IL MODERNO APPROCCIO RADIOTERAPICO AI TUMORI METASTATICI CEREBROSPINALI

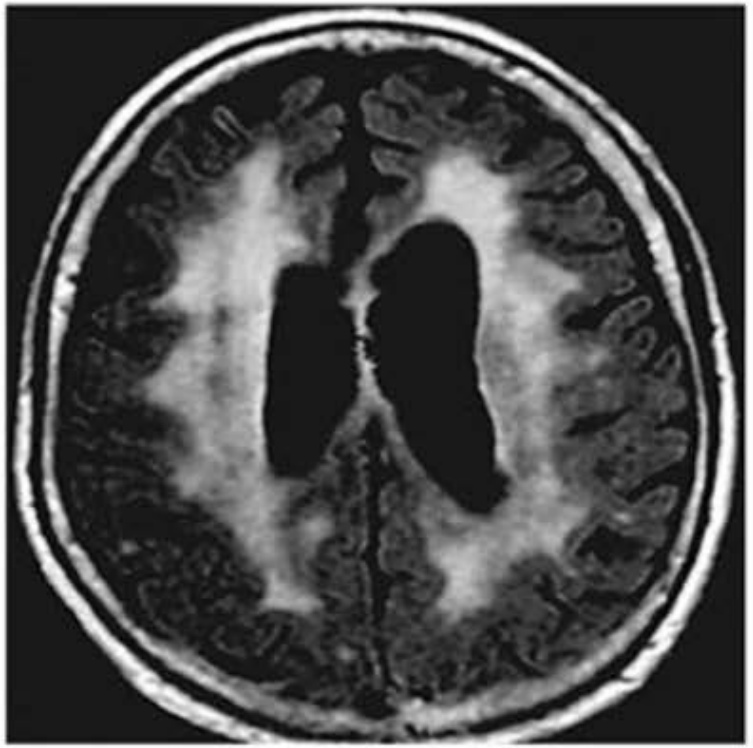
✓ Outline

- *SRS alone for brain metastases*
- *How many metastases can be treated with SRS?*
- *Immunotherapy/targeted therapy for brain metastases*
- *Combining SRS with Immunotherapy/targeted agents*
- *Future research*

✓ Outline

- *SRS for brain metastases*
- *How many metastases can be treated with SRS?*
- *Immunotherapy/targeted therapy for brain metastases*
- *Combining SRS with Immunotherapy/targeted agents*
- *Future research*

✓ Whole Brain Radiation Therapy



Late toxicity

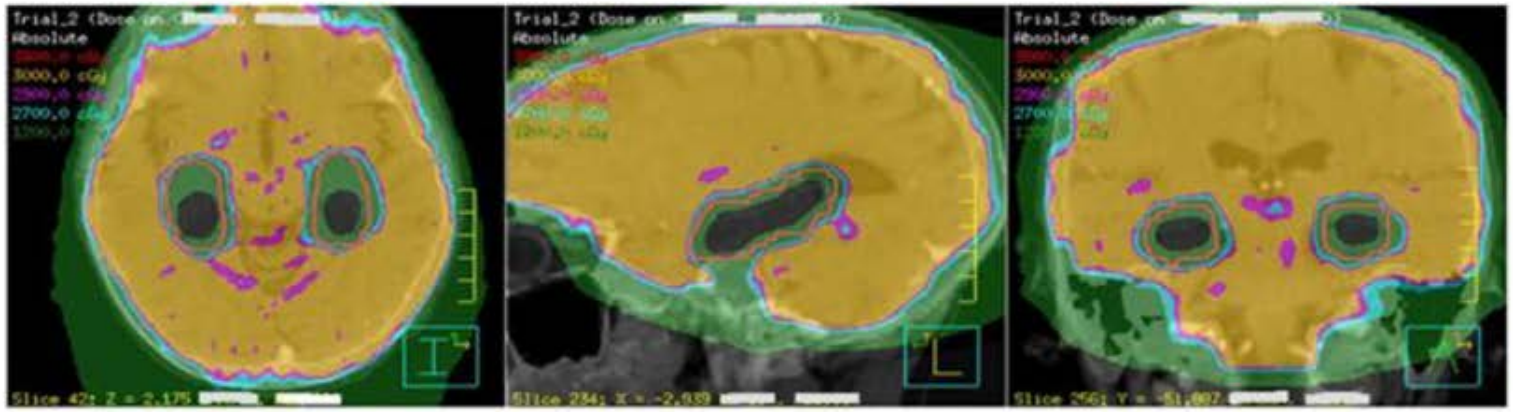
Normal pressure hydrocephalus, causing cognitive, gait and bladder dysfunction

Neuroendocrine dysfunction

Cerebrovascular disease

RTOG 0933: HA-WBRT

- Conformal avoidance of the hippocampus using IMRT during whole brain radiotherapy (HA-WBRT) for brain metastases preserves memory function



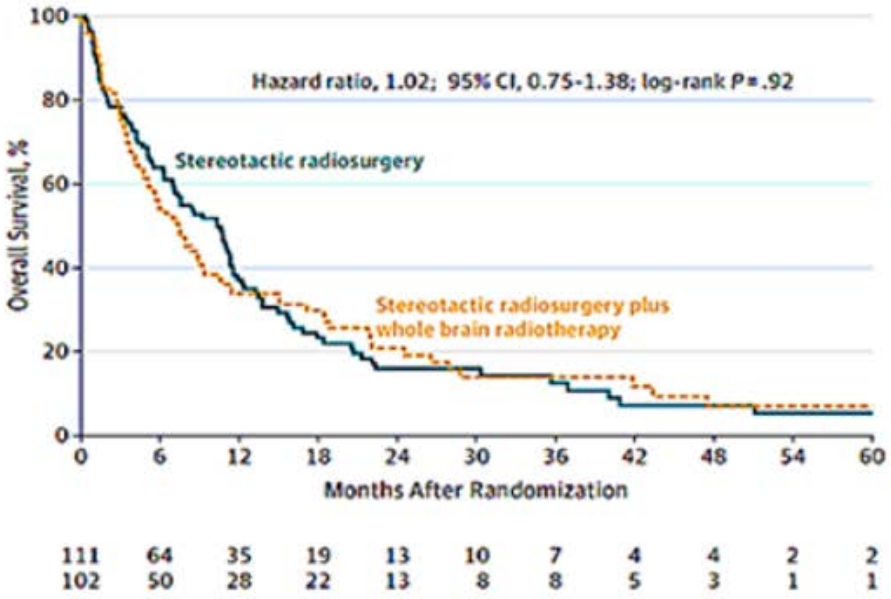
Gondi, et al., Radiother & Oncol 2010, PMID: 20970214

✓ *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	

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



✓ *NCCTG N0574*

Cognitive Test	SRS	SRS+WBRT	P-value
HVLT Total Recall	8.2%	30.4%	0.0043
HVLT Delayed Recall	19.7%	51.1%	0.0009
HVLT Recognition	22.6%	40.4%	0.0585
TMT Part A	16.7%	30.4%	0.1063
TMT Part B	19.0%	37.2%	0.0677
COWA	1.9%	18.6%	0.0098
Pegboard-Dominant	29.3%	47.7%	0.0656

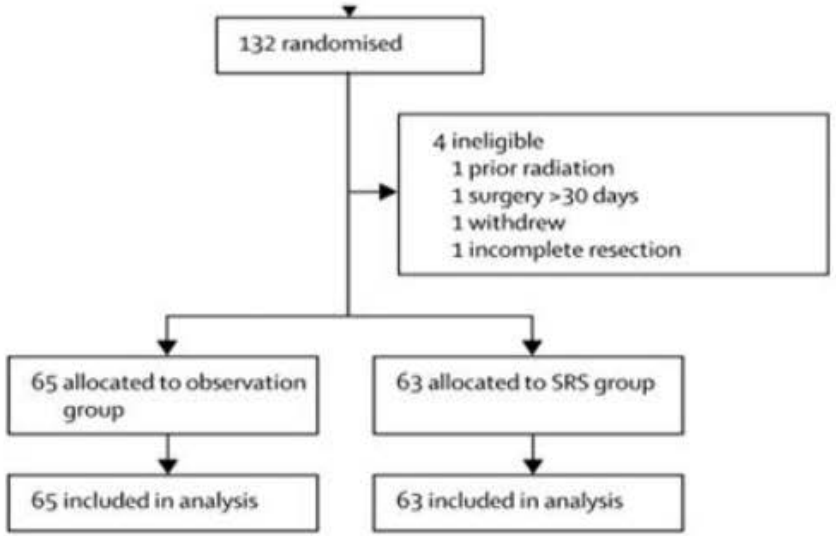
Cognitive Test	SRS	SRS+WBRT	P-value
HVLT Total Recall	0.87	0.12	0.177
HVLT Delayed Recall	-0.05	-0.36	0.631
HVLT Recognition	0.35	-1.43	0.044
TMT Part A	0.33	-0.42	0.498
TMT Part B	1.1	0.01	0.397
COWA	0.34	-0.25	0.071
Pegboard-Dominant	-0.45	-6.46	0.114

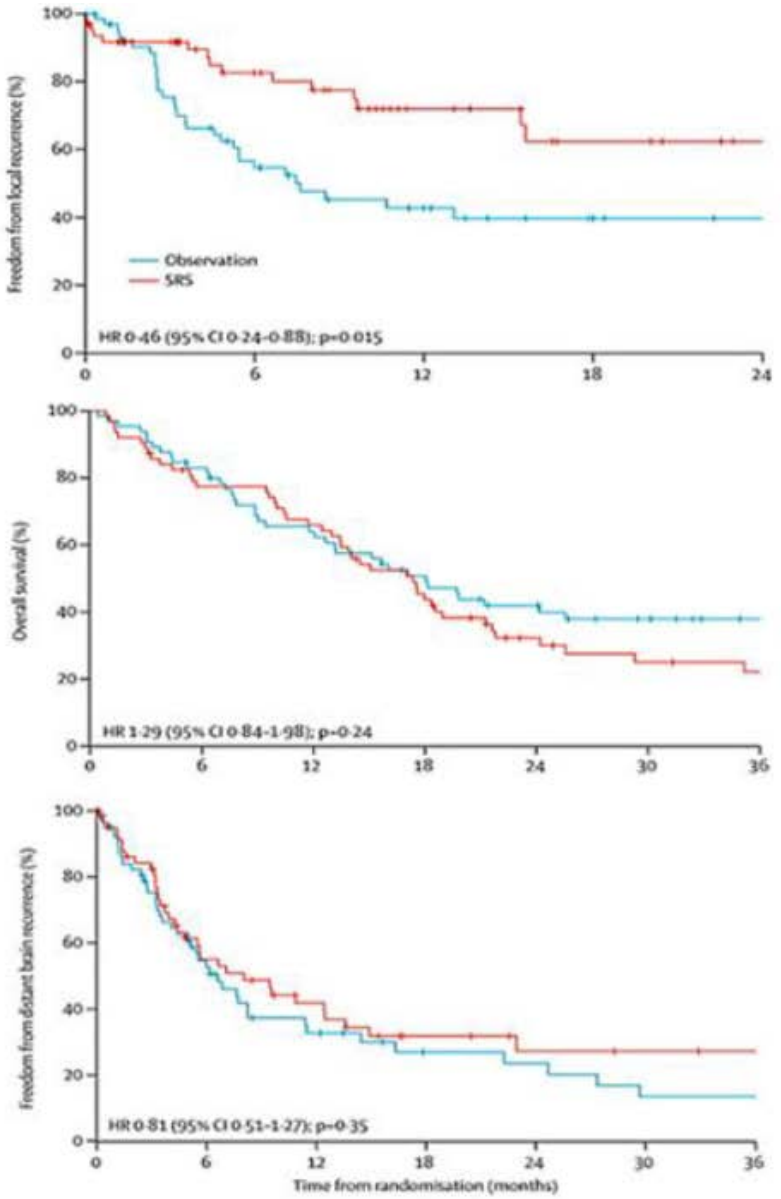
P Brown , JAMA 2016

ASTRO Recommendations

- *Don't routinely add adjuvant WBRT or 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*

