

MANAGEMENT OF PATIENTS WITH BRAIN METASTASES

Focusing on radiotherapy

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BRAIN METASTASES



In 20-40% of adult cancer patients

Limited number of lesions	(1-3 / 1-4)	~40%
Multiple lesions	(≥ 4 / ≥ 5)	~60%

MULTIPLE LESIONS: PROGNOSIS



Median Survival Time:

- ◆ Untreated ~ 1 month
- ◆ Dexamethasone alone 1-2 months
- ◆ WBRT alone Mostly 3-6 months

▶ Short Overall Treatment Time

MULTIPLE LESIONS: FRACTIONATION OF WBRT



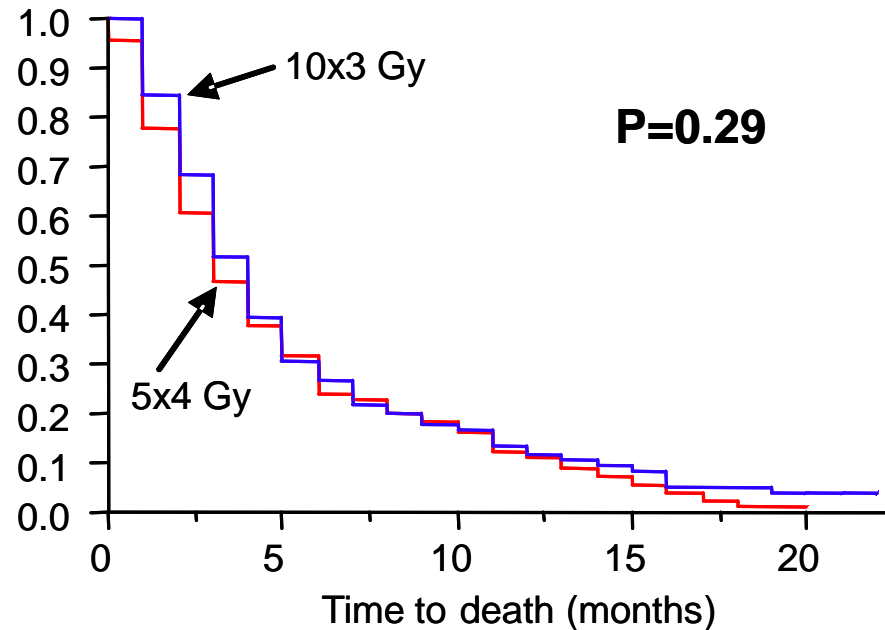
- ♦ 20 x 2 Gy (4 weeks) or 15 x 2.5 Gy (3 weeks)
- ♦ 10 x 3 Gy (2 weeks)

	Overall Survival		p-value
	at 6 months	at 12 months	
10 x 3 Gy (N=257)	33%	20%	
Higher doses (N=159)	29%	18%	0.86

	Local Control		p-value
	at 6 months	at 12 months	
10 x 3 Gy (N=257)	39%	24%	
Higher doses (N=159)	41%	30%	0.61

MULTIPLE LESIONS: FRACTIONATION OF WBRT

- ♦ 10 x 3 Gy (2 weeks)
- ♦ 5 x 4 Gy (1 week)



QUARTZ-TRIAL (N=538)

- ◆ Brain Metastases from NSCLC
- ◆ Phase III non-inferiority trial

	BSC alone	BSC + WBRT
Median OS	57 days	65 days
Mean QALYs	41.4 days	43.3 days

WHY WBRT FOR PATIENTS WITH A POOR SURVIVAL?



Wong J, *et al.*, Int J Radiat Oncol Biol Phys. 2009 Nov 15;75(4):1125-31. (N=129)

Symptom Relief:

- ◆ Headache 41%
- ◆ Discontinuation of Corticosteroids 51%

Komosinska K, *et al.*, Acta Oncol. 2010 Apr;49(3):382-8. (N=91; KPS <70)

Improvement of **Performance Status** 57%

Van Oorschot B, *et al.*, Breast Care (Basel). 2011;6(1):14-19. (Review)

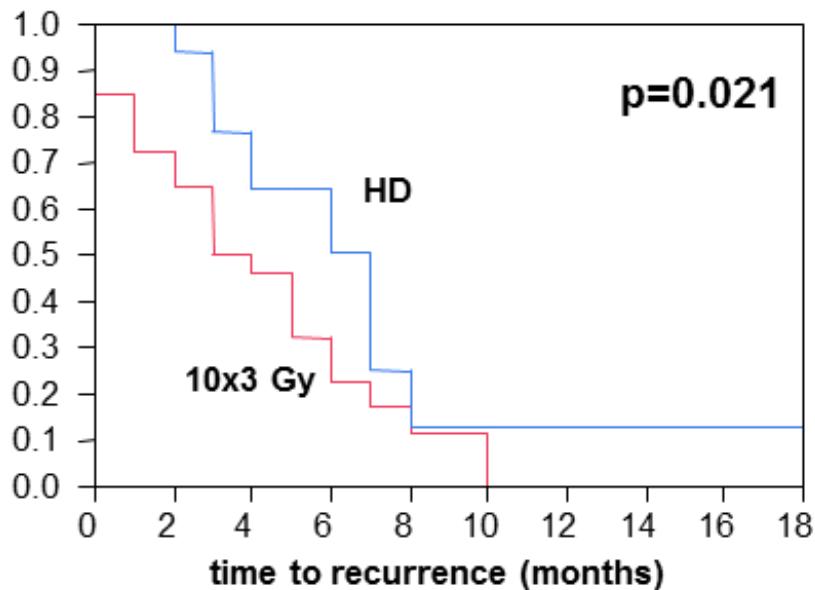
Symptom Relief:

- ◆ Headache 50-70%
- ◆ Cerebral Dysfunction 40-50%
- ◆ Paresis 30-40%

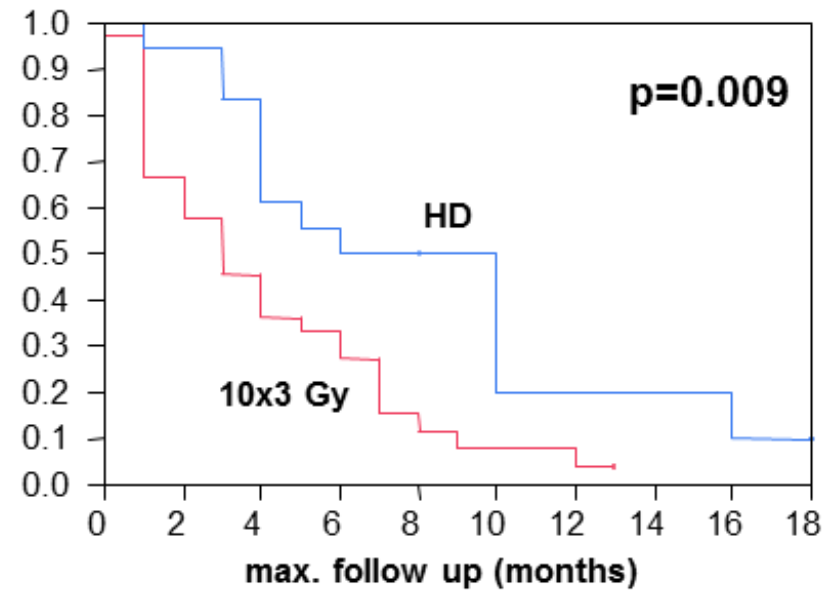
DOSES >30 GY FOR BRAIN METS FROM MELANOMA



