CONVEGNO DEL GRUPPO REGIONALE PIEMONTE-LIGURIA-VALLE D'AOSTA

Associazione Italiana Radioterapia Oncologica

Radiochirurgia e Radioterapia stereotassica: non solo tecnica

RADIOCHIRURGIA E RADIOTERAPIA STEREOTASSICA INTRACRANICA: ESPERIENZE CLINICHE E INTEGRAZIONI CON TERAPIE SISTEMICHE

Letteratura ed esperienza clinica piemontese

C. Mantovani *(Torino)*

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RADIOCHIRURGIA E RADIOTERAPIA STEREOTASSICA: NON SOLO TECNICA

Ospedali Galliera – Salone Congressi
Genova, 25 marzo 2017

La sottoscritta Mantovani Cristina in qualità di relatore, ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 18,19 del Reg. Applicativo dell'Accordo Stato-Regione del 12 aprile 2012, per conto dello Studio E.R. Congressi s.r.l., dichiara che negli ultimi due anni

non ha avuto rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

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Brain metastases: background

- Systemic disease to the brain is unfortunately a quite common event
- Radiotherapy, especially with the great technical development during the past decades, represents a cornerstone of current treatment options
- Despite advances in treatment options, the prognosis is still poor

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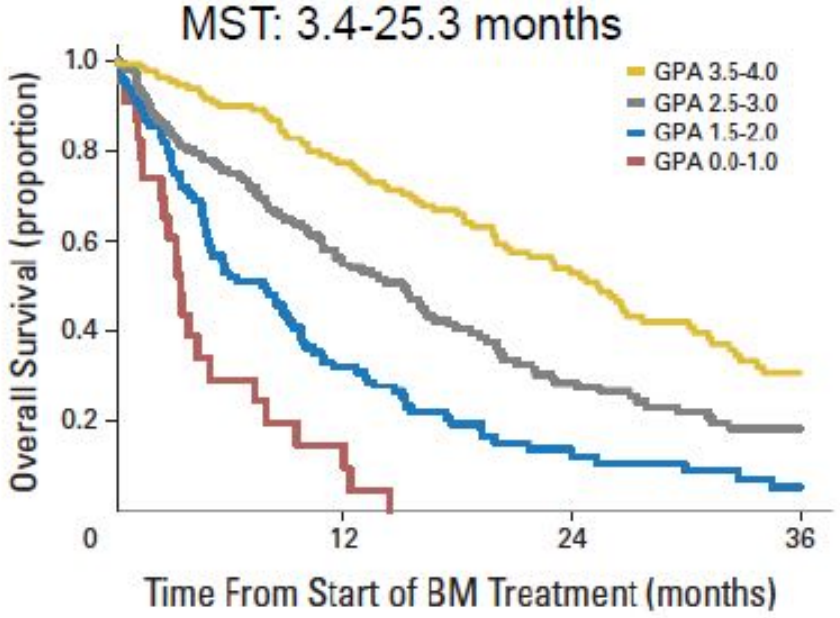
JOURNAL OF CLINICAL ONCOLOGY

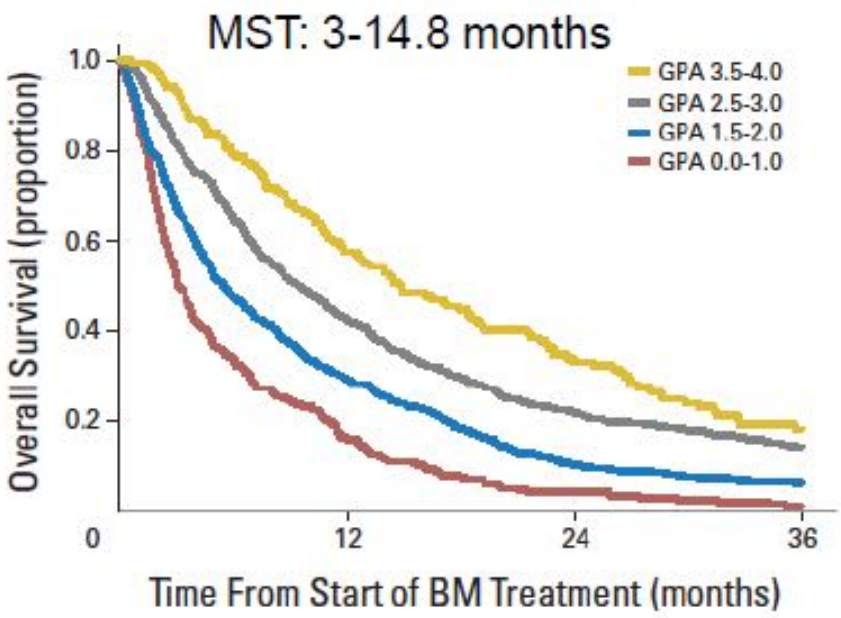
	KPS	Age	Number of mets	Extra - cranial mets	Tumour subtype
Lung	✔	✔	✔	✔	-
Breast	✔	✔	-	-	✔
Melanoma	✔	-	✔	-	-
Renal	✔	-	✔	-	-
GI	✔	-	-	-	-

A



Breast cancer

B



NSCLC

Diagnosis-specific GPA

Sperduto et al.

