Radiotherapy and Brain Metastases

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Possible strategies

- Watchful waiting
- Surgery
- Postop RT to resection cavity or WBRT postop
- SRS (+/- WBRT)
- Staged SRS, Hypofractionated RT
- Partial brain RT
- WBRT
- Systemic treatment
- BSC

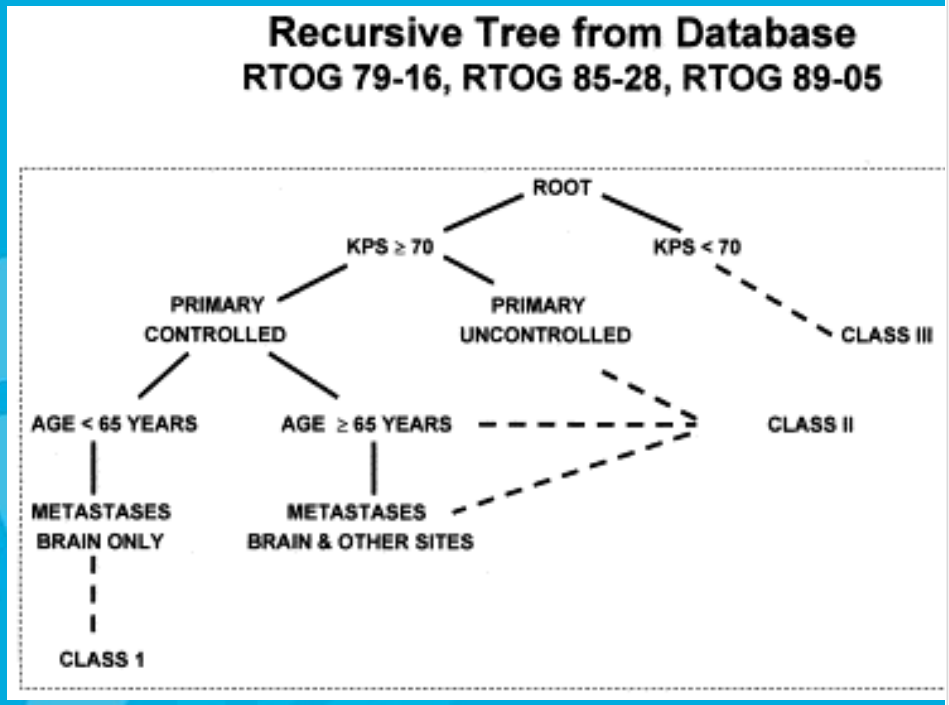

WHICH
WHEN
WHY
WHO
WHERE
WHERE
WHAT
?

Treatment modality depends on prognosis

Prognostic indicators

- Recursive Partitioning Analysis (RPA)
- Disease Specific - Graded Prognostic Assesment (DS-GPA)

RTOG recursive partitioning analysis (RPA) classification for brain metastases



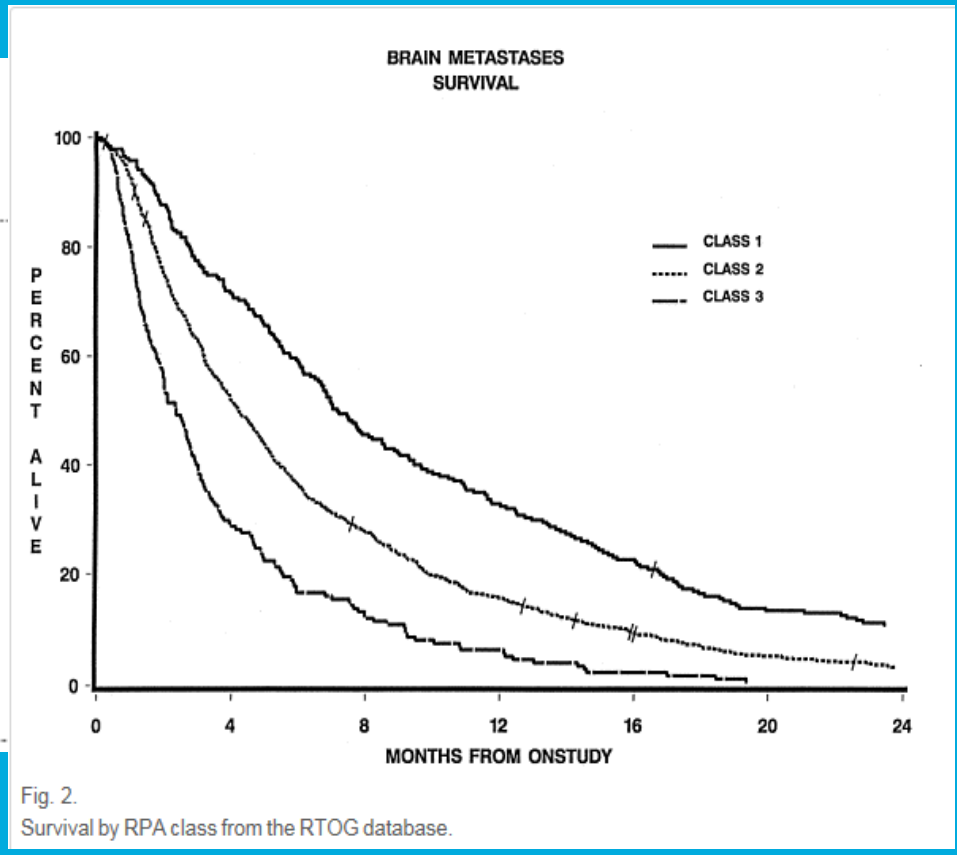


Fig. 2.
Survival by RPA class from the RTOG database.