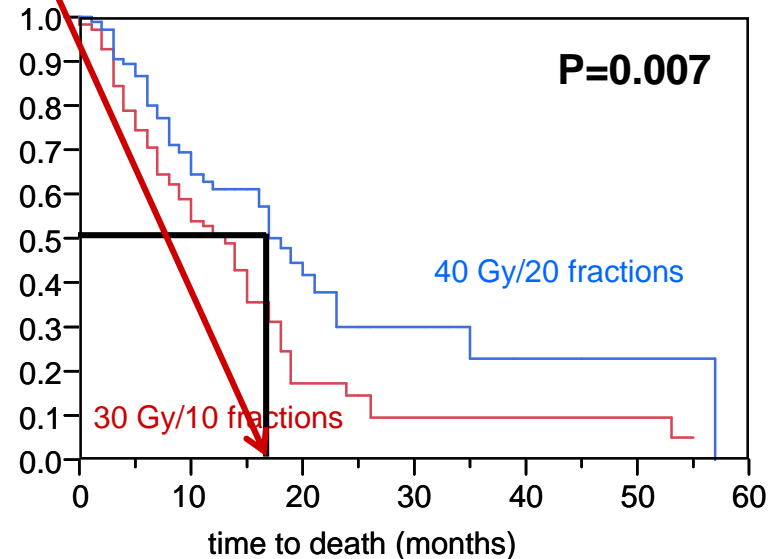
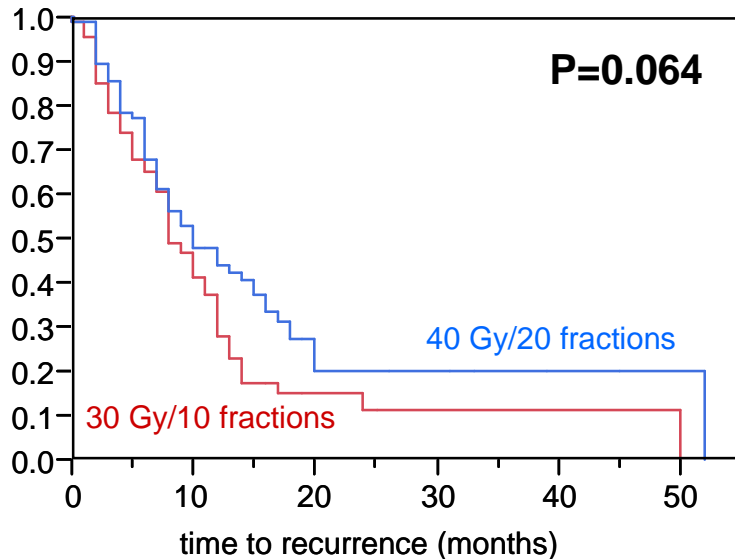
Intracerebral Control



Overall Survival



DOSES >30 GY FOR PATIENTS WITH A MORE FAVOURABLE SURVIVAL PROGNOSIS



RPA-CLASSIFICATION (RECURSIVE PARTITIONING ANALYSIS)

1,200 patients from 3 RTOG trials (WBRT for brain mets.)

- ◆ RTOG 79-16:
 - ◆ 10 x 3 Gy +/- Misonidazole
 - ◆ 6 x 5 Gy +/- Misonidazole
- ◆ RTOG 85-28:
 - ◆ 2 x 1.6 Gy / day
 - ◆ 48.0 Gy vs. 54.4 Gy
 - ◆ 54.4 Gy vs. 64.0 Gy
 - ◆ 64.0 Gy vs. 70.4 Gy
- ◆ RTOG 89-05:
 - ◆ 15 x 2.5 Gy +/- Bromodeoxyuridine

RPA-CLASSIFICATION (RECURSIVE PARTITIONING ANALYSIS)

	RPA I	RPA II	RPA III
Karnofsky PS	≥70	≥70	<70
Age	<65 years	≥65 years	Any
PT controlled	Yes	No	Yes/No
Extracranial mets.	No	Yes	Yes/No
Median OS (months)	7.1	4.2	2.3

RPA-CLASSIFICATION HETEROGENEOUS TREATMENTS



1,200 patients from 3 RTOG trials (WBRT for brain mets.)

- ◆ RTOG 79-16:
 - ◆ 10 x 3 Gy +/- **Misonidazole**
 - ◆ 6 x 5 Gy +/- **Misonidazole**
- ◆ RTOG 85-28:
 - ◆ **2 x 1.6 Gy / day**
 - ◆ 48.0 Gy vs. 54.4 Gy
 - ◆ 54.4 Gy vs. 64.0 Gy
 - ◆ 64.0 Gy vs. 70.4 Gy
- ◆ RTOG 89-05:
 - ◆ 15 x 2.5 Gy +/- **Bromodeoxyuridine**



GPA SCORE (GRADED PROGNOSTIC ASSESSMENT)

1,960 patients from 5 RTOG trials (WBRT for brain mets.)

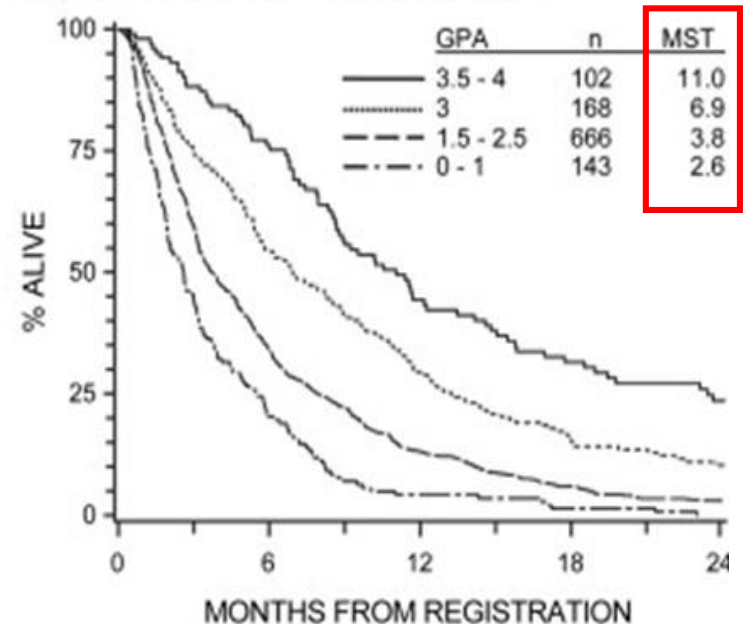
- ◆ RTOG 79-16, RTOG 85-28, RTOG 89-05, RTOG 91-04, RTOG 95-08
- ◆ RTOG 91-04:
 - ◆ 10 x 3 Gy vs. 54.4 Gy (2 x 1.6 Gy / d)
- ◆ RTOG 95-08:
 - ◆ 15 x 2.5 Gy vs. 15 x 2.5 Gy + SRS boost

GPA SCORE (GRADED PROGNOSTIC ASSESSMENT)



	0 points	0.5 points	1 point
Age	>60 yrs	50-59 yrs	<50 yrs
Karnofsky Score	>60	70-80	>80
N metastases	>3	2-3	1
Extracranial mets.	Yes	---	No

GRADED PROGNOSTIC ASSESSMENT





GPA SCORE HETEROGENEOUS TREATMENTS

1,960 patients from 5 RTOG trials (WBRT for brain mets.)