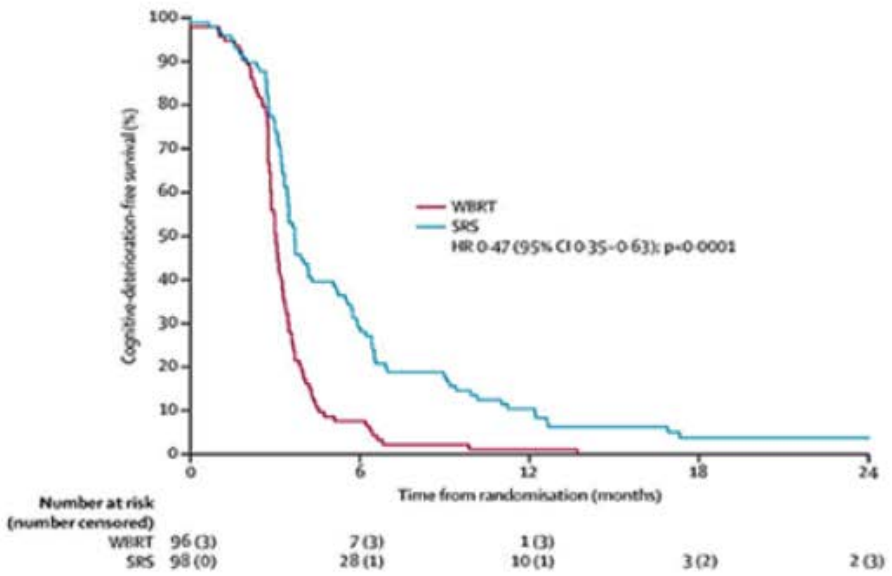
Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

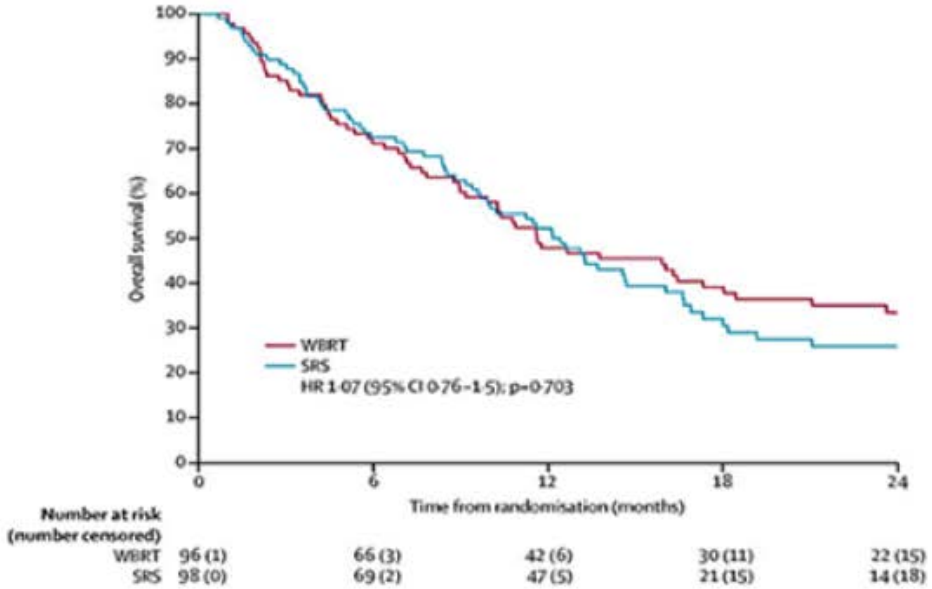




Mahajan et al, Lancet Oncology, 2017

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial



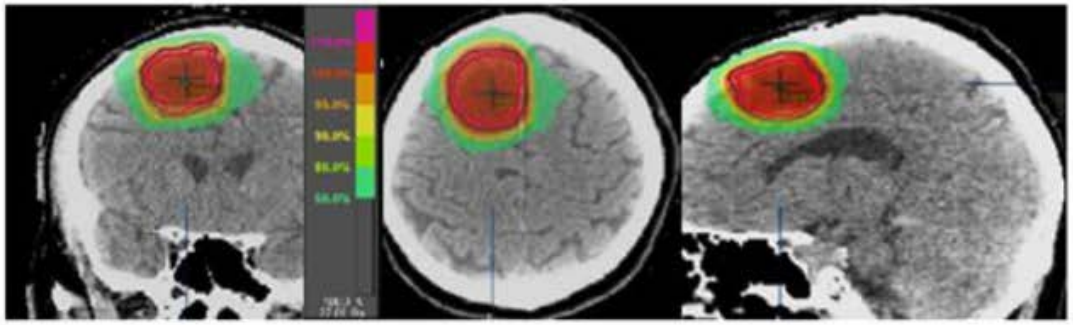


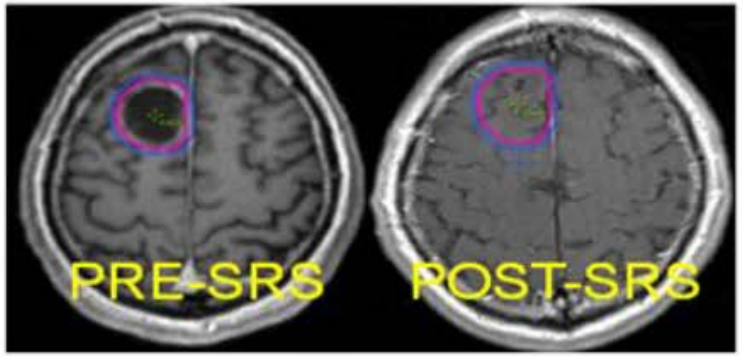
PD Brown et al, Lancet Oncology, 2017

Stereotactic Radiosurgery for Resected Brain Metastases: New Evidence Supports a Practice Shift, but Questions Remain

By Giuseppe Minniti, MD, PhD, Scott G. Soltys, MD, Lia M. Halasz, MD, John C. Breneman, MD, Michael Chan, MD, Nadia N. Laack, MD, John P. Kirkpatrick, MD

International Journal of Radiation Oncology biology • physics
www.redjournal.org





- *Timing of SRS*
- *Which target delineation*
- *Which dose/fractionation*
- *Which histologies can benefit*
- *Post-SRS vs Pre-SRS*

Multicenter Randomized Phase III study on brain metastases susceptible to surgical resection (> 21mm or < with edema unresponsive to medical therapy or with considerable mass effect).

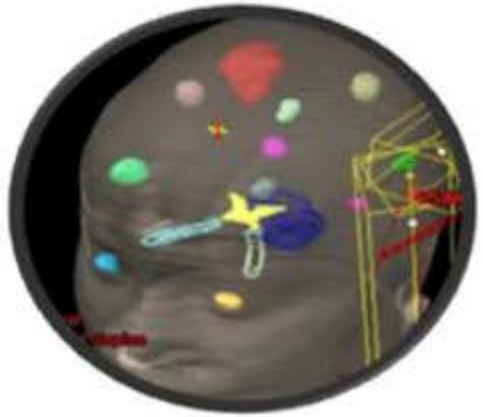
-Diff. Leptomeningea and RN post SRS
-Better target definition
-Cell spilled prevention
-Better oxygenation
-Resection of irradiated tissue

-Control arm: surgery + Fractional SRS
-Experimental arm: fractional SRS + surgery

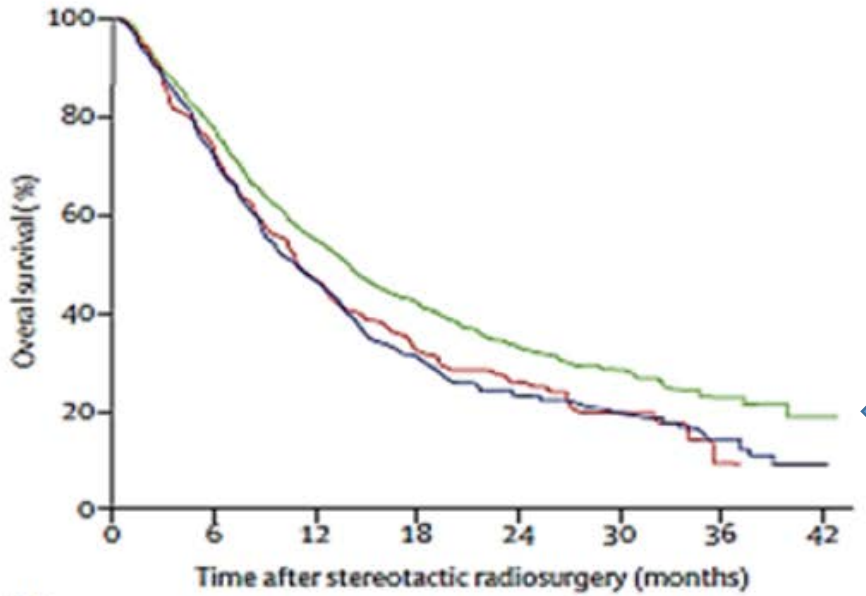
	Scheda di valutazione per partecipazione a studio randomizzato di fase III: radiochirurgia ipofrazionata preoperatoria vs radiochirurgia ipofrazionata postoperatoria in pazienti con BMs suscettibili di trattamento chirurgico.			
istituto e città				
1	N° di pazienti con BM operati all'anno			
2	I casi clinici vengono discussi collegialmente?	SI'	NO	
	Se si, con che frequenza?	settimanale	quindicinale	altro (specificare)
3	Fate a tutti i pazienti una RM post-operatoria entro 48-72 ore?	SI'	NO	
4	Nel vostro centro sono eseguibili le seguenti indagini istopatologiche, biomolecolari ed immunoistochimiche sul campione di tessuto tumorale:			
	□ Ematossilina Eosina □ GFAP			
	□ CD31 □ NG2			
	□ CD3+ □ CD4+ □ CD8+ □ CD68+ □ FOXP3 □ PD-L1.			
	□ BRAF □ EGFR □ KRAS □ ALK			
	□ KRAS □ MSI □ ER □ PgR □ HER-2			
	□ ELISA su fluido cerebrospinale			
5	Nella pratica clinica del reparto viene eseguita la Radioterapia post-operatoria?	SI'	NO	
	Se la risposta alla domanda 5 è SI' che tipo di RT:			
	□ SRS in singola seduta			
	□ SRS ipofrazionata			
	□ WBRT			
6	E' presente presso il vostro centro una NeuroRadiologia?	SI'	NO	
7	E' pratica clinica eseguire presso il vostro centro la RM di simulazione oltre alla TC?	SI'	NO	
8	Viene effettuata una valutazione neuropsicologica del paziente?	SI'	NO	
	Se si, che tipo di test utilizzate?	nome		
9	E' presente presso il vostro centro un data Manager o una persona che si occupa della gestioni dei dati degli studi di ricerca?	SI'	NO	