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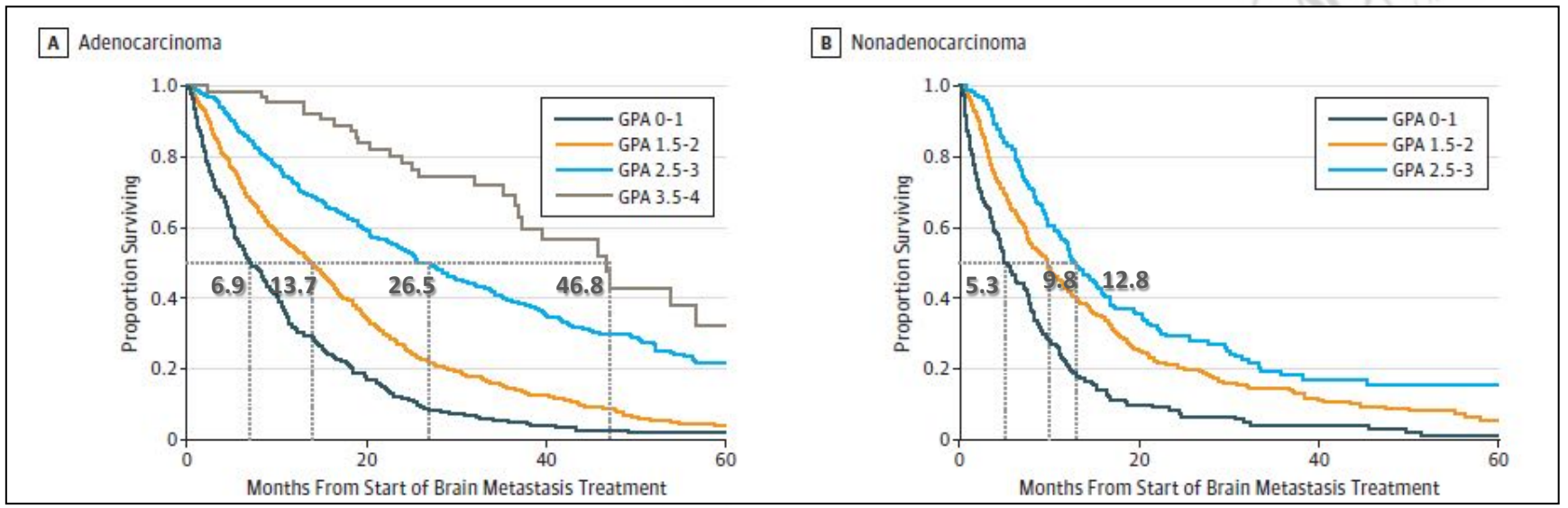
JAMA Oncology | Brief Report

An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA)

Paul W. Sperduto, MD, MPP; T. Jonathan Yang, MD; Kathryn Beal, MD; Hubert Pan, MD; Paul D. Brown, MD; Ananta Bangdiwala, MS; Ryan Shanley, MS; Norman Yeh, MD; Laurie E. Gaspar, MD, MBA; Steve Braunstein, MD; Penny Sneed, MD; John Boyle, MD; John P. Kirkpatrick, MD, PhD; Kimberley S. Mak, MD; Helen A. Shih, MD; Alex Engelman, MD; David Roberge, MD; Nils D. Arvold, MD; Brian Alexander, MD; Mark M. Awad, MD, PhD; Joseph Contessa, MD; Veronica Chiang, MD; John Hardie, MD, PhD; Daniel Ma, MD; Emil Lou, MD; William Sperduto, BA; Minesh P. Mehta, MD

Table 2. Updated DS-GPA for NSCLC With Brain Metastases (Lung-molGPA) Scoring Chart and Worksheet to Estimate Survival

Prognostic Factor	GPA Scoring Criteria[a] 0	0.5	1.0	Patient Score[b]
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	___
Total	NA	NA	NA	___



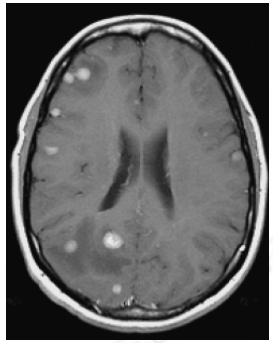
Brain metastases: background

- Many patients affected with brain metastases die as a result of extra-cranial disease progression
- A substantial number of brain metastases patients suffer from the local tumor progression in the CNS
- Optimising local control is thus of paramount importance

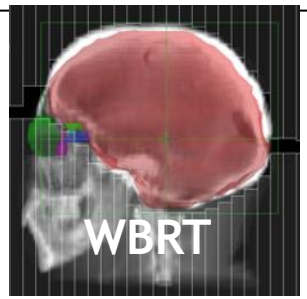
Brain metastases: background

Corollary:

- Development of symptomatic brain metastases has a substantial impact on patient's quality of life (QoL) and neuro-cognitive function



- Treatment decisions must be individualized based on a complex array of both **patient-specific** and **tumor-specific** characteristics