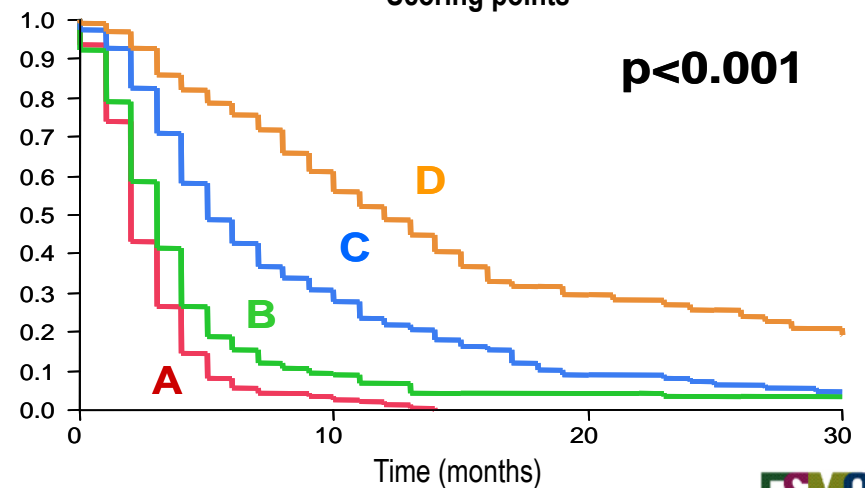
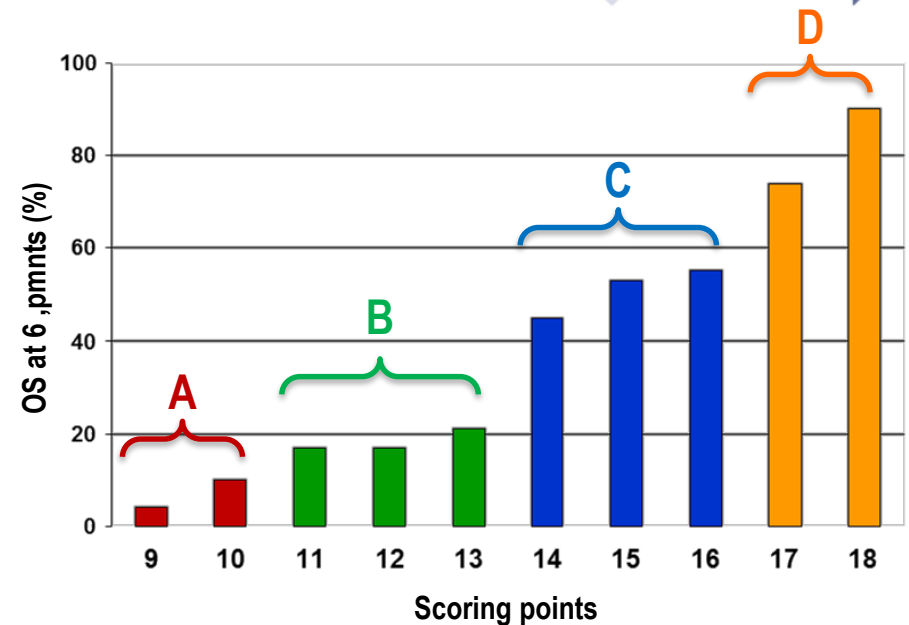
- ◆ **RTOG 79-16, RTOG 85-28, RTOG 89-05, RTOG 91-04, RTOG 95-08**
- ◆ RTOG 91-04:
 - ◆ 10 x 3 Gy vs. 54.4 Gy (**2 x 1.6 Gy / d**)
- ◆ RTOG 95-08:
 - ◆ 15 x 2.5 Gy vs. 15 x 2.5 Gy + **SRS boost**

SURVIVAL SCORE – WBRT ALONE (N=1,085)¹



	Survival at 6 months (%)	Score
Age		
≤ 60 years	43	4
≥ 61 years	25	3
Karnofsky Performance Score		
< 70	8	1
≥ 70	53	5
Extracranial metastases at the time of RT		
No	51	5
Yes	24	2
Interval from tumour diagnosis to WBRT		
≤ 8 months	32	3
> 8 months	36	4

The score has been validated in
350 new patients²



1. Rades D, et al., Strahlenther Onkol 2008;184:251–5. © Urban & Vogel. With permission of Springer;
2. Dziggel L, et al., Strahlenther Onkol. 2013;189:364–6.

DISEASE-SPECIFIC GPA SCORES (DS-GPA)



	Melanoma / Renal Cell Cancer		
Points	0	1	2
KPS	<70	70-80	90-100
N brain mets.	>3	2-3	1

	NSCLC / SCLC		
Points	0	0.5	1
Age	>60	50-60	<50
KPS	<70	70-80	90-100
N brain mets.	>3	2-3	1
Extracranial mets.	Yes	---	No

	Breast Cancer / GI Cancer				
Points	0	1	2	3	4
KPS	<70	70	80	90	100

NEW DS-GPA SCORE FOR BREAST CANCER



	Melanoma / Renal Cell Cancer		
Points	0	1	2
KPS	<70	70-80	90-100
N brain mets.	>3	2-3	1

	NSCLC / SCLC		
Points	0	0.5	1
Age	>60	50-60	<50
KPS	<70	70-80	90-100
N brain mets.	>3	2-3	1
Extracranial mets.	Yes	---	No

	Breast Cancer / GI Cancer				
Points	0	0.5	1	1.5	2
KPS	≤50	60	70-80	90-100	n/a
Subtype	Triple (-)	n/a	HR+, her2-	HR-, her2+	Triple (+)
Age	≥60	<60	n/a	n/a	n/a

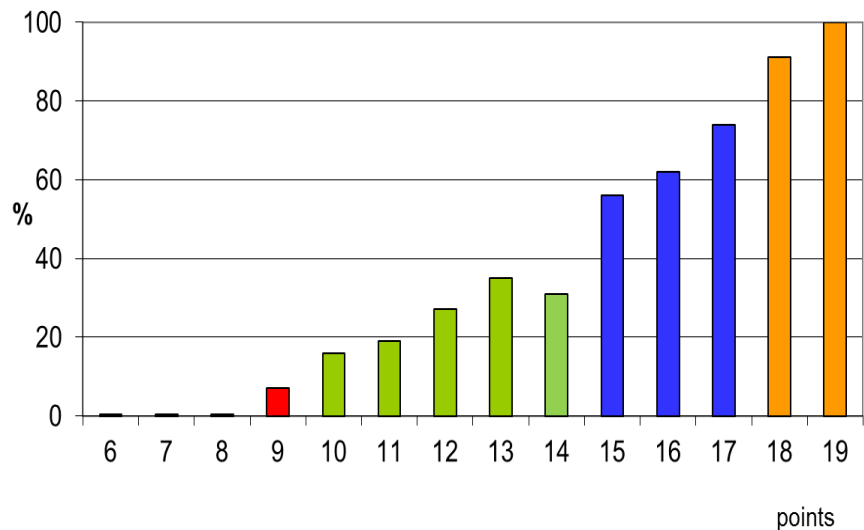
DISEASE-SPECIFIC SCORES: WBRT ALONE

Tumour type	Age	Gender	KPS	N lesions	Extracr. mets.
Breast cancer ¹			X		X
Non-small cell lung cancer ²		X	X		X
Small cell lung cancer ³			X	X	X
Less radiosensitive tumours ⁴	X		X		X
Esophageal cancer ⁵			X	X	X