✓ Outline

- SRS for brain metastases
- How many metastases can be treated with SRS?
- Immunotherapy/targeted therapy for brain metastases
- Combining SRS with Immunotherapy/targeted agents
- Future research



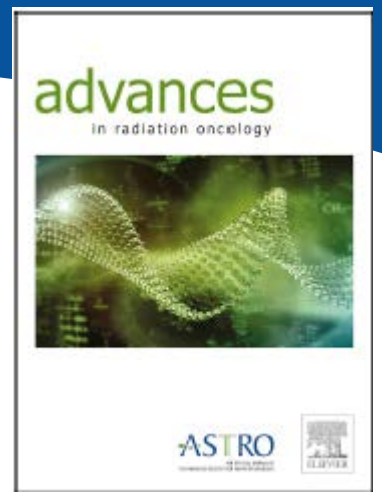
Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



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

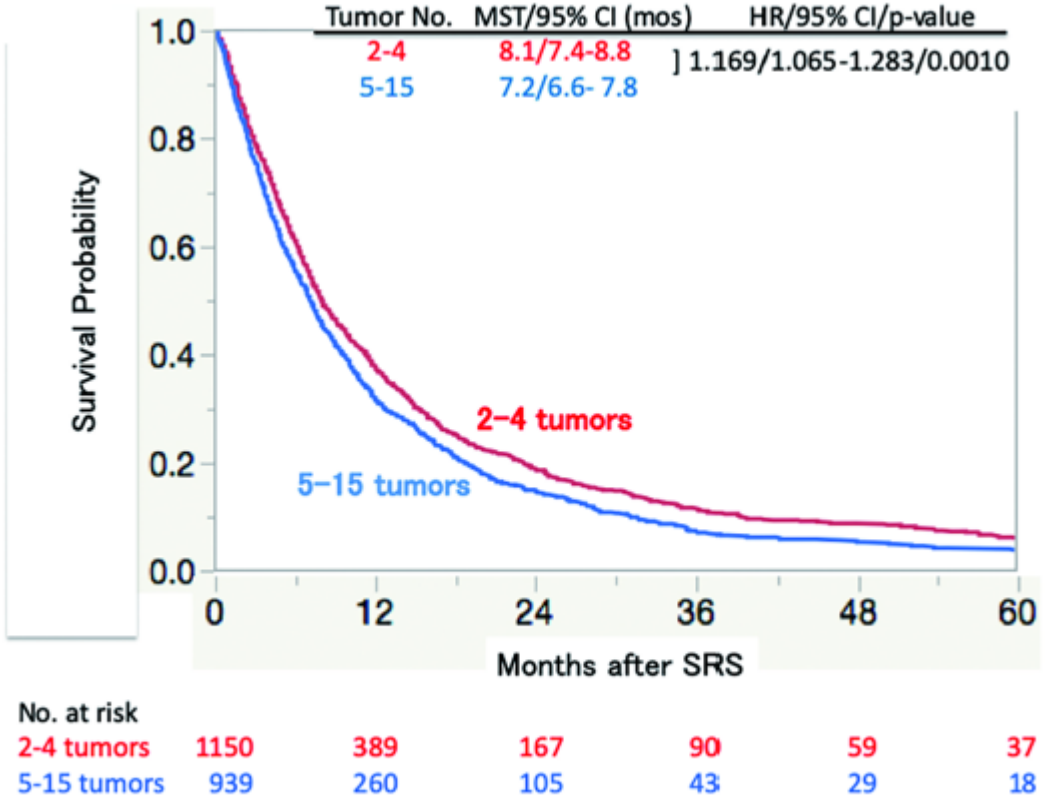
A multi-institutional prospective observational study
-Single fraction 20-22 Gy
-Cumulative volume < o = 15mL
-Resume Several randomized clinical Trials
-1194 patients (455 1 mts, 531 2-4 mts, 208 5-10 mts).
-OS non inferior between 1-4/5-10
BUT
-1-4 BMs fewer neurocognitive sequelae and improved quality of life with SRS

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



A Cohort Study of Stereotactic Radiosurgery Results for Patients with 5-15 versus 2-4 Brain Metastatic Tumors

Masaaki Yamamoto, M.D., Ph.D., Yasunori Sato, Ph.D., Yoshinori Higuchi, M.D., Ph.D., Hidetoshi Kasuya, M.D., Ph.D., Bierta E. Barfod, M.D.



Compared SRS results for 2-4 vs 5-15 BMs based on 1254 patients with 2-4 tumors and 939 with 5-15 BMs

Fig. 3A

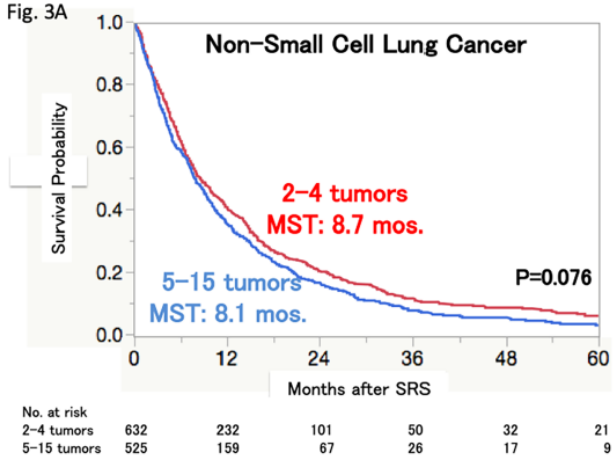


Fig. 3B

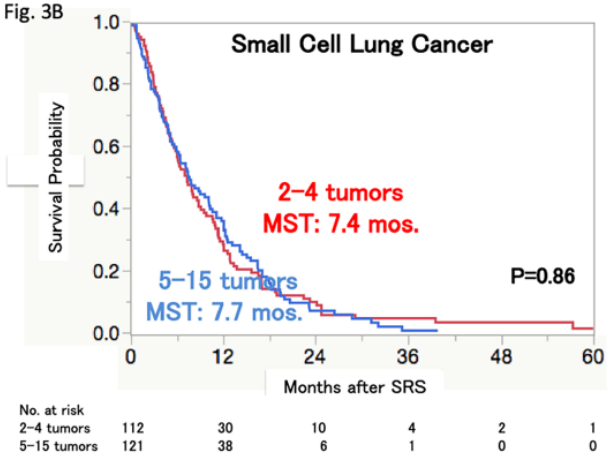


Fig. 3C

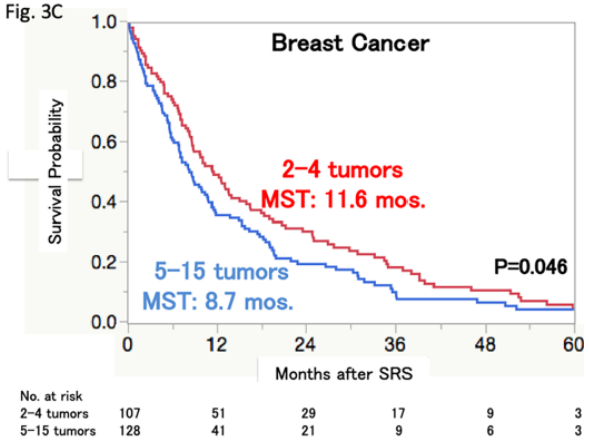


Fig. 3D

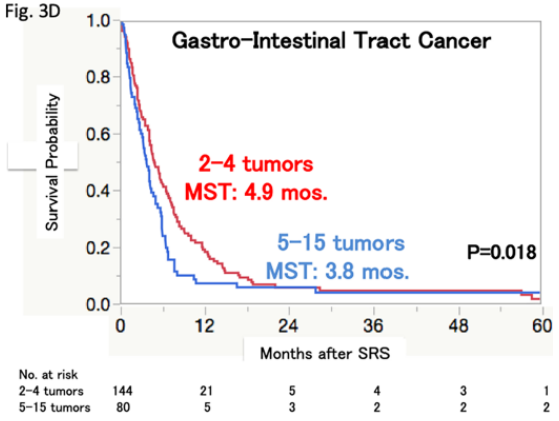


Fig. 3E

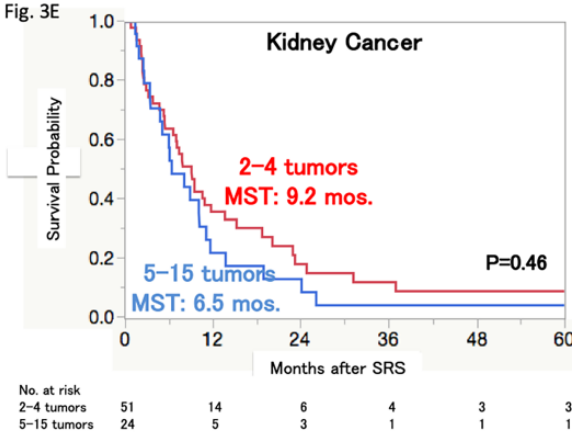
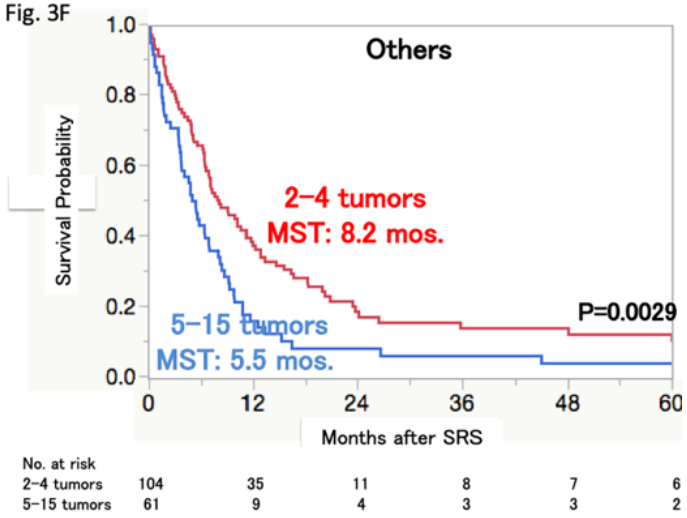


