Management of Brain Metastases

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- Incidence of BM is increasing
- 1.improved systemic therapies -prolong survival but majority cross BBB poorly– brain is thus becoming sanctuary site of metastases
- 2.Imaging more often

- 1/3rd of all adult cancer patients develop BM
- MC primaries are Lung (20%), Breast (10%), melanoma (7%), RCC (7%)
- Incidence of brain Mets in advanced Her2 Neu +ve breast ca is 40-50%
- ALK positive NSCLC , CNS is the first site of progression –up to 45%

Wide variety of treatment options- choose wisely

- WBRT
- WBRT with HA
- WBRT with SIB
- SF-SRS
- MF-SRS
- SRS+ WBRT
- Surgery+ WBRT
- Surgery + Post op SRS
- Pre op SRS + surgery
- BSC + Steroids

- BM management has become complex
- Ideally we needs a Brain tumour MDT

- Shifting goal post from palliation to

- Neurocognition
- Control
- Survival

STUDIES ON SOLITARY BRAIN METASTASES

WBRT +/- Surgery

- WBRT -standard of care for long time
- Patients with solitary BM
- WBRT alone Vs. Surgery + WBRT ?

- Seven Studies including 3 RCTs

Solitary Brain Metastasis-- Role of Surgery

SINGLE LESION; ALL PRIMARIES

TABLE II Randomized trials of surgery plus radiation therapy as compared with radiation therapy alone

Reference	*Treatment*	*Patients (n)*	*Eligibility criteria*	*Steroids*	*Median survival (months)*	*Local recurrence (%)*	*Median functionally independent survival (months)*
Patchell *et al*. 1990 [5]	WBRT	23	KPS≥70,	All	3.5	52	1.8
	WBRT + surgery	25	age≥18		9.2	20	8.8
					$p<0.01$	$p<0.02$	$p<0.005$
Vecht *et al*. 1993 [8]	WBRT	31	WHO PS≤2,	Most	6	NR	3.5
	WBRT + surgery	32	age≥18		10		7.5
					$p=0.04$		$p=0.06$
Mintz *et al*. 1996 [6]	WBRT	43	KPS≥50,	All	6.3	NR	NR
	WBRT + surgery	41	age<80		5.6		
					$p=0.24$		

WBRT = whole-brain radiation therapy; KPS = Karnofsky performance status; WHO PS = World Health Organization performance status; NR = not reported.

Surgery: Improved local control and overall survival

RCT- Patchell et all NEJM 1990

- 48 pts with solitary BM confirmed on MRI
- Arm 1- Stereotactic Biopsy +WBRT (36Gy/12fr)
- Arm2- Complete resection +WBRT (36Gy/12fr)
- All pts had KPS $\geq$70
- Radiosensitive histologies like SCLC, Myeloma, Leukaemia, Lymphoma, GCT were excluded
- Increase in survival in surgical group 40 Vs. 15 weeks

Patchell RA NEJM 322(8):494-500

RCT Canadian Trial

- 84 pts WBRT alone vs Sx +WBRT (30Gy/10fr)
- Pts with good PS/NPS/life expectancy were chosen
- Solitary BM
- SCLC, leukaemia and Lymphoma were excluded
- Gross total resection achieved in 38 out of 40 pts
- No diff in OS (6.3 Mo vs 5.6 Mo for RT vs Surgery arm)
- Possible factors leading to non benefit in surgical arm- More patients with extracranial ds, MRI was not mandatory- its possible that additional lesions were missed on CT scan

Mintz et all ; cancer78(7):1470-76

ANSWER- WBRT +/- Surgery for solitary BM

- Significant survival and LCR benefit with surgery as compared to WBRT alone
- Benefit of surgery may be lost in patients with extracranial ds or poor PS

Surgery Vs. Surgery + WBRT for solitary BM

- One RCT and 3 Retrospective studies
- RCT- Multicentric study from US by Patchell et all
- 95 Pts with solitary BM confirmed on biopsy and KPS $\geq$70
- Complete resection of metastases
- WBRT 50.4Gy/28 fr Vs. no further T/t
- NSCLC was dominant
- >1/3 rd pts in both arms had no extracranial ds

Patchel RA JAMA 280(17):1485-89

	Surgery	Surgery+ WBRT	
Brain recurrence	70%	18%	P <0.001
Recurrence at original site	46%	10%	P<0.001
Distant site in brain	37%	14%	P<0.01
Time to any recurrence in brain was longer in WBRT arm			
Death due to neurological cause	44%	14%	0.003
Median survival	43 weeks	48 weeks	Not different; study was not powered to detect difference in OS

Overall this study has shown benefit of WBRT – however some consider salvage WBRT in view of lack of OS benefit

Message Surgery +/- WBRT

- Surgery alone is not sufficient– even in solitary metastases
- Type of RT can be WBRT/ SRS boost
- RT improves LCR; WBRT prevents distant brain failure
- ?impact on OS

Surgery + WBRT Vs. SRS– SOLITARY BM

- One small RCT and 2 Retrospective studies

Table 2 SRS versus Surgery + WBRT

First author (Year)	Interventions	Median survival	# pts with recurrence/ progression[a]	Median time to recurrenc progression
Randomized controlled trials				
Muacevic [23] (2008)	G1: SRS ($n = 31$) G2: Surgery + WBRT ($n = 33$)	G1: 10.3 months G2: 9.5 months (Log-rank; P = NS)	1 yr local control rate: G1: 97% G2: 82% 1 yr distant recurrence rate: G1: 26% G2: 3%	At original site: Median: NR (LR curves: log-rank; $P = 0.06$, NS) At distant brain sites: Median: NR (DR curves: log-rank; $P = 0.04$)

SRS mean 21Gy (14-27Gy)
WBRT 40Gy/20fr

- RCT is a multicentric study from Germany
- No diff in OS
- Duration of freedom from LR – similar b/w both groups
- Freedom from recurrence at distant brain site was longer in WBRT arm

Muacevic et all Neurooncol 87(3):299-307

Message--Surgery + WBRT Vs. SRS– SOLITARY BRAIN MET

- Equivalent LCR- Surgery is not giving any additional benefit for LCR- Why do Surgery??
- WBRT reduced DBF
- OS similar

Surgery +WBRT Vs. SRS +WBRT- SOLITARY BM

- No prospective studies, 4 retrospective studies
- In 3 studies no diff in OS while in one study OS inferior in SRS arm
- 2 studies showed longer duration of freedom from LR in SRS arm

Table 3 Surgery + WBRT versus SRS + WBRT

First author (Year)	Interventions	Median survival	# pts with recurrence/progression[a]	Median time to recurrence/progression
Retrospective cohort studies				
Bindal [16] (1996)	G1: Surgery ± WBRT[b] (n = 62) [matched to G2] G2: SRS ± WBRT[b] (n = 31)	G1: 16.4 months G2: 7.5 months (Log-rank; $P = 0.0018$)	1 yr freedom from LR rate: G2 poorer than G1 [Data: NR] 1 yr freedom from DR rate: G1: 75% G2: 69%	At original site: G1: Median not reached G2: 6 months (Log-rank; $P = 0.0001$) At distant brain sites: G1: Median not reached G2: Median not reached (Log-rank; P = NS)
Garell [17] (1999)	G1: Surgery + WBRT (n = 37) G2: SRS + WBRT (n = 8)	G1: 8 months G2: 12.5 months (Log-rank P = NS)	NR	NR

Schoggl [18] (2000)	G1: Surgery + WBRT ($n = 66$) G2: SRS + WBRT ($n = 67$)	G1: 9 months G2: 12 months (Test unclear; P = NS)	At original site: G1: 11/66 (17%) G2: 3/67 (5%) (P = NR) At distant brain sites: G1: 10/66 (15%) G2: 7/67 (10%) (P = NR)	At original site: G1: 3.9 months G2: 4.9 months (Test unclear; $P < 0.05$) At distant brain sites: G1: 3.7 months G2: 4.4 months (Test unclear; P = NS)
O'Neill [19] (2003)	G1: Surgery ± WBRT[b] ($n = 74$) G2: SRS ± WBRT[b] ($n = 23$)	Median survival: NR 1 yr survival rate: G1: 62% G2: 56% (Log-rank; P = NS)	At original site: G1: 11/64 (17%) G2: 0/21 (0%) (P = NR) Overall in brain: G1: 19/64 (30%) G2: 6/21 (29%) (P = NR)	NR

Summary of evidence for solitary BM

- WBRT alone is not enough- level I evidence
- Surgical resection alone is not enough- Level I evidence
- Intensify LCR with either SRS or surgery +RT

- Surgery + WBRT Vs. SRS alone- similar LCR

- SRS alone is enough for LCR

- Who should undergo surgery for BM?

Where does surgery stand for BM?

- Tissue diagnosis in pt. with unknown primary or history of primary cancer long time back
- Significant mass effect
- Relieving mass effect in cystic and haemorrhagic mets
- Lesions >3 cm or those with significant mass effect (>1 cm midline shift) do better with surgery

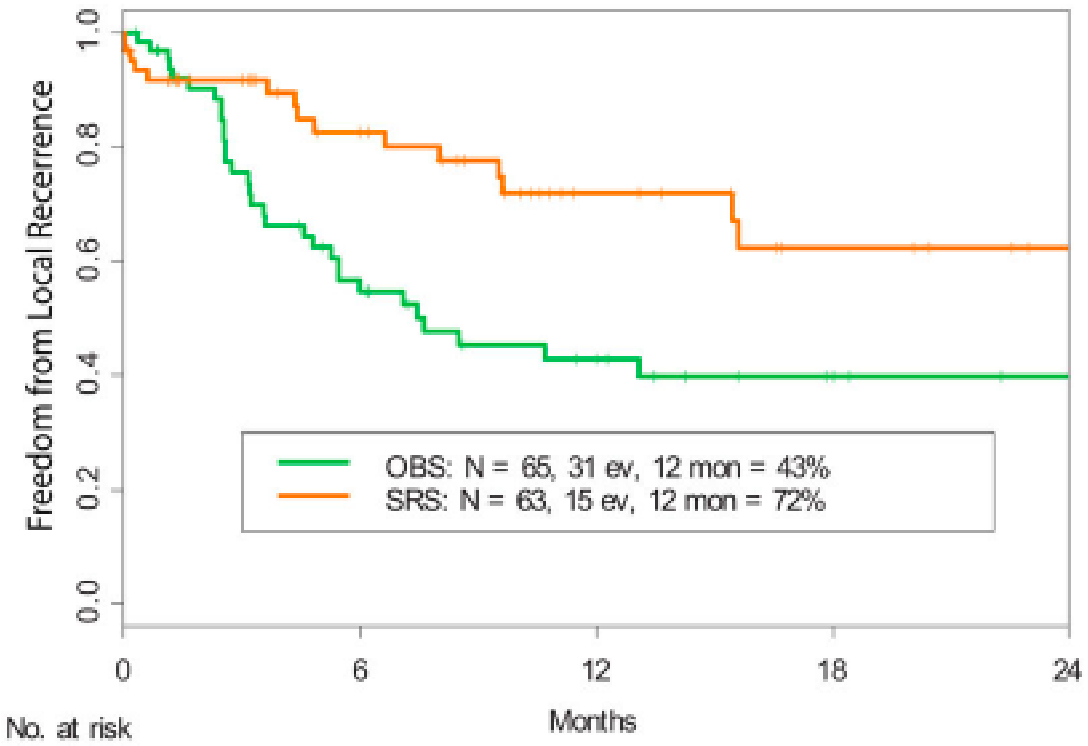
Resection cavity SRS

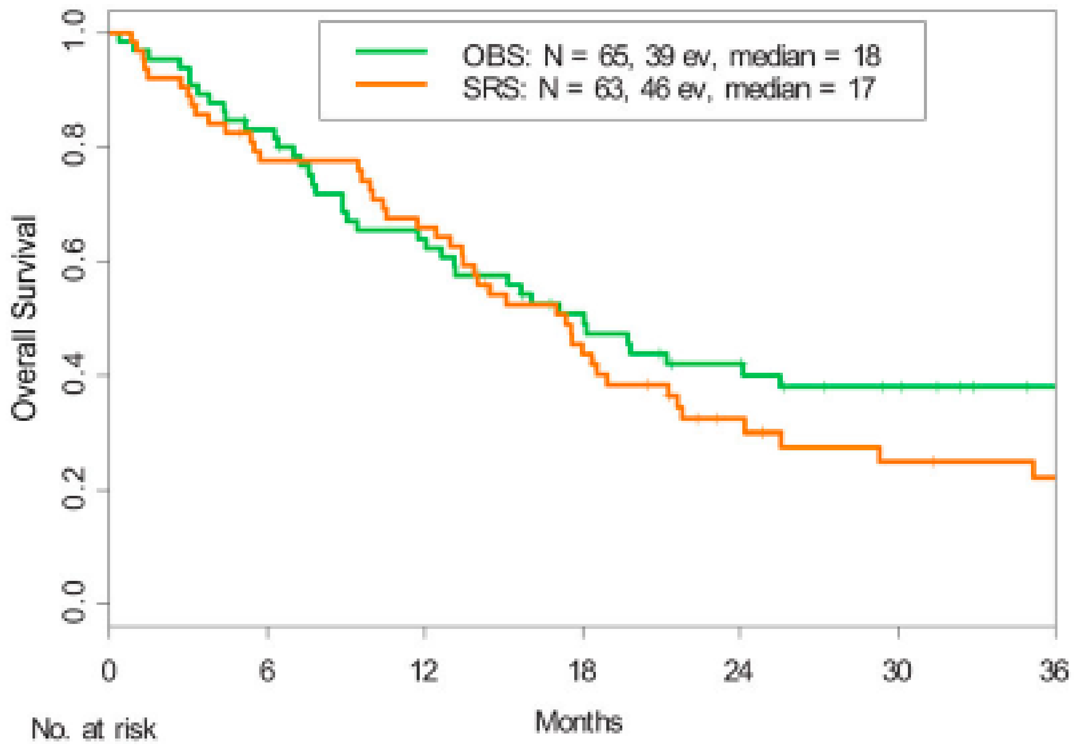
Randomized Trial of Post op SRS Vs Observation for completely resected BM

