Patients with more than five brain metastases: is radiosurgery a reasonable approach?

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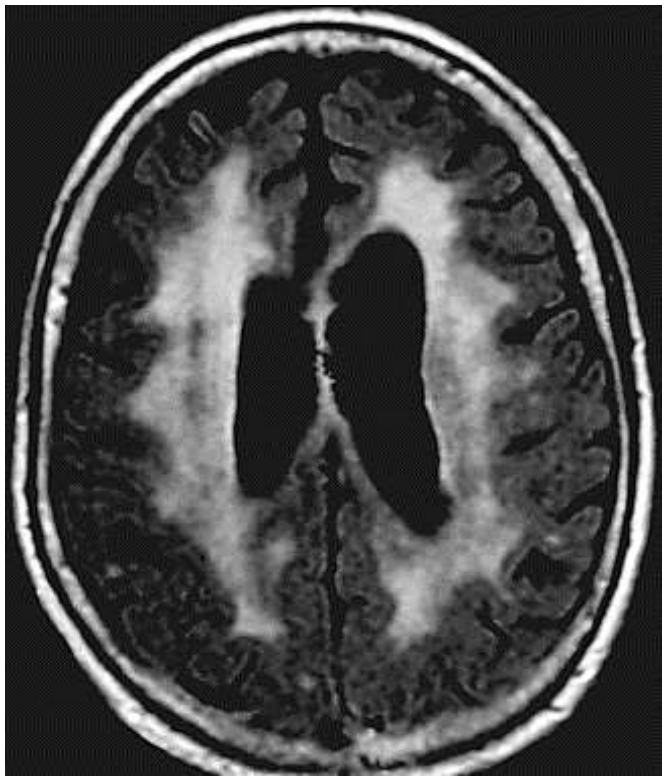
Disclosure: honoraria fees from BrainLab, Elekta, ABBVIE

Milano, 2019

✓ *Outline*

- *SRS for brain metastases*
- *How many metastases can be treated with SRS?*
- *Optimal dose/fractionation*
- *New SRS techniques for multiple brain metastases*

✓ *Whole Brain Radiation Therapy*



Late toxicity

Radiation necrosis

Normal pressure hydrocephalus, causing cognitive, gait and bladder dysfunction

Neuroendocrine dysfunction

Cerebrovascular disease

Gamma Knife SRS

Gamma radiation from Cobalt-60 source

Use multiple beams (4-18 mm)

Fixed frame SRS

High conformality

Accuracy 0.5-1mm

CyberKnife SRS

Industrial robot arm with 6MV X-band linac

Use 100-2000 non-isocentric beams

Frameless SRS/FSRS

High conformality

Accuracy 0.5-1mm

X-ray 6D IGRT

LINAC-based SRS

High-energy X-ray from LINAC

Use shaped beams or dynamic arcs

Frameless SRS/FSRS

High conformality

Accuracy 0.5-1mm

CBCT/ ExacTrac X-Ray

6D IGRT

✓ *The addition of WBRT to SRS/Surgery has never been shown to not improve OS*

Authors	*Arms*	*mOS*	*P value*
Patchell, 1998	*Surgery*	9.9	0.39
	Surgery + WBRT	11.1	
Kocher, 2011	*SRS/Surgery*	10.9	0.89
	SRS/Surgery + WBRT	10.7	
Aoyama, 2006	*SRS*	8.0	0.42
	SRS + WBRT	7.5	
Chang, 2009	*SRS*	15.2	0.003
	SRS + WBRT	5.7	
Brown, 2016	*SRS*	10.4	0.92
	SRS + WBRT	7.4	

Recommendations

- *Don't routinely add adjuvant WBRT to SRS for limited brain metastases*
- *Randomized studies have demonstrated no OS benefit*
- *The addition of WBRT to SRS is associated with diminished cognitive function and worse-patient fatigue and QOL*
- *Surveillance and judicious salvage allows patients to enjoy the highest QOL without a detriment in functional status and OS*

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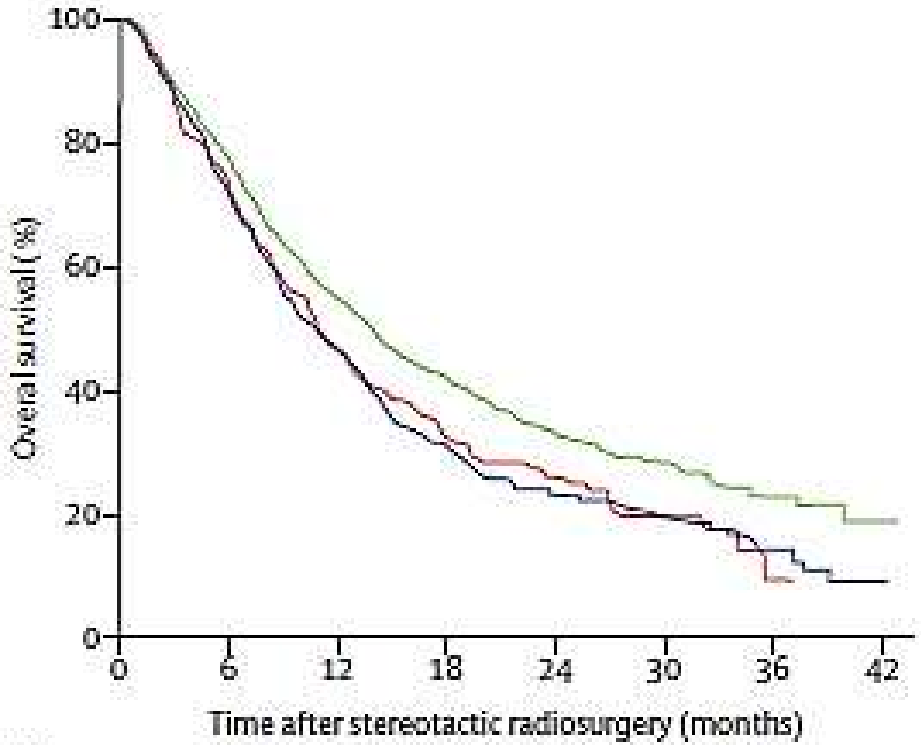
Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78

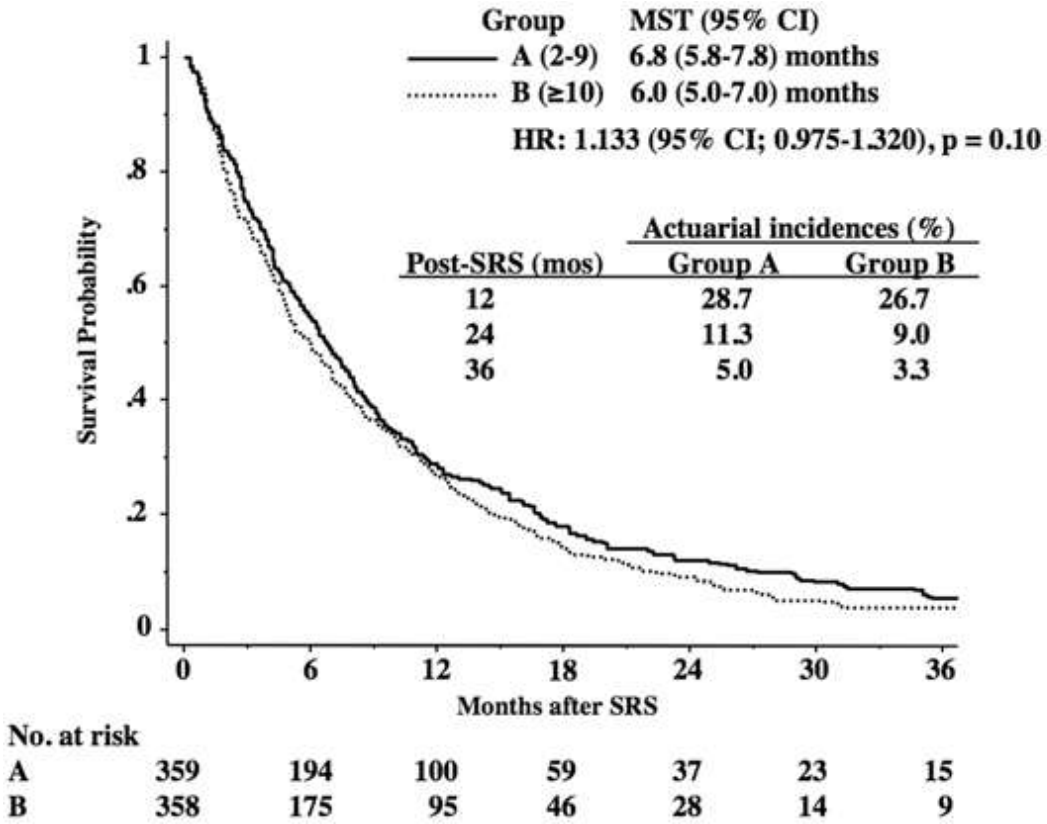


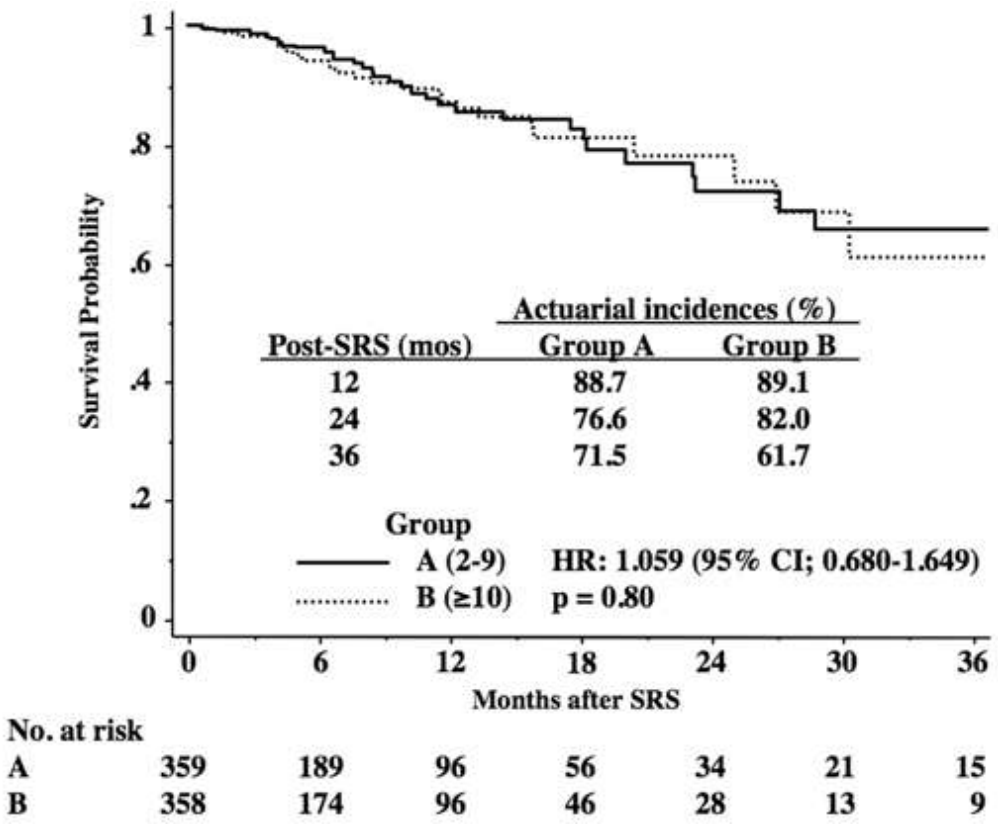
Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

Yamamoto et al, Lancet Oncol 2014; 15: 387–95

Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2–9 versus 10 or more tumors

Yamamoto M et al.





J Neurosurg (Suppl 2) 121:16–25, 2014

Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2–9 versus 10 or more tumors

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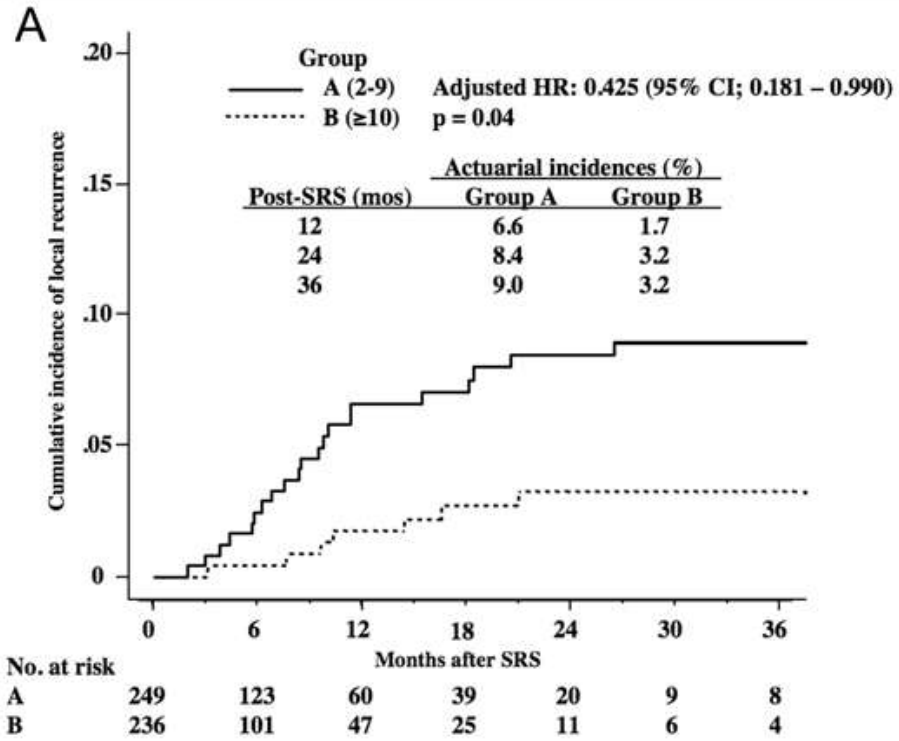