Fig. 3F



Treatment results for patients with 5-10 BMs were not inferior to those for patients with 2-4 BMs, and, notably, found that there was no significant difference in long-term neurocognitive function (NCF) maintenance between the two tumor number groups (GPA prognostic index)

NHS Criteria for commissioning

Patients meeting all of the following criteria will be routinely funded for SRS/SRS:

- MDT discussion
- Systemic disease status controllable/new diagnosis/no extra cranial disease
- Prognosis > 6 months
- PS ECOG ≤ 2
- Total PTV ≤ 20cc
- SRS New BM (> 3 months after)
- RE-RT (> 6 months)

AIM

- The aim of this report is to evaluate the utility of the NHSE selection criteria by comparing outcomes with previously published data.
- We have also sought to identify prognostic factors that may help to further define patient subgroups that may specifically or particularly benefit from radiosurgery for brain metastases.

Dott.ssa C. Reverberi

Treatment's preparation

- CT scan with thermoplastic mask: Axial unenhanced images were acquired at 1.5mm slice-thickness
- The MRI scan images were acquired without immobilisation in the mask, using 1mm slices with intravenous gadolinium contrast.
- All patients underwent SRS/SRT using CyberKnife robotic radiosurgery (Eclipse system) or gantry-based Linac radiosurgery (on Elements System)

Planning procedu

- The dose was prescribed to each PTV volume separately, and the planning team would aim to covered at least 98% of the volume by the 50% isodose at least
- The prescribed doses vary between 16-24Gy for a single fraction of treatment and between 21-25Gy for 3-5 fractions

TABLE 1. STANDARD VOLUME-BASED PRESCRIPTION DOSES (SHAW 2000)

PTV volume	Maximum Prescription dose	No. of fractions
≤ 4 cm3	24Gy	1#
≤ 8 cm3	20Gy	1#
> 8 cm3 and ≤ 14 cm3	18Gy	1#
In conjunction with immediate (within 4-6 weeks) whole brain radiotherapy:		
≤ 1 cm3	20Gy	1#
≤ 4 cm3	18Gy	1#
> 4 cm3 and ≤ 14cm3	16Gy	1#

Summary of dose constraints for organ at risk (Hanna 2018) (Susan 2016 (Apr)) (Mayo 2010) (Lambrecht 128(2018))

Single fraction radiosurgery (1#)

OARs	Dmax Constraint*	Volume constraint
Optic Chiasm	Ideally < 10Gy Acceptable < 12Gy	V8Gy ≤ 0.1cc
Optic Nerve	Ideally < 10Gy Acceptable < 12Gy	V8Gy ≤ 0.1cc
Retina	5Gy	
Lens	2Gy	
Cochlea	9Gy	4Gy D mean for hearing preservation
Facial Nerve	16Gy	
Trigeminal Nerve	20Gy	
Cranial Nerve 3,4,6	26Gy	
Cranial Nerve 9,10,11	12Gy	
Brainstem**	Ideally < 10Gy Acceptable < 12.5Gy	V10 ≤ 0.5cc
Normal brain (no PTV included)	Aim V10Gy ≤ 10cc Acceptable V12Gy ≤ 10cc	V5Gy ≤ 50%

Three fractions radiosurgery (3#)

OARs	Dmax Constraint	Volume constraint
Optic Chiasm	Ideally < 15Gy Acceptable < 17.4Gy	V15.3Gy ≤ 0.1cc
Optic Nerve	Ideally < 15Gy Acceptable < 17.4Gy	V15.3Gy ≤ 0.1cc
Cochlea	17.1Gy	6Gy D mean for hearing preservation
Facial Nerve	26Gy	
Trigeminal Nerve	26Gy	
Brainstem**	Ideally < 18Gy Acceptable < 23.1Gy	
Normal brain (no PTV included)	V19.5Gy ≤ 10cc	V5Gy ≤ 50%

*Dmax to poit dose impies dose to volume < 0.035cc** Where PTV is not inside the brainstem

Table 1. Patient characteristics

No of patients May 2016-Sept 2018	**386**		
Gender	Male 166 (43%)	Female 220 (57%)	
Age	Median: 63 years	M 67 ys (range 21-89)	F 60 ys (28-86)
Karnowski Performance Status (KPS) 348 pts analysed	100	48 pts (13.8%)	
	90	155 pts (44.6%)	
	80	92 pts (26.4%)	
	70	53 pts (15.2%)	
Status extra-cranial disease	Controllable	296 pts (76.7%)	
	No extracranial disease	66 pts (17.1%)	
	New diagnoses	24 pts (6.2%)	
Treatment characteristics			
Number of fractions	**Single** (293 pts – 75.9%)	**Three** (93 – 24.1%)	
Total Dose	16Gy – 19 Gy (24 pts-8.2%) 20Gy – 24 Gy (269pts – 91.8%)	20-23 Gy (7 pts-7.5%) 24 Gy (84 pts-90.3%) 27 Gy (2 pts – 2.1%)	

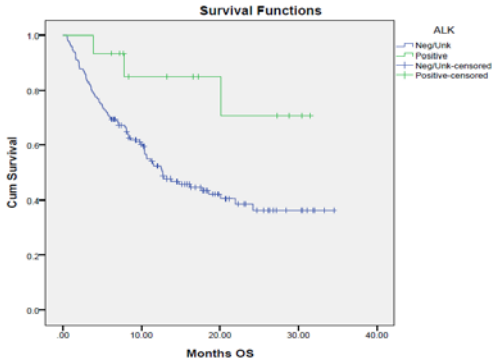
Extra-cranial disease (ECD)					
Controllable	296	12.62 (9.54-15.7)	0.012	2.24	0.003
New diagnosis	24	12.82 (8.31-17.33)		2.01	0.086
No ECD	66	NR		-	0.013
Volume category					
0-4cc	207	19.86	<0.0001	-	0.284
4-8cc	100	10.26 (5.93-14.58)		1.33	0.155
>8cc	79	10.88 (7.67-14.09)		1.38	0.22
Number of met					
1	141	NR	0.008	-	0.003
2-4	165	11.74 (9.48-13.99)		1.75	0.002
>5	80	17.95 (9.86-26.05)		1.1	0.69
Number of fraction					
1#	293	16.011 (11.88-20.14)	0.055		0.99
3#	93	10.88 (7.82-13.94)			

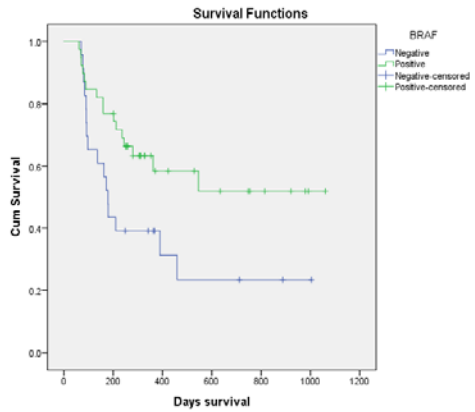
OS & Primary tumour histology

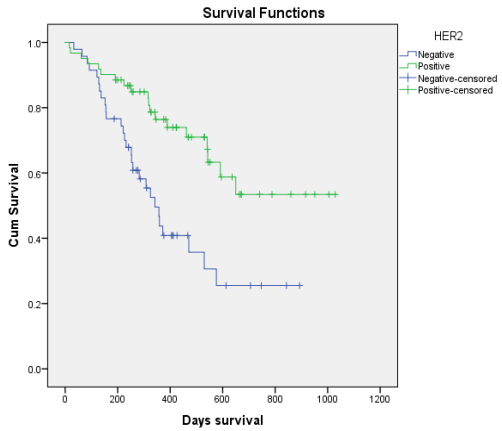
Table 4. Univariate and Multivariate analysis of OS according to the primary tumour.

	No pts	No events (death)	Median OS (95%CI)	Univar anal. (P value)	Multivar anal. (P value)	HR (95% CI)
All	386	196	15.19 (12.0-18.38)	0.012		
Breast	90	37	19.43 (12.86-26.0)		0.002	0.51 (0.34-0.78)
Lung	162	82	14.56 (8.1-21.02)		0.026	0.68 (0.48-0.95)
Melanoma	49	23	15.09 (3.57-26.6)		0.081	0.65 (0.40-1.05)
Others	85	54	9.5 (6.48-12.52)		0.013	-

	n	Overall survival: Median (months)	6 months (%)	12 months (%)	24 months (%)
All	386	15.2	72.5	55.1	38.4
Breast*	90	19.7	84.4	63.9	43.7
HER2 +ve	55	NR	89.1	73.7	51.4
HER2 -ve	32	10.8	75.0	41.9	21.0
Lung*	162	14.8	72.2	55.3	41.4
ALK +ve	15	NR	93.3	84.8	70.7
EGFR +ve	20	20.1	84.4	66.3	48.3
PDL1 +ve	54	22.0	68.5	59.8	45.8
Melanoma*	49	15.3	71.4	59.2	43.8
BRAF +ve	27	NR	81.5	66.7	55.6
BRAF WT	15	13.0	60.0	53.3	40.0