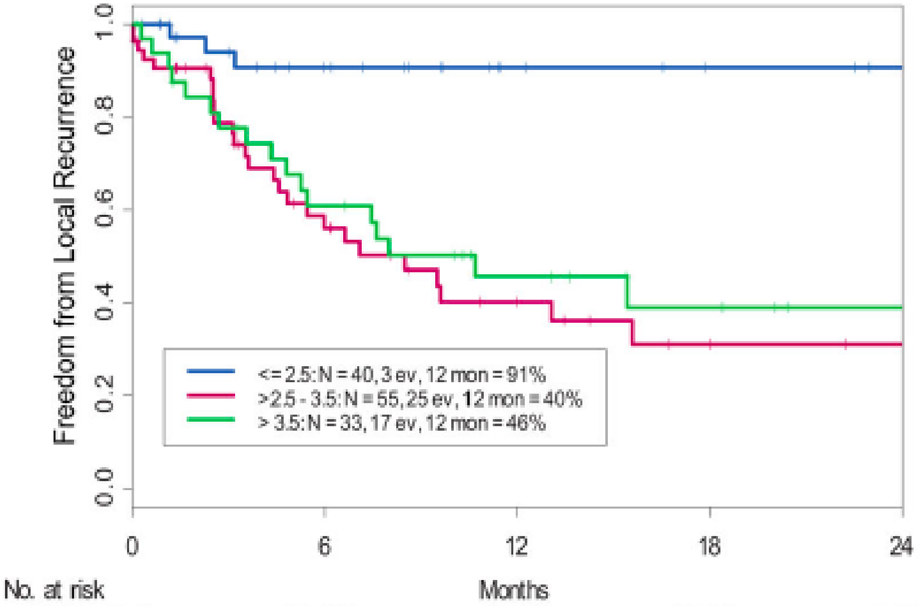
- 132 Pts with 1-3 Brain Mets (2009-2016) MDACC
- Randomized to SRS of resection cavity Vs. Observation
- PTV = Resection Cavity +1mm
- GK RS- Median dose 16Gy (Range 12-18 Gy)

	SRS	Observation	p
1Y Local Recurrence Rate	**43%**	**72%**	**0.015**
Median time to Local Recurrence	**Not Reached**	**7.6 Mo**	
Median OS	**17 Months**	**18 Months**	**0.24**
Death due to neurological cause	**48%**	**64%**	**0.24**

Mahajan A; Lancet Oncology 2017







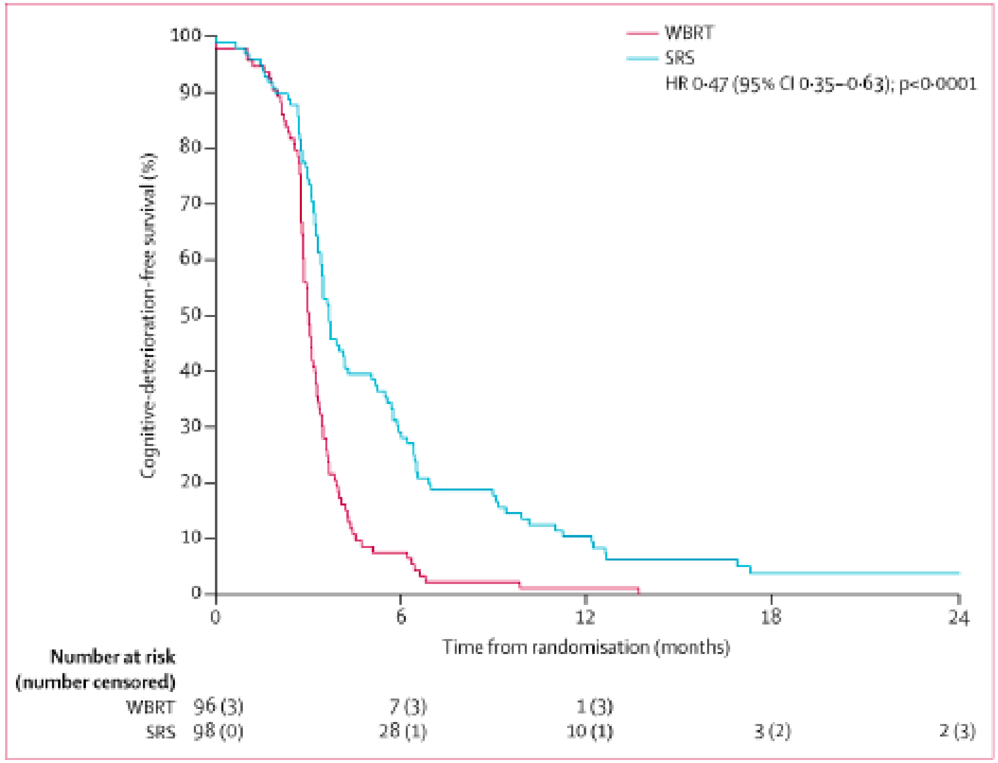
Interpretation

- SRS after surgery significantly decreases local recurrence and can be an alternative to WBRT

NCCTG N107C/CEC -3- Post op SRS Vs. WBRT

- Phase 3 multicentric RCT- 48 institutions across US and Canada
- one resected metastases and resection cavity <5 cm
- Up to 3 BM
- Randomized to post op SRS or WBRT Primary end points- Cognition deterioration free survival (CDFS) and OS
- 194 pts from 2011 to 2015
- Median FU 11.1 Mo
- No diff in OS

Lancet Oncology 2017 August ; 18 (8) 1049-60



- Median CDFS was longer in SRS Vs WBRT (3.7 Mo Vs 3 Mo)
- Amongst long term survivors cognitive decline was less in SRS Vs. WBRT

Cognitive Decline	SRS	WBRT	p
3 Months	37%	89%	0.00016
6 Months	46%	88%	0.0025
9 months	48%	81%	0.020
12 months	60%	91%	0.0188

Summary of evidence

- SRS- Equivalent LCR; no diff in OS (level of evidence- I) as compared to WBRT
- Less neurocognitive decline (level of evidence- I)
- Local Control Rate after cavity SRS-70-90%
- 20-40% require salvage WBRT for DBM/LMD/LR
- Median delay in WBRT 12-15 months

Clinical Investigation

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

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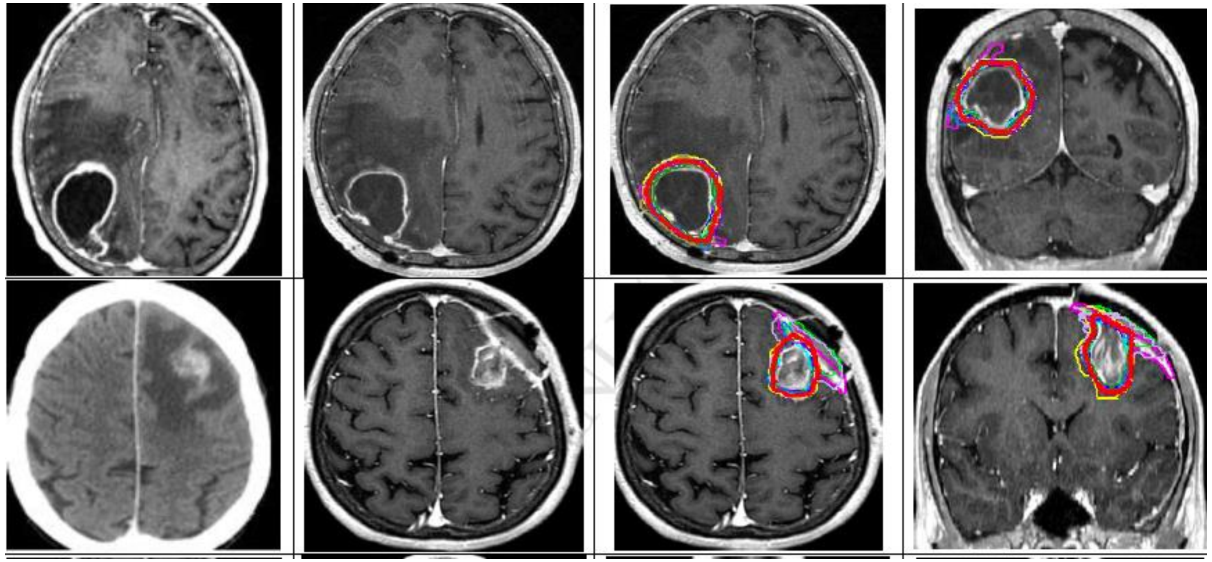
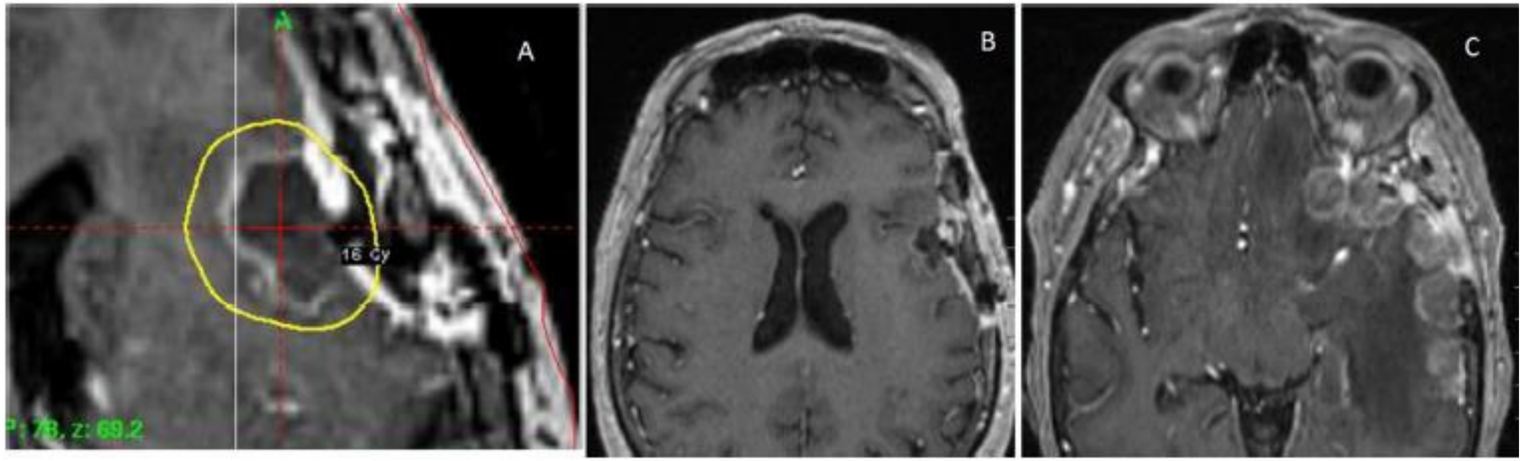
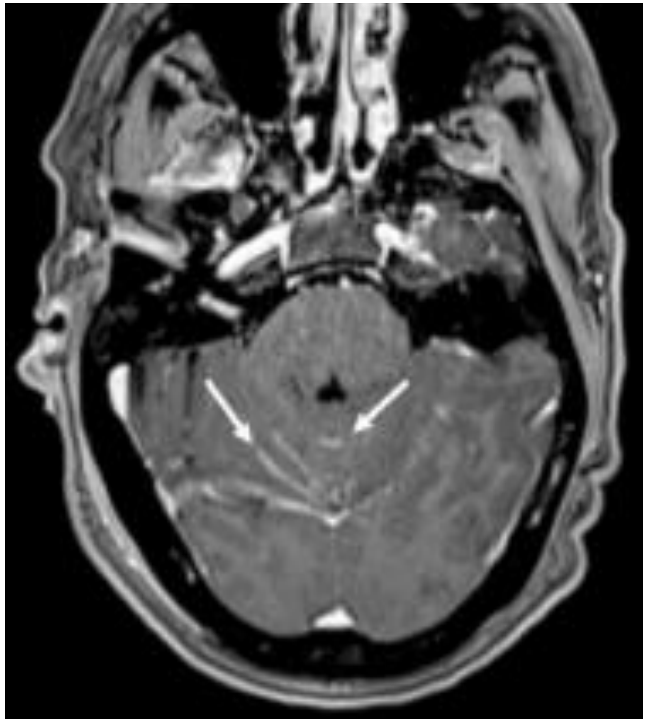