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Radiosurgery (SRS) and FSRT

Author	N patients	N metastases	Diagnoses	Range of diameters/ volumes[b]	Dose/specification isodose	GTV–PTV margin (mm)	% WBI[a] (patients)	RTx Machine	Technique
Matsuo (1999) [31]	92	162	All histologies	<3 cm/<10 cm^3	1 × 25 Gy/50%	0	0%	Lineac	Circular arc
Chang (2003) [25]	135	153	All histologies	<2 cm/<5 cm^3	20–24 Gy/ 70–100%	0	13%	Lineac	Circular arc
Lutterbach (2003) [30]	101	155	All histologies	<3 cm	18 Gy/80%	0–2	0%	Lineac	Circular arc
Chang (2005) [26]	189	264	Melanoma, sarcoma, renal cell carcinoma	<4 cm/27.5 cm^3	RTOG/60–100%	0	8%	Lineac	Circular arc
Ernst-Stecken (2006) [28]	51	72	All histologies	1–5 cm/0.3–65.6 cm^3	5 × 7 Gy/90% or WBI + 5 × 6 Gy/90%	3	57%	Novalis	Conformal beam/ Dynamic arc
Vogelbaum (2006) [34]	202	375	All histologies	<4.5 cm	RTOG/50%	0	76%	GK	GK
Narayana (2007) [32]	20	20	All histologies	2–5 cm	5 × 6 Gy/100%	3	0%	Lineac	IMRT
Chao (2008) [27]	111	?	All histologies	<4 cm	RTOG/?	0	0%	GK	GK
Higuchi (2009) [29]	43	46	All histologies	3–4.5 cm/10–36 cm^3	3 × 10 Gy/50%	0	0%	GK	GK
Molenaar (2009) [16]	86	150	All histologies	<4 cm	RTOG/80%	2	15%	Novalis	Dynamic arc
Saitoh (2009) [33]	49	78	Non small cell lung cancer	<4 cm	3 × 13 Gy/90% or 3 × 14 Gy/90%	3	0%	Lineac	Conformal beam

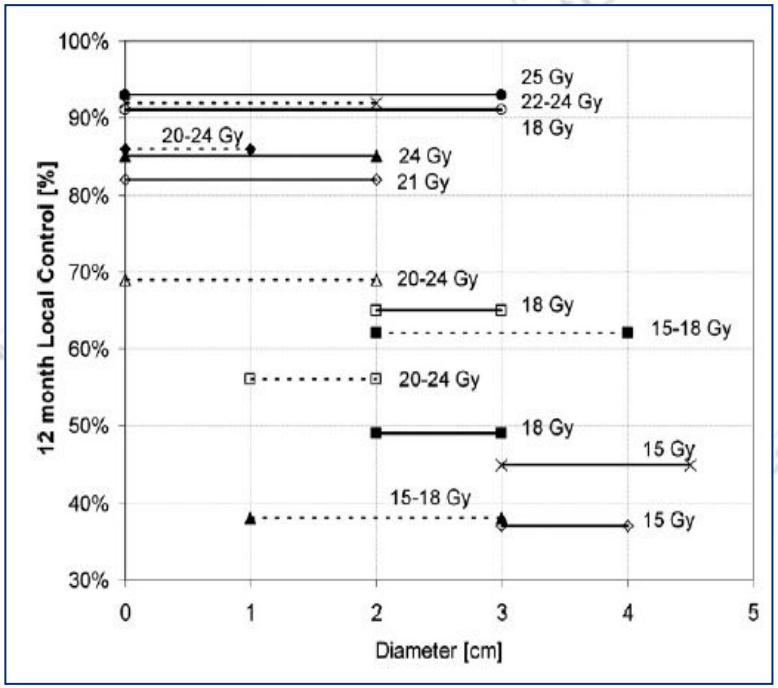
Radiosurgery (SRS) and FSRT

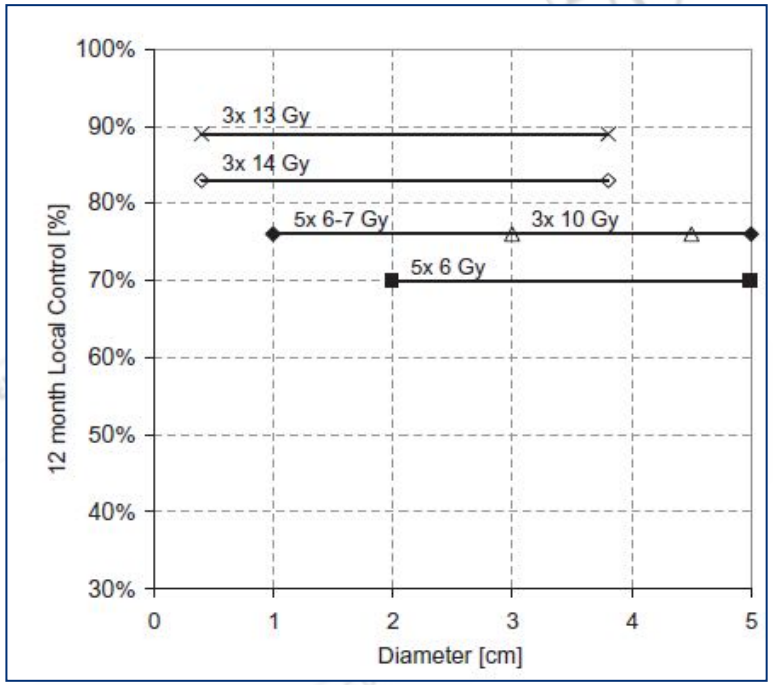
Author	Diameter (cm)	Dose (Gy)	BED_{12} (Gy)	6 month local control (%)	12 month local control (%)	12 month survival (%)	Radiation necrosis rate (%)
Matsuo (1999) [31]	0–3	25	[b]53.0	100	93	40	Na
Chang (2003) [25]	0–2	20–24	41.0–50.7	Na	69	[a]48	[a]1
	0–1	20–24	41.0–50.7	97	86		
	1–2	20–24	41.0–50.7	82	56		
Lutterbach (2003) [30]	0–3	18	[b]36.0	93	91	27	1
Chang (2005) [26]	1–3	15–18	28.6–36.0	Na	38	31	3
Vogelbaum (2006) [34]	0–2	24	[b]50.7	92	85	[a]50	Na
	2–3	18	[b]36.0	87	49		
	3–4.5	15	[b]28.6	71	45		
Chao (2008) [27]	0–2	22–24	45.9–50.7	97	92	[a]32	[a]2
	2–4	15–18	28.6–36.0	83	62		
Molenaar (2009) [6]	0–2	21	[b]43.4	100	82	[a]35	[a]6
	2–3	18	[b]36.0	95	65		
	3–4	15	[b]28.6	95	37		