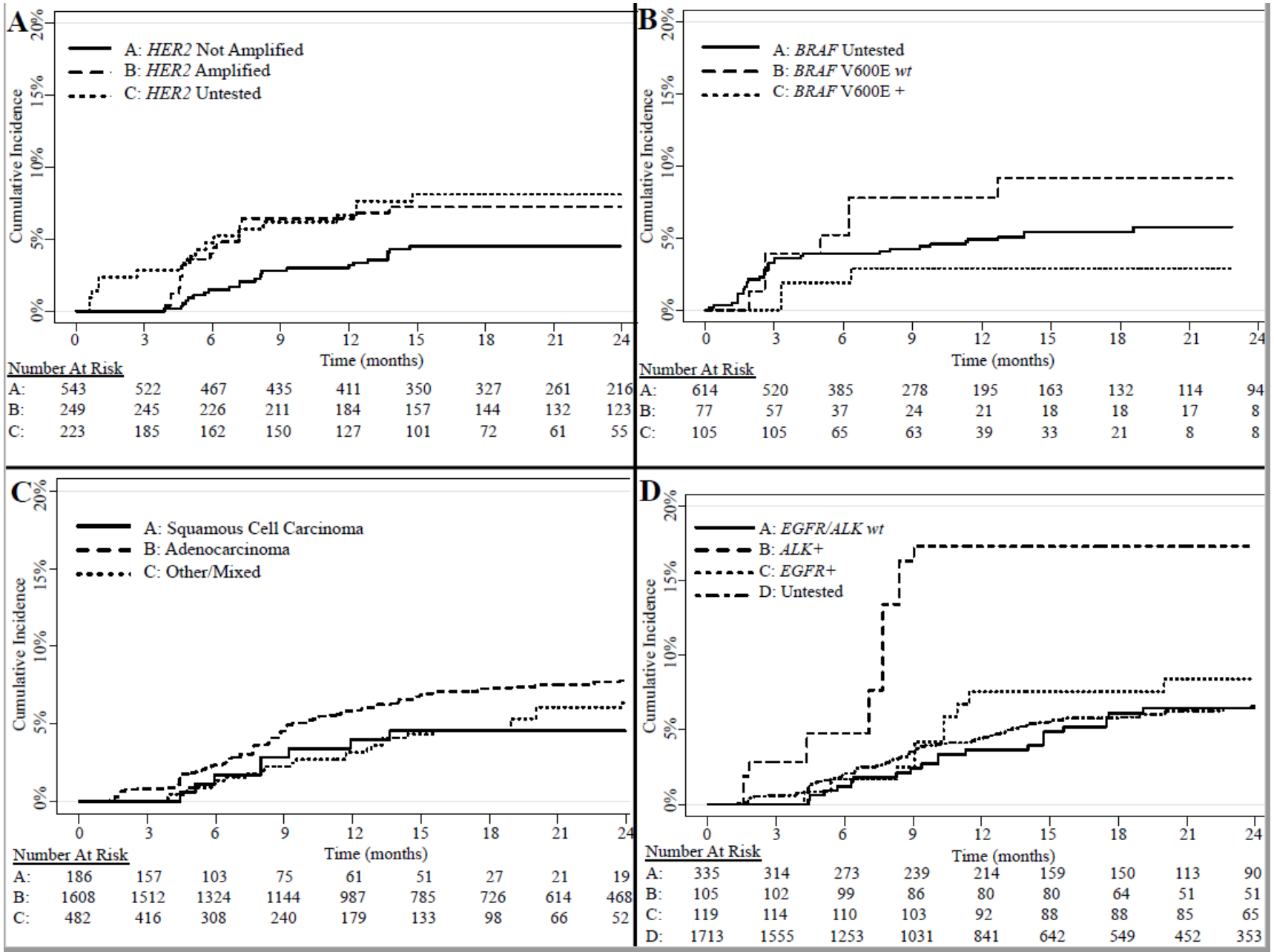




Association between Radiation Necrosis and Tumor Biology following Stereotactic Radiosurgery for Brain Metastasis

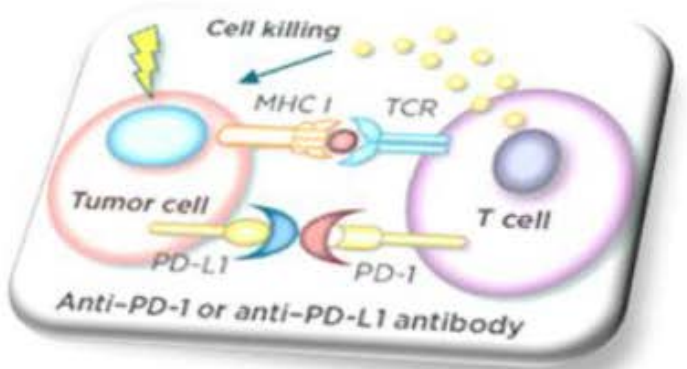
Jacob A.

Characteristic	Cohort		*P*-Value
	Radiation Necrosis	Control	
NSCLC Histology			0.01
Adenocarcinoma	83 (76)	447 (61)	
Squamous Cell	7 (6)	90 (12)	
Mixed/Other	19 (18)	190 (26)	
NSCLC Molecular Status			<0.01
EGFR- / *ALK*-	13 (12)	91 (13)	
EGFR+ / *ALK*-	9 (8)	26 (4)	
EGFR- / *ALK*+	6 (6)	5 (1)	
Unknown	81 (74)	605 (83)	
Breast Receptor Status			
ER+	24 (49)	74 (31)	<0.01
PR+	14 (29)	42 (17)	0.02
HER2-amplified	17 (35)	40 (17)	<0.01
Triple Negative	19 (39)	83 (34)	0.43
Melanoma *BRAF* Status			0.87
BRAF V600+	2 (7)	17 (10)	
BRAF V600 *wt*	4 (15)	21 (13)	
Unknown	21 (78)	129 (77)	


A
A: HER2 Not Amplified
B: HER2 Amplified
C: HER2 Untested
Cumulative Incidence
0% 5% 10% 15% 20%
0 3 6 9 12 15 18 21 24
Time (months)
Number At Risk
A: 543 522 467 435 411 350 327 261 216
B: 249 245 226 211 184 157 144 132 123
C: 223 185 162 150 127 101 72 61 55
B
A: BRAF Untested
B: BRAF V600E wt
C: BRAF V600E +
Cumulative Incidence
0% 5% 10% 15% 20%
0 3 6 9 12 15 18 21 24
Time (months)
Number At Risk
A: 614 520 385 278 195 163 132 114 94
B: 77 57 37 24 21 18 18 17 8
C: 105 105 65 63 39 33 21 8 8
C
A: Squamous Cell Carcinoma
B: Adenocarcinoma
C: Other/Mixed
Cumulative Incidence
0% 5% 10% 15% 20%
0 3 6 9 12 15 18 21 24
Time (months)
Number At Risk
A: 186 157 103 75 61 51 27 21 19
B: 1608 1512 1324 1144 987 785 726 614 468
C: 482 416 308 240 179 133 98 66 52
D
A: EGFR/ALK wt
B: ALK+
C: EGFR+
D: Untested
Cumulative Incidence
0% 5% 10% 15% 20%
0 3 6 9 12 15 18 21 24
Time (months)
Number At Risk
A: 335 314 273 239 214 159 150 113 90
B: 105 102 99 86 80 80 64 51 51
C: 119 114 110 103 92 88 88 85 65
D: 1713 1555 1253 1031 841 642 549 452 353

✓ Outline

- SRS alone for brain metastases
- How many metastases can be treated with SRS?
- *Immunotherapy/targeted therapy for brain metastases*
- Combining SRS with Immunotherapy/targeted agents
- Future research



✓ Outline

- SRS alone for brain metastases
- How many metastases can be treated with SRS?
- Immunotherapy/targeted therapy for brain metastases
- **Combining SRS with Immunotherapy/targeted agents**
- Future research

BRAF and SRS

	# concurrent BRAF/RS	Results
Marseille	20	No increased risk
Emory	15	symptomatic radiation necrosis was more frequent in the BRAF inhibitor group (28.2 vs. 11.1% at 1 year, P <0.001)
Utah	14	1-year rates of freedom from intratumoral hemorrhage were 39.3% and 77.0%
Moffitt	24	No grade 3 or greater toxicity
UVA	17	"acceptable safety profile"
UCSF	Phase II trial NCT01721603	Trial ongoing

Series with at least ten patients are mixed regarding whether concurrent BRAF agents increase risk of toxicity

Gaudy-Marqueste et al, *Annals of Oncology*, *25*(10), 2086–2091
Patel et al, Radium Society 2015 (P0011) and Melanoma Res. 2016 August ; 26(4): 387–394.
Ly et al, **J Neurosurg** 123:395–401, 2015
Ahmed et al, J Neurooncol (2015) 122:121–126
***Anker et al, IJROBP 95(2):632-646, 2016. (ECOG)**

Authors	Type of study	Patients	treatment	CNS-PFS	OS	Toxicity
Ahmed, 2016	Retrospective	21	Pembro/Nivo plus RT	6-month 61%, 12-month 38%	6-month 81%, 12-month 66%	0
						0
Parakh, 2017						NR
Anderson , 2017						0
						0
Goldberg, 2016						12%
Chen, 2018						NR
						NR
Gonzales, 2016						0
Cowey, 2018						NR
Nardin, 2018						6.8%
Qian, 2016						NR
				NR	non-concurrent 9 months	NR
Patel 2015	Retrospective	44	IPI plus SRS	12-month CNScr71.4%	12-month OS 37.1%	NR
Kiess, 2015	Retrospective	46	IPI plus SRS	NR	median OS 12.4 months 12-month OS 60%	17.4%
Queirolo, 2014	Retrospective	146	IPI	CNScr 27%	4.3 months	6%

**within 6 months; *concomitant, within 4 weeks; ^Pts with symptomatic BM had shorter PFS than those without symptoms (2.7 vs 7.4 months, P=0.035)

	6-months PFS	12-month OS
SRS plus ICI	60-80%	65-80%°°
pembro/Nivo alone	30-40%	50-60%

°°cocurrent >75%, nonconcurrent 60-75%

Brain metastases from non-small cell lung cancer with EGFR or ALK mutations: A systematic review and meta-analysis of multidisciplinary approaches

Raj Singh [a], Eric J. Lehrer [b], Stephen Ko [c], Jennifer Peterson [c], Yanyan Lou [d], Alyx B. Porter [e], Rupesh Kotecha [f], Paul D. Brown [h], Nicholas G. Zaorsky [i], Daniel M. Trifiletti [c,*]

[a] Department of Radiation Oncology, Virginia Commonwealth University Health System, Richmond; [b] Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York; [c] Department of Radiation Oncology; [d] Department of Medical Oncology; [e] Department of Neurology, Mayo Clinic, Phoenix; [f] Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida; [h] Department of Radiation Oncology, Mayo Clinic, Rochester; and [i] Department of Radiation Oncology, Penn State Cancer Institute, Hershey, USA

30 Studies (2649 pz)

	TKI Alone	RT Alone (WBRT/SRS)	Vs TKI + SRS
OS	23,3	32,2	28,3
PFS	++	+	++

Robin, et al. (2018) *	Osimertinib, ceritinib, alectinib, brigatinib, and lorlatinib	35 patients *ALK* +: 19 patients *EGFR* +: 16 patients All received SRS 28 – no prior WBRT 6 – WBRT before SRS 1- WBRT after SRS 20 – TKI during treatment course	53 (24–79)	N/A	N/A	6 (4–26)	4.1 years	Median freedom from CNS progression: 7.8 months, followed by 6.8 months, followed by 3.2 months 5-year freedom from WBRT (FFWBRT): 97%	Median OS: 3 years *ALK* + patients: 4.2 years *EGFR* + patients: 2.4 years 5-year freedom from neurologic mortality: 84%	7/516 lesions with RN (1.4%) and 4/35 patients (11.4%) occurring at a median of 9.9 months (range: 4.6–17.8 months)	Receipt of CNS-active TKIs at diagnosis associated with improved OS ($p < 0.01$)