- Internationally recognized experts contoured 10 post op – completely resected cases
- Level of agreement was adequate (mean sensitivity and specificity 0.75 and 0.98)
- To cases in infra tentorial compartment – significant difference in contours were detected along CTV margin towards bone flap

Author Year No of Pts	TV size	Dose and Fractionation	1 YLC	IY RN
Minniti 2019 N=95 Linac	2-4 cm	9Gyx 3 fraction	83%	15%
Martinage 2019 N=160 CK	All post op cavities	9-10 Gy x 3fr (22%) 8Gy x 3 fr (33%) 6Gyx 5fr (23%) 5Gy x 6fr (12%)	I YLC- 88% 2Y LC 81%	8.9%
Ling DC 2015 N= 99	>3cm	15-21Gyx 1fr (26%) 10-12Gy x 2fr (14%) 6-9 Gy x 3fr (56%)	1Y LC 72% 2Y LC 55%	9%
Keller 2017 N=181 Linac	All post op cavities	11 Gy x 3fr	1 YLC 88% 2YLC 87%	19%
Sahgal 2018 N=122 Linac	All post op cavities	5-7Gy x5fr	1YLC 84%	6%
Specht2016 N=46	>3cm	7Gy x5 r	1YLC 88%	

Leptomeningeal Metastases





Overall 1-2 Y LMD after post op SRS- 11-17%

1 Y LMD intact mets SRS Vs Post op SRS - 5% Vs 17% ($p<0.01$)

1 Y LMD post op SRS vs Post op WBRT- 13% Vs 3% ($p=0.045$)

Possible cause- Iatrogenic tumour dissemination in CSF

Atalar B et al IJROBP 2013, Johnson MD et al IJROBP 2016
Patel KR et al Neurosurgery 2016, Patel KR et al J Neuro Oncol 2014

High Risk pts for post SRS LMD

- Breast Cancer/Melanoma
- Infra tentorial location
- Cystic Metastases
- Hemorrhagic Mets

Pre Surgery SRS

- Advantages-
- Easily identifiable tumour
- CTV= GTV– Less normal Brain radiated
- Decreased risk of LMD
- Oxygenated tumour- better local Control
- Resection of majority of radiated tissue- reduced RN
- Better Compliance

Concerns

- Lack of pathologic confirmation before RT
- May not be suitable in emergency situation
- Wound healing issues

Published evidence of Pre OP SRS

Author and study	Intervention	LC	LMD	RN
Asher et al Ph II + Retrospective N=47	• Pre op SRS– surgery within 48hours • GTV=PTV • Dose 20% reduction	1Y LC - 85.6%	1 YLMD-0%	Not reported
Patel et all Retrospective study Pre op (n=71) vs Post op SRS (n=114)	• Pre op SRS– surgery within 48hours • GTV=PTV • Dose 20% reduction Post op PTV= Cavity +1-2mm single fraction SRS	Pre op- 1YLR-16% Post op 1YLR 12.6%	2YLMD Preop 3.2% Post op 16.6%	2Y RN Pre op 4.9% Post op 16.4%
Patel et al Retrospective study Pre op (n=71) vs Post op WBRT (n=42)	WBRT 30-37.5Gy/10-15fr	2YLR Pre op- - 24.5% WBRT 25%	2YLMD Preop 3.5% WBRT 9%	1Y RN Pre op 9.9% WBRT 0%

Summary of evidence for solitary BM

- WBRT alone/ Surgical resection alone is not enough- level I evidence
- Intensify LCR with either SRS or surgery +RT
- SRS alone is enough for LCR
- Or Surgery + Resection Cavity SRS

2-4 Brain metastases

- Question- Is WBRT alone enough or is there any advantage of doing WBRT + SRS?

- There are 3 RCT and MA

RCT I –(2-4 Mets)

- University of Pittsburgh – RCT
- WBRT alone vs WBRT (30Gy/12fr) +SRS (16Gy) in 2-4 BM
- High control rates in SRS arm (100% vs 8%; p 0.0005)
- trial closed prematurely
- No diff in OS (11months in SRS arm and 7.5 months in WBRT arm; p 0.22)

Kondziolka IJROBP vol45 no 2 pp427-434; 1999

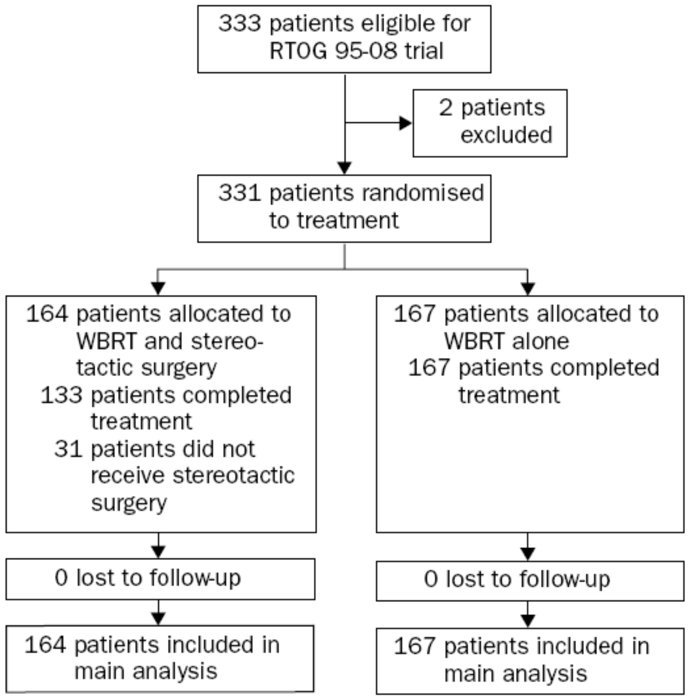
RTOG 95-08– Most robust and compelling evidence (primary end point OS, large pt number)

- RTOG 9508
- 331 pts
- WBRT (37.5Gy/15fr) +/- SRS
- Included pts up to 3 BM
- Primary end point- OS
- Secondary endpoint- tumour response, LCR, Intracranial recurrence, cause of death, change in PS

D W Andrews The Lancet 363 no 9422, pp1665-1672, 2004

RTOG9508

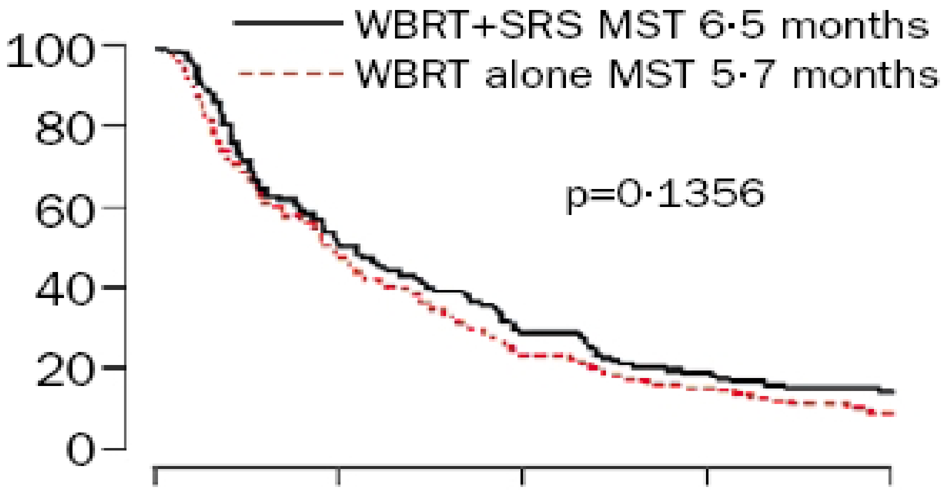
Unresectable 1-3 metastases



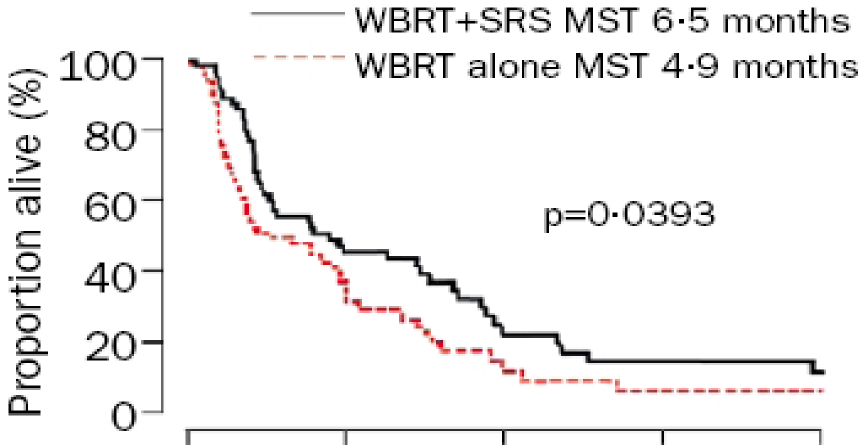
WBRT+SRS

WBRT

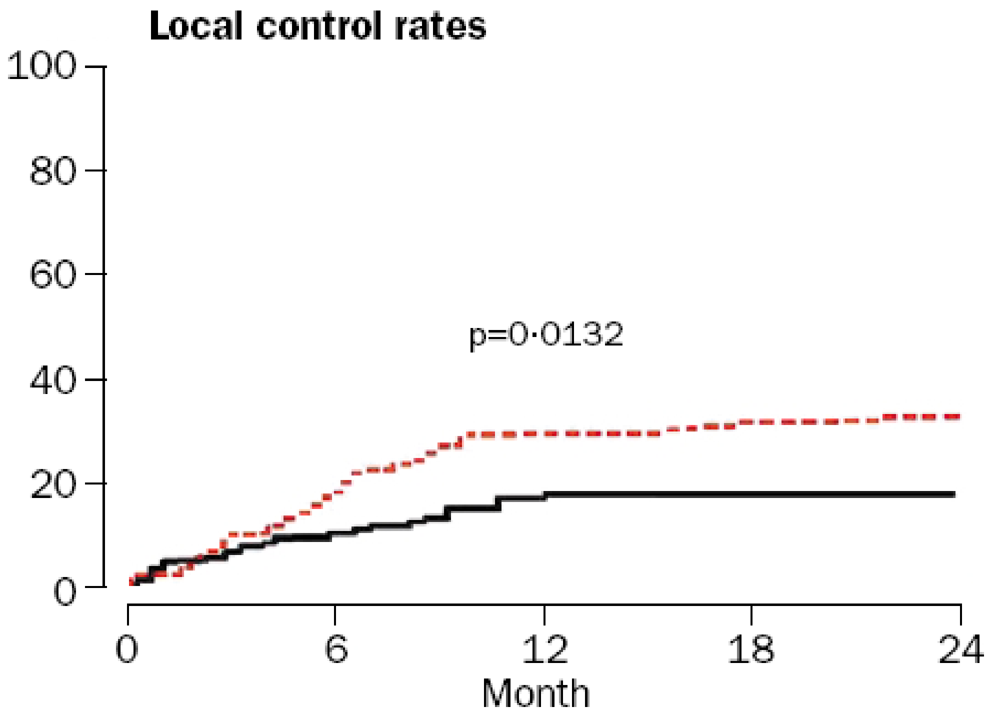
Overall survival



Survival in patients with single metastasis



Andrew D, Lancet 2004



- Significant benefit of LCR with SRS
- WBRT+SRS: standard of care for patients with single metastasis
- Should be considered for patients with 2-3 metastases in view of higher local control

Table 4: RTOG 9508 [30]. SRS improved survival in patients with a single BrM. Subset analysis suggested there was a potential benefit for patients with NSCLC, RPA class I, or patients that were <50 years old with 2 to 3 metastasis. Patients in the study receiving SRS also had improved KPS with decreased steroid dependence.