L. Gaspar et al. IJROBP 2000

Diagnosis-specific GPA

Table 3 Diagnosis-specific GPA[15,20,21]

GPA	Significant prognostic factors	GPA scoring criteria				
NSCLC/SCLC		0	0.5		1	
	Age	>60	50-60		<50	
	KPS	<70	70-80		90-100	
	ECM	Present	—		Absent	
	#BM	>3	2-3		1	
Melanoma/RCC		0	1		2	
	KPS	<70	70-80		90-100	
	#BM	>3	2-3		1	
Breast cancer		0	0.5	1.0	1.5	2.0
	KPS	<60	60	70-80	90-100	
	ER/PR/Her2	Triple negative		ER/PR + Her2 -	ER/PR – Her2 +	Triple positive
	Age	≥ 70	<70			
GI		0	1	2	3	4
	KPS	<70	70	80	90	100

ECM, extracranial metastases; ER, estrogen receptor; GPA, graded prognostic assessment; Her2, human epidermal growth factor receptor 2; KPS, Karnofsky performance status; #BM, number of brain metastases; NSCLC, non-small cell lung cancer; PR, progesterone receptor; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

Tsao et al, ASTRO guideline 2012

Table 4 Median survivals stratified by diagnosis and diagnosis-specific GPA score for patients with newly diagnosed brain metastases[15,20,21]

Diagnosis	Overall median survival (mo)	Diagnosis-specific GPA			
		GPA: 0-1 Median survival (mo)	GPA: 1.5-2.0 Median survival (mo)	GPA: 2.5-3.0 Median survival (mo)	GPA: 3.5-4.0 Median survival (mo)
NSCLC	7.0	3.0	5.5	9.4	14.8
SCLC	4.9	2.8	4.9	7.7	17.1
Melanoma	6.7	3.4	4.7	8.8	13.2
Renal cell	9.6	3.3	7.3	11.3	14.8
GI	5.4	3.1	4.4	6.9	13.5
Breast	13.8	3.4	7.7	15.1	25.3
Total	7.2	3.1	5.4	9.6	16.7

GI, gastrointestinal; GPA, graded prognostic assessment; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Favorable prognosis

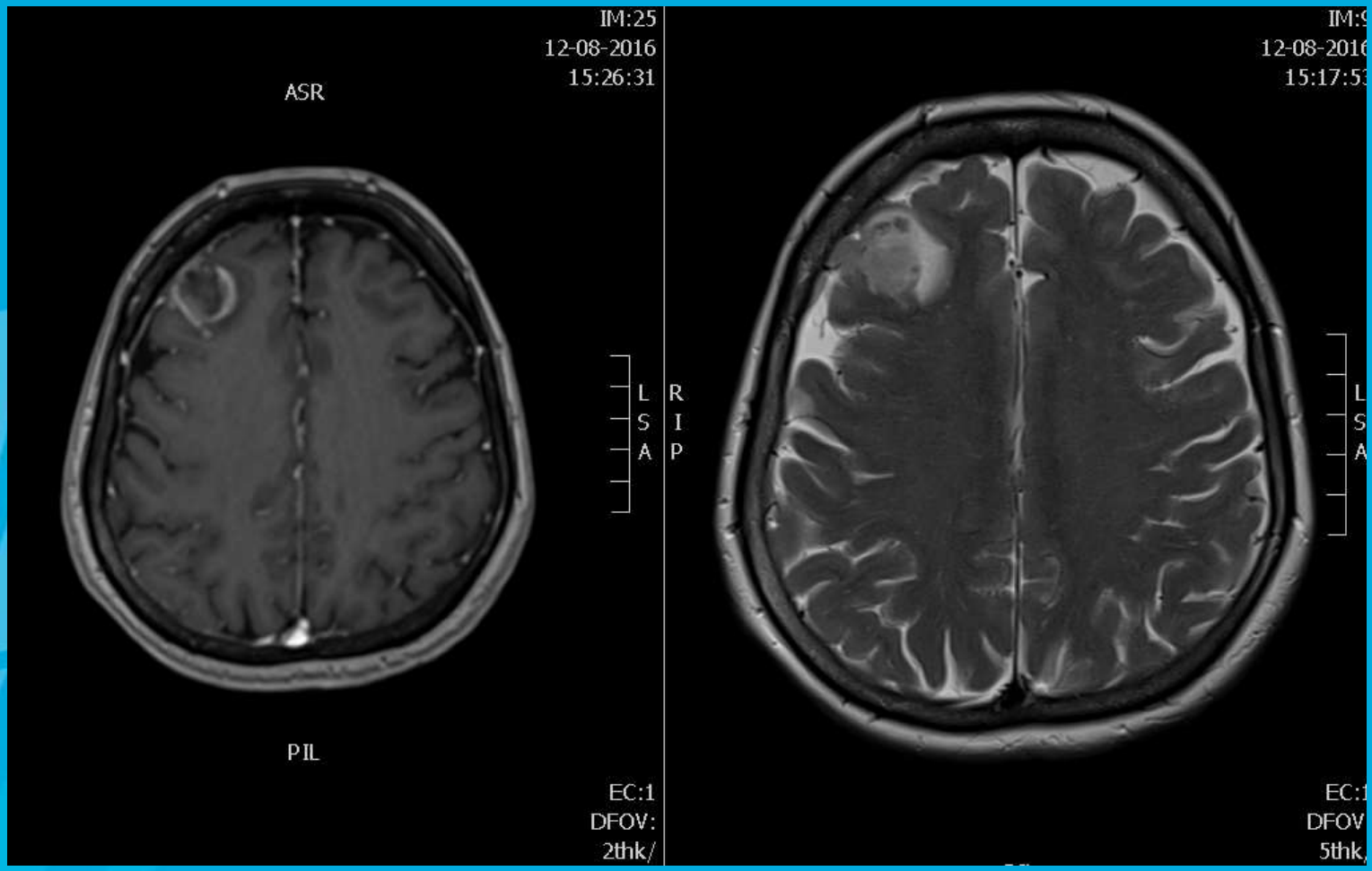
- Age < 65 years
- KPS > 70
- Controlled primary tumor
- Stable / absent extracranial disease