Author	Diameter (cm)	Dose (Gy)	BED_{12} (Gy)	6 month local control (%)	12 month local control (%)	12 month survival (%)	Radiation necrosis rate (%)
Ernst-Stecken (2006) [28]	1–5	5 × 6–7	43.3–52.8	89	76	Na	Na
Narayana (2007) [32]	2–5	5 × 6	[b]43.3	90	70	42	Na
Higuchi (2009) [29]	3–4.5	3 × 10	[b]50.4	90	76	30	0
Saitoh (2009) [33]	0.4–3.8	3 × 13	[b]71.1	90	89	[a]61	[a]12
		3 × 14	[b]78.3	100	83		

Actuarial local control and survival rates and crude radiation necrosis rates about SRS and FSRT

Radiosurgery (SRS) and FSRT

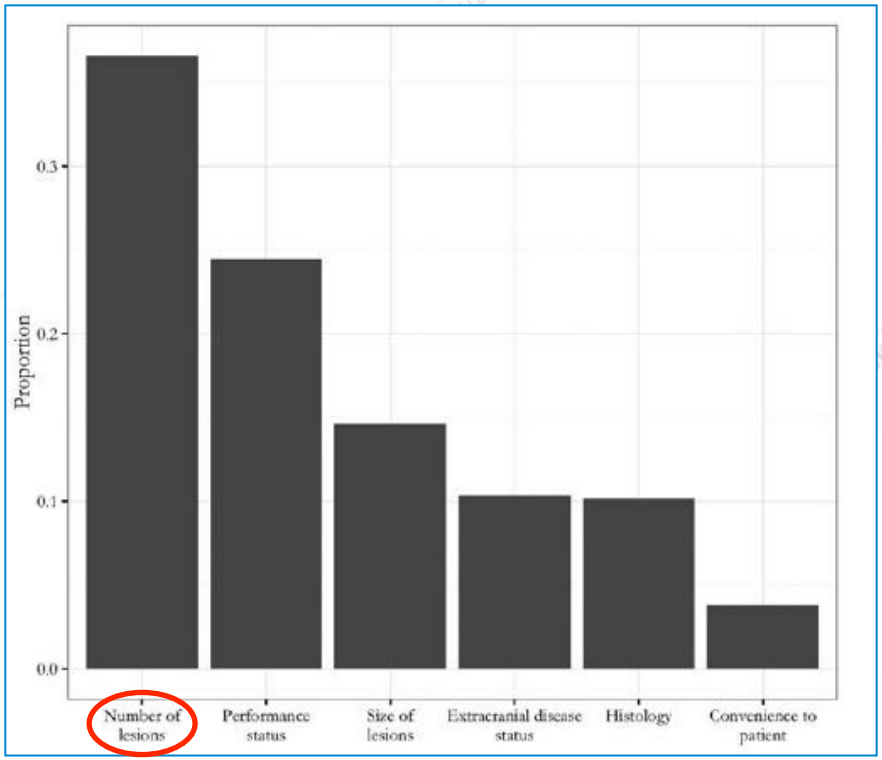




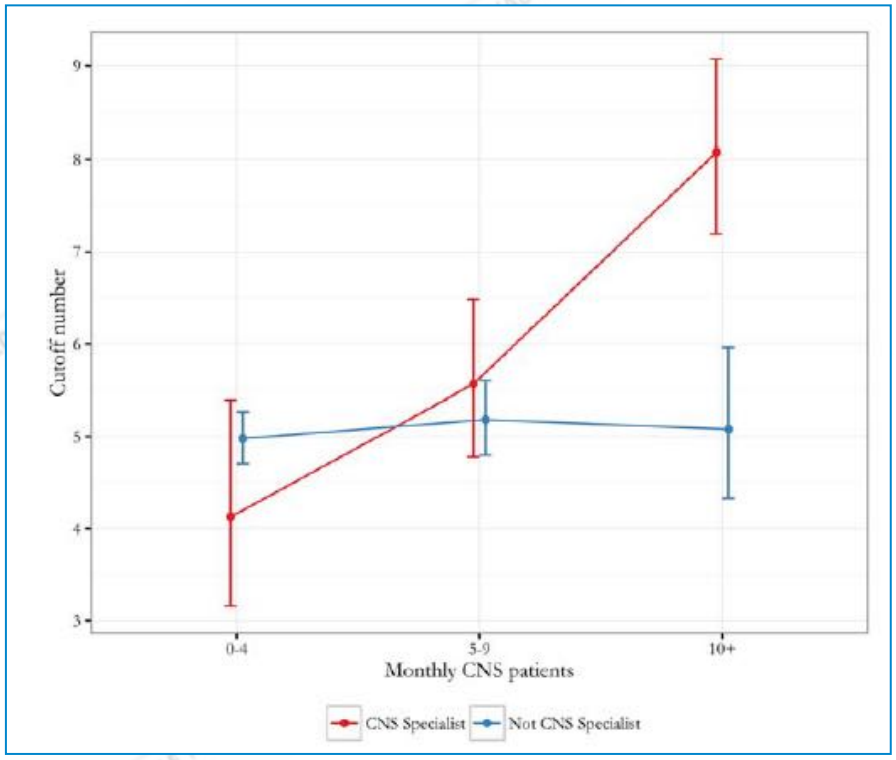