Study	TKI	*n* (Patients)	Median Age (range)	Median GTV/PTV	Treatment Planning	Number of BM (range)	Median Follow-up (range)	CNS-PFS (95% CI)	OS (95% CI)	Toxicities	Additional Notes/ Comments
Doherty, et al. (2017)*	*EGFR*: Erlotinib or gefinitib afatanib osimertinib or rocelitinib *ALK*: crizotinib and ceritinib	184 *EGFR* + and *ALK* +: 163 WBRT and TKI: 98 WBRT, surgery, and TKI: 16 WBRT, surgery, SRS, and TKI: 1 WBRT and SRS: 5 SRS and TKI: 37 TKI alone: 20	59 (29–86)	N/A	SRS: 15–21 Gy depending on GTV WBRT: 30 Gy/10 fractions or 20 Gy/5 fractions	One: 46 2–4: 48 >4: 82 SRS: 94% with 1–4 WBRT: 61% with >4	N/A	Median time to intracranial progression WBRT + TKI: 50.5 months ($p = 0.0038$) SRS + TKI: 12 months TKI alone: 15 months *EGFR* +: Significant trend maintained as above ($p = 0.0064$) *ALK* +: NS	Median OS: WBRT + TKI: 21.6 months SRS + TKI: 23.9 months TKI alone: 22.6 months No association on MVA of first-line treatment on OS	N/A	
Wang, et al. (2018)*	Icotinib, erlotinib or gefitinib osimertinib	45 all *EGFR* + Upfront RT (interval between diagnosis and RT of <3 months): 30 Deferred RT for chemotherapy or TKI: 15	46 (58–70)	N/A	WBRT: 30 Gy/10 fractions SRS: N/A	One: 14 Two: 5 >2: 26	N/A	Median intracranial PFS: 17.7 months (12.4–23)	($p = 0.083$) Median OS: 28 months (17.3–38.7) Upfront RT: 26.5 months Upfront TKI: 28 months	N/A	
Xie, et al. (2018)	Osemertinib	40 all *EGFR* + treated with osemertinib Progressing BMs with TKI only (Group A): 11 Progressing BMs with TKI and SRS (Group B): 9 Stable BMs with TKI only (Group C): 20	63 (32–81)	(SD: 1.1) Median GTV: Group A: 9 cc (3–25 cc) Group B: 11 cc (4–30 cc)	N/A	N/A	N/A	Median intracranial PFS: 8.8 months (6.2–12.1) Group A: 8.8 months (4.3–13.4) Group B: Not reached Group C: 8.4 months (5.6–11.1)	($p = 0.19$) Median OS: 16.2 months Group A: Not reached Group B: 16.2 months Group C: Not reached	N/A	

(continued on next page)

Preliminary experience of the concurrent use of radiosurgery and T-DM1 for brain metastases in HER2-positive metastatic breast cancer

Toxicity

J Neurooncol. 2017 May;132(3):525. doi: 10.1007/s11060-017-2405-0. Epub 2017 Mar 23.

Arthur Geraud[1] · H

Radio-sensitising effect of T-DM1 should not be discarded for the efficacy of radiosurgery in the management of brain metastases in patients with HER2-positive metastatic breast cancer.

Altundag K[1].

Results

Author information

Response

Comment on
Preliminary experience of the concurren
Neurooncol. 2017]

After radiosurgery and concurrent T-DM1 (r

Neuro Oncol. 2014 Jul;16(7):1006-9.

Trastuzumab emtansine and stereotactic radiosurgery for brain metastases: report of a case with significant brain edema.

Carlson JA, Nooruddin Z, Rusthoven C, Elias A, Borges VF, Diam

Abstract

BACKGROUND: In the last 10 years, multiple new targete
factor receptor 2-positive (HER2+) breast cancer. Up to
requiring some form of radiation therapy. The interaction
unreported.

METHODS: In this series, we describe 4 patients who de
These patients were treated with stereotactic radiosurge
metastatic HER2+ breast cancer. Additionally, we presen
patients treated during this same time period.

RESULTS: Using previously published clinical and preclin
interaction.

CONCLUSION: Increased awareness of potential interact

y was low for most
patients in the con-
uential group. The

Combination of Trastuzumab Emtansine and Stereotactic Radiosurgery Results in High Rates of Clinically Significant Radionecrosis and Dysregulation of Aquaporin-4.

Stumpf PK[1], Cittelly DM[2], Robin TP[3], Carlson JA[4], Stuhr KA[3], Contreras-Zarate MJ[2], Lai S[2], Ormond DR[5], Rusthoven CG[3], Gaspar LE[3], Rabinovitch R[3], Kavanagh BD[3], Liu A[3], Diamond JR[6], Kabos P[7], Fisher CM[1].

Author information

Abstract

PURPOSE: Patients with human EGFR2-positive (HER2$^+$) breast cancer have a high incidence of brain metastases, and trastuzumab emtansine (T-DM1) is often employed. Stereotactic radiosurgery (SRS) is frequently utilized, and case series report increased toxicity with combination SRS and T-DM1. We provide an update of our experience of T-DM1 and SRS evaluating risk of clinically significant radionecrosis (CSRN) and propose a mechanism for this toxicity.

EXPERIMENTAL DESIGN: Patients with breast cancer who were ≤45 years regardless of HER2 status or had HER2$^+$ disease regardless of age and underwent SRS for brain metastases were included. Rates of CSRN, SRS data, and details of T-DM1 administration were recorded. Proliferation and astrocytic swelling studies were performed to elucidate mechanisms of toxicity.

RESULTS: A total of 45 patients were identified; 66.7% were HER2$^+$, and 60.0% were ≤ 45 years old. Of the entire cohort, 10 patients (22.2%) developed CSRN, 9 of whom received T-DM1. CSRN was observed in 39.1% of patients who received T-DM1 versus 4.5% of patients who did not. Receipt of T-DM1 was associated with a 13.5-fold (P = 0.02) increase in CSRN. Mechanistically, T-DM1 targeted reactive astrocytes and increased radiation-induced cytotoxicity and astrocytic swelling via upregulation of Aquaporin-4 (Aqp4).

CONCLUSIONS: The strong correlation between development of CSRN after SRS and T-DM1 warrants prospective studies controlling for variations in timing of T-DM1 and radiation dosing to further stratify risk of CSRN and mitigate toxicity. Until such studies are completed, we advise caution in the combination of SRS and T-DM1.

RESEARCH ARTICLE Open Access

Stereotactic radiosurgery combined with nivolumab or Ipilimumab for patients with melanoma brain metastases: evaluation of brain control and toxicity

Giuseppe Minniti[1*], Dimitri Anzellini[2], Chiara Reverberi[2], Gian Carlo Antonini Cappellini[3], Luca Marchetti[1], Federico Bianciardi[1], Alessandro Bozzao[4], Mattia Osti[2], Pier Carlo Gentile[1] and Vincenzo Esposito[5]

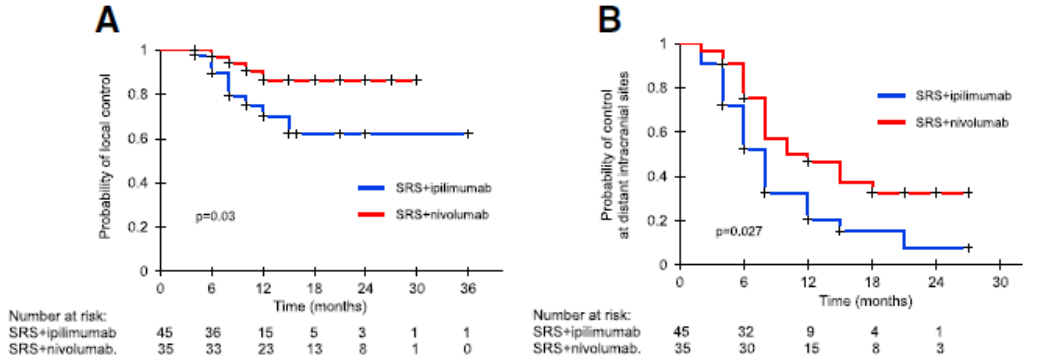


Fig. 2 Kaplan-Meier analysis of local control (LC, **a**) and distant brain control (DBC, **b**) after concurrent SRS and ipilimumab (blue li nivolumab (red line). LC and DBC were significantly better in SRS and nivolumab group

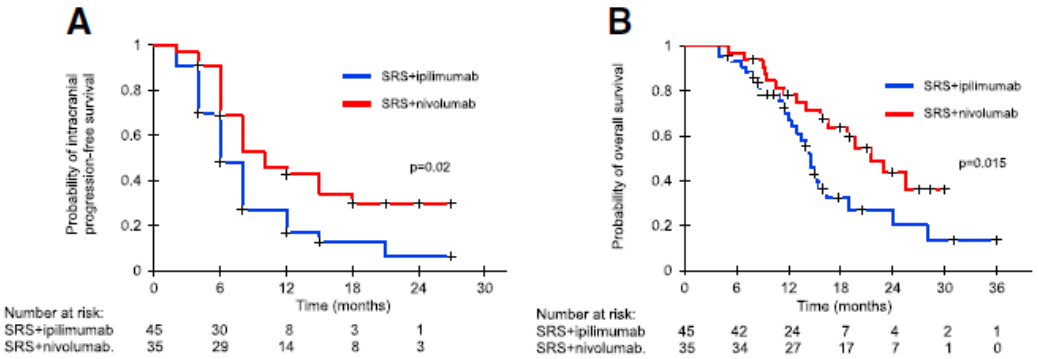


Fig. 1 Kaplan-Meier analysis of overall survival (OS, **a**) and intracranial progression-free survival (PFS, **b**) for patients receiving concurrent SRS and ipilimumab (blue line) or nivolumab (red line). OS and intracranial PFS were significantly better in SRS and nivolumab group

CNS event				
Headache	8 (18%)	2 (4%)	4 (12%)	1 (3%)
Hemorrhage	3 (7%)	1 (2%)	2 (6%)	1 (3%)
Seizure	3 (7%)	2 (4%)	2 (6%)	1 (3%)
Diziness	4 (9%)	0	2 (6%)	0
Brain necrosis	13 (29%)	5 (11%)	7 (20%)	3 (9%)
Discontinuation of treatment	5		3	