✓ Surgery
✓ Postop RT to resection cavity
✓ SRS Staged SRS,
Hypofractionated RT

Resection

- Tumor size and location
- Mass effect
- Symptoms
- Functional status
- Extent of systemic disease
- Pathology (dd other etiology, abscess, subacute infarction, …)

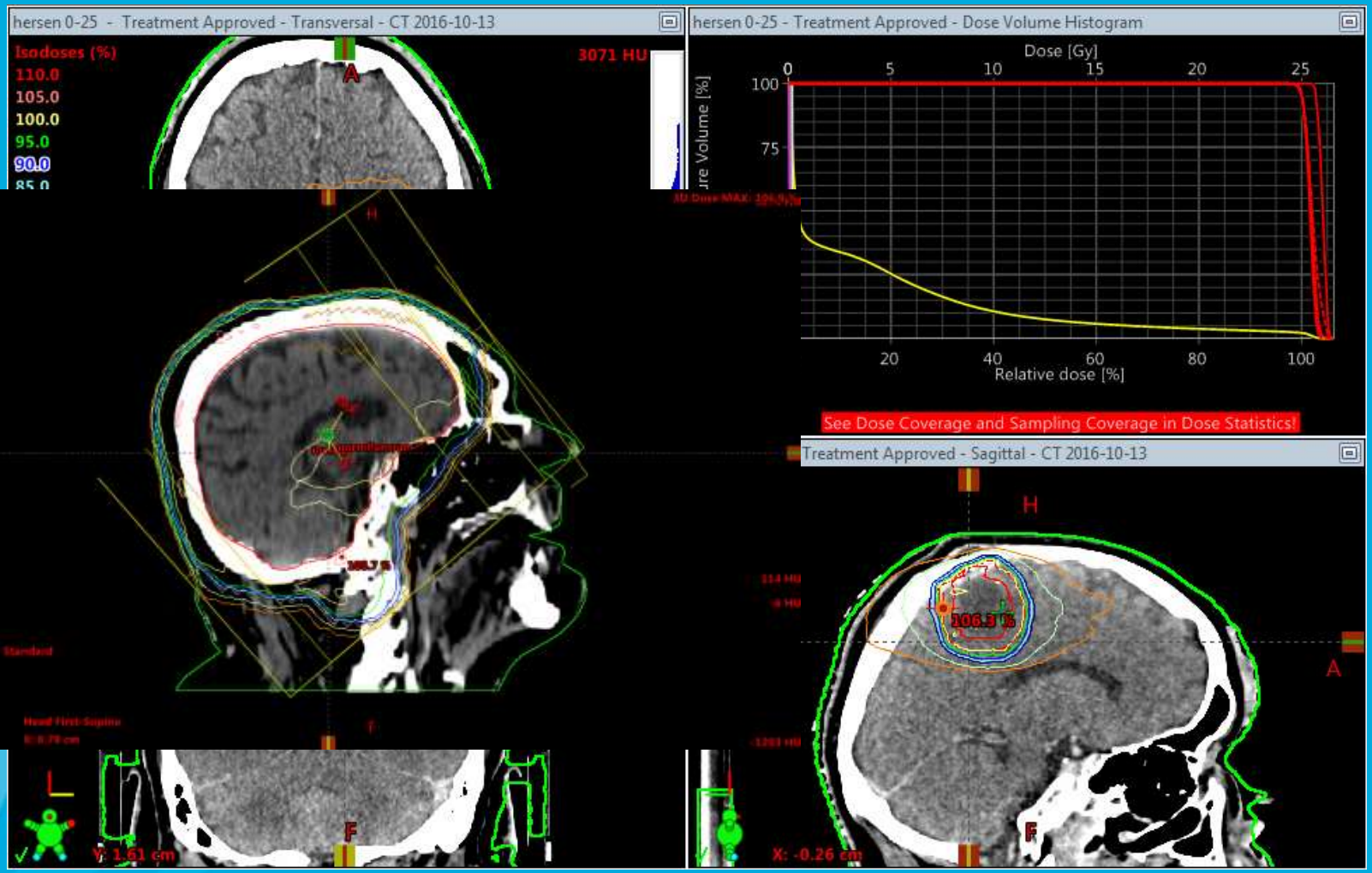
60 y old female, cT1N0M0 hormone-dependent, Her -