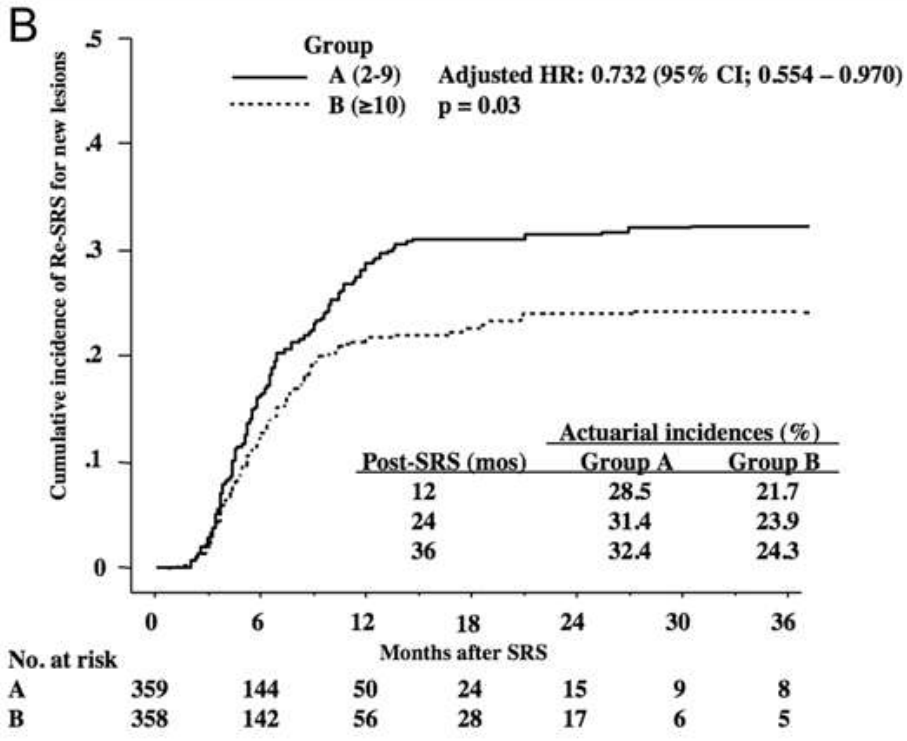

J Neurosurg (Suppl 2) 121:16–25, 2014

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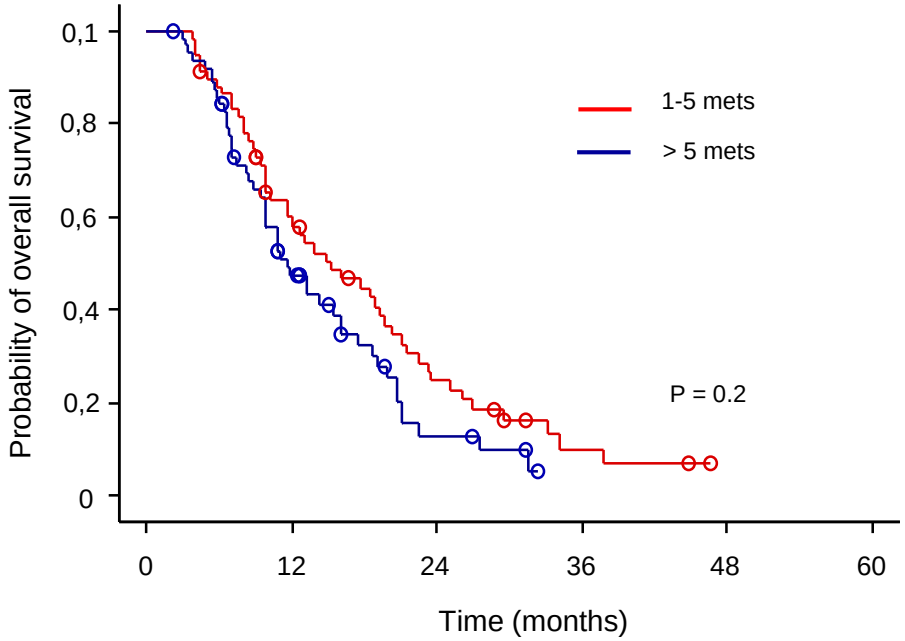
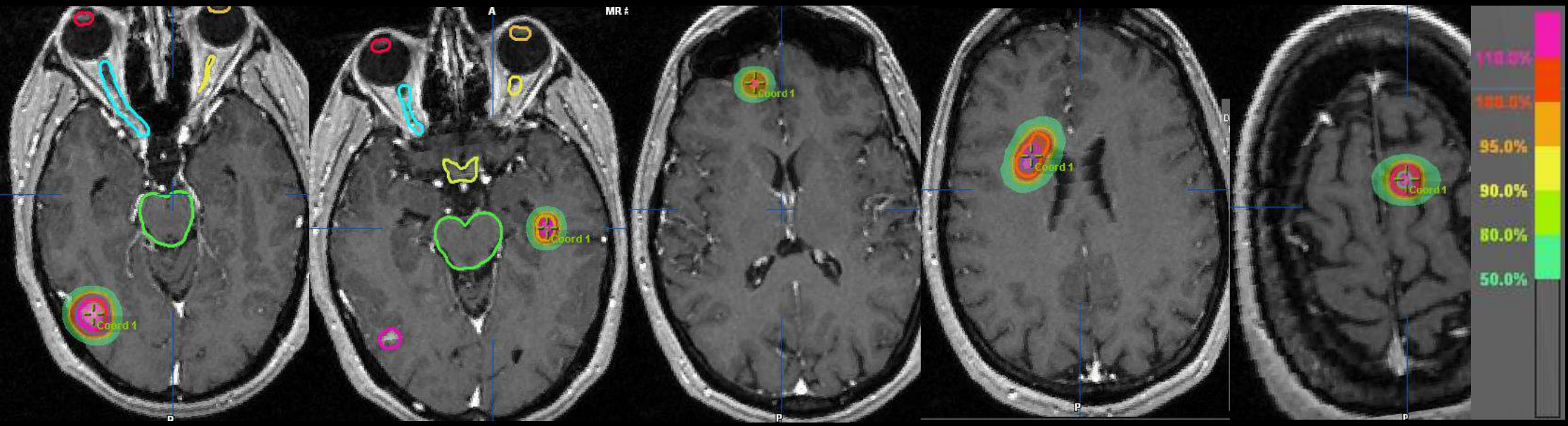
✓ *Patients treated for BM at UPMC San Pietro FBF January 2015 - June 2018*

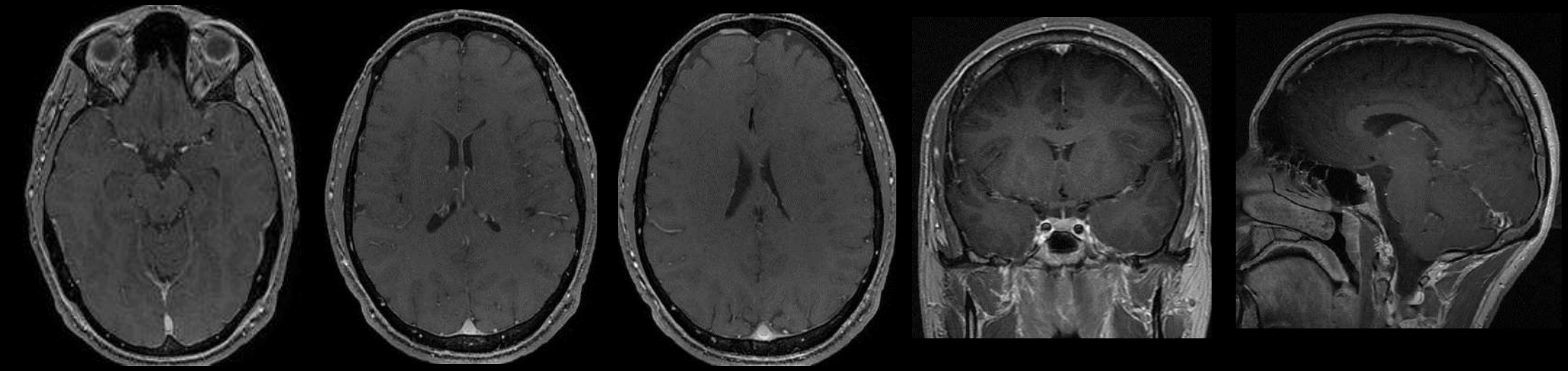
- *263 patients with 1274 brain mets*

- *1 met (n= 61)*
- *2-5 mets (n= 117)*
- *6-10 mets (n= 60)*
- *> 10 mets (n= 25)*



Treatment planning in a patient with 6 mets treated with SRS





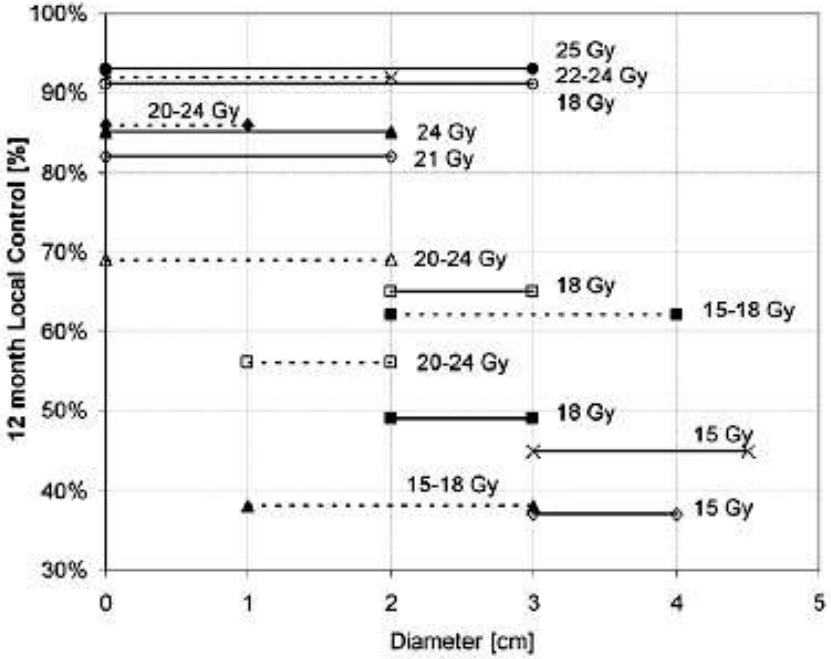
24-month post- SRS MRI

✓ *Outline*

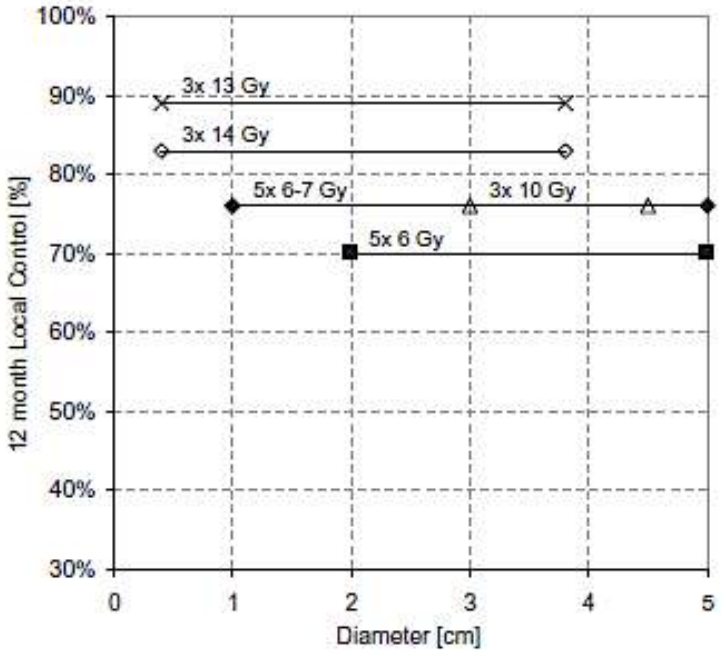
- *SRS for brain metastases*
- *How many metastases can be treated with SRS?*
- *Optimal dose/fractionation*
- *New SRS techniques for multiple brain metastases*

Dose–effect relation in stereotactic radiotherapy for brain metastases. A systematic review

