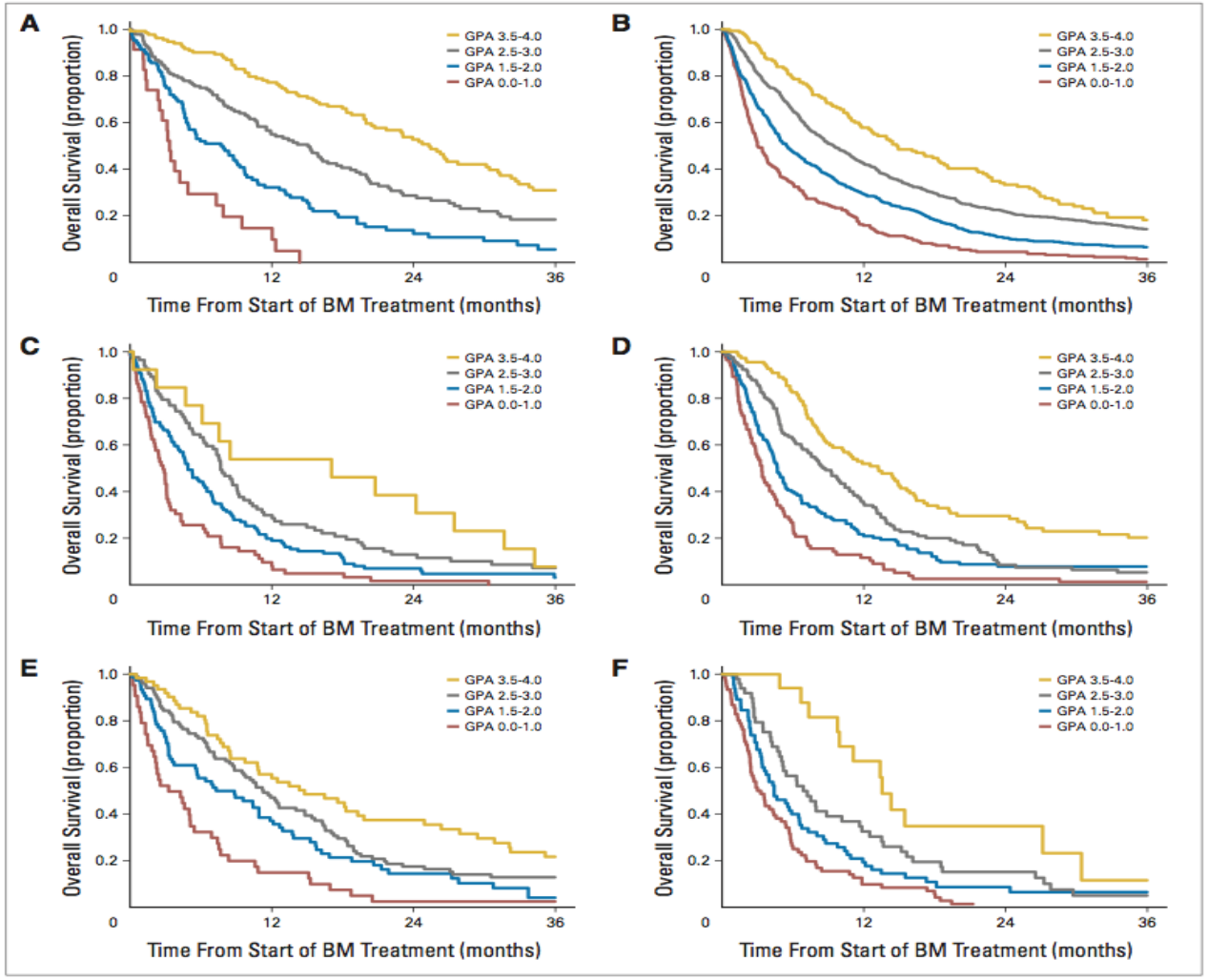
Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Prognostication: Graded Prognostic Assessment (GPA)