[a]Treatment-related adverse events of any grade occurring in at least 5% of patiens in either cohorts. Some patients had more than one event. No grade 4 events were reported in both cohorts

Single-fraction versus multi-fraction (3 x 9 Gy) stereotactic radiosurgery for large (> 2 cm) brain metastases: a comparative analysis of local control and risk of radiation-induced brain necrosis

Giuseppe Minniti, M.D,

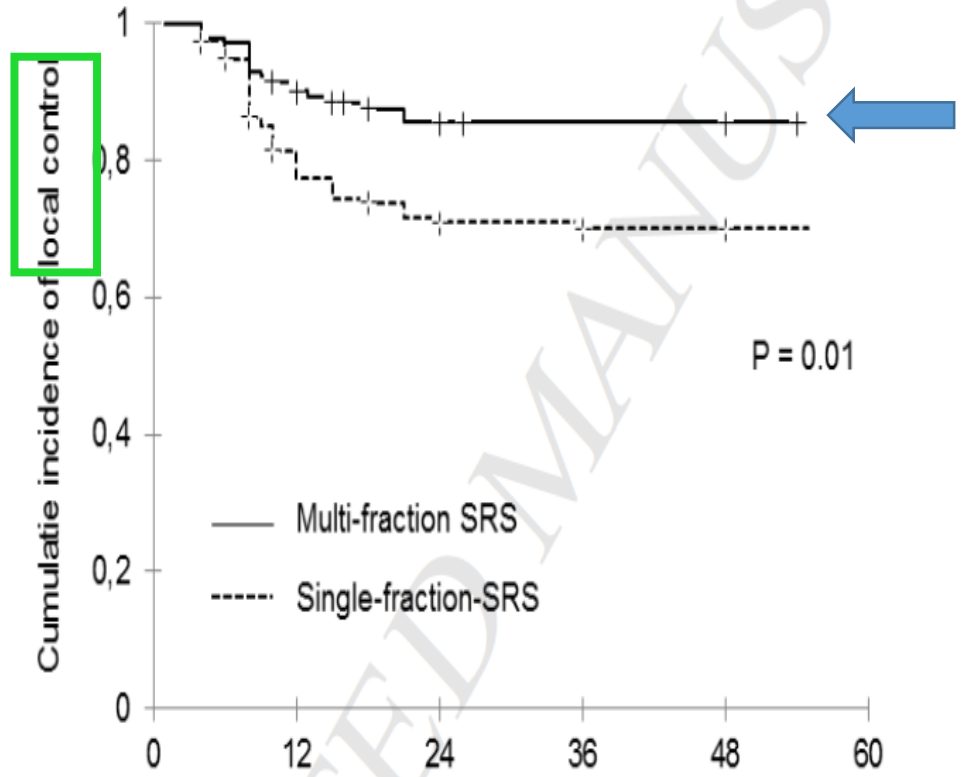
Table 2. Effect of single-fraction SRS and multi-fraction SRS on LC and RN risk [a,b]

Outcome	HR*	95% CI	p
Local control			
Unadjusted cohort	0.43	0.21 to 0.9	0.03
Propensity score matching	0.35	0.13 to 0.76	0.01
IPTW propensity score	0.33	0.16 to 0.68	0.007
RN risk			
No adjustment	0.42	0.21 to 0.83	0.03
Propensity score matching	0.22	0.14 to 0.73	0.005
IPTW propensity score	0.23	0.18 to 0.66	0.001

Abbreviations: SRS, stereotactic radiosurgery; LC, local control; RN,radiation-induced brain necrosis; HR, hazard ratio; CI, confidence interval; * Single-fraction SRS is the reference group;
a Propensity score-matching and inverse-probability-of-treatment weighting (IPTW) propensity score
b age at diagnosis, gender, histology, number of metastases, extracranial disease, and tumor volumes

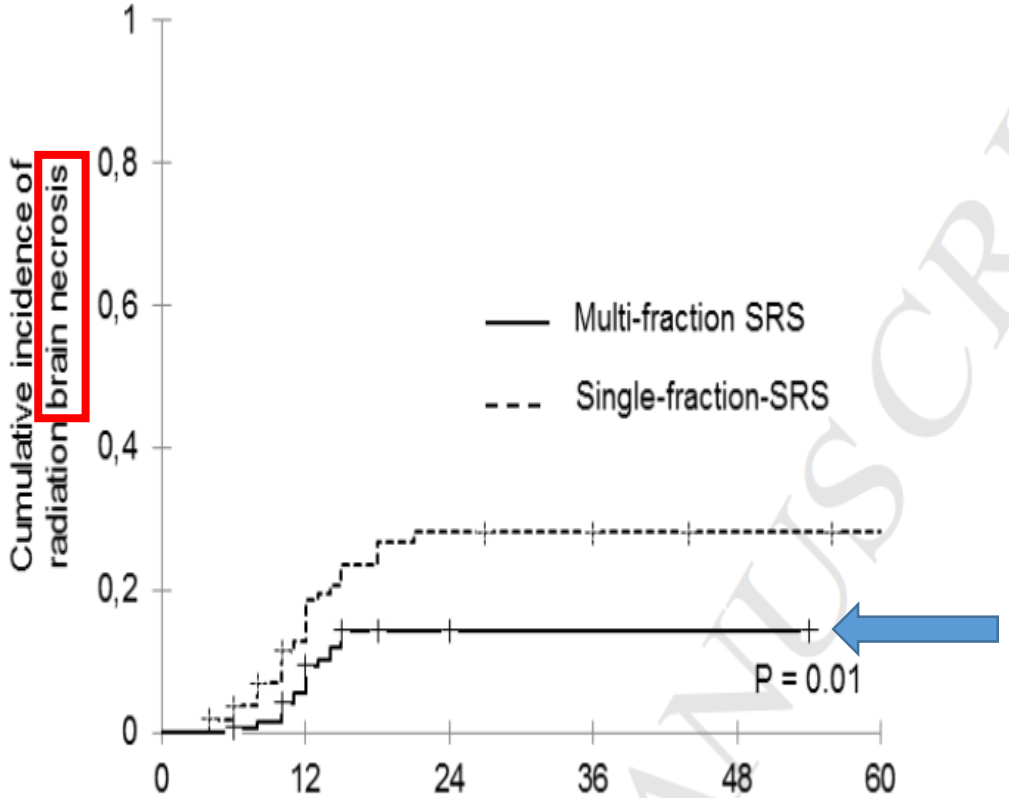
- Different radiation schedules used to treat large metastasis (3x7Gy n=11)
- V12 e V18 Gy most significant predictors of RN
- BED: 108 — 9Gyx3
  EQD2: 64,8
- BED:70 — 7Gyx3
  EQD2:42
  BED: 153
  EQD2: 92

  a/b 3
- WBRT 30Gy:BED 60 EQD2 36



Number at risk:

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



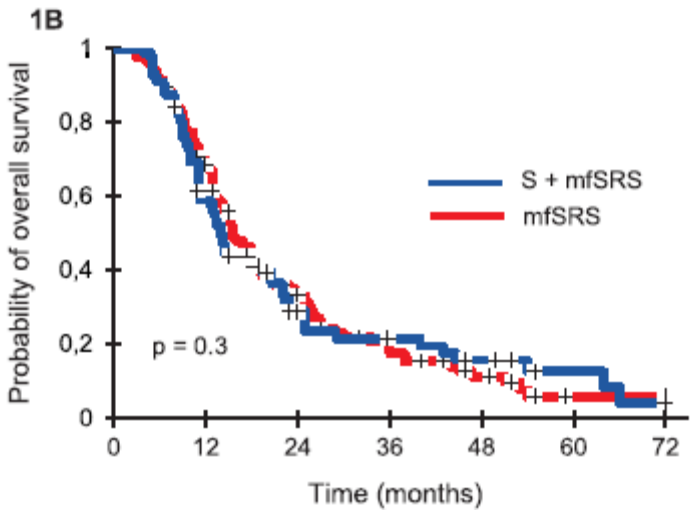
Number at risk:

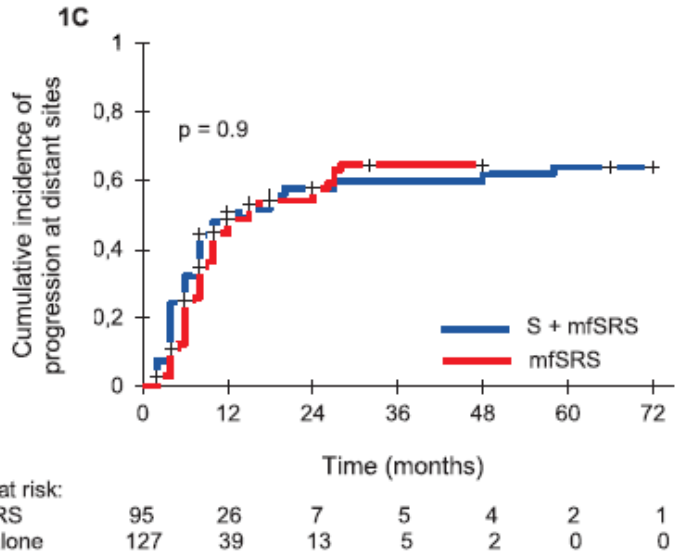
Single-fraction SRS	179	64	17	6
Multi-fraction SRS	164	60	14	5

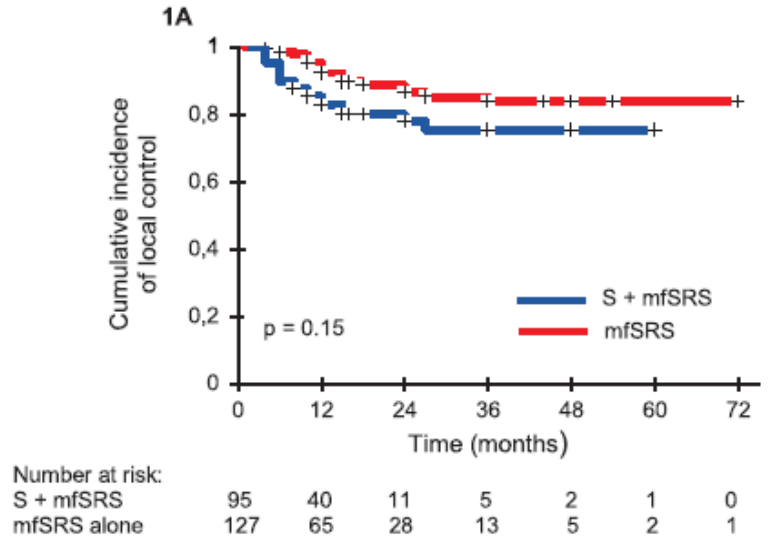
Comparative effectiveness of multi-fraction stereotactic radiosurgery for surgically resected or intact large brain metastases from non-small-cell lung cancer (NSCLC)

Giuseppe Minniti[a,*], Claudia Scaringi[a], Gaetano Lanzetta[b], Dimitri Anzellini[c], Federico Bianciardi[a], Barbara Tolu[a], Roberta Morace[b], Andrea Romano[d], Mattia Osti[a], PierCarlo Gentile[a], Sergio Paolini[b]

[a] *Radiation Oncology Unit, UPMC Hillman Cancer Center, San Pietro Hospital FBF, Rome, Italy*
[b] *IRCCS Neuromed, 86077 Pozzilli IS Italy*
[c] *Radiation Oncology Unit, Sant' Andrea Hospital, University Sapienza, 00100 Rome, Italy*
[d] *Neuroradiology Unit, Sant' Andrea Hospital, University Sapienza, 00189 Rome, Italy*







Int J Radiat Oncol Biol Phys. 2011 Jun 1;80(2):362-8. doi: 10.1016/j.ijrobp.2010.02.028.