*RS data**



*mf-RS data**

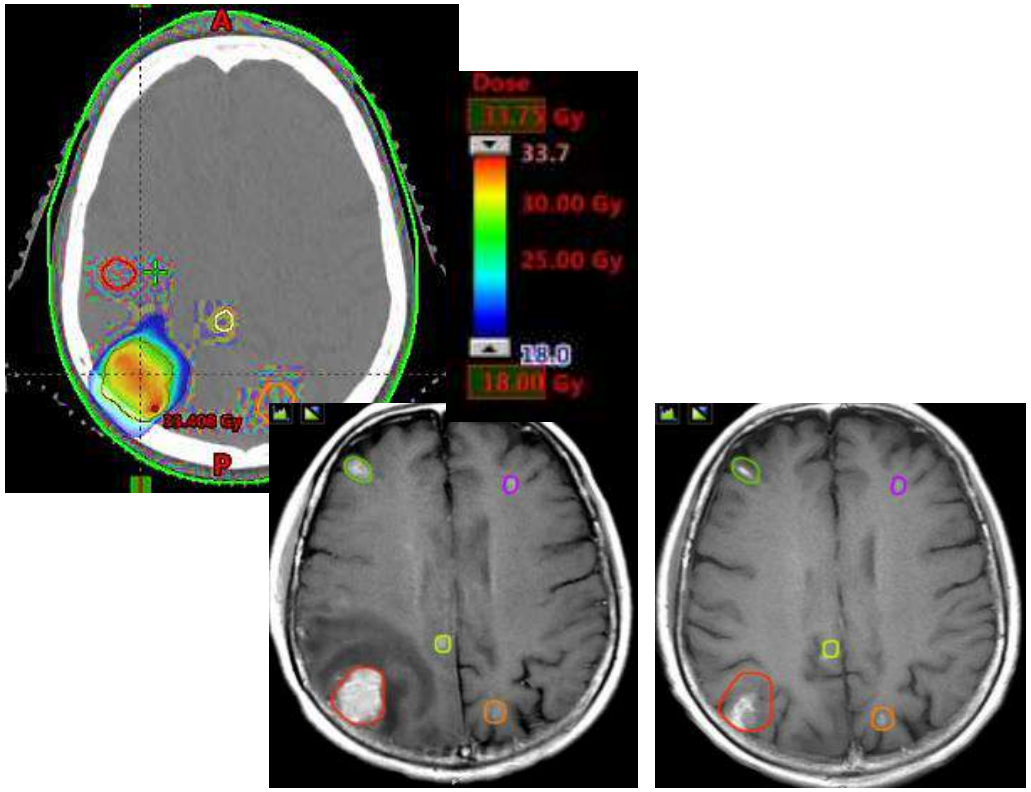


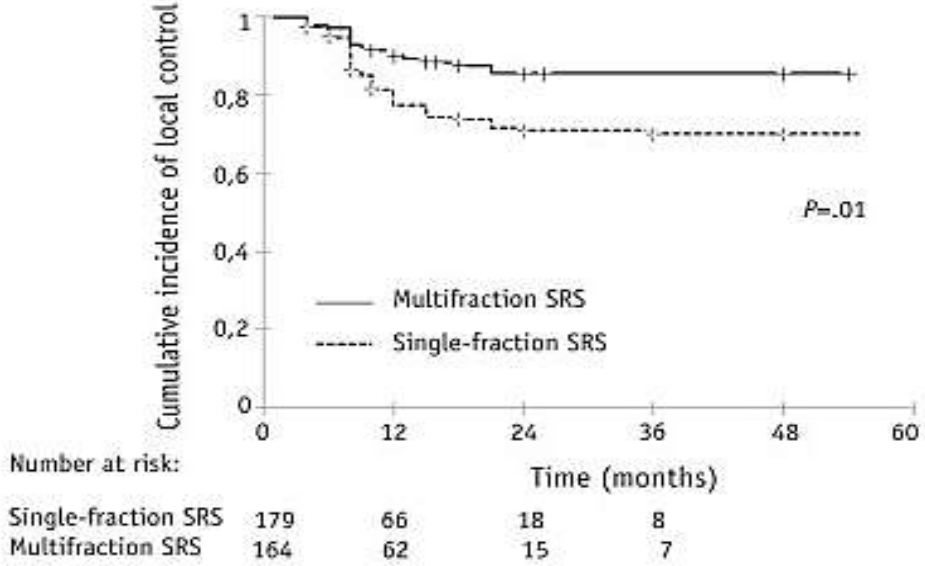
**12 months*

11 selected publications

Wiggenraad 2011

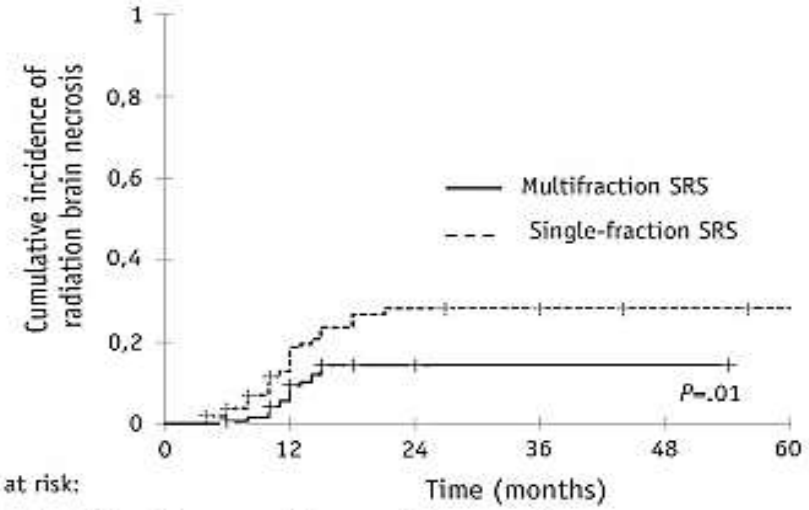
Single-fraction vs multi-fraction SRS





Number at risk:

Single-fraction SRS	179	66	18	8
Multifraction SRS	164	62	15	7



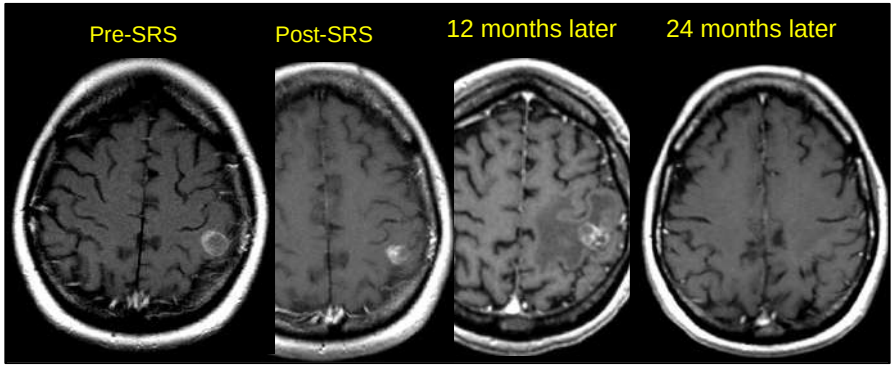
Number at risk:

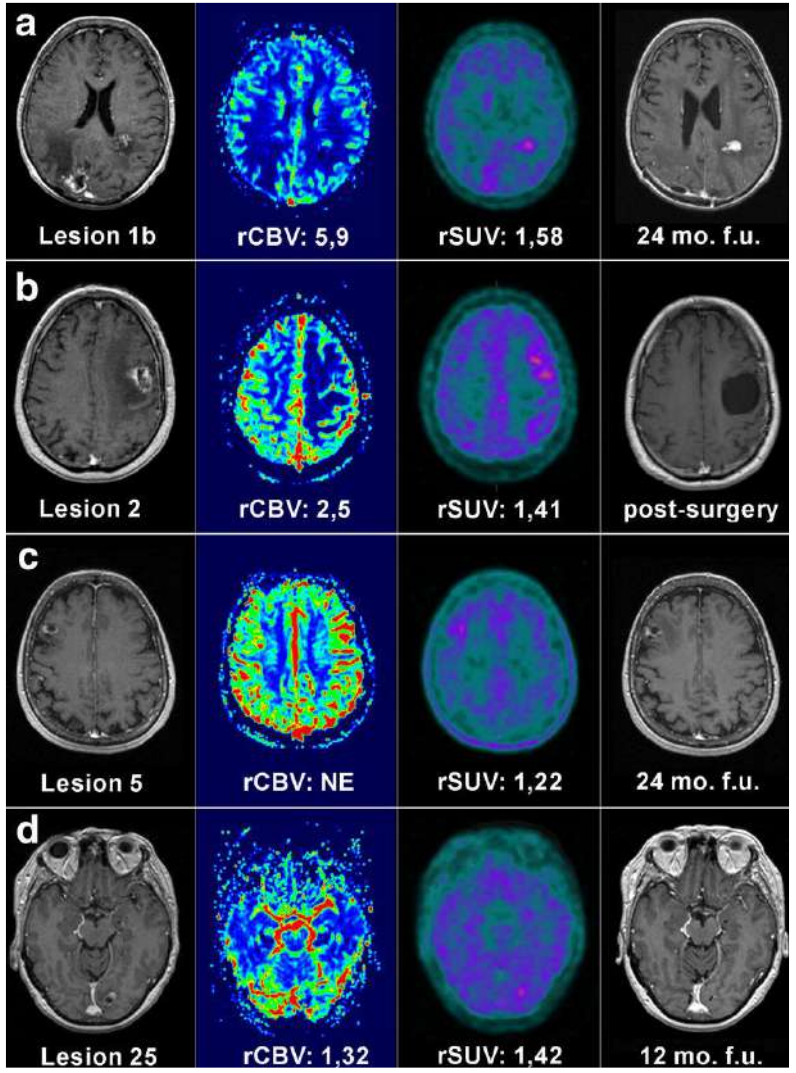
Single-fraction SRS	179	64	17	6
Multifraction SRS	164	60	14	5

Minniti et al., IJROBP 2016

Accuracy of F-DOPA PET and perfusion-MRI for differentiating radionecrotic from progressive brain metastases after radiosurgery

Francesco Cicone · Giuseppe Minniti · Andrea Romano · Annalisa Papa · Claudia Scaringi · Francesca Tavanti · Alessandro Bozzao · Riccardo Maurizi Enrici · Francesco Scopinaro





Semiquantitative PET parameter	AUC	Asymptotic significance	Standard error	95 % Confidence interval		Best differentiating cut-off value	Sensitivity (%)	Specificity (%)	Accuracy (%)
				Lower limit	Upper limit				
$SUVL_{max}/Bkgr_{max}$ (rSUV)	0.924	0.0001	0.065	0.798	1	1.59	93.3	90.9	91.9
rCBV	0.808	0.002	0.079	0.653	0.962	2.14	86.7	68.2	75.6

✓ *Outline*

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- *How many metastases can be treated with SRS?*
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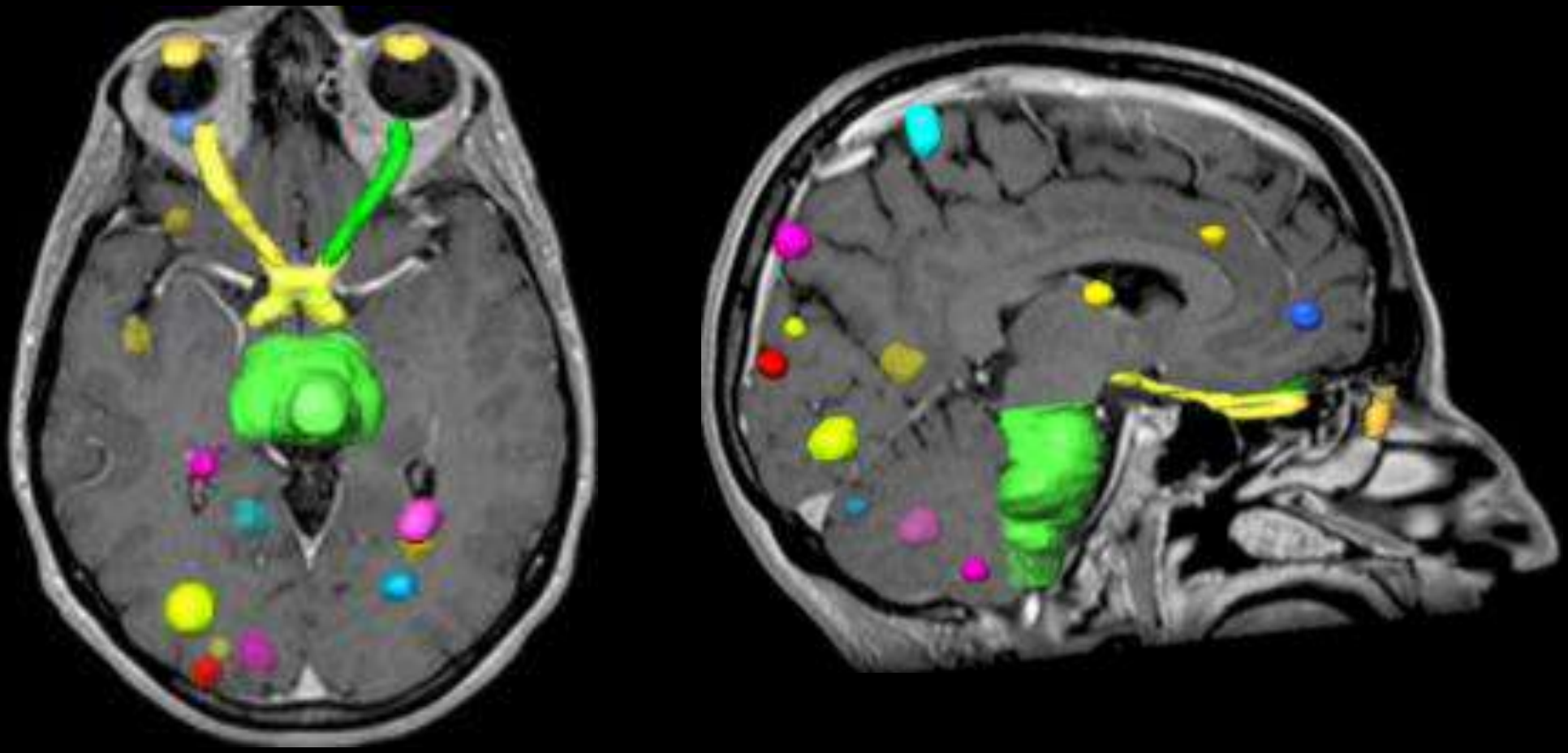
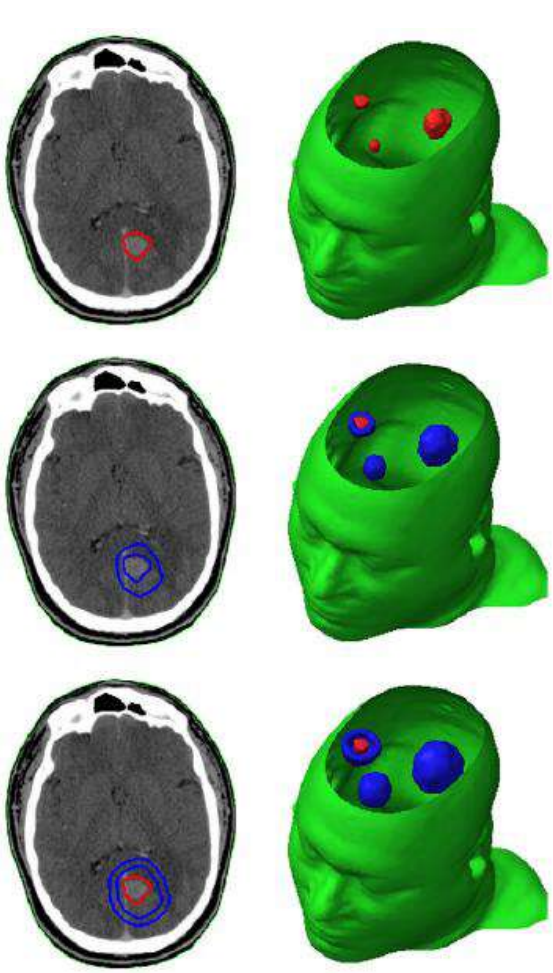
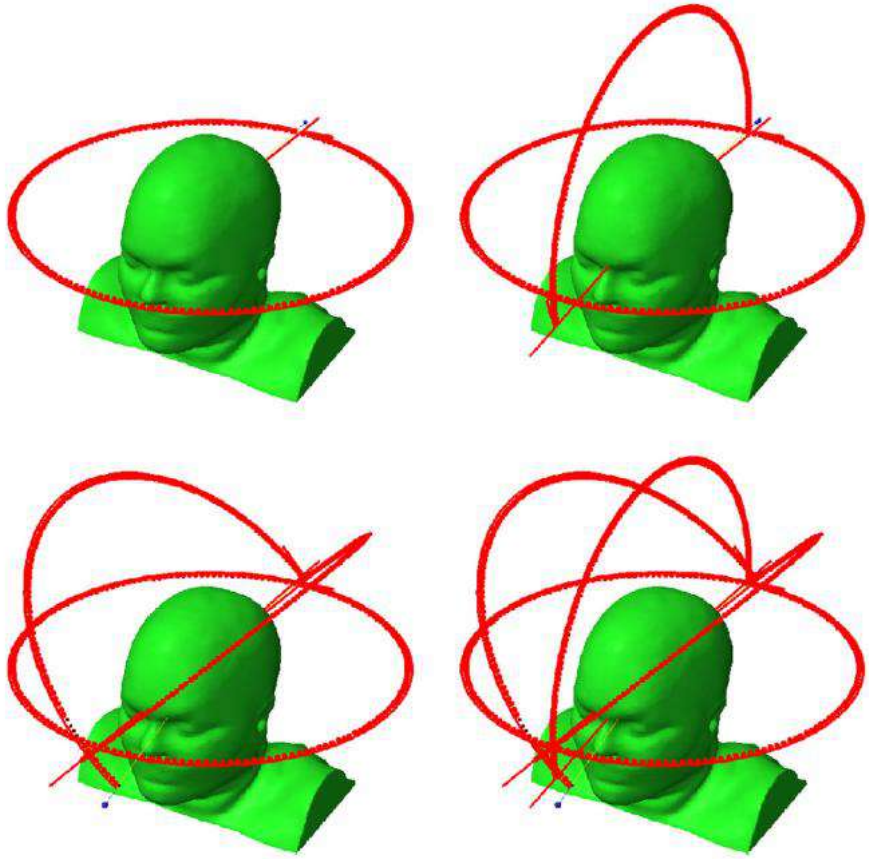
SRS for multiple brain mets