Local control is highly dependent upon dose!!!

Treatment Trends for Patients With Brain Metastases: Does Practice Reflect the Data?

Kiri A. Sandler, MD[1]; Narek Shaverdian, MD[1]; Ryan R. Cook, MSPH[2]; Amar U. Kishan, MD[1]; Christopher R. King, PhD, MD[1]; Isaac Yang, MD[3,4]; Michael L. Steinberg, MD[1,3]; and Percy Lee, MD[1,3]

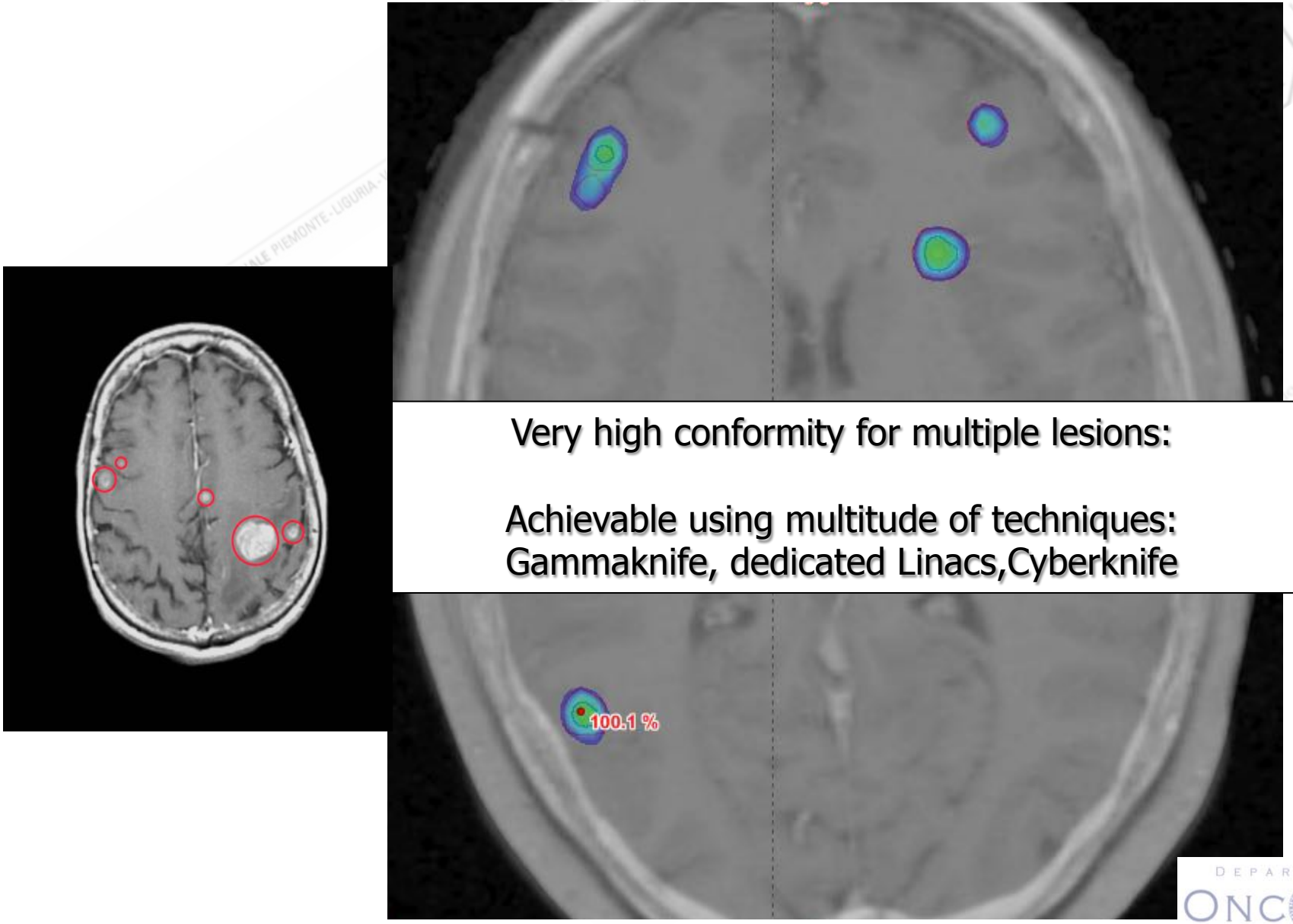


Decision-making factors



The cutoff number used when switching from SRS to WBRT compared with the number of patients with brain mets treated per month

Innovations in Radiosurgery:
Radiosurgery for multiple brain mets: > 3-4 mets eligible to SRS?