GBM grIV

Postoperative RT

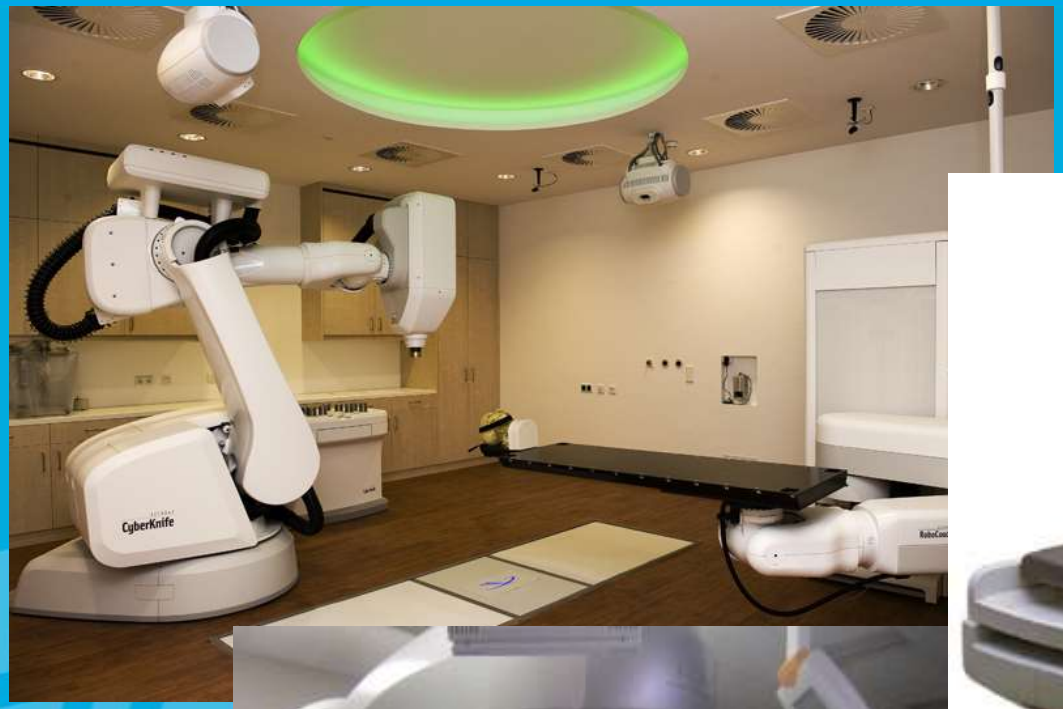
- 50% local recurrence within 6-12m
- Surgery + WBRT vs WBRT alone: fewer local recurrence and improved OS (Patchell NEJM 1990)
- Focal RT to resection cavity or WBRT?
- If focal RT: SF-RT or fractionated?


hersen 0-25 - Treatment Approved - Transversal - CT 2016-10-13
Isodoses (%)
110.0
105.0
100.0
95.0
90.0
3071 HU
hersen 0-25 - Treatment Approved - Dose Volume Histogram
Dose [Gy]
0
5
10
15
20
25
100
75
20
40
60
80
100
Relative dose [%]
See Dose Coverage and Sampling Coverage in Dose Statistics!
Treatment Approved - Sagittal - CT 2016-10-13
106.3 %
Y: 1.61 cm
X: -0.26 cm

Radiosurgery

- Who?
- What? (don’t treat incidental, asymptomatic brainM+)
- When?
- How?

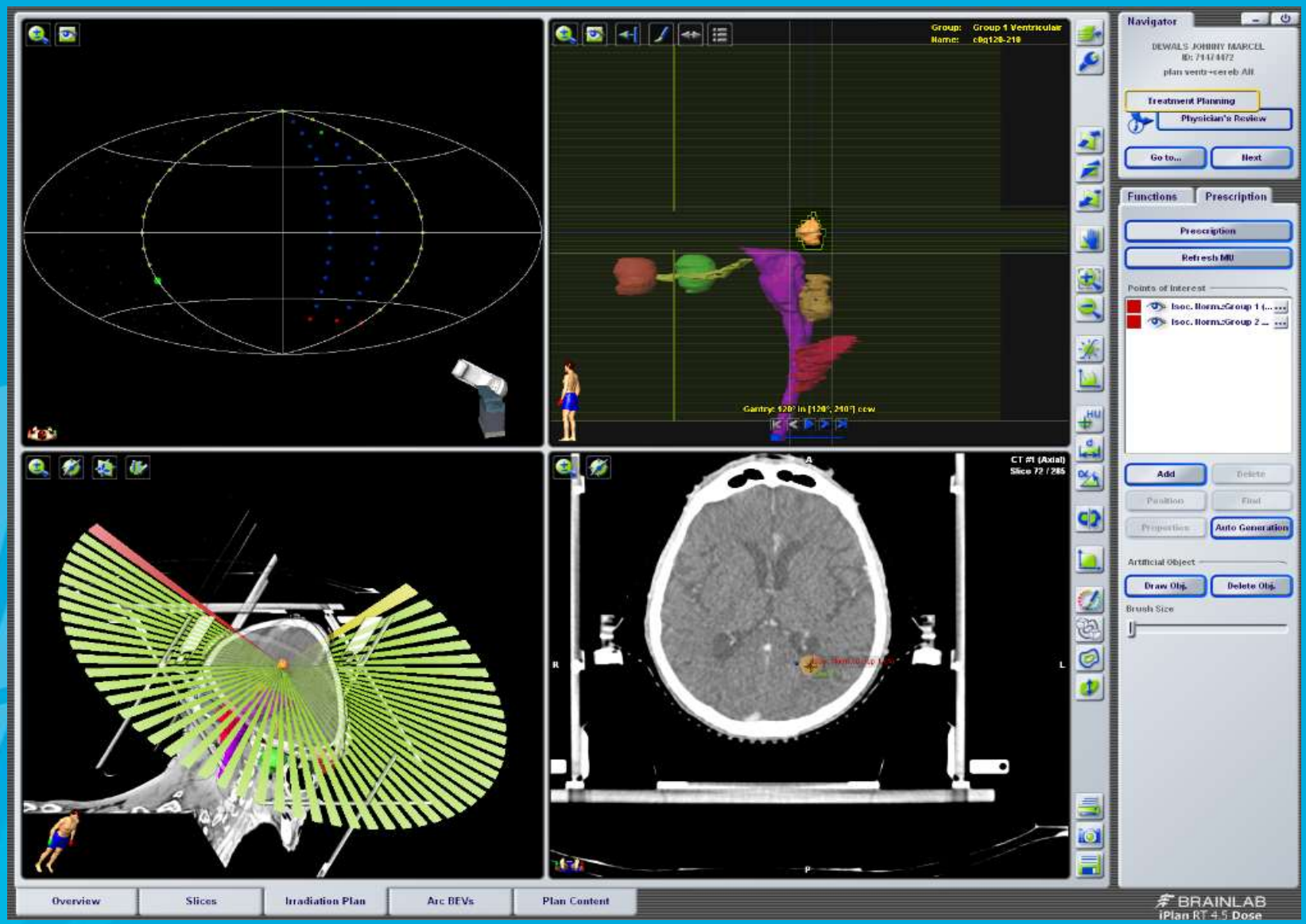
- Single fraction, hypofractionated, staged SRS