✓ *Single isocenter multiple targets technique*

Single-and multibeam geometries utilized for the single isocenter volumetric modulated arc therapy radiosurgery technique.



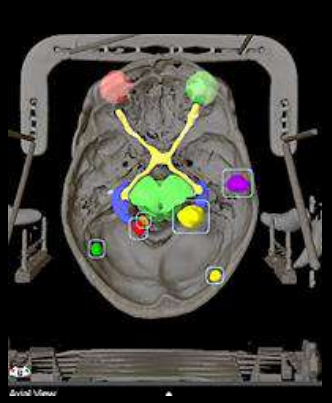


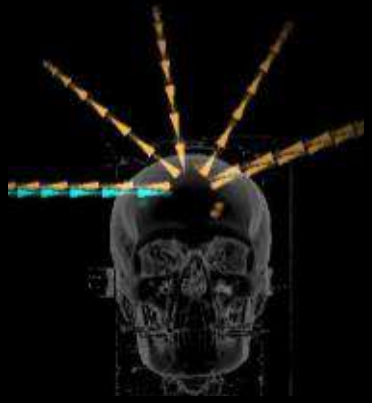
Clarke et al.

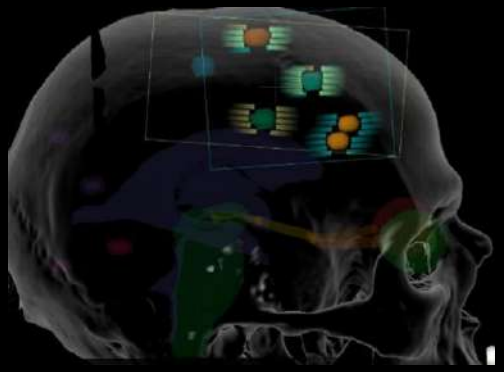
Practical Radiation Oncology (2012) **2**, 306–313

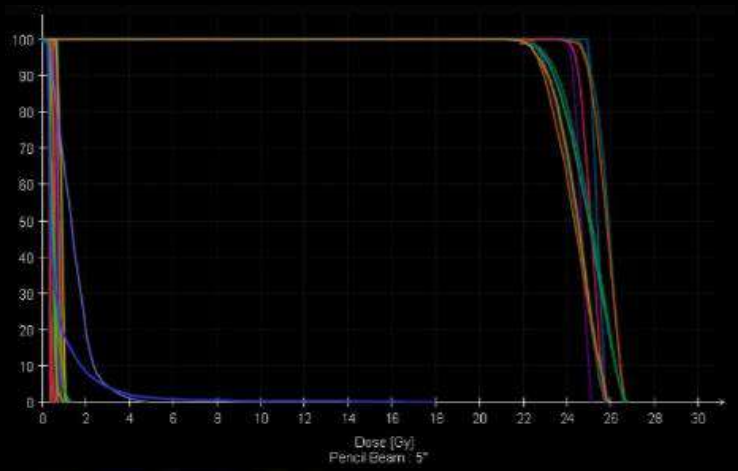
Conclusions: We have outlined a practical approach to cranial radiosurgery treatment planning using the single isocenter VMAT platform. One or 2 arc single isocenter plans are often adequate for treatment of single targets, while 2-4 arcs may be more advantageous for multiple targets. Given the high plan quality and extreme clinical efficiency, this single isocenter VMAT approach will continue to become more prevalent for linac-based radiosurgical treatment of 1 or more intracranial targets and will likely replace multiple isocenter techniques.

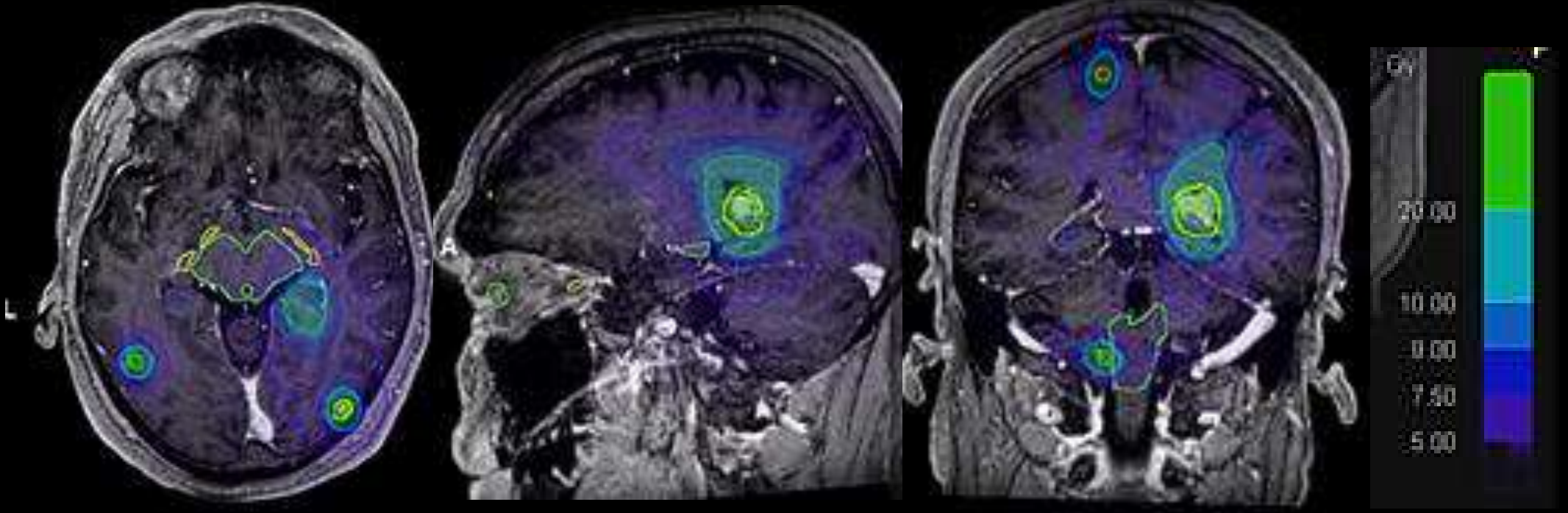
Brain Elements, version 1.5
Single-isocenter DCA SRS for multiple brain metastases











Preliminary Experience with Brain Elements Treatment Planning at UPMC Hillman Cancer Center, San Pietro Hospital, Rome: Evaluation of patient's repositioning accuracy and clinical efficacy

Table 1. Summary of patient charaterictiscs and treatment parameters

Parameter	No
number of patients	26
median age	52
sex (F/M)	14/12.
histology	
lung	12
breast	4
melanoma	6
kidney	3
ovary	1
no of lesions per patient	
2-5 lesions	8
6-10 lesions	18
tumor location	
frontal	20%
parietal	24%
temporal	19%
cerebellar	15%
occipital	17%
radiosurgical dose	
22 Gy	55
20 Gy	115
18 Gy	11
GTV (cm3)	
mean (SD)	0.34 (0.56)
median	0.29
range	0.17-4.86
total volume	2.2
PTV (cm^3)	
mean (SD)	0.60 (0.7)
median	0.54
range	0.27-5.92
total volume	3.7
Conformity index	
median	1.27
range	1.07-1.55
Gradient index	
median	3.92
range	2.78-5.56
D95 (%)	
mean (SD)	97.7 (4.5)
median	97.8 (91.6-107)
V95 (%)	
mean (SD)	99.7 (1.1)
median	99.5 (92.4-101)