Very high conformity for multiple lesions:

Achievable using multitude of techniques:
Gammaknife, dedicated Linacs,Cyberknife

SRS vs WBRT: it's not a numbers game!

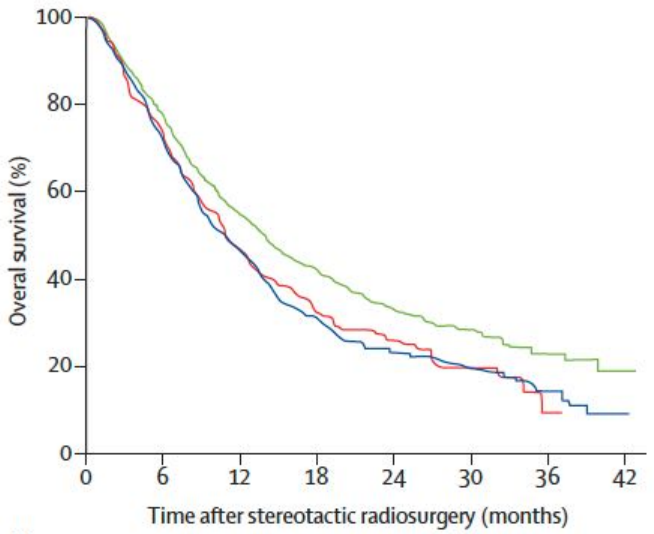
Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto

Lancet Oncol 2014; 15: 387–95

	Median overall survival, months (95% CI)			
	Total (n=1194)	1 tumour (A) (n=455)	2–4 tumours (B) (n=531)	5–10 tumours (C) (n=208)
Lung	12·5 (11·2–13·4)	13·4 (11·7–15·5)	11·4 (9·5–13·1)	12·5 (10·3–14·9)
Breast	14·8 (11·9–24·4)	27·2 (8·2–NE)	13·7 (10·9–23·6)	10·5 (5·2–NE)
GI tract	6·7 (5·7–8·7)	14·4 (6·7–18·2)	5·7 (4·7–7·9)	5·7 (1·5–7·9)
Kidney	13·7 (6·0–17·0)	16·3 (6·0–NE)	13·7 (5·1–17·0)	3·8 (2·3–5·4)
Others	8·4 (6·1–10·3)	7·3 (3·3–24·3)	8·6 (1·0–14·8)	9·0 (2·9–27·3)

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

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A Meta-Analysis Evaluating Stereotactic Radiosurgery, Whole-Brain Radiotherapy, or Both for Patients Presenting with a Limited Number of Brain Metastases

Cancer Month 00, 2011

May Tsao, MD[1]; Wei Xu, PhD[2]; and Arjun Sahgal, MD[1,3]

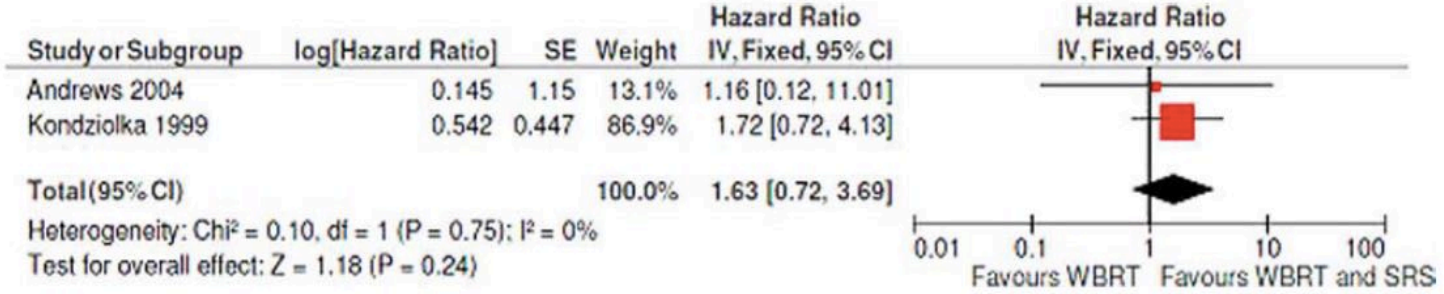


Figure 1. Overall survival: whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) boost versus WBRT alone.