WBRT-30: WBRT WITH 10X3 GY ALONE (N=882)

- Age, gender, KPS, PT, extracranial mets., N brain mets., interval FD to WBRT, systemic treatment prior to WBRT, controlled PT

	Survival at 6 months (%)	Score (points)
Age		
< 50 years	45	5
51-60 years	42	4
61-70 years	27	3
> 70 years	14	1
Karnofsky Performance Score		
KPS < 70	8	1
KPS = 70	36	4
KPS > 70	60	6
Extracranial metastases		
No	46	5
Yes	24	2
Systemic treatment prior to WBRT		
No	24	2
Yes	33	3



WBRT-30 – TEST GROUP VS. VALIDATION GROUP

Survival at 6 months

	Test group	Valid. group	P
6 - 9 points	4%	3%	0.91
10 - 14 points	29%	28%	0.89
15 - 17 points	62%	54%	0.53
18 - 19 points	93%	96%	0.96

WBRT-30 – COMPARISON TO OTHER SCORES

Positive Predictive Value (PPV)

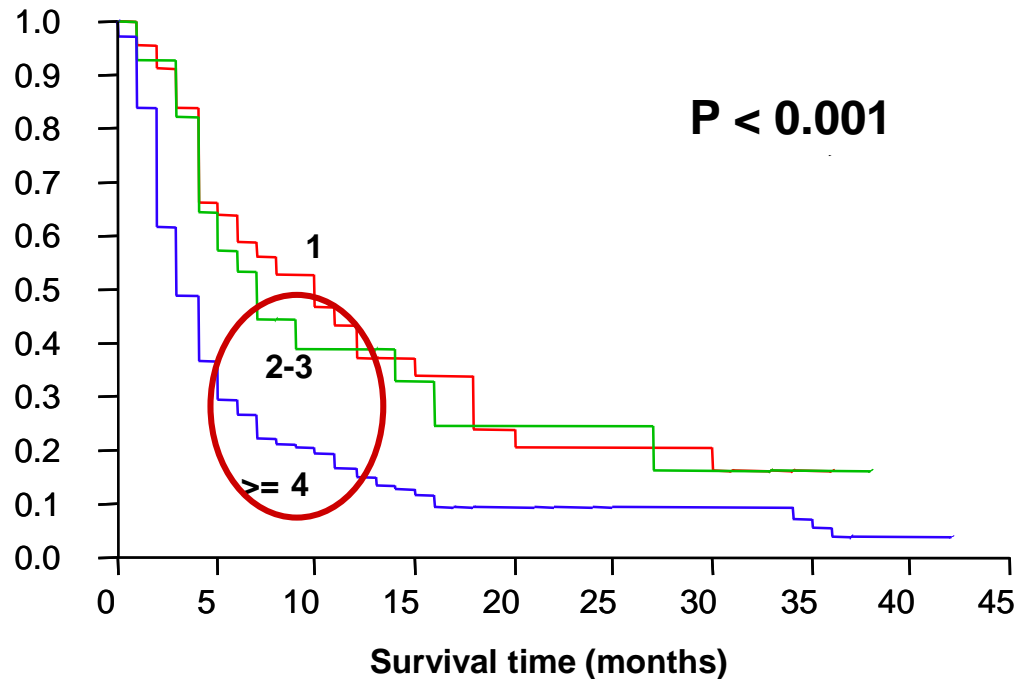
	To die \leq 6 mos.	To live \geq 6 mos.
WBRT-30	97%	96%
RPA	92%	75%
GPA	85%	64%
Rades 2008	96%	73%

WBRT +/- SYSTEMIC AGENTS (PHASE II/III-STUDIES)



Author	N	Agent	Median OS
Verger, 2005	82	Temozolomide	4.5 vs. 3.1 mos. (n.s.)
Mehta, 2003	401	Motexafin-Gd	5.2 vs. 4.9 mos. (n.s.)
Knisely, 2008	183	Thalidomide	3.9 vs. 3.9 mos. (n.s.)
Neuhaus, 2009	96	Topotecan	2.9 vs. 3.1 mos. (n.s.)
Lee, 2014	80	Erlotinib	3.4 vs. 2.9 mos. (n.s.)
Zhuang, 2013	54	Erlotinib	10.7 vs. 8.9 mos. (p=0.02)
[Lin, 2013 (Phase I)]	35	Lapatinib	Feasibility criteria not met (tox.!)]

SURVIVAL PROGNOSIS DEPENDS ON THE NUMBER OF BRAIN METASTASES



Patients with a limited number of brain metastases may benefit from

Local Treatments

(Resection, Stereotactic Radiosurgery, Fractionated Stereotactic RT)

NEUROSURGICAL RESECTION: PROS AND CONS

Pros:

1. Immediate mass reduction
(in particular for lesions >3 cm not suitable for SRS)
2. Confirmation of diagnosis (~5% of brain primaries = secondary tumours)
(new technologies reduce mortality to <2%, morbidity to <8%)

Cons:

1. Surgery (particularly in the posterior fossa) may cause leptomeningeal spread
[van der Ree, JNNP 1999, Siomin, JNO 2004]
2. Craniotomy = invasive, entails significant risks
3. Not suitable for all locations (brain stem etc.)
4. **Improved OS only, if all metastases are removed => 1 lesion (2 lesions)**

STEREOTACTIC RADIOSURGERY (SRS)



Rationale for SRS vs. Neurosurgical Resection:

1. Treatment of multiple lesions in one session
 2. Treatment of surgically inaccessible lesions (e.g. brain stem);
- ◆ Fuentes, Neurosurgery 2006
 - ◆ 92% LC of brain stem mets, only 2/16 patients died due to brain stem problems
“argument pro Surgery”: Rapid relief of symptoms, **however**: Hoshi, J Urol 2002: rapid relief in 80% of 42 RCC patients after GK-RS

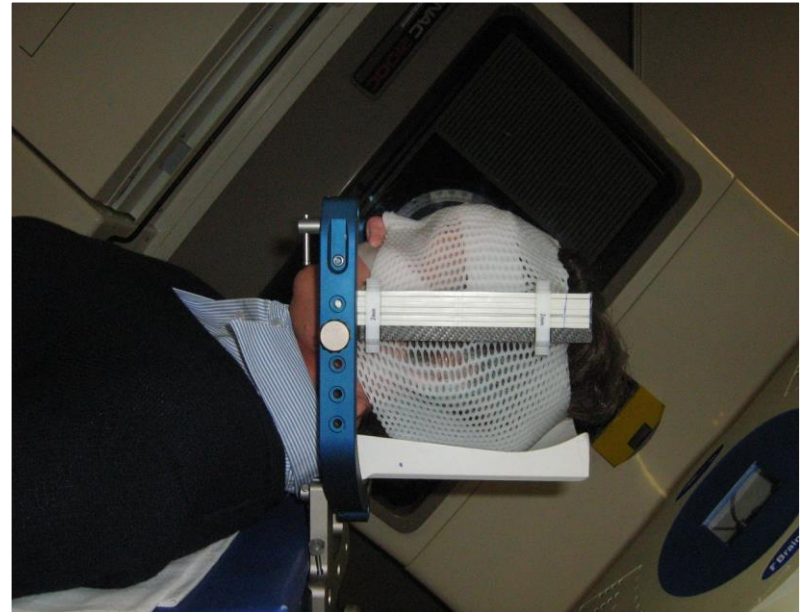
STEREOTACTIC RADIOSURGERY (SRS): LIMITATIONS



- ◆ **Large Metastases** (>4 cm)
and/or
- ◆ **Brain Stem Lesions** (small therapeutic ratio)