Med OS	All pts	Single brain met	1–3 mets, age <50	1–3 mets, NSCLC	1–3 mets, RPA class I
WBRT alone	5.7 mos	4.9 months	8.3 months	3.9 months	9.6 months
WBRT + SRS	6.5 mos	6.5 months	9.9 months	5.0 months	11.6 months
P value	0.14	**0.04**	**0.04**	**0.05**	**0.05**

SRS boost showed survival advantage over WBRT in

- **Single brain met**
- **1-3 mets with RPA class I**
- **Largest tm <2cm**
- **NSCLC**

Pts in SRS arm had significantly better or stable KPS score at 6 months (43% vs 27%; p=0.03) and reduced steroid requirement

- Message about SRS with WBRT in 2-4 BM

- There is a LCR and OS advantage of SRS over WBRT in pts with single BM
- 2-4 BM advantage of SRS in NSCLC, young pts, RPA class I-II, Small mets

2-4 Brain Metastases

- Question- Is SRS alone enough or is there any advantage of adding WBRT to SRS?

RCT -Japanese study – JROSG 99-1

- 132 pts with up to 4 lesions
- SRS alone vs SRS +WBRT
- Concluded – use of WBRT delayed occurrence of need of salvage brain T/t
- No diff in OS

Table 5: JROSG 99-1 [31] study comparing SRS with or without WBRT. Omission of WBRT was found to decrease intracranial control, and, as a result, the authors recommended SRS + WBRT for patients with up to 4 brain metastases.

	MS	OS @ 1 yr	Freedom from new brain mets @ 1 mos	Salvage brain tx	Neuro death
SRS	8.0 months	28.4%	46.8%	43%	19.3%
SRS + WBRT	7.5 months	38.5%	76.4%	15%	22.8%
P value	0.42	0.42	**<0.001**	**<0.001**	0.64

Aoyama H The J of American Medical Association, vol 295 no 21, pp 2483-2491 , 2006

Retrospective study

- MDACC Chang et al- single institution RCT
- 58 pts with 1-3 brain mets
- RPA class 1-2
- SRS alone vs SRS +WBRT
- *Trial stopped early due to decreased survival in WBRT arm (15.2 months vs 5.7 months)*
- Criticism- there were more visceral mets in WBRT arm
- This is the only trial supporting SRS alone (Level 1 evidence)

E L Chang The lancet Oncology vol10 no 11, pp1037-44; 2009

European Trial EORTC 22952-26001

- Kocher et all- SRS or surgical resection followed by WBRT vs Observation in pts with 1-3 BM
- 359 pts (199 SRS and 160 Surgery)
- Adjuvant WBRT reduced IC relapse- Surgery vs Sx +WBRT (59% vs 27%, p <0.001)
- SRS vs SRS+WBRT (31% vs 19%, p=0.040)
- No impact on functional dependence or OS

M Kocher JCO Vol29 no2 pp134-141, 2011

Message about role of WBRT after SRS in 2-4 BM

- All three studies showed that adding WBRT results in modest improvement in LCR and DBF; even WBRT does not eliminate local recurrence

- WBRT comes at a cost of NC decline

- No Change in OS

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Clinical Investigation

Phase 3 Trials of Stereotactic Radiosurgery With or Without Whole-Brain Radiation Therapy for 1 to 4 Brain Metastases: Individual Patient Data Meta-Analysis

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Included 3 studies – JRSOG99-1, MDACC and EORTC 22952-26001

Total 359 pts

Table 1 Descriptive statistics for 364 patients and those stratified by SRS versus SRS plus WBRT age groups

Factor	Total no. of patients (n=364)	SRS alone (n=186)	SRS plus WBRT (n=178)	SRS alone age >50 yr (n=155)	SRS plus WBRT age >50 yr (n=141)	SRS alone age ≤50 yr (n=31)	SRS plus WBI age ≤50 yr (n=37)
No. of females/ males (%/%)	128/236 (35/65)	65/121 (35/65)	63/115 (35/65)	47/108 (30/70)	47/94 (33/67)	18/13 (58/42)	16/21 (43/57
Median age, yr (range)	62 (33-86)	62 (33-86)	61 (35-78)	64 (51-86)	65 (51-78)	45 (33-50)	45 (35-50
Age ≤50 yr (%)	68 (19%)	31 (17%)	37 (21%)				
RPA1/RPA2 (%/%)	149/215 (41/59)	73/113 (39/61)	76/102 (43/57)	56/99 (36/64)	50/91 (35/65)	17/14 (55/45)	26/11 (70/30
No. of brain metastases (%)							
1	217 (60%)	111 (60%)	106 (60%)	92 (59%)	80 (57%)	19 (61%)	26 (70%)
2	88 (24%)	44 (24%)	44 (25%)	36 (23%)	36 (26%)	8 (26%)	8 (22%)
3	47 (13%)	24 (13%)	23 (13%)	21 (14%)	21 (15%)	3 (10%)	2 (5%)
4	12 (3%)	7 (4%)	5 (3%)	6 (4%)	4 (3%)	1 (3%)	1 (3%)
Extracranial metastases	202 (56%)	100 (54%)	102 (58%)	82 (52%)	77 (55%)	18 (58%)	25 (68%)
Cancer type							
Lung	214 (59%)	109 (59%)	105 (59%)	100 (65%)	84 (60%)	9 (29%)	21 (57%)
Breast	43 (12%)	22 (12%)	21 (12%)	12 (8%)	11 (8%)	10 (32%)	10 (27%)
Kidney	24 (6%)	11 (6%)	13 (7%)	6 (4%)	13 (9%)	5 (16%)	0 (0%)
Other	83 (23%)	44 (23%)	39 (22%)	37 (24%)	33 (23%)	7 (23%)	6 (16%)
Local failures (%)	72 (20%)	51 (27%)	21 (12%)	41 (26%)	17 (12%)	10 (32%)	4 (11%)
Salvage treatment after local failures (%)	45 (63%)	37 (73%)	8 (38%)	29 (71%)	7 (41%)	8 (80%)	1 (25%)
Distant brain failures (%)	156 (43%)	98 (53%)	58 (34%)	78 (50%)	39 (28%)	20 (65%)	19 (51%)
Salvage treatment after distant failures (%)	100 (64%)	72 (73%)	28 (48%)	56 (72%)	19 (49%)	16 (80%)	9 (47%)
Total deaths (%)	314 (86%)	157 (84%)	157 (88%)	135 (87%)	126 (89%)	22 (71%)	31 (84%)
Neurologic deaths (%)	99 (27%)	55 (30%)	44 (25%)	43 (28%)	36 (26%)	12 (39%)	8 (22%)

Results

- Age <50 years showed significant OS benefit with SRS (p=0.04)
- Patients with single BM had significantly better survival than 2-4 mets
- Pts with single brain mets had significantly lower risk of distant brain failure than 2-4 mets
- Local control rate significantly favoured additional WBRT across all age groups

SRS in up to 10 BM

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto*, Toru Serizawa*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya

Summary

Background We aimed to examine whether stereotactic radiosurgery without whole-brain radiotherapy (WBRT) as the

Lancet Oncol 2014; 15: 387–95

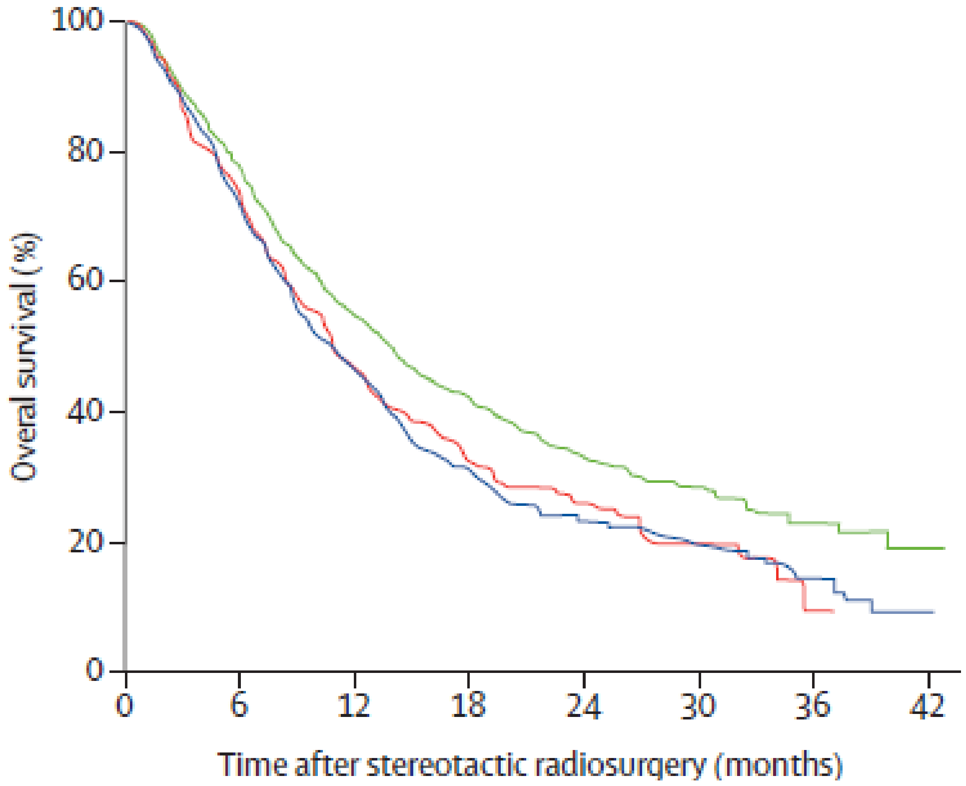
Majority investigators are Neurosurgeons

- Study by Japanese Leksell Gamma Knife (JLGK) society
- Aim- To examine whether SRS without WBRT as initial treatment for pts with 5-10 brain mets is non inferior to pts with 2-4 mets in terms of OS
- Prospective Observational multicentric study (23 Centres) (not a randomized study)
- KPS >70
- 1-10 mets
- Largest tm <10 ml in volume and <3 cm in longest diameter; total cumulative volume <15 ml

Fortis

- SRS dose -20-22Gyat periphery
- All lesions detected by MRI with slice thickness of $\leq$2mm with no gap
- All pts treated with Gamma Knife
- N=1194 from 2009-2012

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



Median OS after SRS was

OS did not differ b/w 2-4 mets vs 5-10 mets

Conclusion- SRS without WBRT in pts with 5-10 brain mets is non inferior to 2-4 mets

Caveats

- Study was confined to small volume ds with largest tm <10 ml and <3 cm in longest diameter
- Cumulative volume of all lesions <15 ml

	Salvage WBRT	Re SRS	LM Ds
5-10 lesions	8%	43%	19%
2-4 lesions	10%	42%	13%

Randomized data still needed but its reasonable to offer SRS alone for small volume ds up to 10 lesions

Question

- How to objectively choose optimal technique/combination of techniques for a given patient?

- Answer – Use appropriate prognostic indices
- Go through the evidence of benefit of each technique or its combination

RPA- 1997

Int. J. Radiation Oncology Biol. Phys., Vol. 37, No. 4, pp. 745–751, 1997

0360-3016/97 $17.00 + .00
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PII S0360-3016(96)00619-0

• *Clinical Investigation*

RECURSIVE PARTITIONING ANALYSIS (RPA) OF PROGNOSTIC FACTORS IN THREE RADIATION THERAPY ONCOLOGY GROUP (RTOG) BRAIN METASTASES TRIALS

- Question – Promising results from newer approaches such as SRS are being reported. Are these results due to therapy alone or can these results be attributed in part to patient selection?