Minimized doses for linear accelerator radiosurgery of brainstem metastasis.

Valery CA[1], Boskos C, Boisserie G, Lamproglou I, Cornu P, Mazeron JJ, Simon JM.

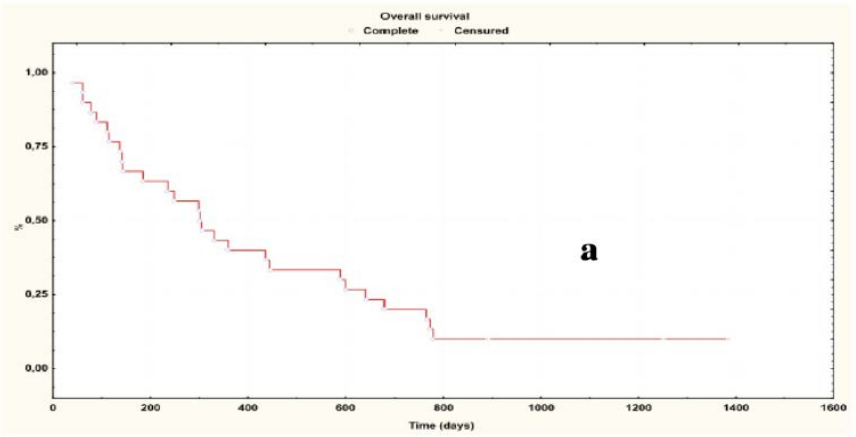
Table 2. Neurological status before and after treatment

		Post-SRS status		
		No change	Improvement	Deterioration
Pre-SRS status	No symptoms	12	—	4
	Hemiparesis	1	2	2
	Cranial nerve palsy	1	3	1
	Cerebellar syndrome	1	3	0

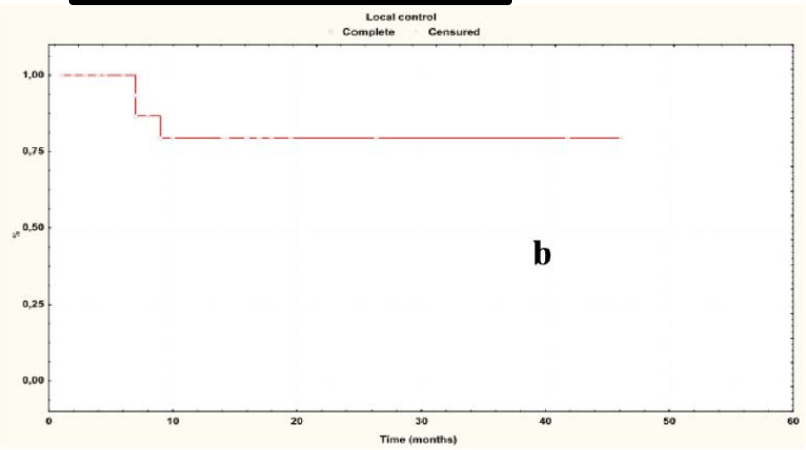
CONCLUSION

Brainstem metastases are known to be challenging lesions. They are difficult to control with conventional treatments but nevertheless require optimized local control before a significant influence on patient survival can be achieved. In our study, we show that reduced doses, compared with those usually administered, can achieve the same local control of brainstem lesions with no side effects. This could well minimize the risk of neurological deterioration, and could lead to possibilities for further local treatment with second radiosurgery or conformal radiotherapy to the area if required.

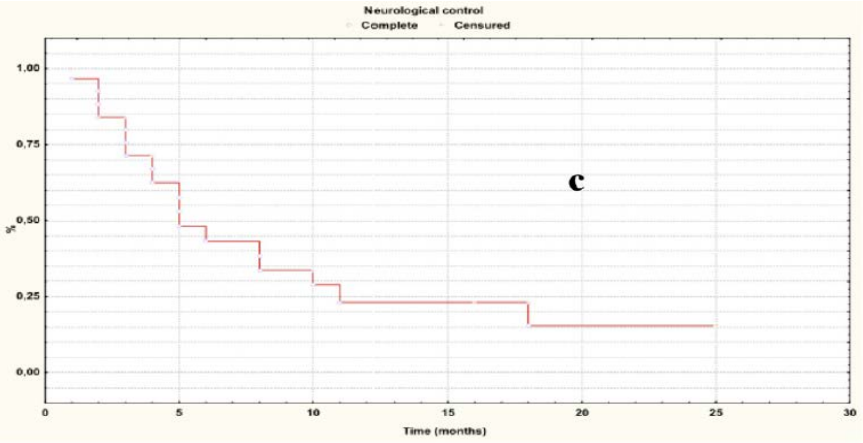
Overall Survival



Local Control



Neurological control



Research Project: MF-SRS concomitant with Immunotherapy or Target therapy

Anzellini D., Reverberi C., Bozzao A., Botticelli A., Pellegrini P., De Sanctis V., Osti M.F.

Overview of the research proposed at national and internationale level

-SRS Vs WBRT
-SRS Vs MF-SRS
-IT/TT: LC 22 al 93%

% PD (Manteinance of the treatment line)
Symptomatic

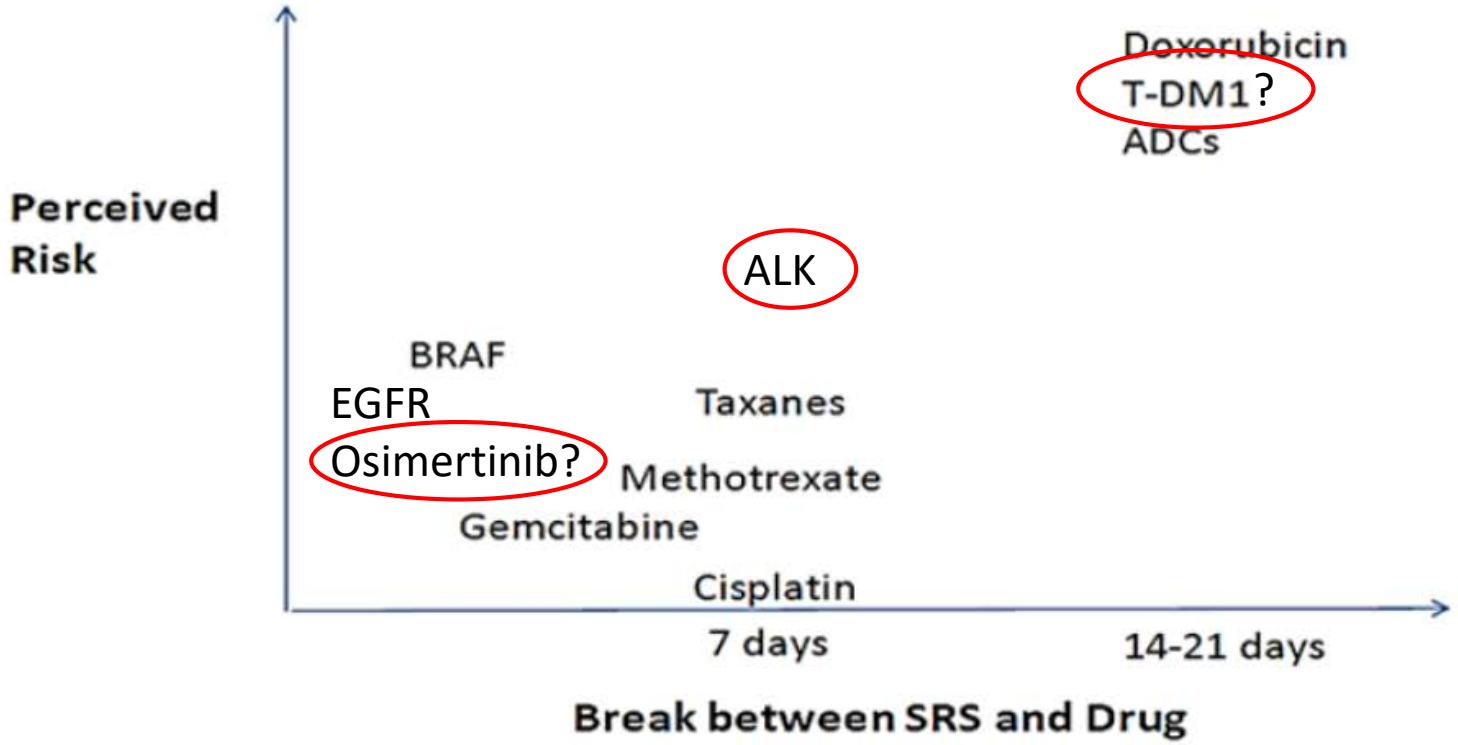
Objectives and methodology

Inclusion criteria
-age =/> 18 anni
-KPS =/> 70
-BMs (V=/< 15 mL)
-No pre-SRS o Ch

-MF-SRS 9Gy x 3/ 8Gy x3
- GTV T1 volumetric
-PTV 2mm
-q21, q15
-7d (ALK)

-IRANO
-PET/TC

MF-SRS Plus Drug



No break:

- **anti-PD1**
- **anti-PDL1**
- **anti-CTLA-4**
- **capecitabine**
- temozolomide
- etoposide
- vinorelbine
- pemetrexed
- lapatinib
- trastuzumab
- hormonal agents
- sunitinib
- **bevacizumab**
- mTor

Future research

- *Optimal timing between SRS and immunotherapy/targeted agents*
- *Optimal dose/fractionation for BM according to size and immunotherapy/targeted agents* → Radiotherapy techiques
- *Neurocognitive status and quality of life for patients with BM treated with SRS and immunotherapy/targeted therapy*
- *Share our experience with other centers and create «big prospective database» to improve our knowledge and testing new technologies*

Grazie per l'attenzione