Solution: Fractionated Stereotactic RT

- ◆ => 3-7 fractions
- ◆ Better therapeutic ratio (EQD2)
- ◆ Non-invasive fixation
- ◆ Lesions >4 cm
- ◆ Local control (1 yr.) 75-85%
- ◆ Acute-toxicity $\leq 5\%$
- ◆ Late-toxicity $\leq 3\%$



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RATIONALE FOR SRS / FSRT VS. WBRT



Rationale for SRS / FSRT vs. WBRT:

1. Steep dose gradient: High dose to lesions, sparing of normal tissues
2. Higher dose per fraction => higher biological effective dose => higher tumour cell killing potential

RATIONALE FOR SRS / FSRT VS. WBRT

$EQD2 = GD \times [(ED + \alpha/\beta) / (2 \text{ Gy} + \alpha/\beta)]$ for tumour cell kill

Fractionation	EQD2
10 x 2 Gy = 20 Gy	20 Gy
1 x 20 Gy = 20 Gy (1x20 Gy \approx 3x10 Gy)	50 Gy

} x 2.5

1-3 METASTASES (RPA 1-2): SRS VS. WBRT



	Overall Survival		p-value
	at 6 months	at 12 months	
WBRT (N=91)	59%	33%	
SRS (N=95)	68%	52%	0.045

	Intracerebral Control		p-value
	at 6 months	at 12 months	
WBRT (N=91)	55%	23%	
SRS (N=95)	74%	49%	0.005

	Local Control		p-value
	at 6 months	at 12 months	
WBRT (N=91)	57%	26%	
SRS (N=95)	84%	64%	<0.001

1-4 METASTASES: WBRT+SRS VS. SRS ALONE



	Design	Patients	1-year overall survival	1-year local control	1-year cerebral control
Aoyama, JAMA 2006	RCT	SRS SRS+WBRT (N=132)	8% 39% (P=0.42)	70% 86% (P=0.019)	24% 53% (P<0.001)
Rades, STO 2008	Retrospective	SRS SRS+WBRT (N=144)	53% 56% (P=0.24)	66% 87% (P=0.003)	51% 66% (P=0.015)
Kocher, JCO 2011	RCT	SRS SRS+WBRT (N=199)		~71% ~84% (P=0.040)	~57% ~70% (P=0.023)*

*new sites

1 LESION: RESECTION + WBRT VS. RESECTION



	Design	Patients	Overall Survival	Local Control	Cerebral Control
Patchell, JAMA 1998	RCT	Resection Res. + WBRT (N=95)	Median ~11 mos. ~11 mos. (n.s.)	At 1 year 54% 90% (P<0.001)	At 1 year 30% 82% (P<0.001)
Smalley, IJROBP 1987	Retrospect.	Resection Res. + WBRT (N=85)	Median 11.5 mos. 23 mos. (P<0.05)	at 1 year 15% 79% (P<0.05)	

SRS / FSRT FOLLOWING RESECTION



Single-arm Studies¹

- ◆ Local Control at 1 year: 71 - 93%
- ◆ **New Brain Metastases at 1 year: 39 - 64%**
- ◆ Overall Survival at 1 year: 50 - 69%

Comparative Study (N = 132)²: Surgery +WBRT +SRS

- ◆ Local Control at 1 year: 83% 74%
- ◆ **New Brain Metastases at 1 year: 30% 52%**
- ◆ Overall Survival at 1 year: 56% 55%

1. Robbins JR, *et al.*, 2012, Neurosurgery. 2012 Nov;71(5):937-43; Steinmann D, *et al.*, J Cancer Res Clin Oncol. 2012 Sep;138(9):1523-9; Connolly RP, *et al.*, Neuro Oncol. 2013 May;15(5):589-94; Minniti G, *et al.*, Int J Radiat Oncol Biol Phys. 2013 Jul 15;86(4):623-9; Ahmed KA, *et al.*, Neurooncol. 2014 May;118(1):179-86; Ling DC, *et al.*, Neurosurgery. 2015 Feb;76(2):150-6.

2. Patel KR, *et al.*, J Neurooncol. 2014 Dec;120(3):657-63.

NEURO-COGNITIVE DEFICITS FOLLOWING WBRT

- ◆ Chang EL, *et al.*, Lancet Oncol. 2009 Nov;10(11):1037-44. [N=58]
 - ◆ SRS vs. WBRT + SRS
 - ◆ Neuro-cognitive Deficits at 4 mos. 24% vs. **96%** (p<0.001)
 - ◆ Intracerebral Control at 12 mos. 27% vs. **73%** (p<0.001)

- ◆ Aoyama H, *et al.*, Int J Radiat Oncol Biol Phys. 2007 Aug 1;68(5):1388-95.
 - ◆ WBRT + SRS vs. SRS
 - ◆ N=132 (total); N=92 (Follow up of MMSE)

	Preservation of neuro-cognitive function (MMSE ≥27)		
	12 mos.	24 mos.	36 mos.
WBRT + SRS	79%	79%	23%
SRS	53%	43%	43%

NCCTG N0574 (ALLIANCE): PHASE III TRIAL (N=213)

WBRT + SRS vs. SRS alone for 1-3 brain metastases (<3 cm)