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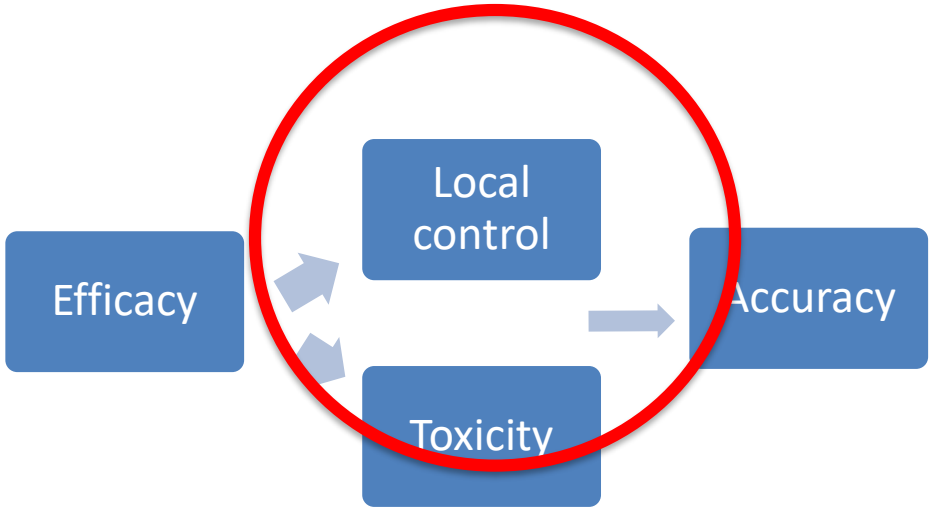
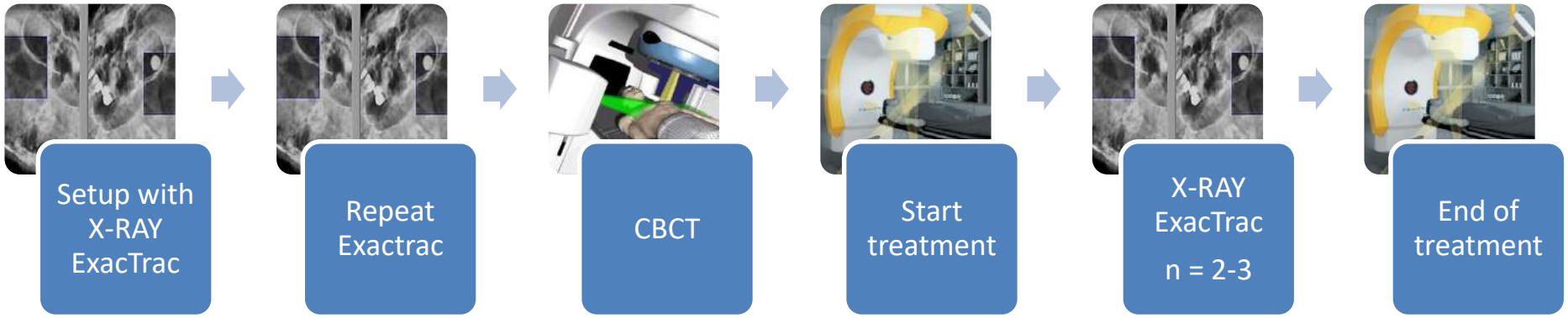
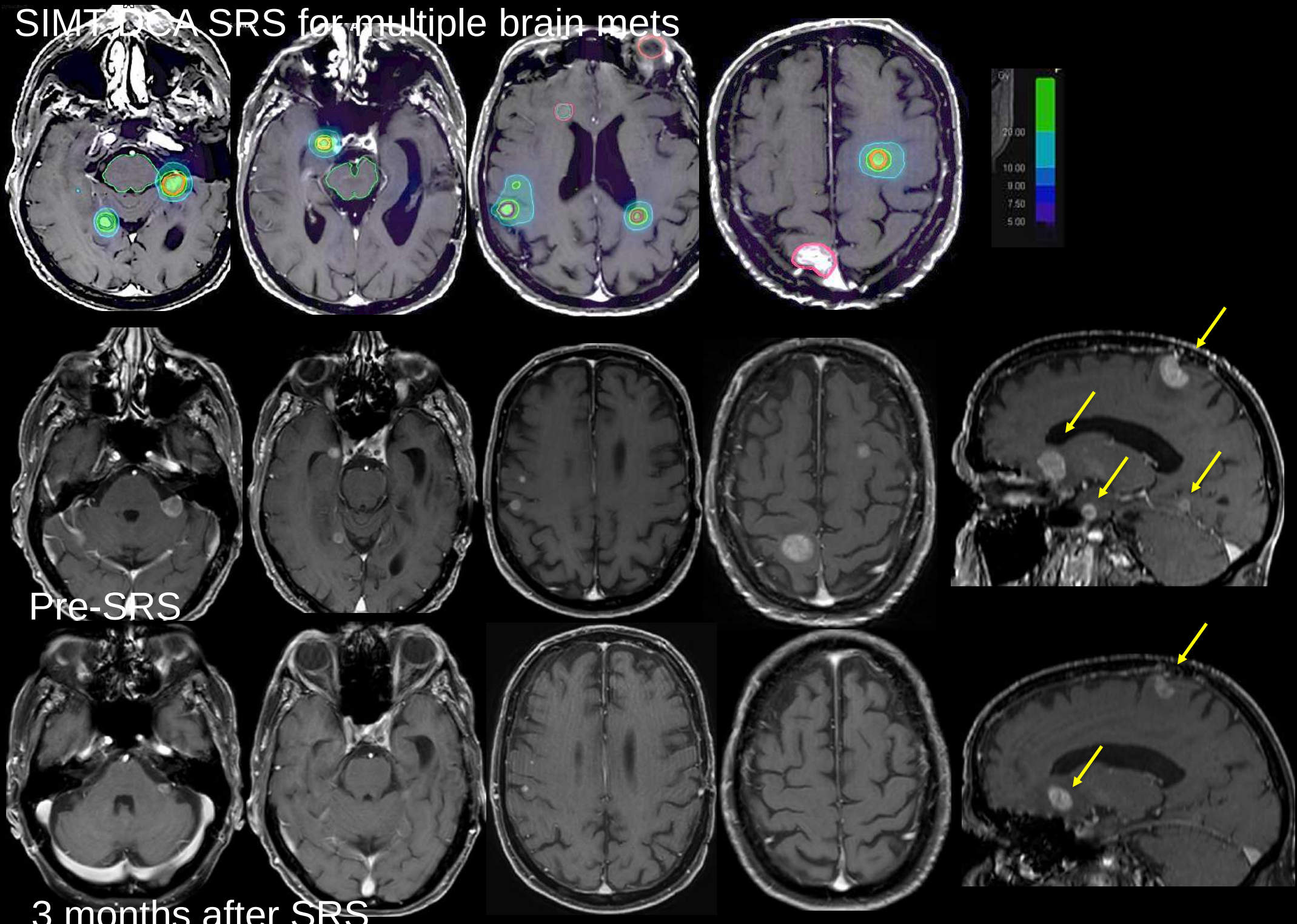
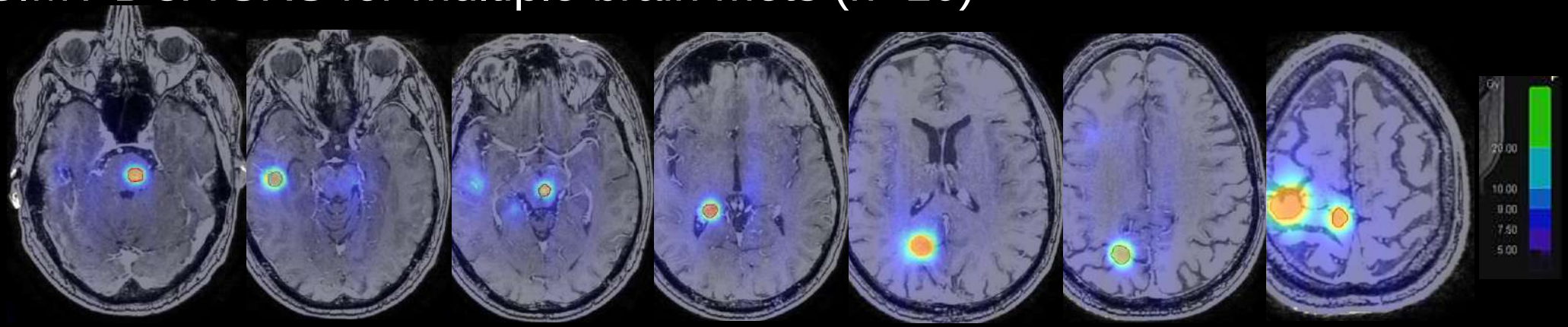


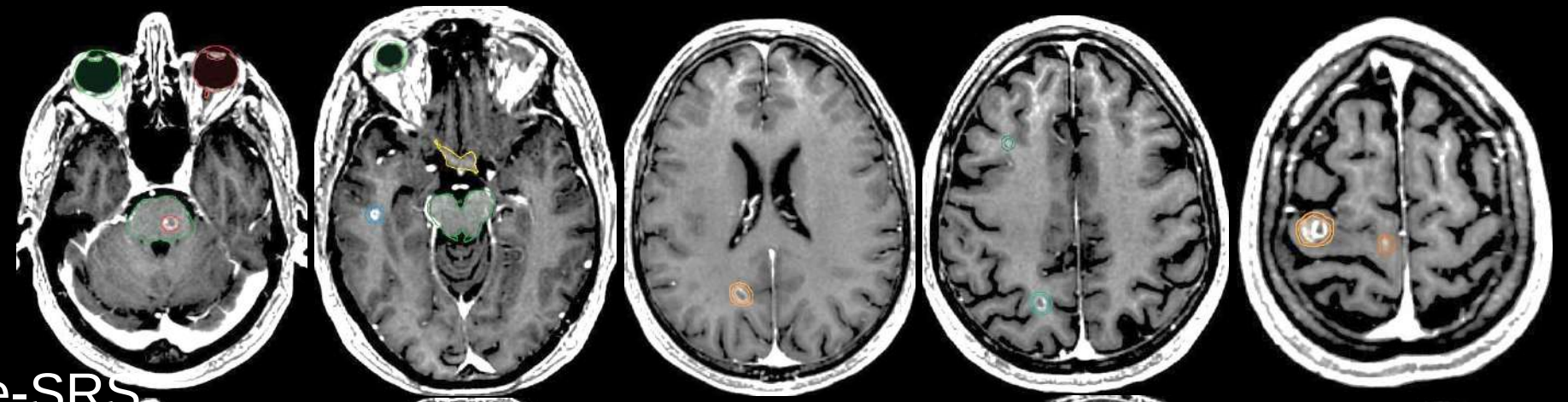


SIMT DCA SRS for multiple brain mets

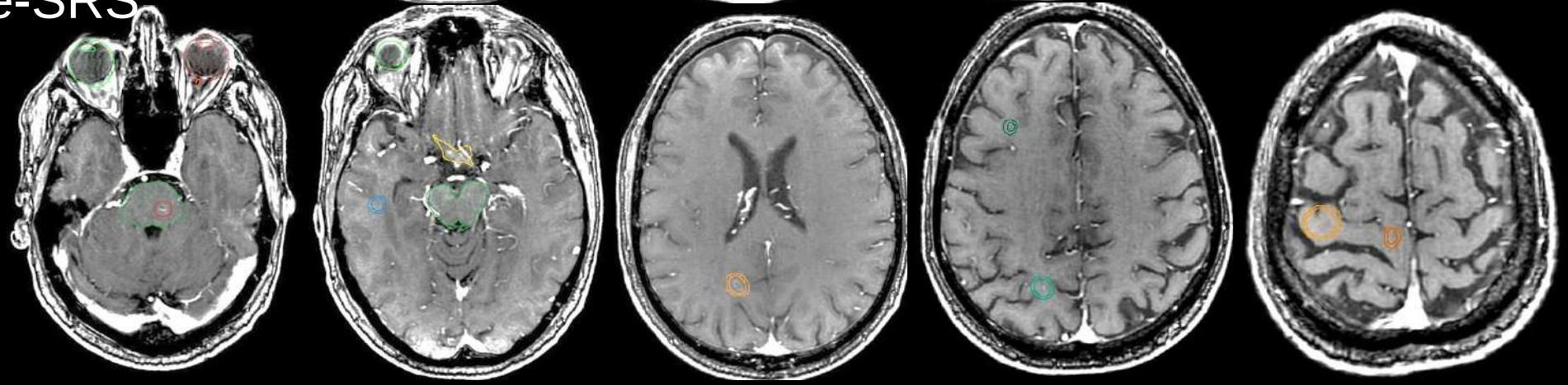


SIMT DCA SRS for multiple brain mets (n=10)





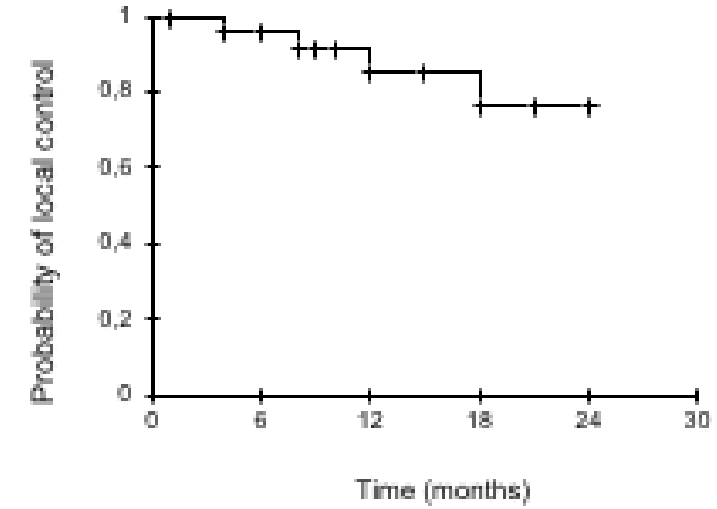
Pre-SRS

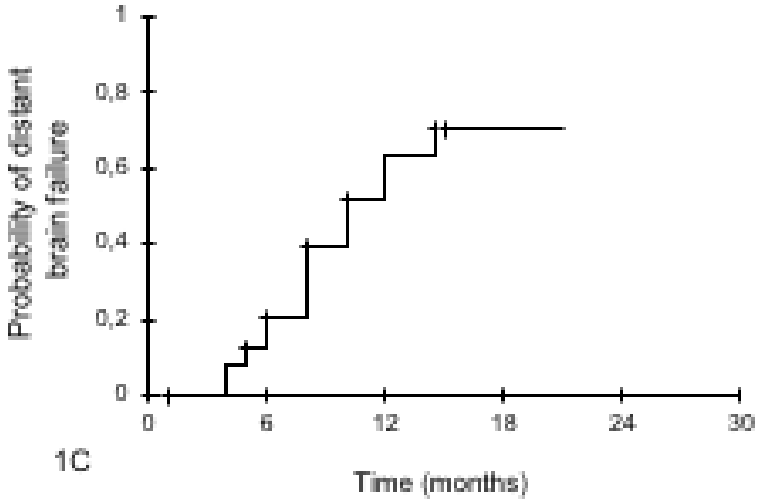


6 months after SRS

Preliminary Experience with Brain Elements Treatment Planning at UPMC Hillman Cancer Center, San Pietro Hospital, Rome:

Clinical outcomes





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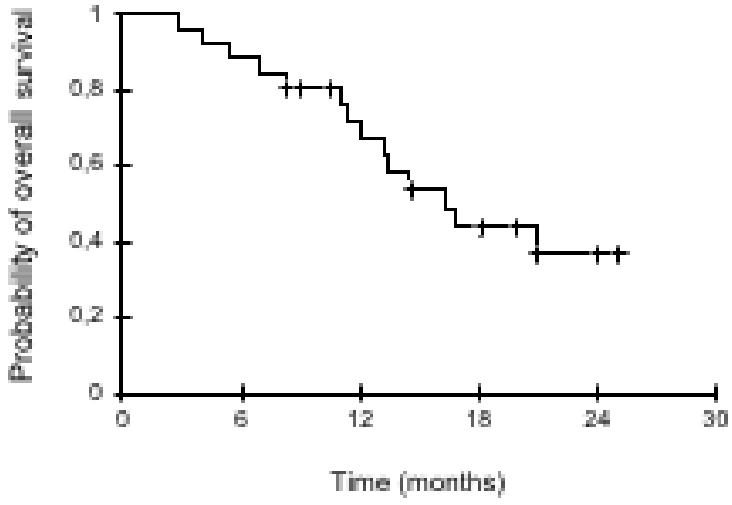