- 1200 pts from 3 consecutive RTOG protocols were included

- Using RPA, a statistical methodology which creates regression tree – 18 pre treatment characteristics and 3 treatment related variables were analyzed

- Class I – KPS $\geq$70 +Age <65 +with controlled primary and no extracranial mets – MS 7.1Mo
- Class III- KPS <70 – MS 2.3 Mo
- Class II- All pts not in class II or III -MS 4.2Mo

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 2, pp. 510–514, 2008

0360-3016/08/$–see front matter
ELSEVIER
doi:10.1016/j.ijrobp.2007.06.074

CLINICAL INVESTIGATION **Brain**

A NEW PROGNOSTIC INDEX AND COMPARISON TO THREE OTHER INDICES FOR PATIENTS WITH BRAIN METASTASES: AN ANALYSIS OF 1,960 PATIENTS IN THE RTOG DATABASE

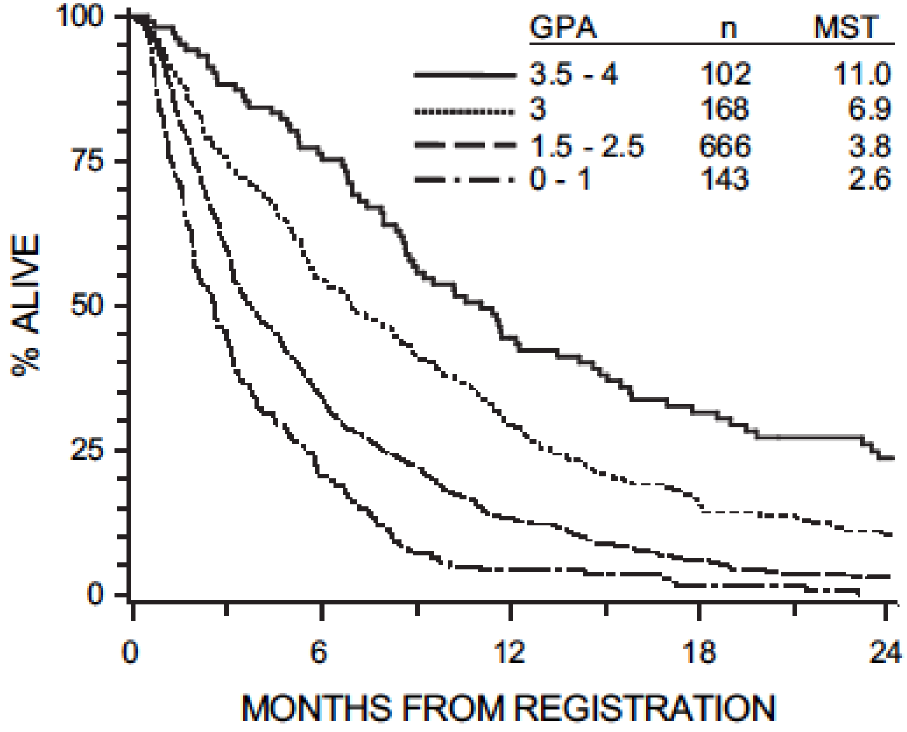
Paul W. Sperduto, M.D.,* Brian Berkey, M.S.,† Laurie E. Gaspar, M.D.,‡ Minesh Mehta, M.D.,§ and Walter Curran, M.D.||

Table 4. Graded Prognostic Assessment

	Score		
	0	0.5	1.0
Age	>60	50–59	<50
KPS	<70	70–80	90–100
No. of CNS metastases	>3	2–3	1
Extracranial metastases	Present	—	None

Genesis – RTOG 9508 study showed survival advantage of using SRS + WBRT Vs WBRT alone in pts with solitary brain mets and trend towards improvement in OS for pts with 2-3 mets

GRADED PROGNOSTIC ASSESSMENT



Primary	Median survival (Months)	95% CI
Non-small-cell lung cancer	7.00	6.53–7.50
Small cell lung cancer	4.90	4.30–6.20
Melanoma	6.74	5.90–7.57
Renal cell carcinoma	9.63	7.66–10.91
Breast cancer	11.93	9.69–12.85
Gastrointestinal cancer	5.36	4.30–6.30
Unknown	6.37	5.22–7.49

VOLUME 30 · NUMBER 4 · FEBRUARY 1 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases

Paul W. Sperduto, Norbert Kased, David Roberge, Zhiyuan Xu, Ryan Shanley, Xianghua Luo, Penny K. Sneed,

Fortis

Renal cell carcinoma

Prognostic Factor	GPA Scoring Criteria 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	GPA Scoring Criteria 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

Non–small-cell and small-cell lung cancer

Prognostic Factor	GPA Scoring Criteria 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	GPA Scoring Criteria 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

Diagnosis Specific GPA (DS GPA)

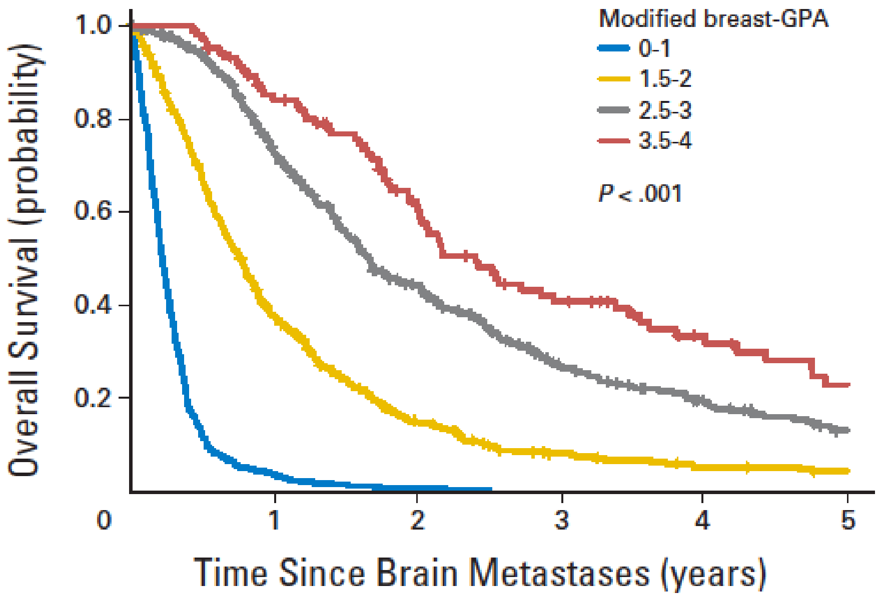
Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

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

Modified Breast GPA

Factor	0	0.5	1.0	1.5
KPS	≤50	60	70-80	90-100
Subtype	TNBC	HR+/HER2-	HR-/HER2+	HR+/HER2+
Age (Y)	>50	≤50	-	-
No of Brain Mets	>3	1-3	-	-

GPA	MS
0-1	2.6 Mo
1.5-2	9.2 Mo
2.5-3	19.9 Mo
3.5-4	28.8 Mo



JCO Tripathi D et all 33:2239-2245; 2015

Patrikidou et al. BMC Cancer (2020) 20:117
https://doi.org/10.1186/s12885-020-6548-6

BM

RESEARCH ARTICLE

Development of a disease-specific graded prognostic assessment index for the management of sarcoma patients with brain metastases (Sarcoma-GPA)

	Score			
	0	0.5	1	2
Histology	H1	H2	H3	H4
PS	3,4	2	0,1	-
No of CNS metastases	>4	2-4	1	-

H1	Adipocytic tumours- Liposarcoma, Myxoid LPS
H2	Smooth &skeletal ms sarcoma- Leiomyosa, RMSOS, FibroSa, MFH, Pleomorphic Sa, Angio Sa
H3	Uncertain differentiation- Synovial Sa, MPNST, Neurofibro Sa, Cystosarcoma Breast
H4	Alveolar Soft part Sa, Haemagiopericytoma

Lung Molecular Graded Prognostic Assessment

	GPA Scoring Criteria[a]		
Prognostic Factor	0	0.5	1.0
Age, y	≥70	<70	NA
KPS	<70	80	90-100
ECM	Present		Absent
Brain metastases, No.	>4	1-4	NA
Gene status	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* pos

	Adenocarcinoma	Non Adeno
0-1	6.9 Mo	5.3
1.5-2	13.7 Mo	6.8
2.5-3	26.5 Mo	12.3
3.5-4	46.8 Mo	

JAMA Oncology Published online November 17, 2016

Guide clinical decisions

- In pts with unfavourable outcome- goal is clear palliation
- In pts with favourable outcome (RPA Class I and some class II)- Increasing OS and functional neurological survival is a goals
- Some of these mol GPAs need more validation in prospective database

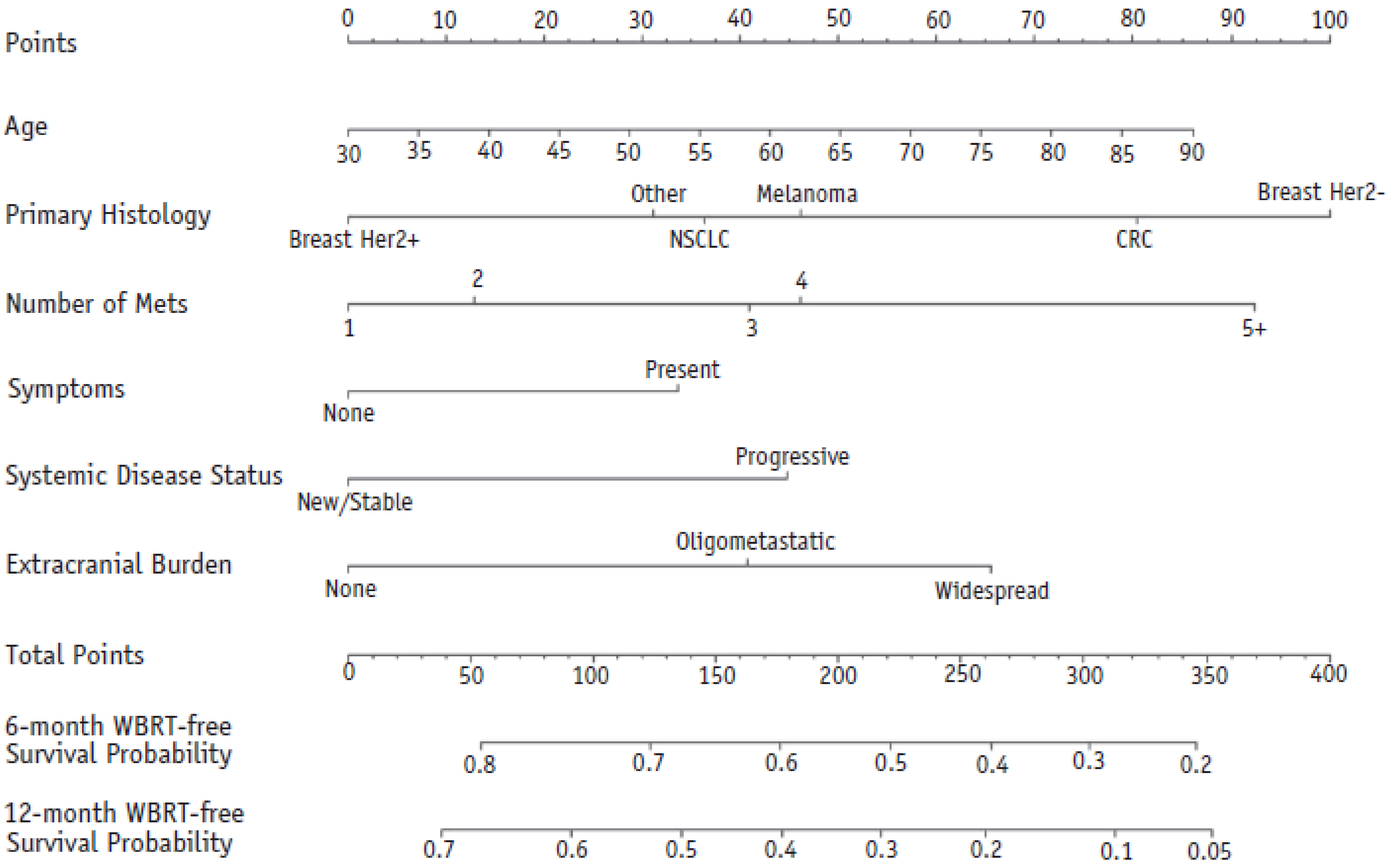
How do you decide whether to offer SRS alone Vs SRS + WBRT?