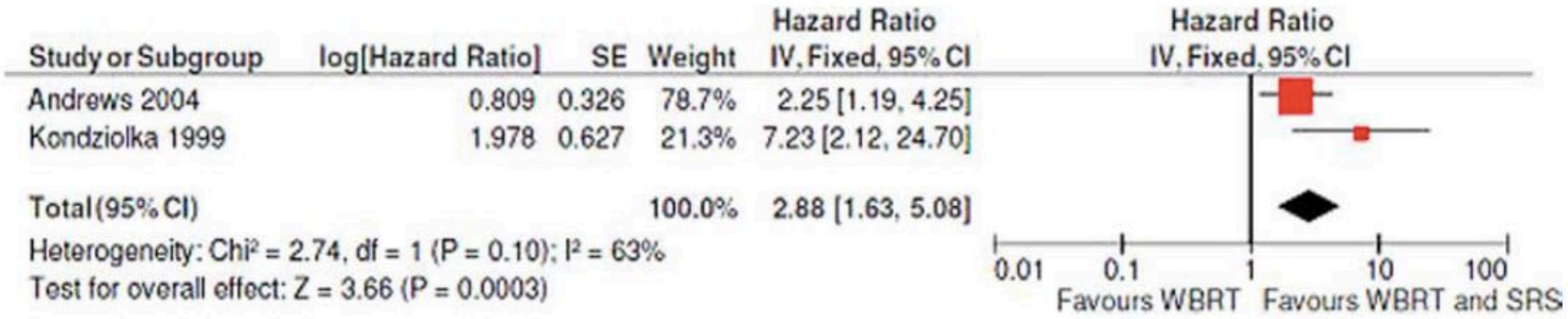


Figure 2. Local Control: WBRT and SRS boost versus WBRT alone.

RCT in oligometastatic patients

Exclusive local treatment (surgery or radiosurgery) vs WBRT + local treatment (surgery or radiosurgery)

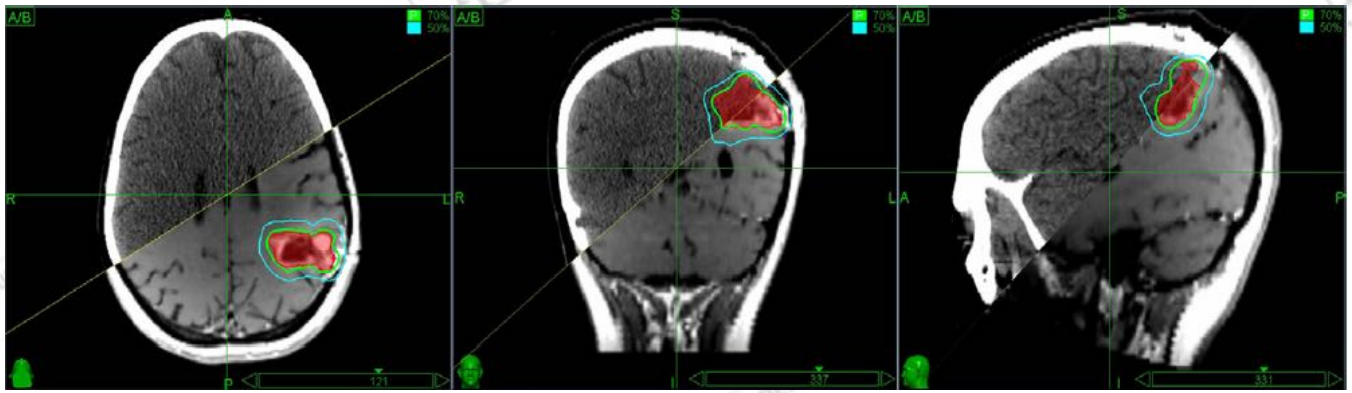
Trials comparing exclusive local therapy vs. (whole brain radiotherapy + local treatment.

Author	Treatment arms	Prescribed dose	*n*	Inclusion criteria	Local control	Freedom from new brain metastases	Brain tumor control	Neurologic death rate	Survival
Patchell [14]	S	–	95	Single lesion	54.0%	63.0%	30.0%	44.0%	NS
	S + WBRT	WBRT: 50,4 Gy in 28 fr		All the primaries	90.0%	86.0%	82.0%	14.0%	
Aoyama [15]	RS	RS:⩽2 cm: 22–25 Gy;>2 cm: 18–20 Gy	132	1–4 lesions	72.5% @ 1 y	36.3% @ 1 y	23.6% @ 1 y	NS	NS
	RS + WBRT	RS: dose reduction by 30% WBRT: 30 Gy in 10 fr or 12 fr		All the primaries	88.7% @ 1 y	58.5% @ 1 y	53.2% @ 1 y		
Chang [16]	RS	RS:<2 cm: 18 Gy; 2–3 cm: 15 Gy; 3–4 cm: 12 Gy	58	1–3 lesions	67.0% @ 1y	45.0% @ 1y	27.0% @ 1y	NS	15.2 m
	RS + WBRT	RS:<2 cm: 18 Gy; 2–3 cm: 15 Gy; 3–4 cm: 12 Gy WBRT: 30 Gy in 12 fr		All the primaries	100.0% @ 1y	73.0% @ 1y	73.0% @ 1y		5.7 m
Mueller and Kocher [20,21]	RS or S	RS: 20 Gy	359	1–3 lesions	68.7% @ 2 y	67.6% @ 2 y	46% @ 2y	44.0%	NS
	RS or S + WBRT	RS: 20 GyWBRT: 30 Gy in 10 fr		All the primaries	83.6% @ 2 y	82.4% @ 2 y	68.6% @ 2 y	28.0%	
Roos [22]	RS or S	RS: n.a.	19	Single lesion	n.a.	n.a.	NS	n.a.	NS
	RS or S + WBRT	WBRT: 36 Gy in 18 fror 30 Gy in 10 fr		All the primaries					

S, surgery; WBRT, whole brain radiotherapy; RS, radiosurgery; fr, fractions; w, weeks; m, months; y, year; n.a., not available; NS, not statistically significant difference.