Radiosurgery:

- Cyberknife
- Gamma Knife
- Linac based SRS
- Proton beam

Linac-based frameless radiosurgery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Isoc. Norm.:Group 2 ...
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Artificial Object
Draw Obj.
Delete Obj.
Brush Size
CT #1 (Axial)
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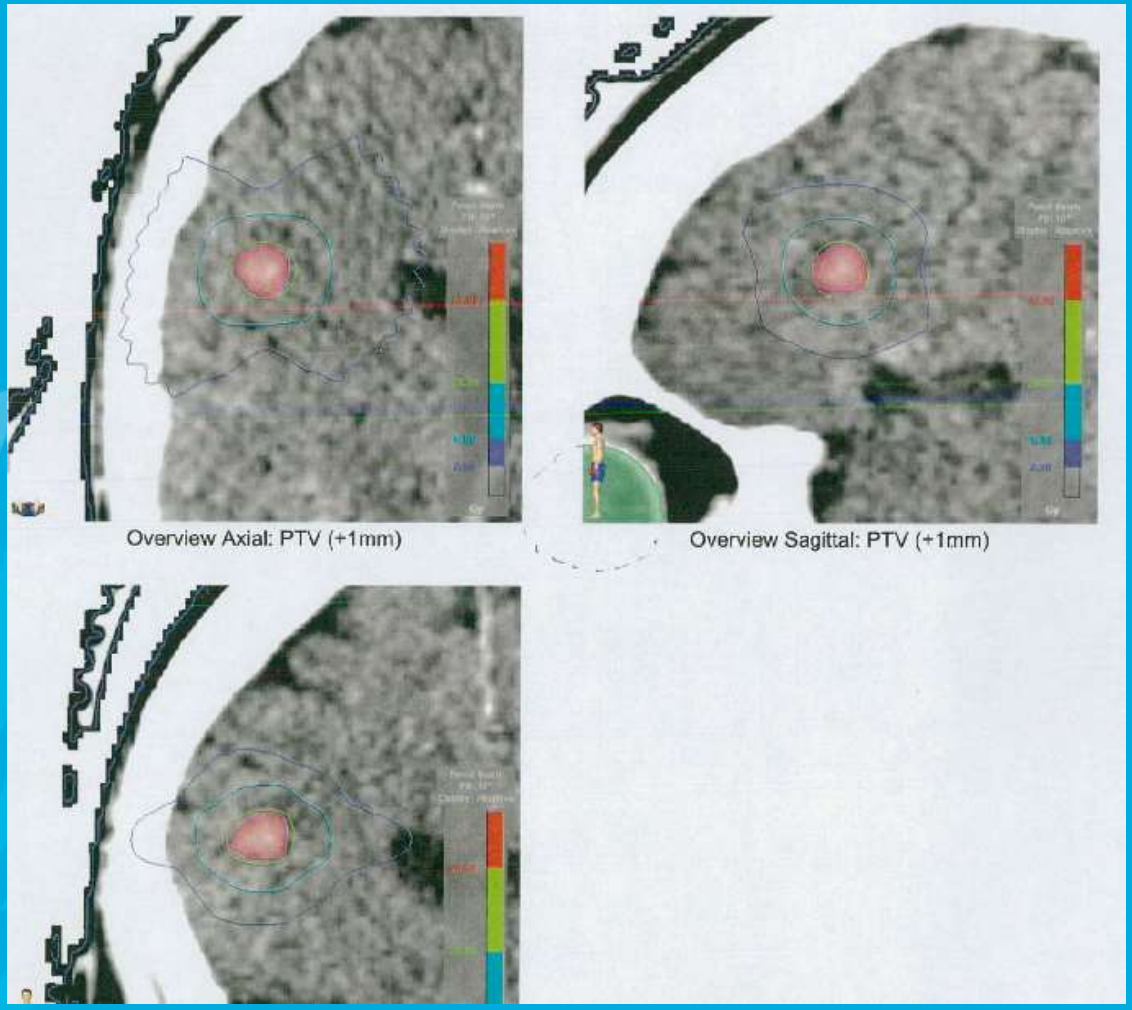
Slices
Irradiation Plan
Arc BEVs
Plan Content
BRAINLAB
iPlan RT 4.5 Dose



Overview Axial: PTV (+1mm)