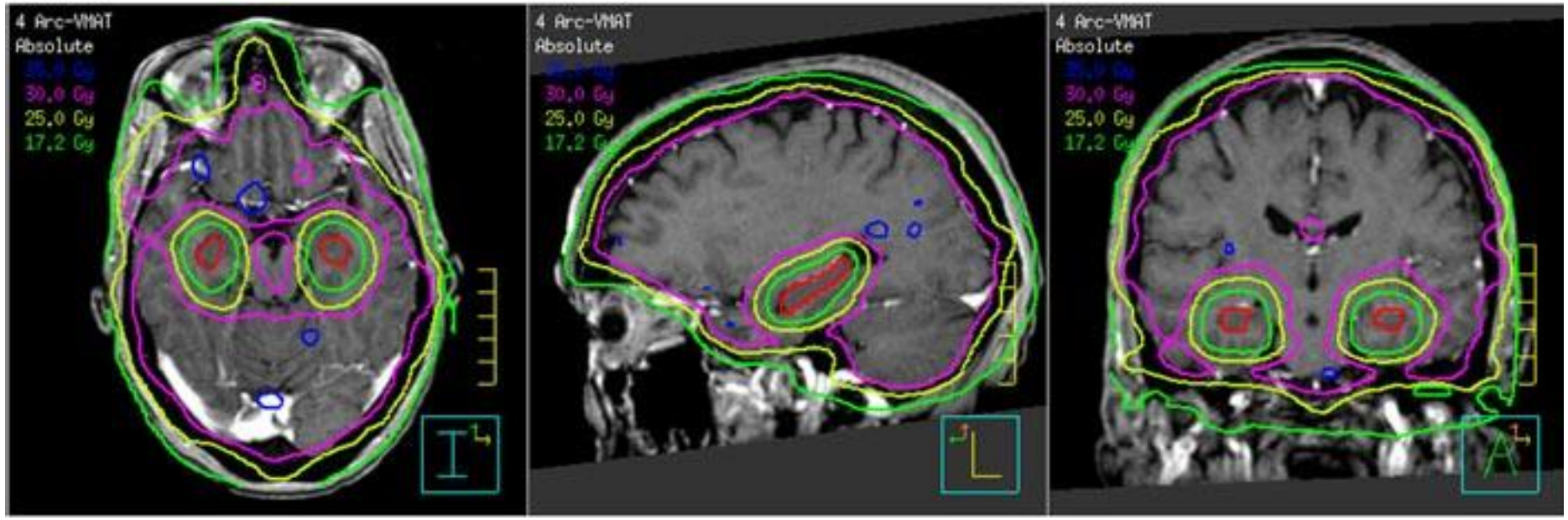


- (A) breast cancer
- (B) non–small-cell lung cancer
- (C) small-cell lung cancer
- (D) melanoma
- (E) renal cell carcinoma
- (F) GI cancer

RTOG0933: Does hippocampal sparing decrease neurocognitive decline after WBRT?

RTOG 0933:
WBRT + Hippocampal Avoidance

- Patients:
  - 113 patients with brain metastases, RPA I-II, no LMS, no prior radiation, SRS, or surgery, disease >5mm away from hippocampus
- Rationale: Hippocampal dose during WBRT hypothesized to be relevant in cognitive decline
- Design: single arm phase II study of using IMRT for WBRT with hippocampal avoidance
- Treatment: WBRT 30 Gy in 10 fractions with IMRT; hippocampal 100% dose and max dose not to exceed 10 Gy and 17 Gy respectively.
- Primary endpoint: HVLT-DR at 4 months with a comparison to historical control (PCI-P-120-9801 study, which showed 30% mean relative decline in HVLT-DR from baseline to 4 months). Also assessed at 2, 4 and 6 mo.