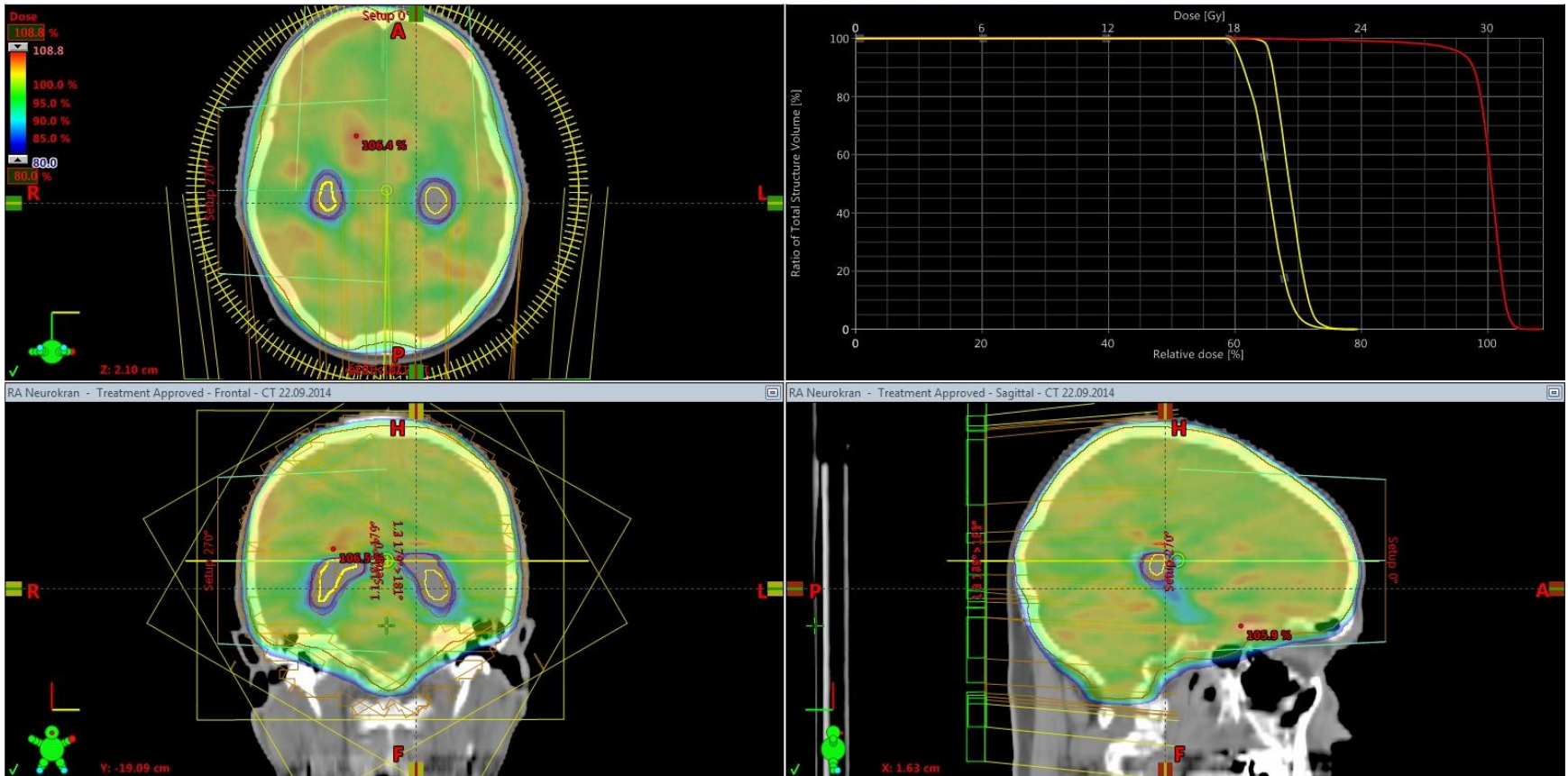
	WBRT+SRS	SRS alone	P
Cognitive Deterioration at 3 mos.	91.7%	63.5%	<0.001
Deterioration in Immediate Recall	30.4%	8.2%	0.004
Deterioration in Delayed Recall	51.1%	19.7%	<0.001
Deterioration in Verbal Fluency	18.6%	1.9%	0.01
Intracranial Progression at 6 mos.	11.6%	35.3%	<0.001
Intracranial Progression at 12 mos.	15.0%	49.5%	<0.001

LATE TOXICITY: WBRT+SRS VS. SRS ALONE



	WBRT+SRS	SRS alone	P
Brain Necrosis	5%	1%	0.32
Leukoencephalopathy	11%	3%	0.16
Any Late Toxicity	17%	7%	0.19

HIPPOCAMPAL SPARING



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HIPPOCAMPAL SPARING

- ◆ **RTOG 0933; N=113** (42 analyzable at 4 months)
- ◆ Hopkins Verbal Learning Test - Revised Delayed Recall (HVLT-R DR)
- ◆ Decline from baseline to 4 months
- ◆ **7%** with hippocampus sparing vs. **30%** historical control ($p < 0.001$)

Gondi V, *et al.*, J Clin Oncol 2014 Dec 1;32(34):3810-6.

Australian Experience

- ◆ 30 patients (26 with melanoma) with a total of 73 brain metastases
- ◆ 80% of evaluable metastases controlled (mean follow up = 3.5 months)
- ◆ Median survival = 9.4 months, 1 patient with grade 4 toxicity

Awad R, *et al.*, Radiat Oncol 2013 Mar 18;8:62.

MEMANTINE: RTOG 0614 (N=508)



- ◆ WBRT: 37.5 Gy in 15 fractions
- ◆ Memantine (20 mg/d, starting 3 days prior to WBRT for 24 weeks) vs. placebo
- ◆ Hopkins Verbal Learning Test - Revised for Delayed Recall (HVLТ-R DR) plus other instruments
- ◆ **Decline in Delayed Recall at 24 weeks** (N=149): 54% vs. 65% (p=0.059)
- ◆ Decline in Delayed Recognition at 24 weeks: 2% vs. 13% (p=0.002)

DISTANT BRAIN METS FOLLOWING SRS ALONE (N=214)

Number of brain metastases

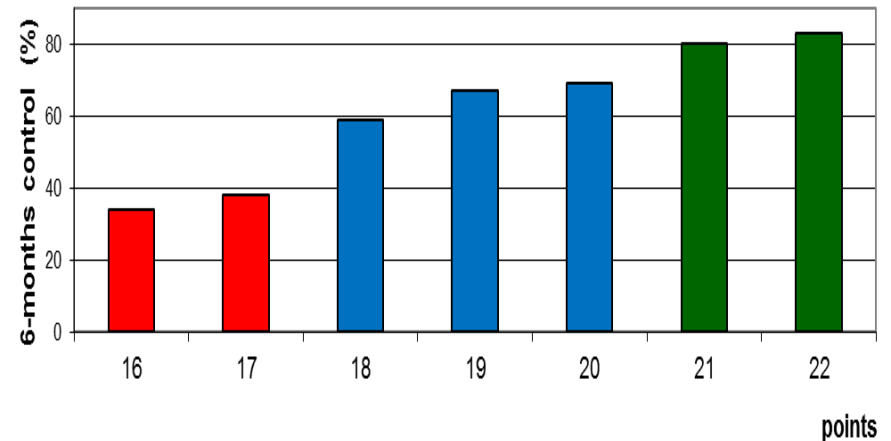
- ◆ N=1 70% 7 points
- ◆ N=2-3 48% 5 points

Extracranial metastases

- ◆ No 69% 7 points
- ◆ Yes 56% 6 points

Primary tumour type

- ◆ Breast cancer 80% 8 points
- ◆ NSCLC 67% 7 points
- ◆ Melanoma 54% 5 points
- ◆ Others 57% 6 points



16-17 points 36%

18-20 points 65%

21-22 points 80%

1-3 METS: RESECTION+WBRT VS. WBRT+SRS

	Design	Patients	Survival at 1 year	Local control at 1 year	Brain control at 1 year
O'Neill et al. IJROBP, 2003	Retrospect.	Res. + WBRT: 74 WBRT + SRS: 23	62% 56% (P=0.15)	42% 100% (P=0.020)	
Rades et al. EJC, 2009	Matched pairs	Res. + WBRT: 52 WBRT + SRS: 52	41% 56% (P=0.08)	66% 87% (P=0.021)	47% 66% (P=0.13)