Overview Sagittal: PTV (+1mm)

Advantage SRS

- More effective for radio-resistant or hypoxic cells
- Steep dose gradient – sparing normal brain tissue
- Outpatient setting
- Equally effective for small lesions as surgery
- Option to continue / short disruption of systemic treatment

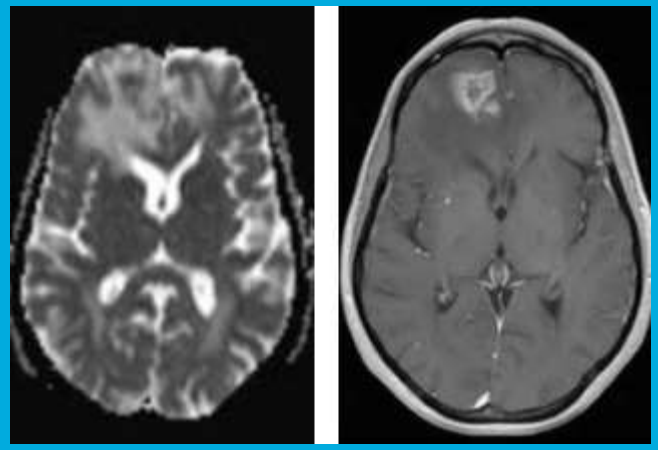
Disadvantages SRS

- More intracranial relapse: close follow up
- Sometimes prolonged edema – long term steroids
- Slower relief of mass effect
- Risk for lepto-meningeal spread

Delayed and late side-effects

Pseudoprogression:

- Increase in or new contrast enhancement on MRI
- Weeks-months after RT
- Asymptomatic



Radionecrosis:

- Months - years after RT
- Develops at or adjacent to original site
- Symptoms depend on location

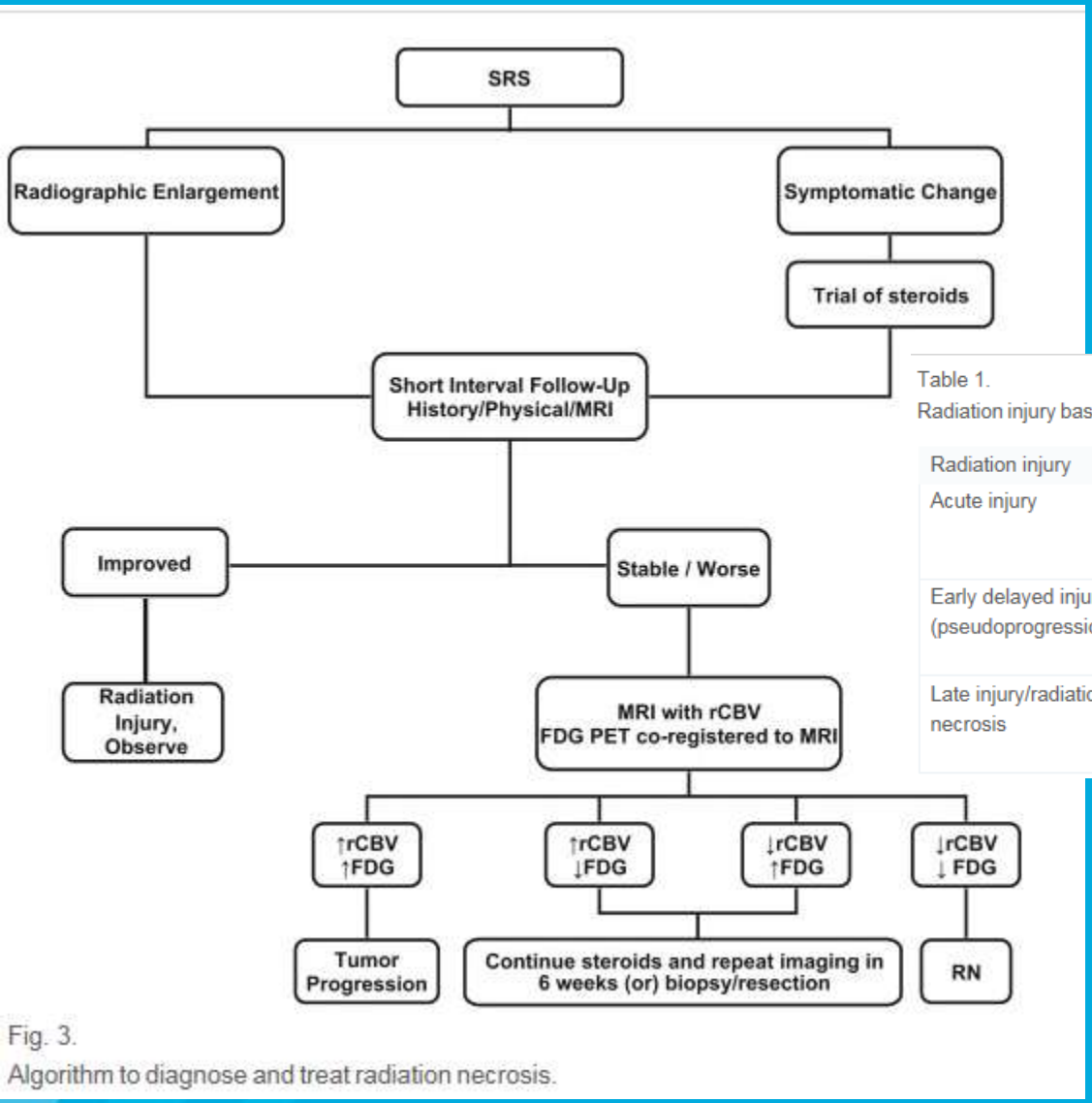


Fig. 3.
Algorithm to diagnose and treat radiation necrosis.