Clinical Investigation

Multi-institutional Nomogram Predicting Survival Free From Salvage Whole Brain Radiation After Radiosurgery in Patients With Brain Metastases

CrossMark

Daniel Gorovets, MD,[*,†] Diandra Ayala-Peacock, MD,[‡,§] David J. Tybor, MPH, PhD,[||] Paul Rava, MD, PhD,[*,¶] Daniel Ebner, BS,[*] Deus Cielo, MD,[#] Georg Norén, MD, PhD,[#] David E. Wazer, MD,[*] Michael Chan, MD,[‡] and Jaroslaw T. Hepel, MD[*]


Points
0
10
20
30
40
50
60
70
80
90
100
Age
30
35
40
45
50
55
60
65
70
75
80
85
90
Primary Histology
Other
Melanoma
Breast Her2-
Breast Her2+
NSCLC
CRC
Number of Mets
2
4
1
3
5+
Symptoms
Present
None
Systemic Disease Status
Progressive
New/Stable
Extracranial Burden
Oligometastatic
None
Widespread
Total Points
0
50
100
150
200
250
300
350
400
6-month WBRT-free Survival Probability
0.8
0.7
0.6
0.5
0.4
0.3
0.2
12-month WBRT-free Survival Probability
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.05

Radiomics- Milliary pattern of brain and lung mets seen MC in EGFR mutated NSCLC

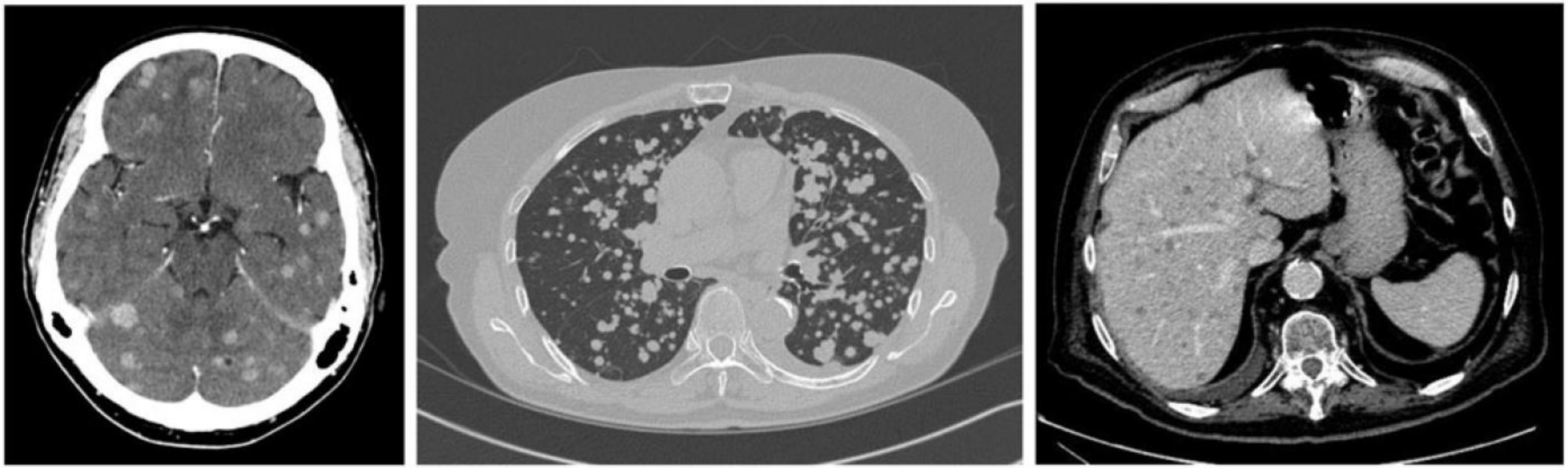
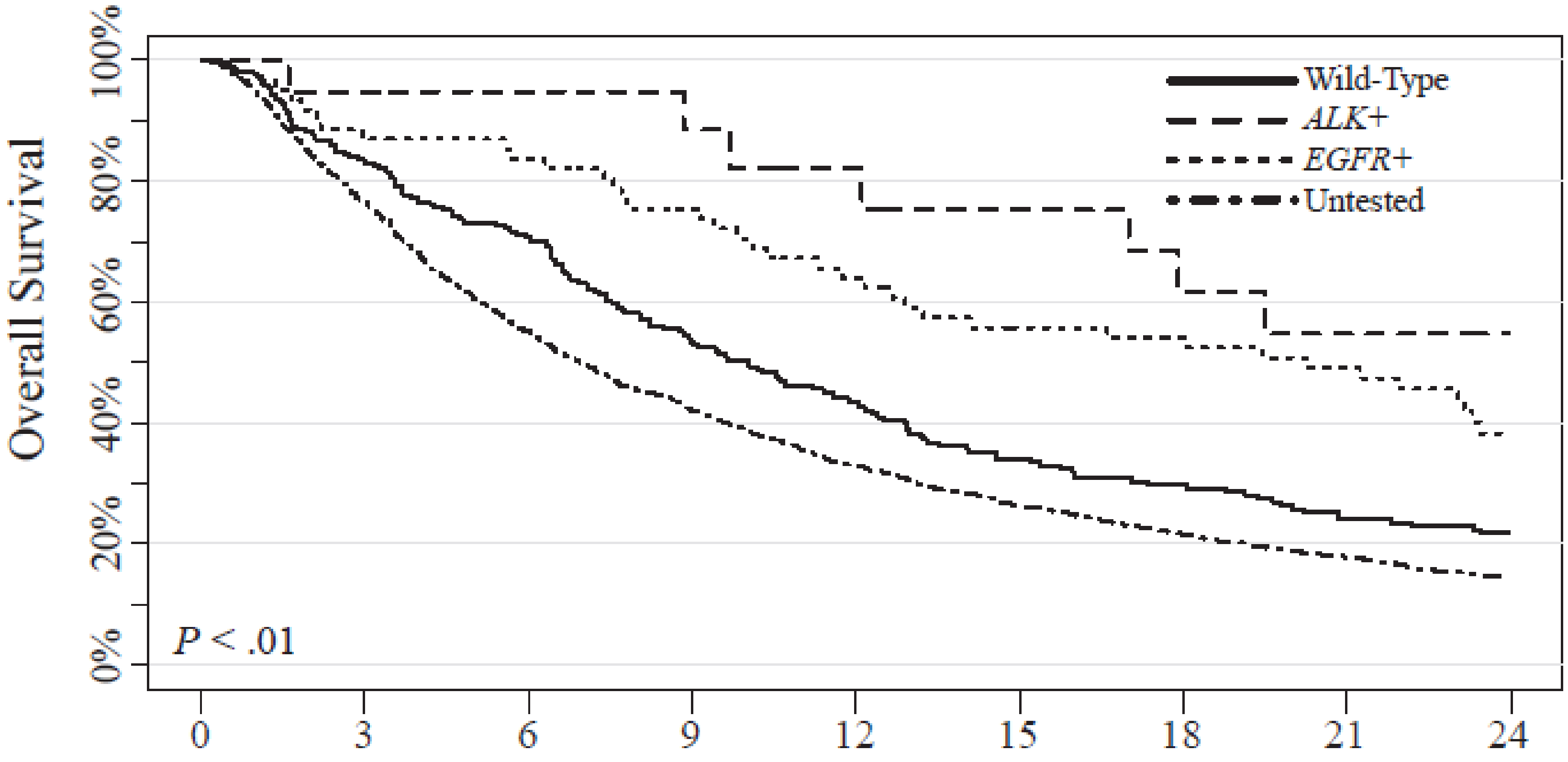


Figure 1. (Left to right) axial computed tomography imaging demonstrating miliary metastases in the brain, lung and liver from non-small cell lung cancer.

The impact of tumor biology on survival and response to radiation therapy among patients with non–small cell lung cancer brain metastases

Jacob A. Miller BS [a], Rupesh Kotecha MD [b], Manmeet S. Ahluwalia MD [a, c, d],

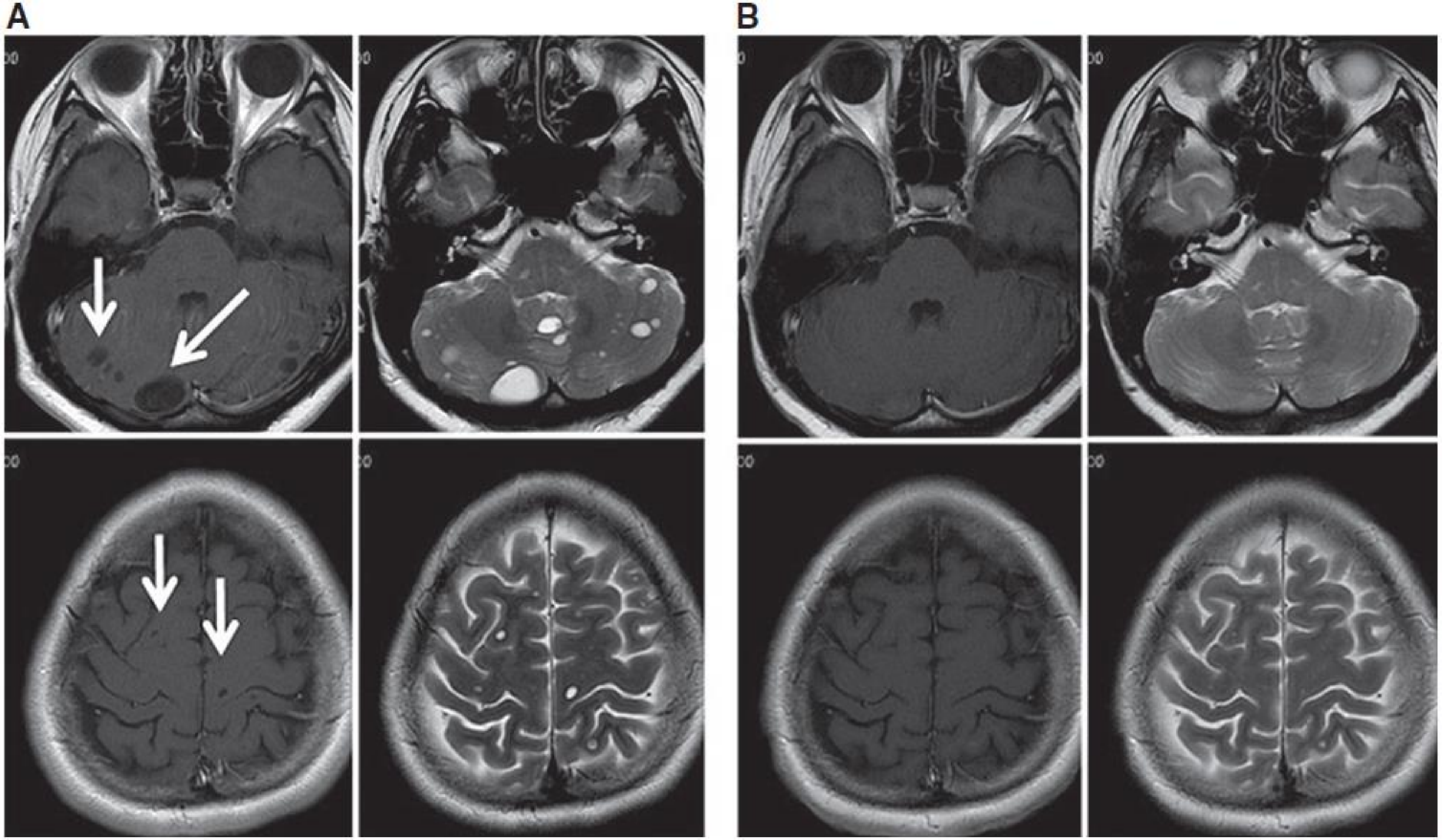
B



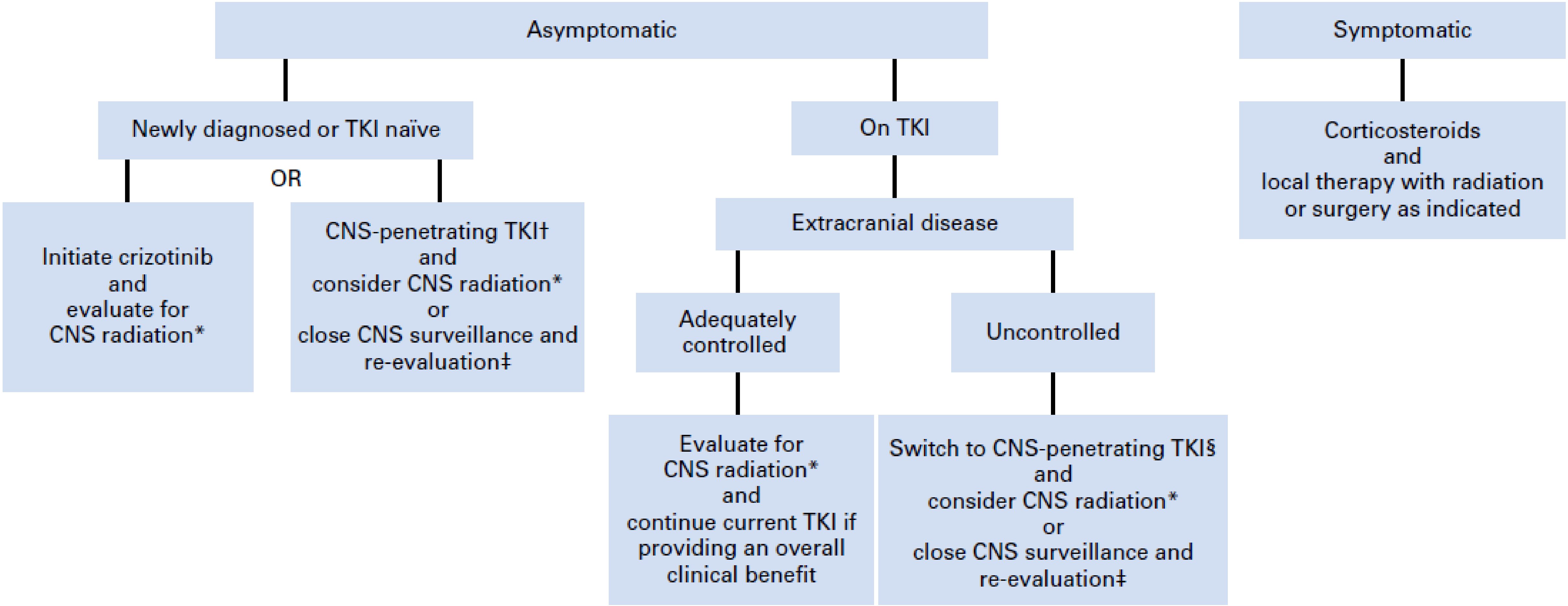
ALK + 49.2 Mo
EGFR 20.3 Mo
Wild 10 Mo

Clinico Radiological Features

- Cystic Brain Mets in ALK positive NSCLC- show interesting feature
- Pathologically – abundant Mucin formation
- MRI T2 – Hyperintensity
- T1 Hypointensity
- Minimal or no T1 Contrast enhancement /vasogenic edema
- Indolent course
- Generally asymptomatic