RESECTION + WBRT ± BOOST (RPA 1-2)

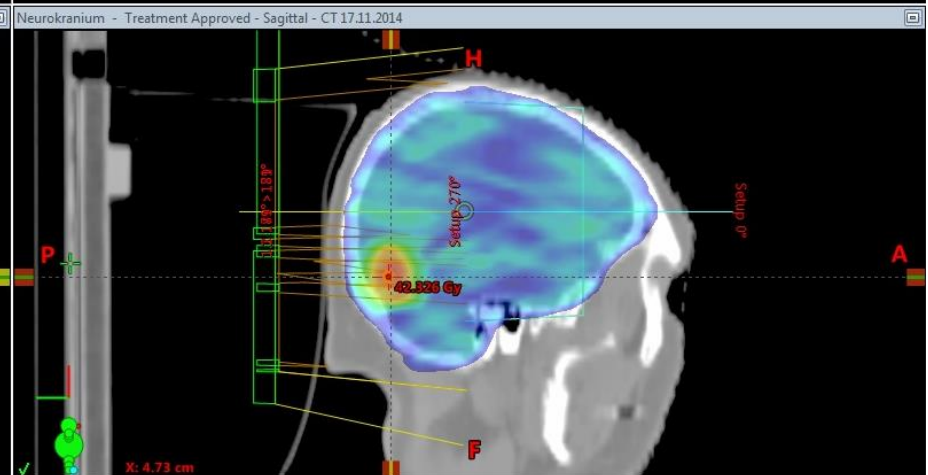
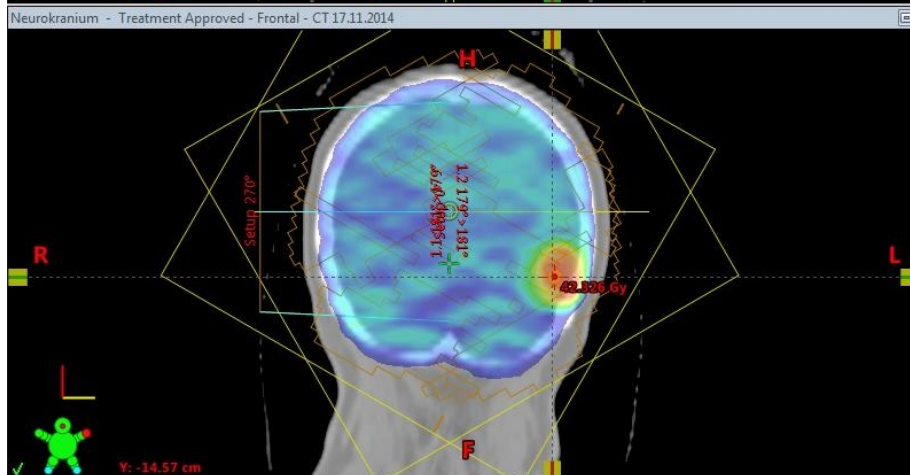
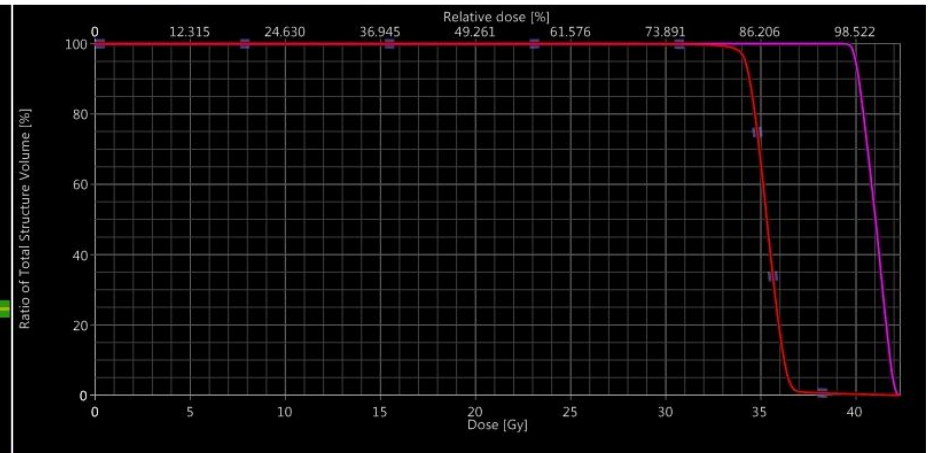
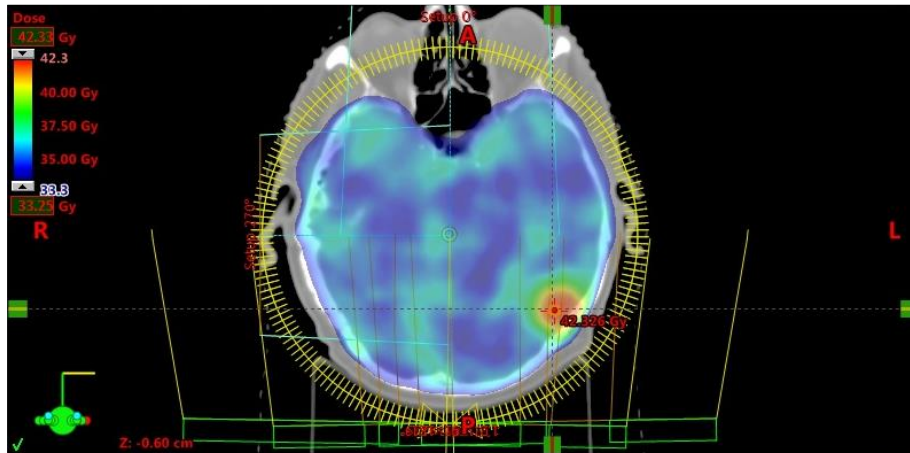


	Overall Survival		p-value
	at 6 months	at 12 months	
S+WBRT (N=99)	59%	41%	
S+WBRT+Boost (N=102)	82%	66%	<0.001

	Intracerebral Control		p-value
	at 6 months	at 12 months	
S+WBRT (N=99)	66%	43%	
S+WBRT+Boost (N=102)	81%	71%	<0.001