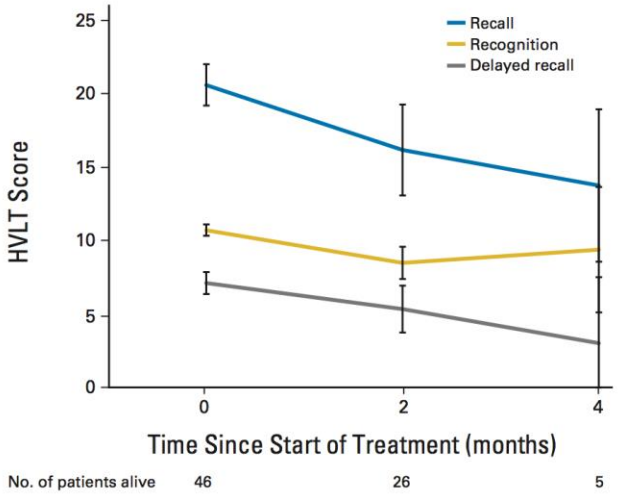


RTOG 0933 → Hippocampal-sparing WBRT using IMRT

Hippocampus:
D100% < 10 Gy
Dmax < 17 Gy

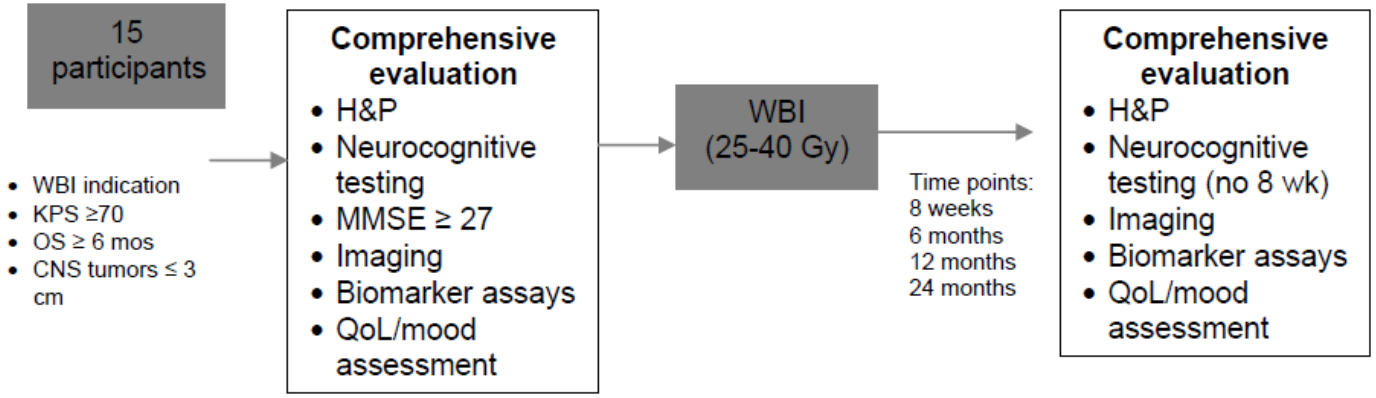
RTOG 0933: Results

- Results:
  - Mean relative decline in HVLT-DR (baseline to 4 mo):
    - Hippocampal-sparing: 7% (95%CI: -4.7% to 18.7%)
    - Historical control: 30% (P = .0003)
  - 3 pts (4.5%) had progression in the hippocampal avoidance region
- Conclusions: conformal avoidance of the hippocampus during WBRT is associated with memory preservation at 4 and 6 month follow up.



Protocol14-372:Pilot study for novel imaging/biochemical markers to identify and predict neurotoxicity in patients undergoing WBRT

Study Schema



Labs: standard CMP with additional vitamin profiling, CoQ, CPA, MMA etc under investigation

Imaging:
-Standard MR MPRAGE, T1/T2
-Arterial spin labeling perfusion studies
-Blood oxygen level dependent sequences
-Susceptibility weighted imaging