MRI- multiple cystic SOLs with central hypointensity in T1, hyperintense in T2
D/D Abscess/TB/Parasitic infection
Since No signs of infection were present, WBRT was given and all SOLS resolved


Asymptomatic
Symptomatic
Newly diagnosed or TKI naïve
On TKI
Corticosteroids
and
local therapy with radiation
or surgery as indicated
OR
Initiate crizotinib
and
evaluate for
CNS radiation*
CNS-penetrating TKI†
and
consider CNS radiation*
or
close CNS surveillance and
re-evaluation‡
Extracranial disease
Adequately
controlled
Uncontrolled
Evaluate for
CNS radiation*
and
continue current TKI if
providing an overall
clinical benefit
Switch to CNS-penetrating TKI§
and
consider CNS radiation*
or
close CNS surveillance and
re-evaluation‡

Concerns with WBRT

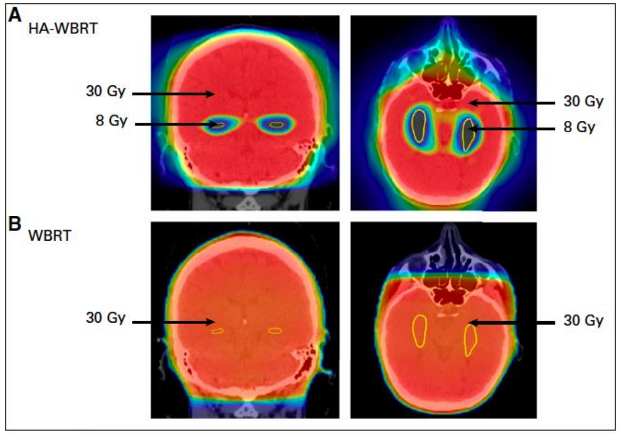
- Decline in neurocognition
- Decline in QoL
- Fatigue
- Decline in PS
- Delay in systemic Treatment

VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY · ORIGINAL REPORT

Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

Vinai Gondi, Stephanie L. Pugh, Wolfgang A. Tome, Chip Caine, Ben Corn, Andrew Kanner, Howard Rowley, Vijayananda Kundapur, Albert DeNittis, Jeffrey N. Greenspoon, Andre A. Konski, Glenn S. Bauman, Sunjay Shah, Wenyin Shi, Merideth Wendland, Lisa Kachnic, and Minesh P. Mehta



- Hippocampus- B/L Subcortical structure which plays fundamental role in learning and memory

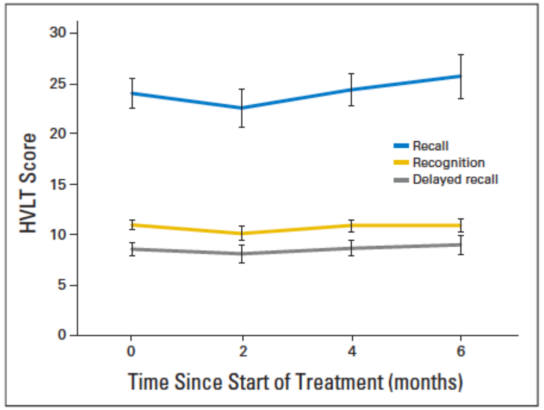


Fig 1. Hopkins Verbal Learning Test (HVLT) scores for 50 patients alive at 6 months.

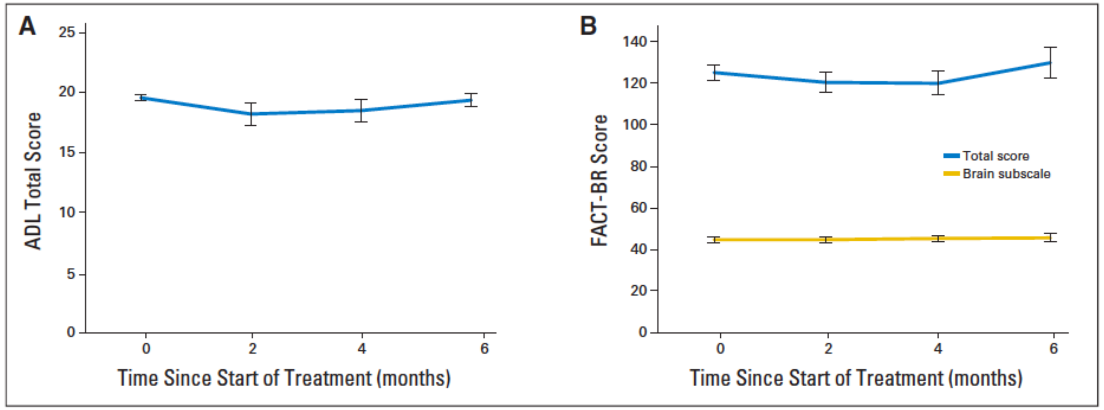
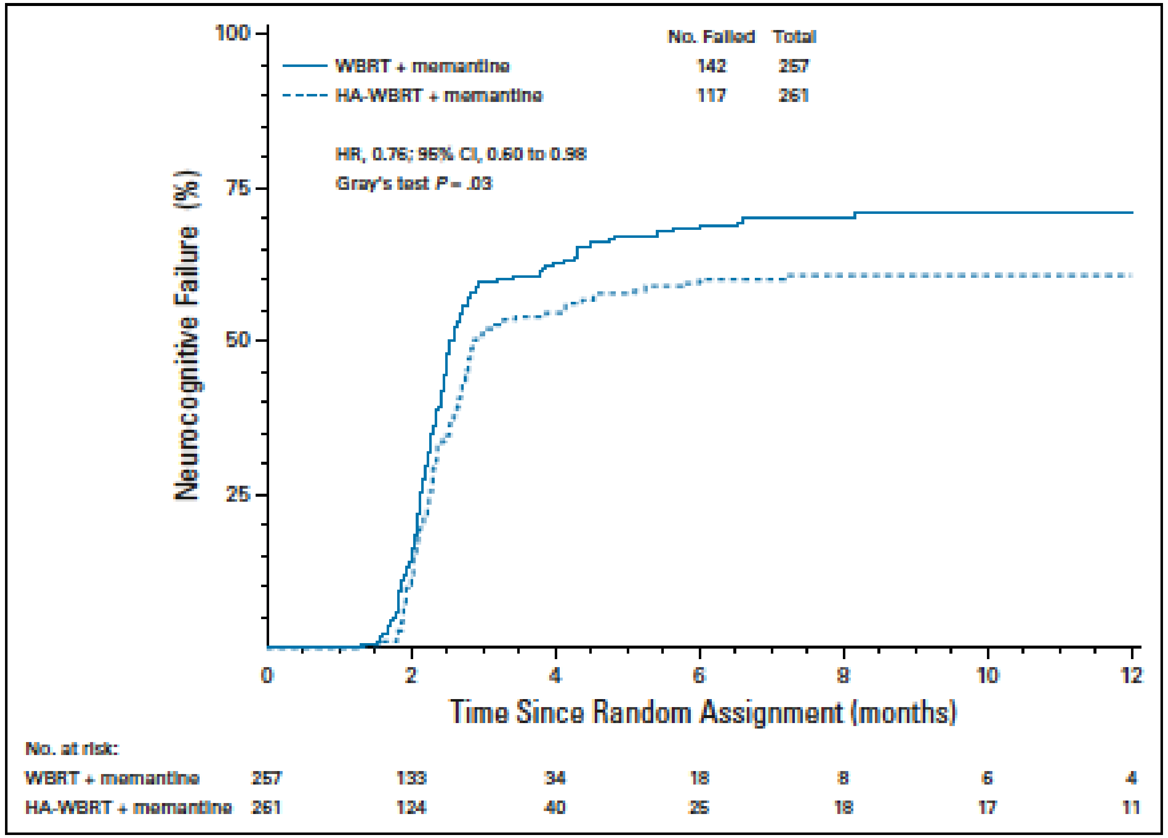


Fig 3. Quality of life assessed using (A) Barthel's Index of Activities of Daily Living (ADLs) and (B) Functional Assessment of Cancer Therapy–Brain subscale (FACT-BR).

original reports

Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001

Paul D. Brown, MD[1]; Vinai Gondi, MD[2]; Stephanie Pugh, PhD[3]; Wolfgang A. Tome, PhD[4]; Jeffrey S. Wefel, PhD[5]; Terri S. Armstrong, PhD[6]; Joseph A. Bovi, MD[7]; Cliff Robinson, MD[8]; Andre Konski, MD, MBA[9]; Deepak Khuntia, MD[10]; David Grosshans, MD, PhD[5]; Tammie L. S. Benzinger, MD, PhD[8]; Deborah Bruner, PhD[11]; Mark R. Gilbert, MD[6]; David Roberge, MD[12]; Vijayananda Kundapur, MD[13]; Kiran Devisetty, MD[14]; Sunjay Shah, MD[15]; Kenneth Usuki, MD[16]; Bethany Marie Anderson, MD[17]; Baldassarre Stea, MD, PhD[18]; Harold Yoon, MD[19]; Jing Li, MD[5]; Nadia N. Laack, MD[1]; Tim J. Kruser, MD[20]; Steven J. Chmura, MD, PhD[21]; Wenyin Shi, MD[22]; Snehal Deshmukh, MS[3]; Minesh P. Mehta, MD[23]; and Lisa A. Kachnic, MD[24] for NRG Oncology



RT causes damage to brain by a cascade of ischemia hypoxic injury leading to increased glutamate levels which leads to excessive stimulation of NDMA receptors

Memantine works as NMDA receptor anatgonist

FIG 3. Kaplan-Meier graph showing time to cognitive failure. HA, hippocampal avoidance; WBRT, whole-brain radiotherapy.

Why SRS is good for brain?

- SRS allows high dose radiation by sharply focussed beams in a single fraction to a discrete tumour volume with steep dose gradient beyond edges of tm
- Brain mets are ideal target coz

1. Majority are small
2. Spherical/pseudospherical
3. Distinct margins on contrast enhanced imaging
4. Displace rather than infiltrate adjacent normal brain parenchyma
5. Fixed organ- no movement

Prerequisite for SRS

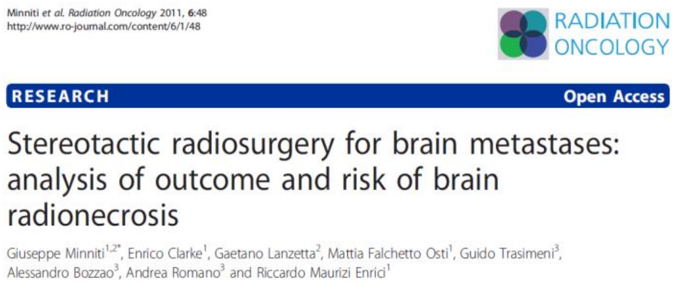
- High quality MRI – Double contrast, Delayed contrast, 3 D sequences
- OBI

SRS Dose Defining study

- RTOG 9005 Shaw et al
- 100 pts with BM
- Dose escalation done in 3Gy increments
- Conclusion
- <20mm- 24Gy
- 21-30 mm-18 Gy
- 31-40 mm- 15Gy

Tumor diameter ≤20 mm		21–30 mm		31–40 mm	
Dose	Toxicity	Dose	Toxicity	Dose	Toxicity
18 Gy	8%	15 Gy	13%	12 Gy	10%
21 Gy	11%	**18 Gy**	20%	**15 Gy**	14%
24Gy	10%	21 Gy	38%	18 Gy	50%
		24 Gy	58%		