Table 1.
Radiation injury based on time from radiation (2)

Radiation injury	Time frame	Characteristic
Acute injury	During or after completion of radiation	Reversible; characterized by edema
Early delayed injury (pseudoprogression)	Up to 12 weeks after radiation	Reversible; characterized by increased signal on fluid-attenuated inversion recovery abnormalities and T2
Late injury/radiation necrosis	Few months to years	Irreversible; focal pattern characterized by circumscribed lesion; diffuse pattern characterized by periventricular white matter changes

Chao et al. IJROBP 2013

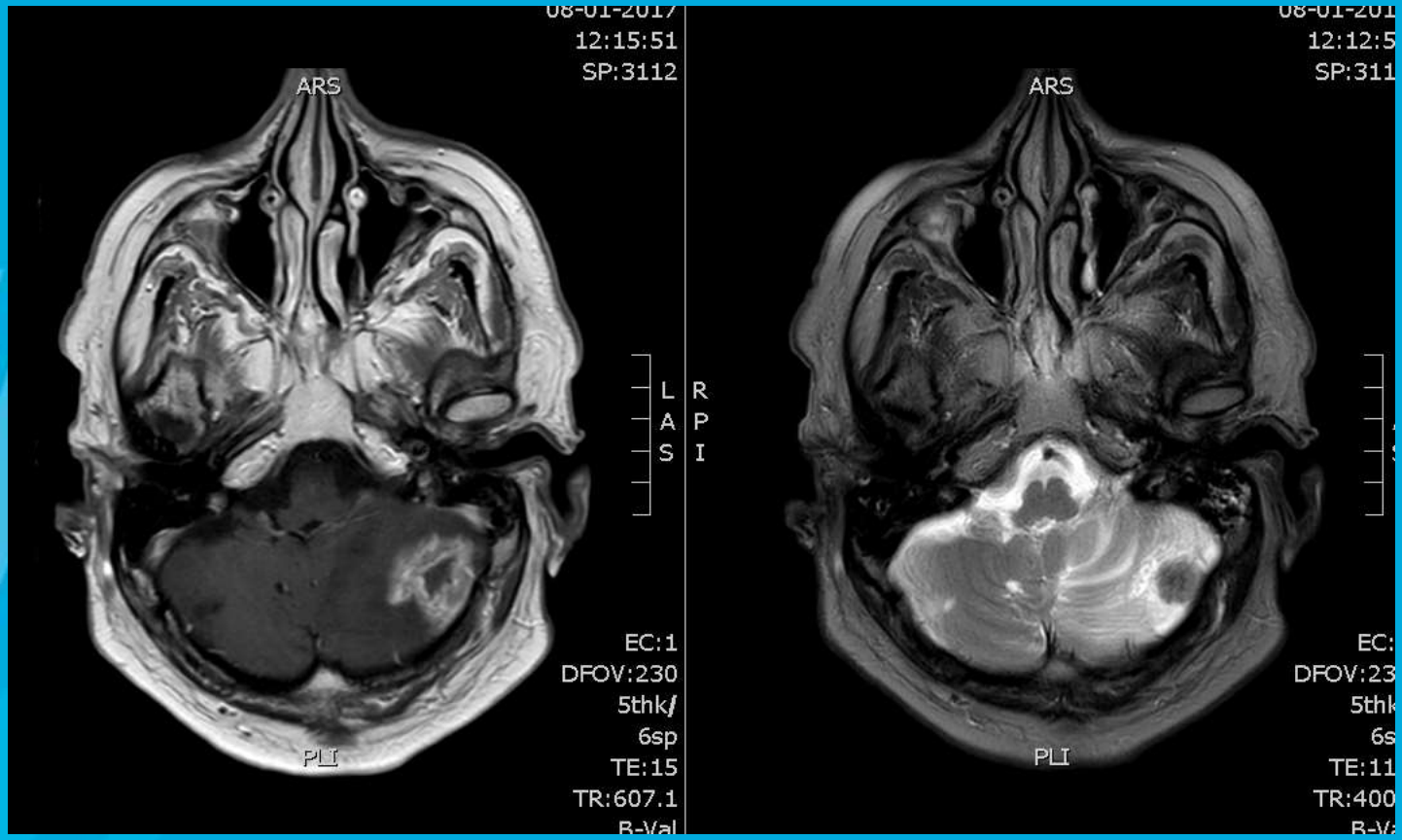
Radionecrosis

- Lipid peak ↑
- rCBV ↓
- Diffusion ↓
- T1 contrast enhancement
- T1/T2 mismatch

Treatment RN

- Biopsy
- Resection to reduce mass effect
- Self-limiting
- Moderate doses of steroids
- Laser therapy
- Bevacucimab

RN after PCI + SIB -> Resection planned



Poor prognosis

- KPS < 70

WBRT

- Aim: survival and quality of life by alleviating symptoms, decreasing use of steroids
- Treats gross tumor and presumed microscopic disease
- Remains standard approach
- Median survival 4-6 months
- ORR 40-60%
- 25-40% stable or improved symptoms

Neurocognitive decline with WBRT

- Early delayed and long term effects on neurocognitive functioning
- BUT multiple factors may impact cognition:
  - ✓ BM
  - ✓ Concurrent treatment
  - ✓ Comorbidities (diabetes, vascular risk factors, genetics)

Methods to improve WBRT

To decrease morbidity of WBRT (reducing late toxicity)