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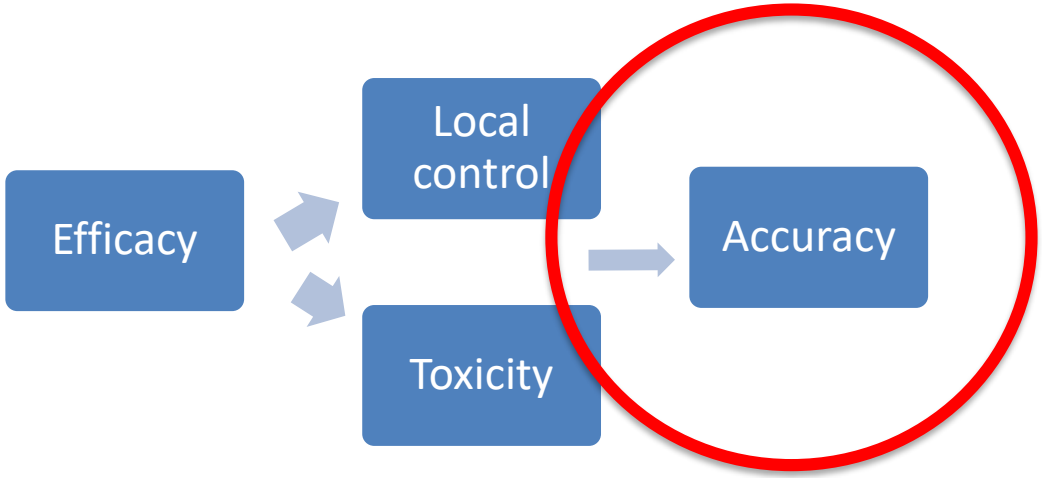
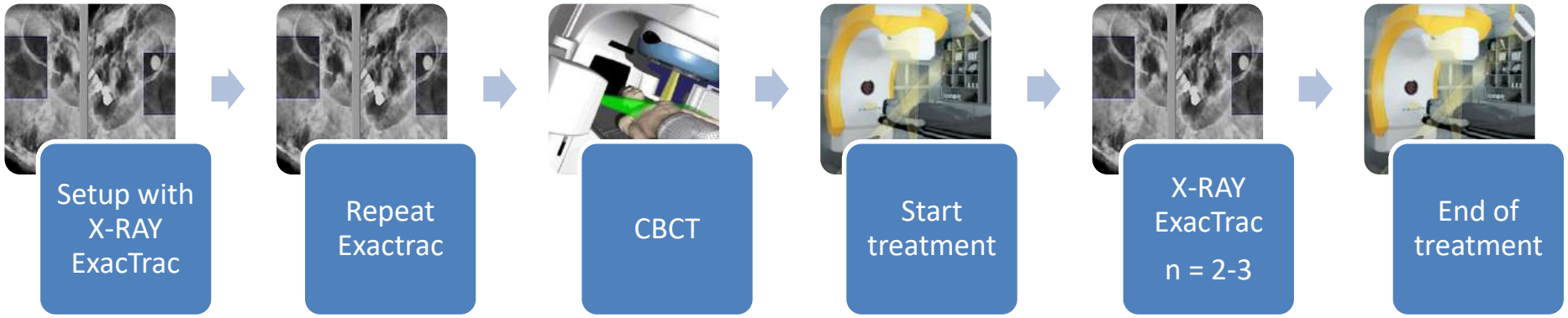
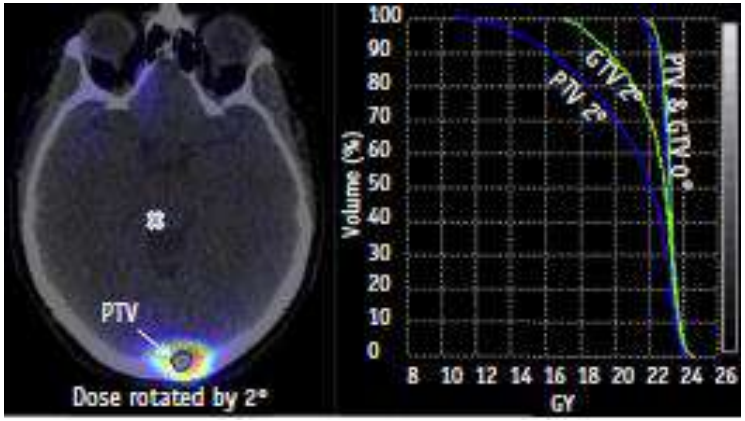
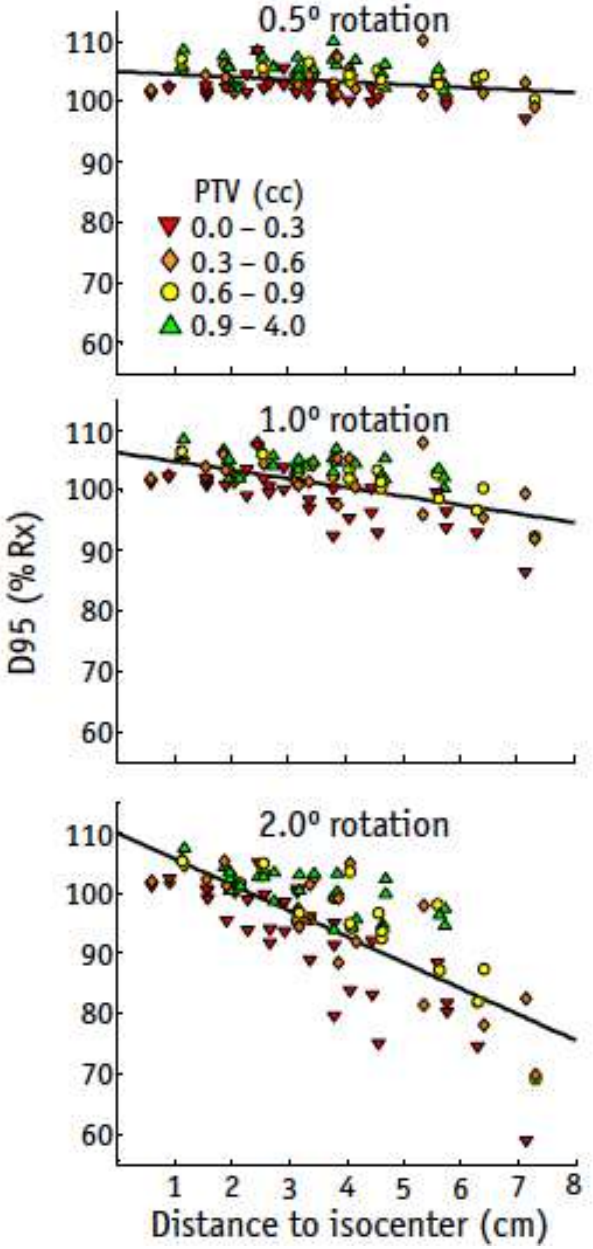


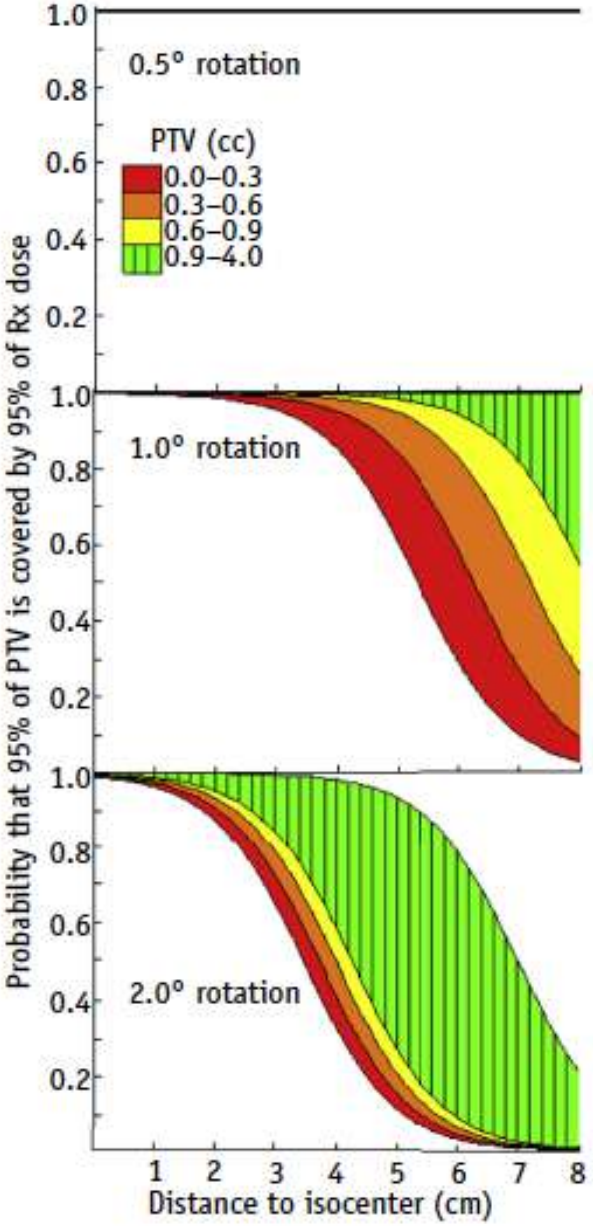


Single-Isocenter Multiple-Target Stereotactic Radiosurgery: Risk of Compromised Coverage

Justin Roper, PhD,* Vorakarn Chanyavanich, PhD,* Gregory Betzel, PhD,* Jeffrey Switchenko, PhD,† and Anees Dhabaan, PhD*







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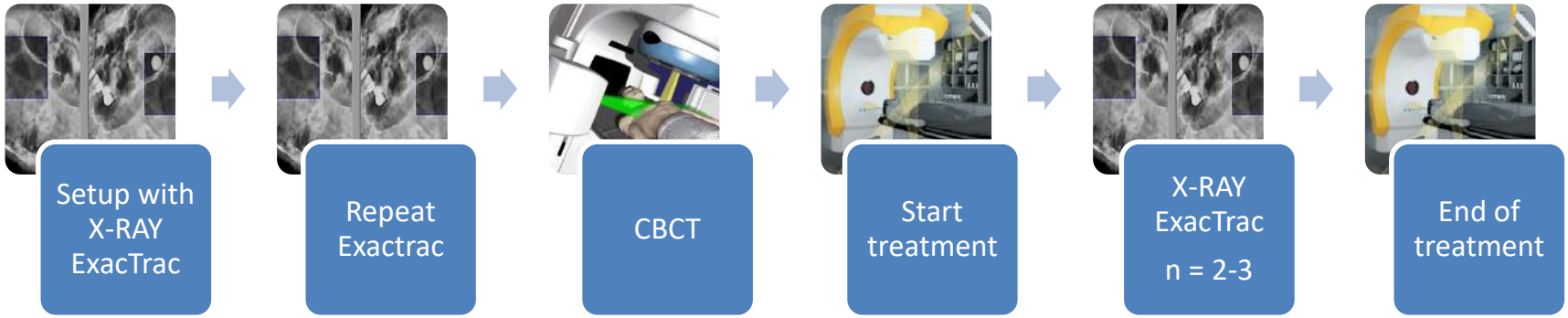


Table 2. Effect of residual isocenter deviations evaluated by the ExacTrac kV X ray 6D imaging system on geometric and dosimetric accuracy of SRS treatment

Parameter	mean distance from isocenter (SD)	x (lateral)	y (vertical)	z (longitudinal)	3D vector	Pitch (x)	Yaw (y)	Roll (z)	Non-overlapping GTV volume %	Non-overlapping PTV volume %	V95 variation %	Mean dose variation %
mean	34.7	-0.085	0.156	-0.23	0.42	-0.13	-0.08	0.1	12.6^	6.1*	1.34**	0.7
SD	17.1	0.3	0.25	0.44	0.30	0.28	0.25	0.32	19	10	2.3	1.2
range	0.22 - 76.3	-0.41 - 0.49	-0.46-0.38	-0.48-0.5	0.05-0.8	-0.42-0.48	-0.4-0.4	-0.5-0.5	0-58	0-44	0-9.2	0-4

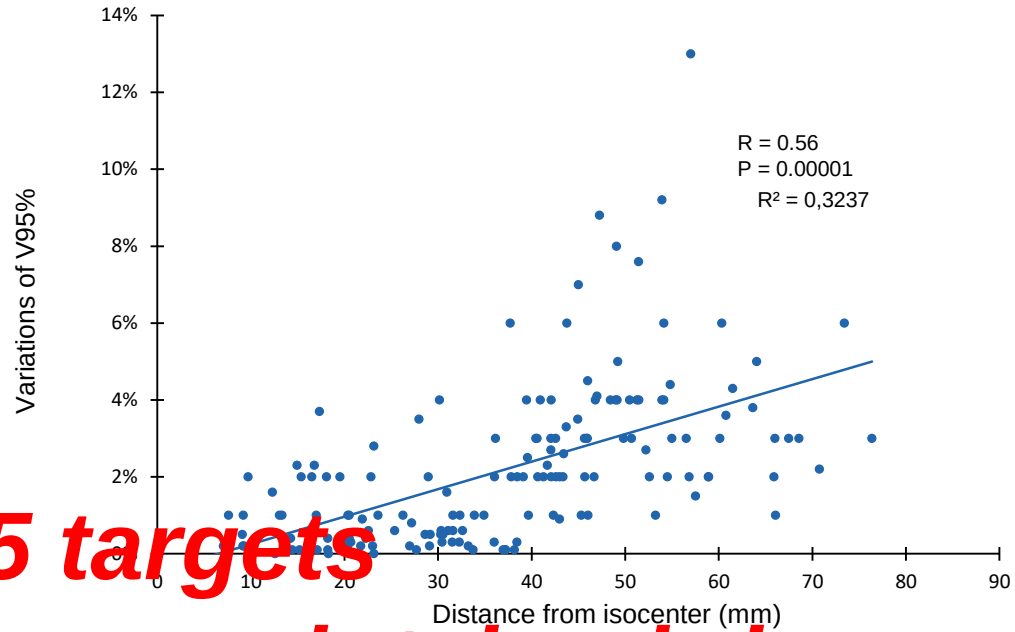
Preliminary Experience with Brain Elements Treatment Planning at UPMC Hillman Cancer Center, San Pietro Hospital, Rome:

- Impact of isocenter residual errors on target geometry and dosimetry

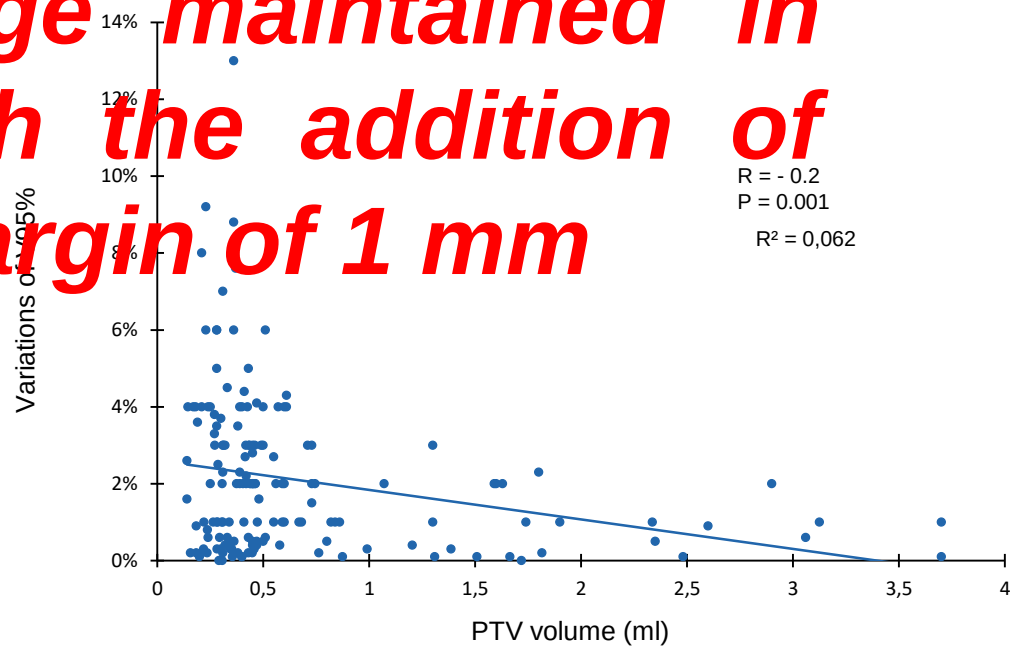
UPMC LIFE CHANGING MEDICINE

Preliminary Experience with Brain Elements Treatment Planning at UPMC Hillman Cancer Center, San Pietro Hospital, Rome:

- ✓ Correlation with distance from plan isocenter and target volume



- ***V95 < 95% in 25 targets***
- ***Target coverage maintained in all targets with the addition of GTV-to-PTV margin of 1 mm***



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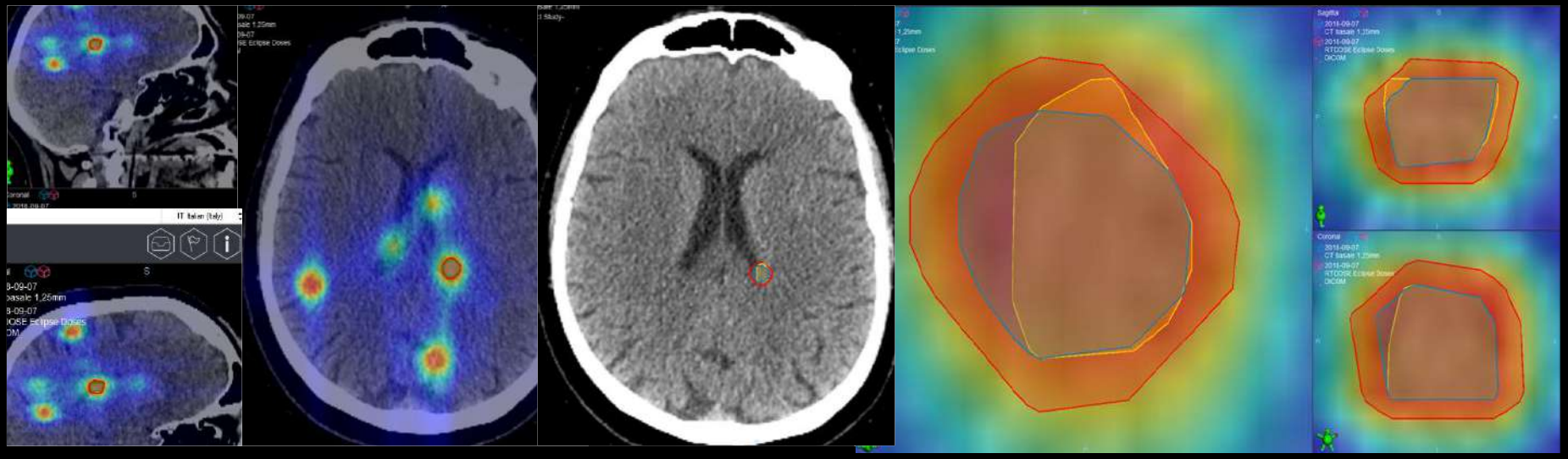
Single-isocenter multi-target DCA SRS

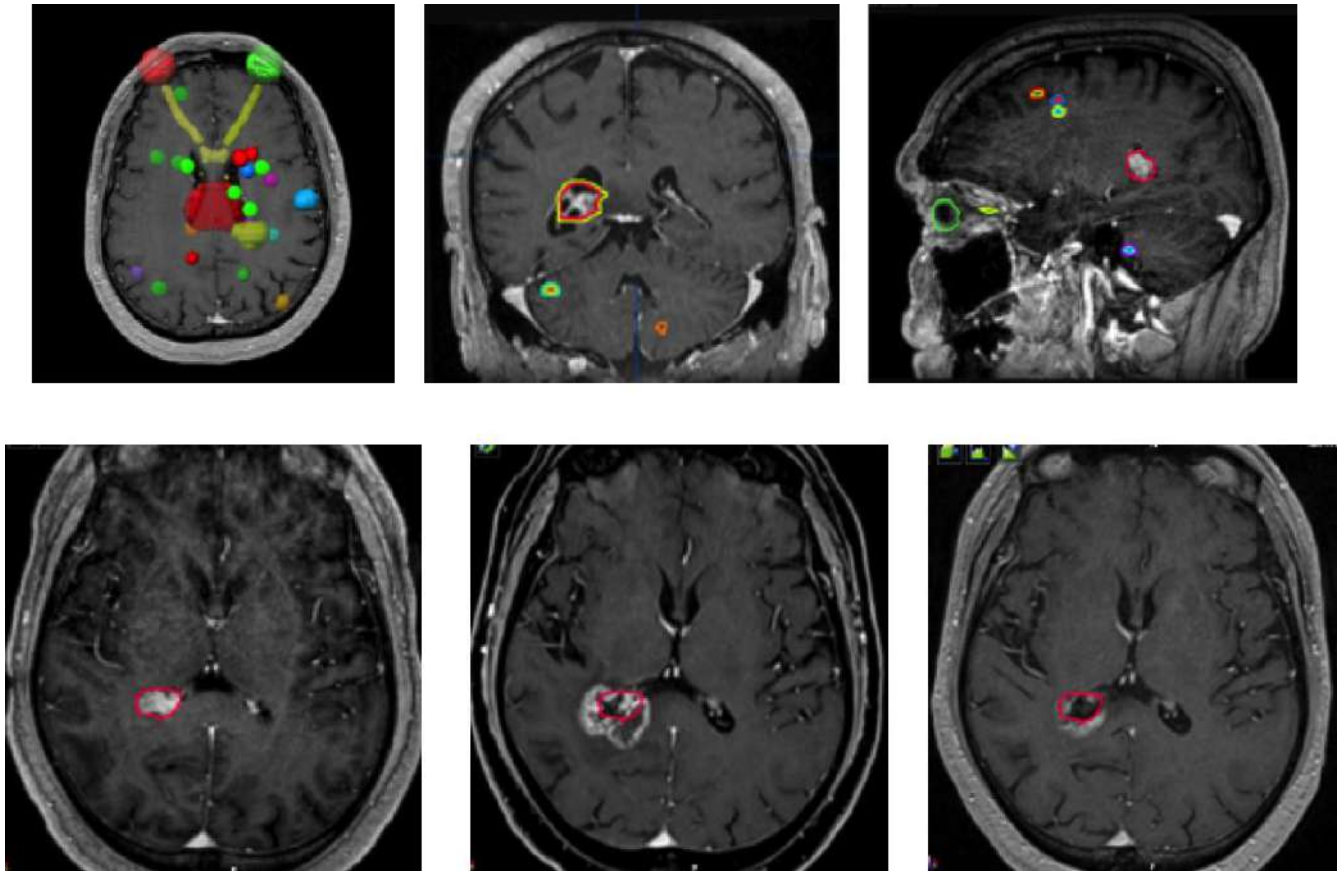


large GTV geometric variations (blue area and orange area) as result of translational and rotational isocenter residual errors.

Risk of radiation-induced brain necrosis

Estimated risk of RN

12-month 9% (3%)
24-month 14% (5%)



Pre-SRS **Post- 12 m** **Post- 18 m**

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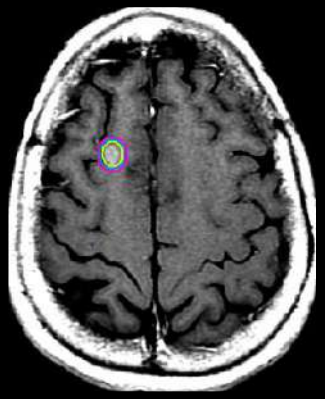
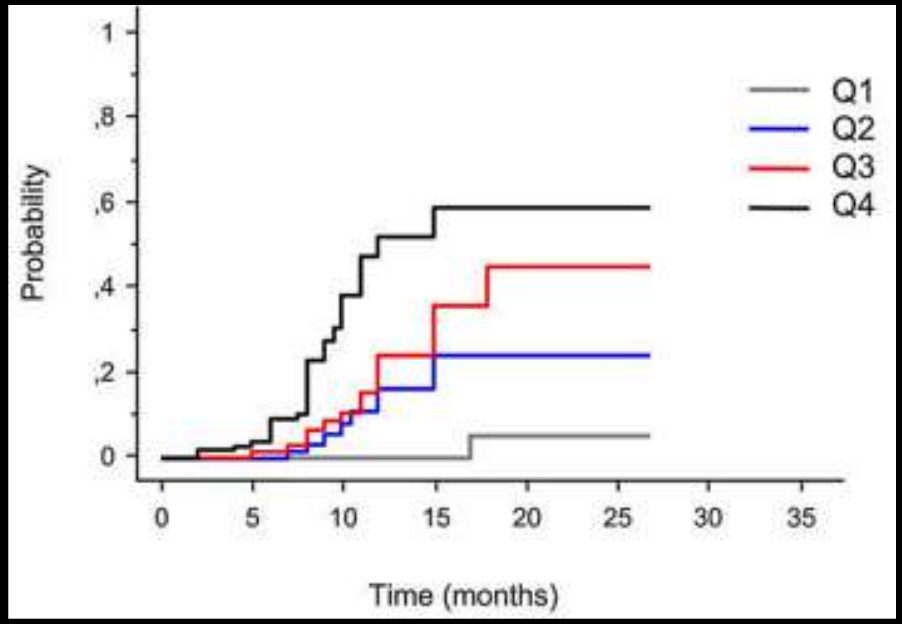
Margins add a significant amount of normal tissue to the treatment volume.



GTV = 1.3 cc

PTV 1mm = 1.9 cc ($V_{12\ Gy}$ 4.7 cc)

PTV 2mm = 2.8 cc ($V_{12\ Gy}$ 8.4 cc)



1-year risk of radionecrosis was 24% for V12 Gy of 6.0-10.9 cm^3 and 51% for V12 Gy >10.9 cm^3, respectively.

Minniti et al., Rad Oncol 2011

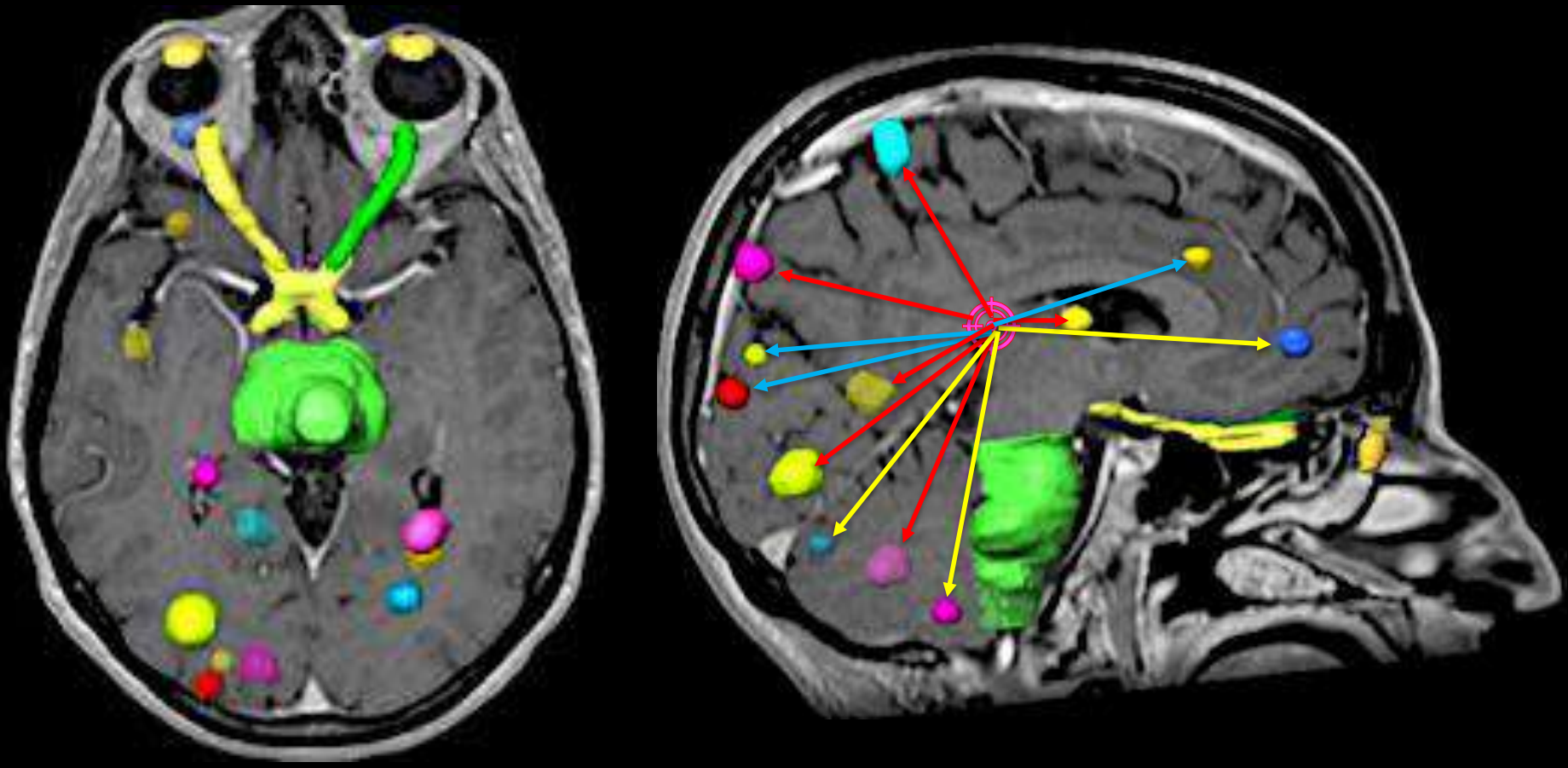
Preliminary Experience with Brain Elements Treatment Planning at UPMC Hillman Cancer Center, San Pietro Hospital, Rome:

Table 3. Target loss coverage (v95 < 95%) according to the size and the distance from isocenter

Parameter	Distance from isocenter < 3.9 cm		Distance from isocenter ≥ 3.9 cm	
Size of GTV	< 0.29 mm	≥ 0.29mm	< 0.29 mm	≥ 0.29 mm
1 mm GTV-to-PTV margins	0	0	0	0
0.5 mm GTV-to-PTV margins	2	0	4	1
No GTV-to-PTV margins	6	1	16	2

Accuracy of treatment: loss target coverage (V95<95%)

Single-isocenter multiple-targets SRS technique

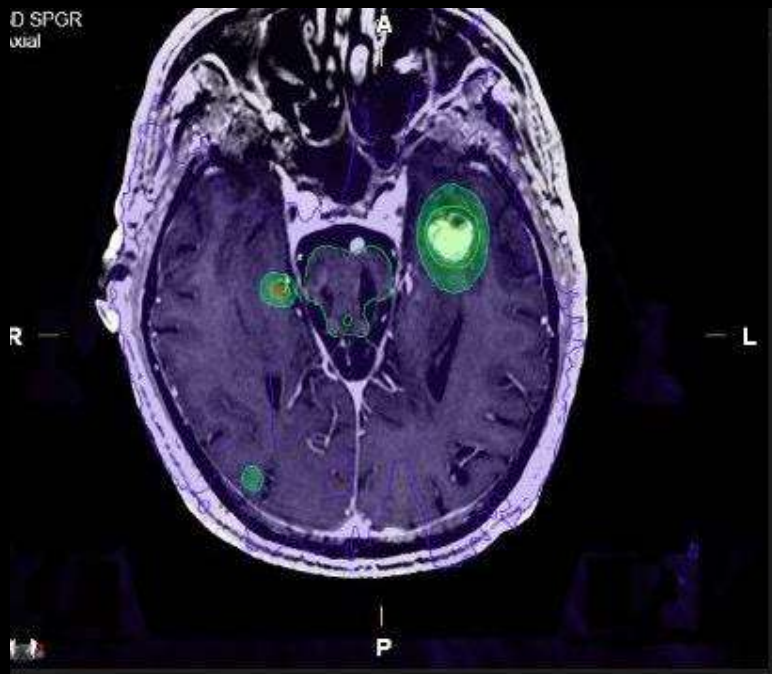


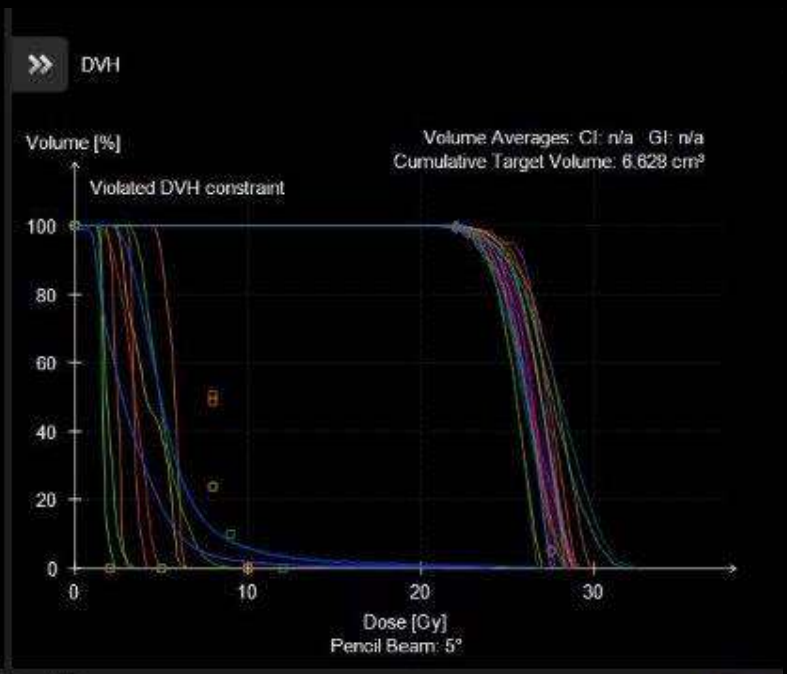
GTV-to-PTV 1 mm

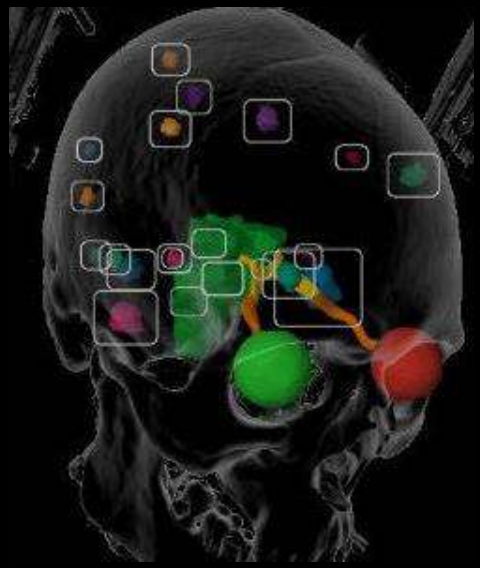
GTV-to-PTV 0.5 mm

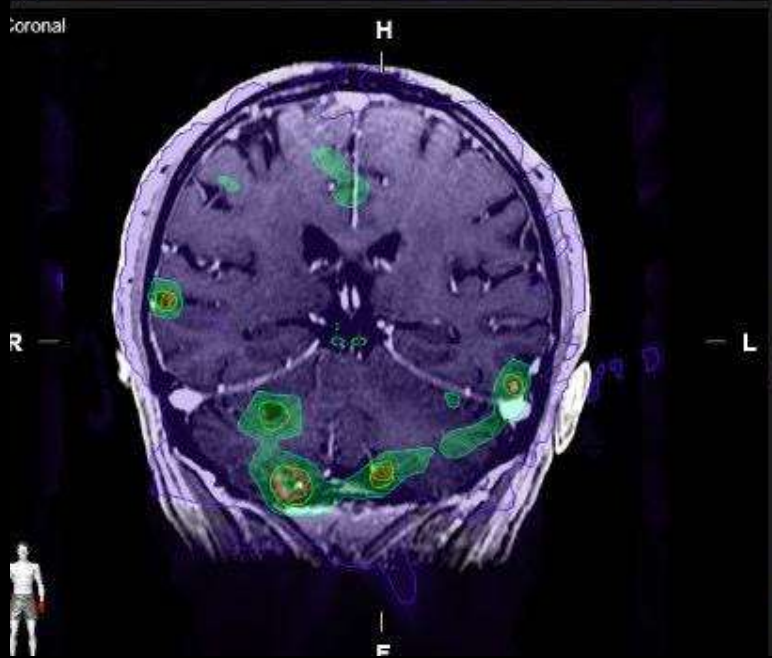
GTV-to-PTV 0 mm

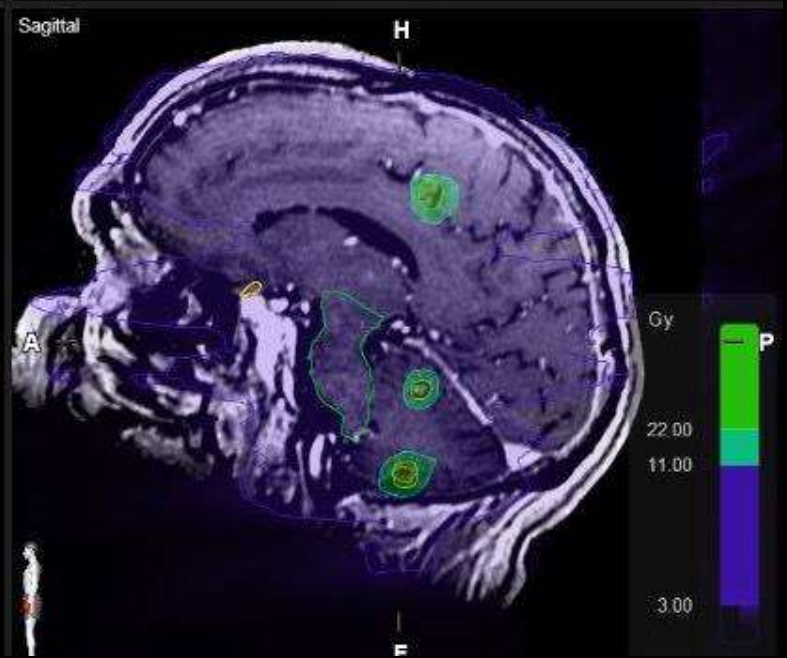
SIMT DCA SRS for multiple brain mets (n=21)

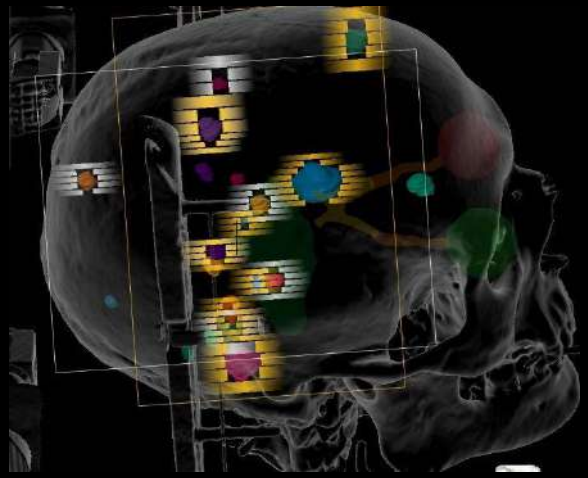












Preliminary Experience with Elements at UPMC Hillman Cancer Center, San Pietro Hospital, Rome

Factors correlated with the risk of neurotoxicity

Sex	lesions (n)	Dp (Gy)	Volume GTV	Vol Tot PTV (cm3)	V12 Brain	V10 Brain	V8 Brain	V5 Brain
M	6	20	1,3	2,1	7,10	9,60	13,80	32,62
F	9	20	3,9	6,8	21,70	29,80	45,10	88,70
M	9	22	2,6	4,2	15,80	21,58	33,28	78,00
M	5	22	1,4	2,3	10,40	14,30	20,40	45,20
F	8	20	8,9	13,1	46,80	64,80	94,80	204,00
M	10	22	2,6	4,1	15,60	20,80	31,90	72,80
M	9	22	1,7	2,7	10,10	13,20	19,90	49.4
M	5	20	1,4	2,1	5,70	7,90	11,70	25,40
F	6	22	3,9	6,4	17,50	22,30	33,70	68,70
F	5	22	1,3	2,1	7,10	9,70	14,60	38,60
M	3	20	0,6	1,3	3,20	4,60	7,10	22,10
M	4	20	0,7	1,5	2,78	3,64	4,94	10,60
M	4	22	5,7	8,26	22,30	28,70	48,50	100,40
M	7	22	2,7	4,22	14,60	19,37	27,30	60,70
F	6	20	1,56	3,12	14,80	20,80	33,60	92,70
F	7	22	3,9	6,2	15,60	20,40	30,40	87,90
F	10	20	2,95	5,5	16,70	22,60	33,60	95,80
M	9	20	3,7	6,6	23,4	32,4	47,9	120,8
M	6	20	1,33	2,28	6,5	9,1	12,8	35,6
F	9	20	6,1	10,4	36	51,6	84,1	208
F	5	20	1,17	2	3,6	6,1	8,9	29,6
F	4	20	1,65	2,8	8,1	11,1	16,2	39,5
F	10	20	1,7	2,6	7,7	10,6	15,7	41,8
F	10	20	2,5	4,7	17	15,8	45,1	132
F	6	20	1,6	2,4	8,40	12,00	18,20	42,10
M	9	20	4,1	7,7	19,50	27,80	16,10	66,30

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Summary

- ✓ SIMT DCA SRS is a fast and effective approach for patients with up to ten brain metastases.
- ✓ Using the ExacTrac X-Ray 6D imaging system, the impact of residual translational and rotational errors on target coverage is modest.
- ✓ A GTV-to-PTV margin of 1 mm permits to avoid loss target coverage, although smaller margins may be used for treating lesions within a few centimeters (< 4 cm) to the plan isocenter without decreasing the accuracy and precision of the treatment.
- ✓ The neurocognitive outcome of treatments with regard to the number and total volume of lesions needs to be evaluated in future clinical studies.

Thank you for your attention

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