E C shaw- IJROBP vol 47 no2 pp291-298, 2000

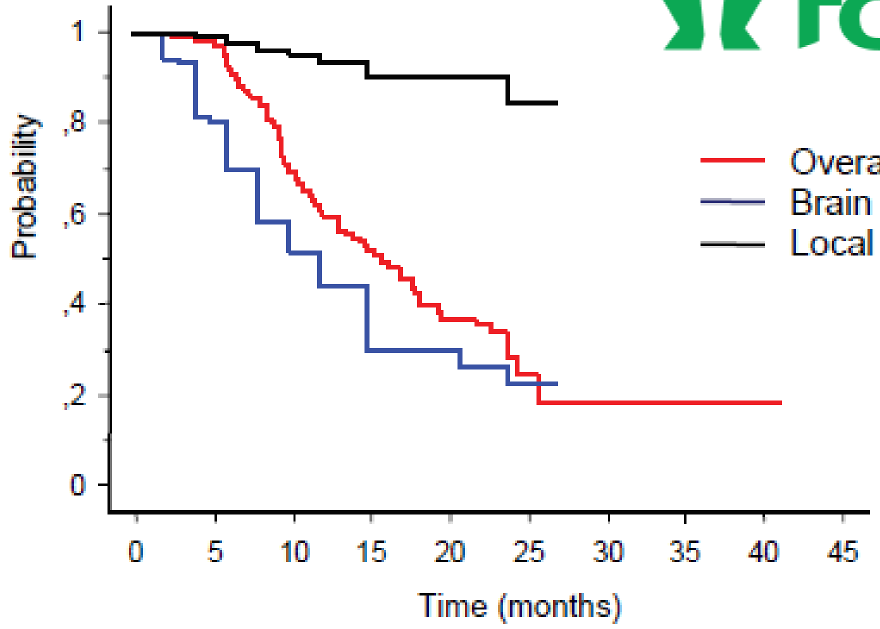

Minniti et al. Radiation Oncology 2011, 6:48
http://www.ro-journal.com/content/6/1/48

RADIATION ONCOLOGY

RESEARCH Open Access

Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis

Giuseppe Minniti[1,2*], Enrico Clarke[1], Gaetano Lanzetta[2], Mattia Falchetto Osti[1], Guido Trasimeni[3], Alessandro Bozzao[3], Andrea Romano[3] and Riccardo Maurizi Enrici[1]



- 206 pts with 1-3 mets < 3.5 cm treated with SRS alone
- No WBRT
- Dose – 15-20Gy GTV delineated on CE MRI and PTV 1-2 mm
- Dose prescribed to 80-90% isodose lines
- 1YLCR and 2 YLCR was 92 and 84%
- CR-305, 34%PR and 36% SD

Complications

- Radio Necrosis on MRI or by HPR (n=12) together was seen in 75 (24%) pts
- Symptomatic in 31 (10%)
- Median time to Radio Ne- 11 months

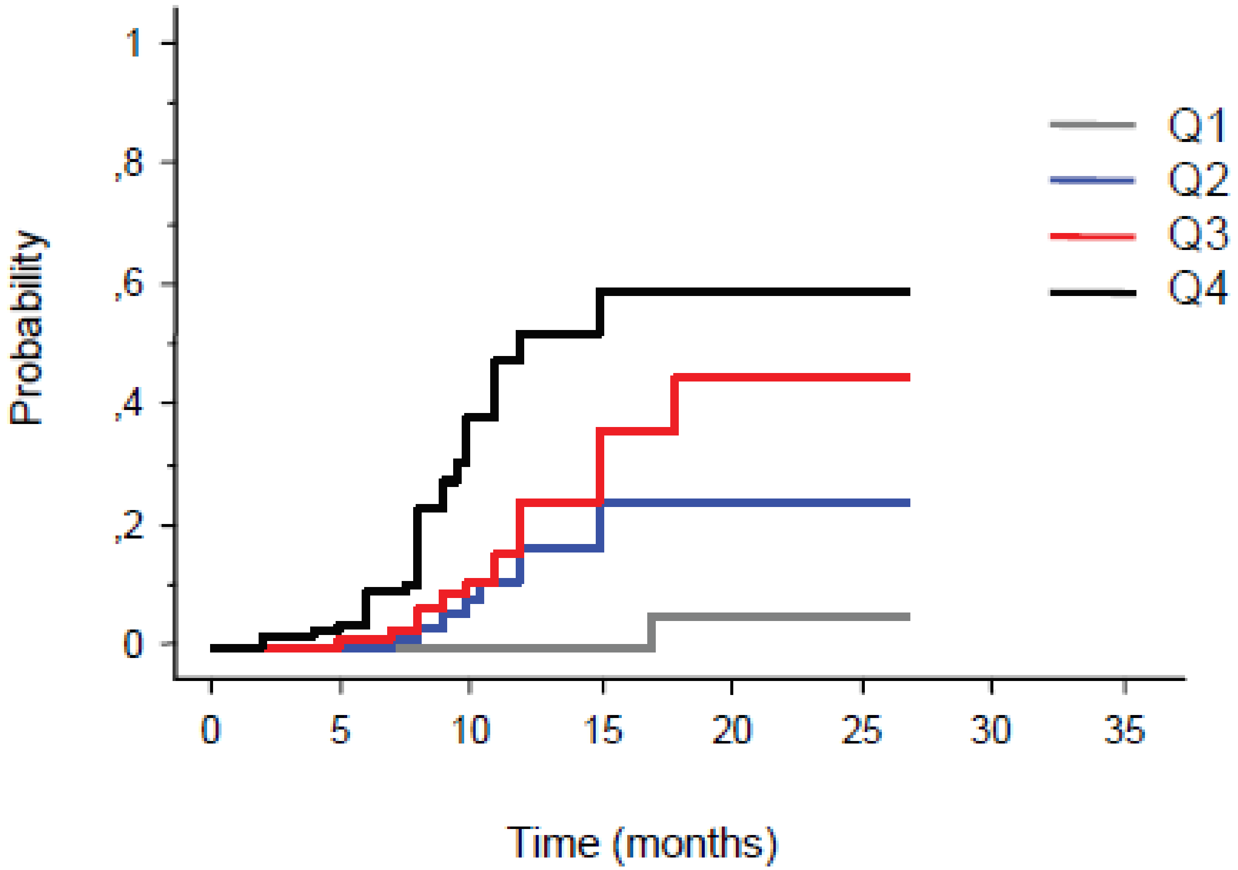


Figure 2 Risk of brain radionecrosis after stereotactic radiosurgery for brain metastases in relation to brain volumes receiving 12 Gy (V12 Gy) stratified for quartiles (Q1-Q4). The risk increased significantly through Q1-Q4, corresponding to V12 Gy < 3.3 cm^3, 3.3-5.9 cm^3, 6.0-10.9 cm^3, and >10.9 cm^3, respectively. The actuarial risk at 1 year was 0% for Q1, 16% for Q2, 24% for Q3, and 51% for Q4

12Gy		Risk at 1 year
Q1	<3.3 cm3	0%
Q2	3.3-5.9 cm3	16%
Q3	6-10.9 cm3	24%
Q4	>10.9 cm3	51%

10Gy		Risk at 1 year
Q1	<4.5 cm3	2.6%
Q2	4.5-7.7. cm3	11%
Q3	7.8-12.6 cm3	24%
Q4	>12.6 cm3	47%

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Clinical Investigation

Single-Fraction Versus Multifraction (3 × 9 Gy) Stereotactic Radiosurgery for Large (>2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis

CrossMark

- 289 pts matched with propensity scoring
- All mets >2 cm; PTV=GTV+1-2mm
- SF SRS dose- 18Gy for 2-3cm mets and 15-16Gy >3cm
- 1YLCR was 77% in single fraction and 91% in MF SRS (p=0.01)
- Radio necrosis- 31 pts (20%) in SFSRS and 11 pts (8%) in MF SRS (p=0.004)
- 1Y Incidence of radionecrosis- 18% and 9% in SF and MF SRS (p=0.01)

- BED 12 of 9Gyx3 fr= 47Gy (equivalent of 22Gy/single fr)

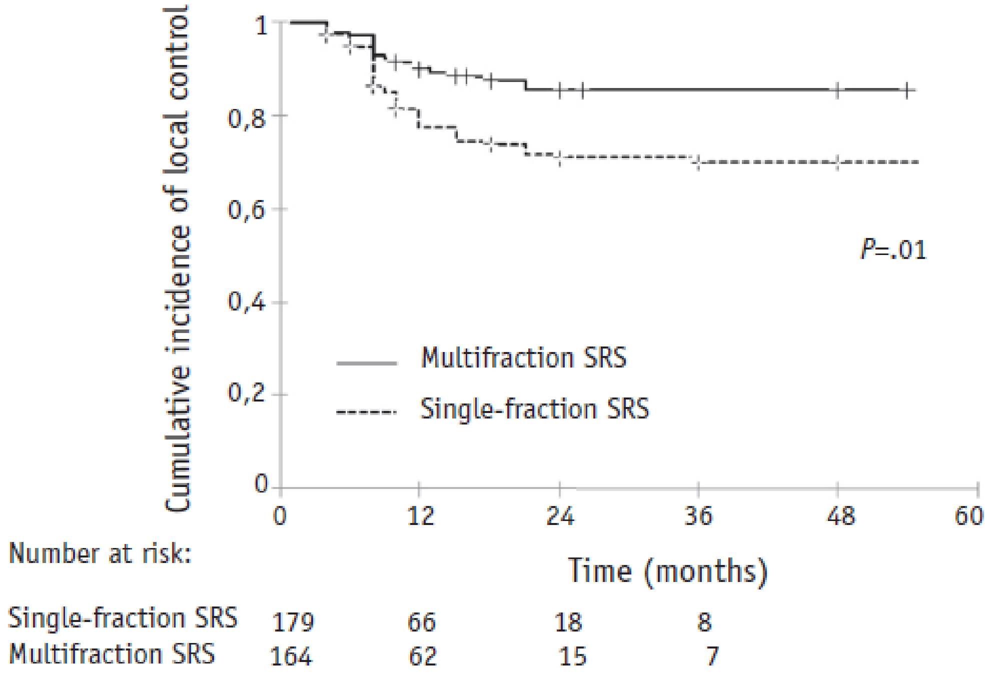

Fig. 3. Cumulative incidence of local control after single-fraction and multifraction stereotactic radiosurgery (SRS). Local control was significantly higher in the multifraction SRS group ($P=.01$).

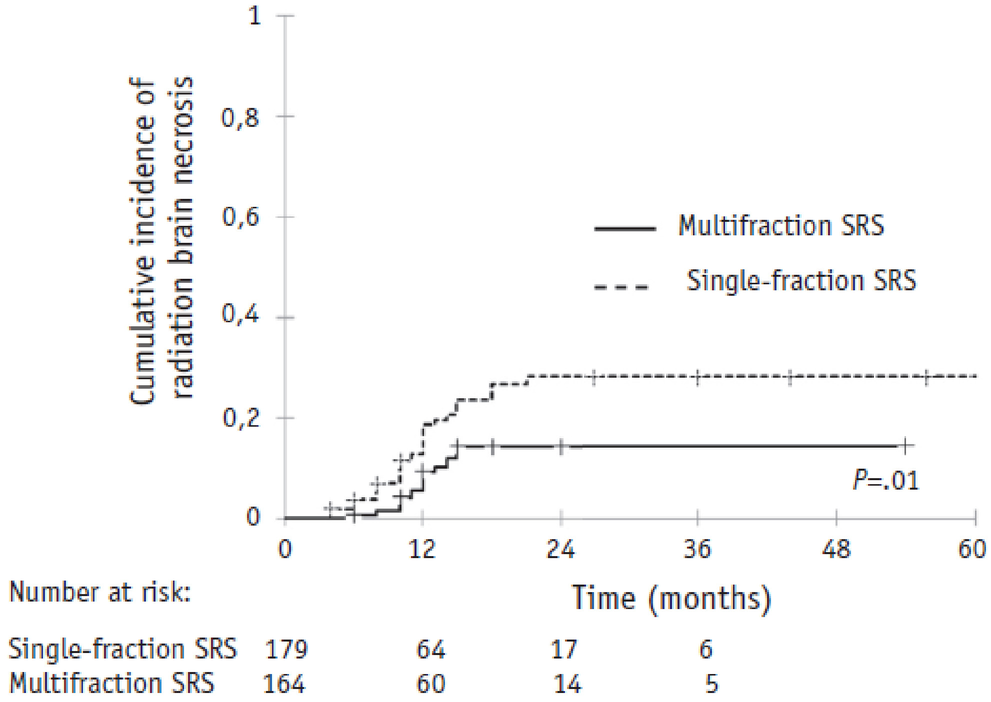

Fig. 4. Cumulative incidence of brain radionecrosis after stereotactic radiosurgery (SRS). The difference between the single-fraction and the multifraction SRS groups was significant ($P=.01$).

MF SRS gives equivalent LCR with lesser incidence of complications

- Management of BM is complex and every patient requires MDT
- Pay attention to molecular subtype of tumour

THANK YOU