To improve efficacy

- RTOG 0614 trial: **memantine** with WBRT → significantly longer time to cognitive decline compared with WBRT alone
- RTOG 0933 trial: avoidance of the hippocampal neural stem-cell compartment during WBRT → significantly better preservation of memory and quality of life than seen in historical series
- WBRT with simultaneously Integrated Boost (SIB)

Best Supportive Care

- Quartz trial (Mulvenna et al. The Lancet 2016)

Dexamethasone and supportive care with or without WBRT (NSCLC with brain metastases unsuitable for resection or stereotactic radiotherapy)

No difference in overall survival, overall quality of life, or dexamethasone use between the two groups

Follow Up

- When no WBRT:

Contrast-enhanced MRI or CT to detect early recurrence or new lesions

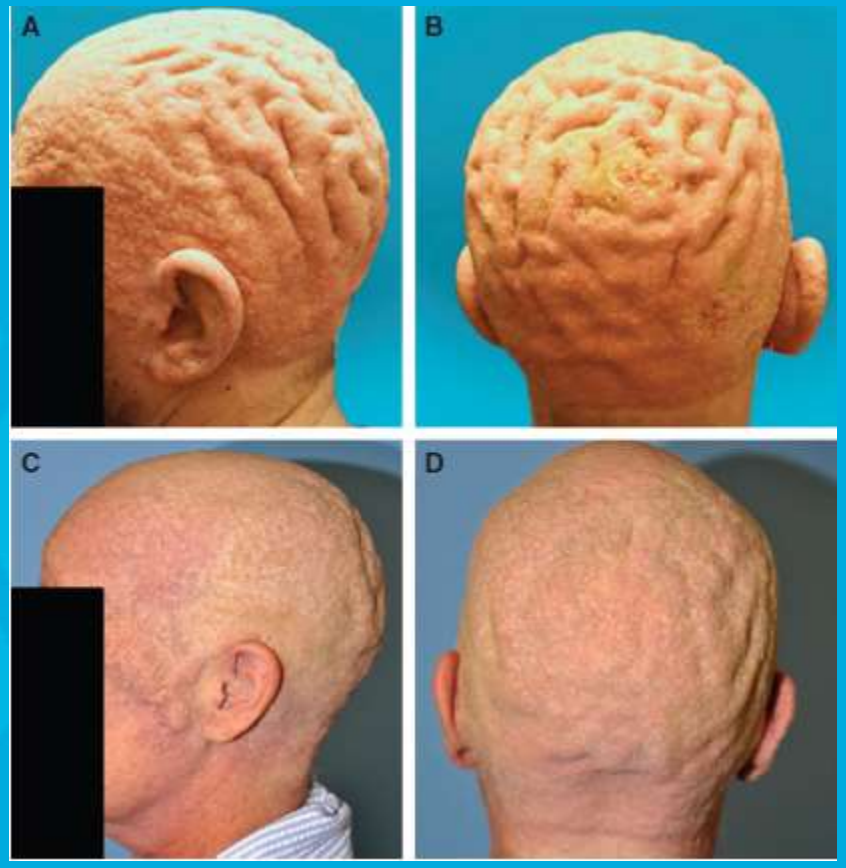
Every 2-3 months

Future developments

- Newer generation of TKIs are likely to have increased CNS activity (eg. ceritinib)
- Combination-sequence RT and TT – immunotherapy?
- Better intracranial control through concurrent use of biologic modifiers, TKIs + WBRT (potential synergistic effect)
- SRS instead of WBRT for 4 -10 M+

(eg. NCT01644591 Trial to Determine Local Control and Neurocognitive Preservation After Initial Treatment With Stereotactic Radiosurgery (SRS) for Patients With >3 Melanoma Brain Metastases)

Vemurafenib and WBRT: Cutis verticis gyrata



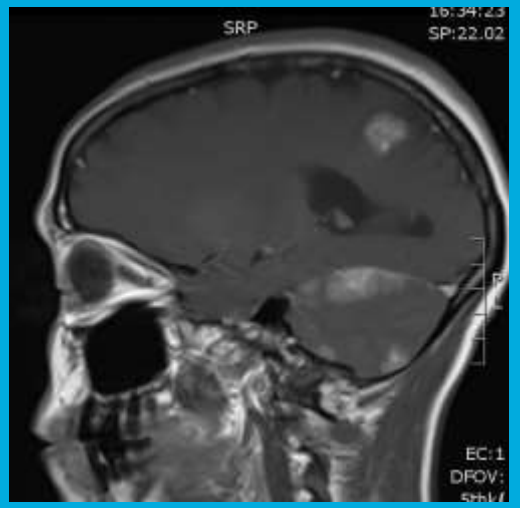
Harding et al. JCO 2014

Relapse

- Cave: recurrence or treatment effect?
- Surgery
- (Re-)irradiation: WBRT, re- WBRT (interval 4-6m), (repeat-) SRS (single fraction or hypofractionated)
- Systemic therapies: EGFR, ALK, PDL-1, …

Leptomeningeal disease

- WBRT
- Palliative focal RT to symptomatic or bulky spinal sites
- Rare craniospinal RT (more toxicity, myelosuppression, nausea, …)

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Conclusion

- Aggressive therapy for those expected to survive long enough
  - KPS
  - Younger age
  - Controlled extracranial disease
- Single M+: surgery (+ focal RT) or upfront SRS
- Limited (≤3), small M+: SRS
- Bulky disease, more M+: WBRT

The brain is a most amazing organ, it works all day, everyday, for all your live