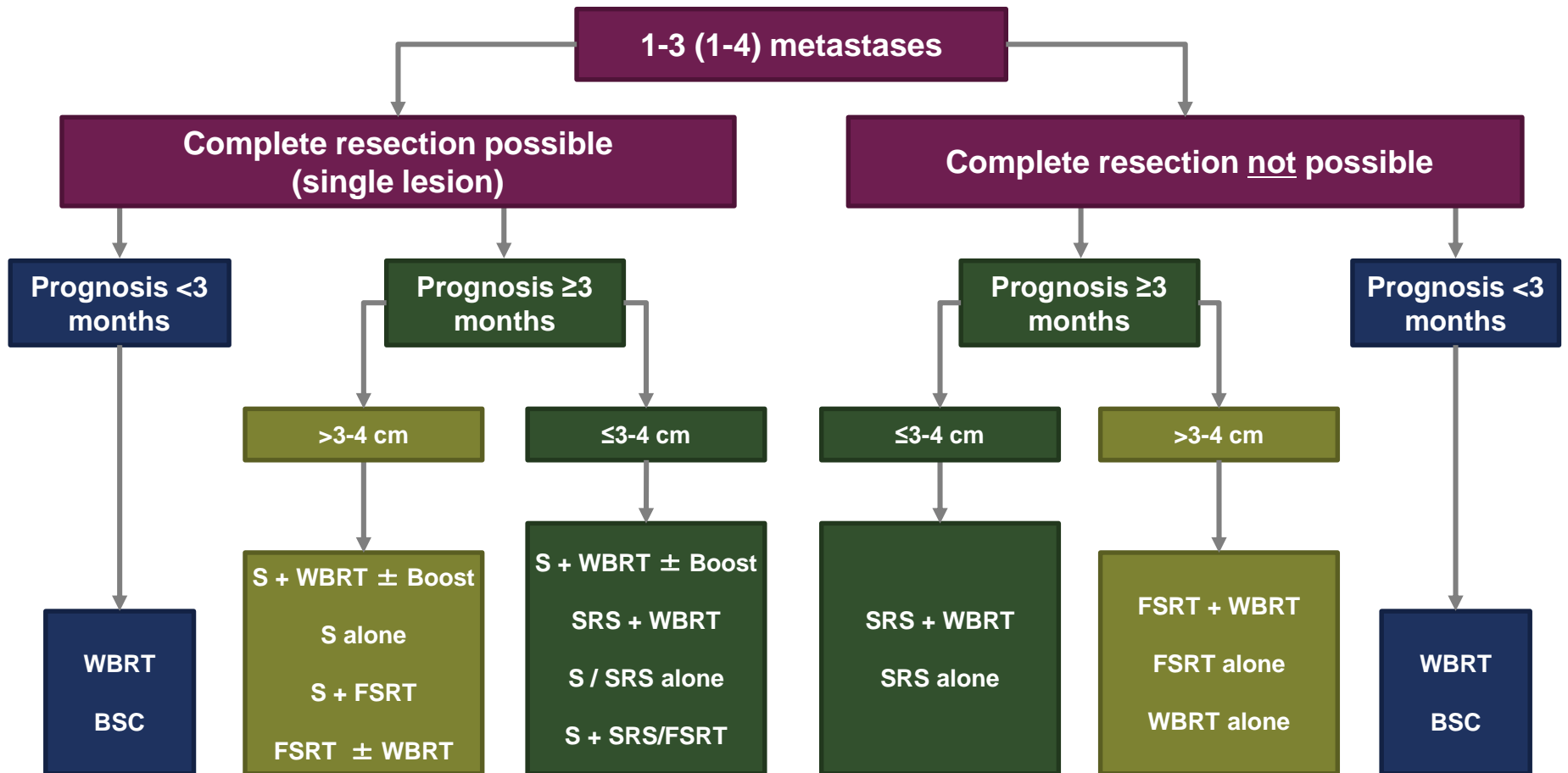
	Local Control		p-value
	at 6 months	at 12 months	
S+WBRT (N=99)	75%	54%	
S+WBRT+Boost (N=102)	86%	78%	<0.001

SIMULTANEOUS INTEGRATED BOOST (SIB)



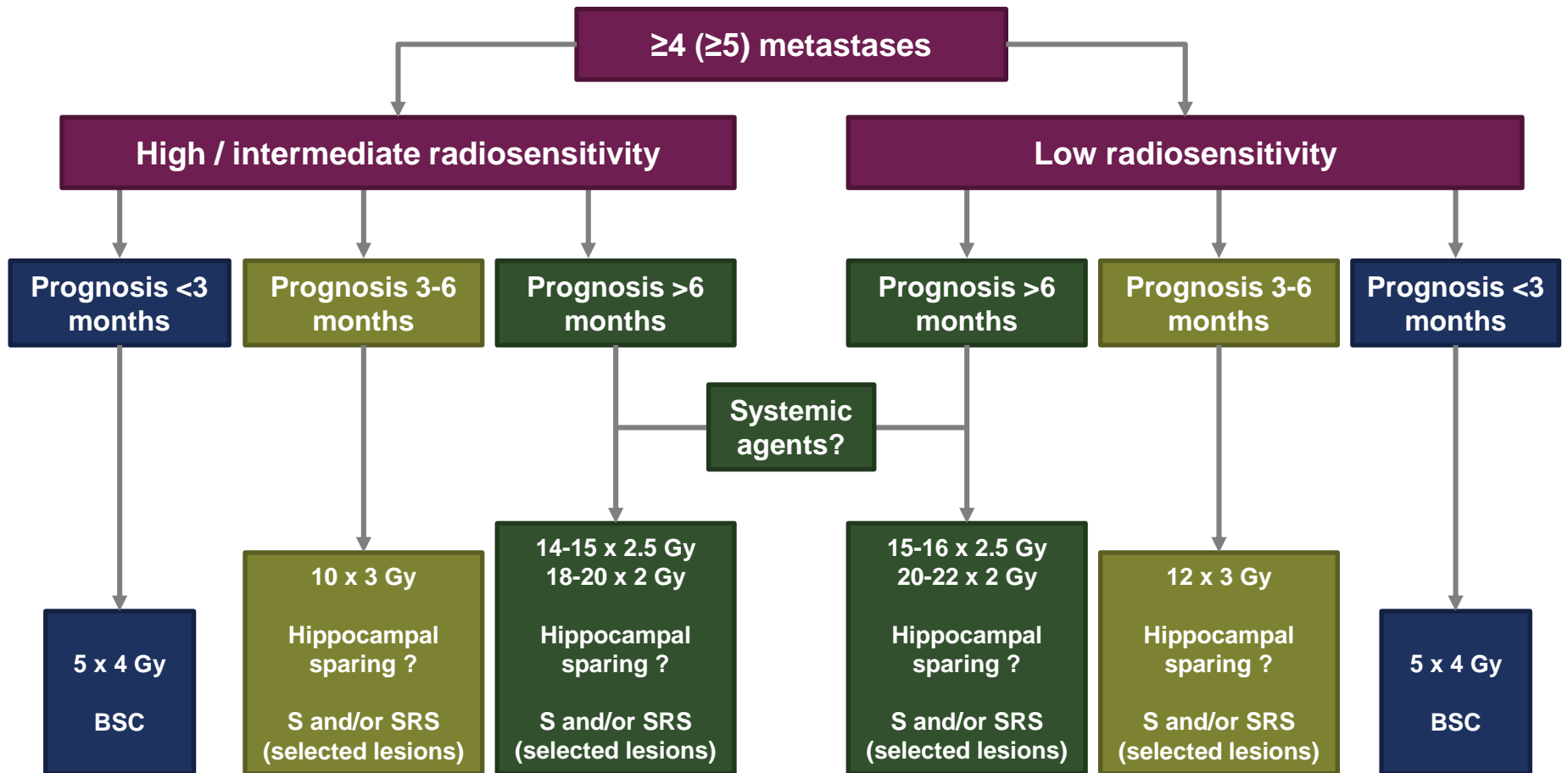
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Algorithm for treatment of 1-3 (1-4) brain metastases



Abbreviations: BSC = best supportive care; FSRT = fractionated stereotactic radiotherapy; S = surgery; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy

Algorithm for treatment of ≥ 4 (≥ 5) brain metastases



Abbreviations: BSC = best supportive care; S = surgery; SRS = stereotactic radiosurgery



Thank you!