S. Scoccianti and U. Ricardi, Radiother Oncol 2011

Post-operative radiotherapy: SRS to resection cavity



Challenging the tradition of adjuvant WBRT???

Neurosurgery. 2016 Aug;63 Suppl 1:184. doi: 10.1227/01.neu.0000489784.83922.17.

215 Postoperative Stereotactic Radiosurgery vs Observation for Completely Resected Brain Metastases: Results of a Prospective Randomized Study.

Rao G, Ahmed S, Hess K, Mahajan A.

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PRE-operative SRS?
SRS administered shortly before surgery

Rationale

- To improve LC due to improved targeting of an intact mets
- To reduce the risk of leptomeningeal dissemination and radionecrosis

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Comparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis

Kirtesh R. Patel[1] · Stuart H. Burri[2] · Danielle Boselli[3] · James T. Symanowski[3] · Anthony L. Asher[4] · Ashley Sumrall[5] · Robert W. Fraser[2] · Robert H. Press[1] · Jim Zhong[1] · Richard J. Cassidy[1] · Jeffrey J. Olson[6] · Walter J. Curran[1] · Hui-Kuo G. Shu[1] · Ian R. Crocker[1] · Roshan S. Prabhu[2]

Comparing Preoperative With Postoperative Stereotactic Radiosurgery for Resectable Brain Metastases: A Multi-institutional Analysis

Kirtesh R. Patel, MD; Stuart H. Burri, MD; Anthony L. Asher, MD; Ian R. Crocker, MD; Robert W. Fraser, MD; Chao Zhang, PhD; Zhengjia Chen, PhD; Shravan Kandula, MD; Jim Zhong, MD; Robert H. Press, MD; ... Show more

Neurosurgery (2016) 79 (2): 279-285.

Brain mets in breast cancer

- In pts with triple negative breast cancer, the risk of CNS relapse may be as high as 46%, and CNS involvement often occurs in the setting of active systemic disease

- In pts with HER2-positive disease, up to 40%–50% will develop BM often despite controlled systemic disease.

- Clinical trials of lapatinib in combination with capecitabine have demonstrated activity with a CNS objective response rate of 20% in patients with previously treated BM

- Afatinib (alone or in combination with vinorelbine) did not demonstrate efficacy and was not as well tolerated. Single-agent neratinib had low efficacy in previously treated BM (CNS objective response rate of only 8%) but neratinib in combination with chemotherapy may prove more efficacious.

Brain mets in breast cancer

- Other promising agents in clinical trials for breast cancer pts with BM include trastuzumab + emtansine (for HER2+ disease), pathway inhibitors of phosphatidylinositol 3-kinase–mammalian target of rapamycin, CDK4 inhibitors, and poly(ADP-ribose) polymerase inhibitors.

- No increased toxicity of cranial SRT combined with Anti-Her2 (trastuzumab); however very limited available data

- No studies with concurrent lapatinib and RT

Toxicity of concurrent SRT and TKIs

- EGFR-inhibitors (gefitinib, erlotinib, lapatinib):

No increased toxicity in cranial SRT
(Phase 1 trials and retrospective data)

- ALK-Inhibitors (crizotinib, ceritinib, alectinib):

Available data does not allow for a robust conclusion on safety of combined crizotinib, ceritinib, alectinib and SRT.

Expert Review of Anticancer Therapy

Radiosurgery/stereotactic radiotherapy in combination with immunotherapy and targeted agents for melanoma brain metastases

Elisabetta Trino, Cristina Mantovani, Serena Badellino, Umberto Ricardi & Andrea Riccardo Filippi

- Anti-CTLA-4 (ipilimumab): the available studies are small but suggest that concurrent cranial SRT with ipilimumab is safe.

- Anti-PD-1/PD-L1 (nivolumab, pembrolizumab): the data on combined SRT and nivolumab is insufficient for conclusions

- BRAF-Inhibitors (vemurafenib, dabrafenib): data on CNS toxicity after combined cranial SRT and BRAF-inhibitors is conflicting. However, high rates of toxicity reported in some studies warrant caution.

- MEK-inhibitors (trametinib): the very small number of patients treated with combined SRT and MEK inhibitors does not allow to draw any conclusions about its safety.

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Summary and Conclusions
what type of RT is indicated in brain mets?

- Neurosurgery has an important role
- SRS represents the best option for small and/or unresectable mets (maximum number < 4-5 and maximum size < 3 cm)
- Probably safe and effective to treat multiple small deposits
- Role of adjuvant irradiation (post-op WBRT? Pre or post-op SRS? Observation?)
- WBRT with hippocampal sparing may be useful in multiple mets where SRS not feasible (remind results of QUARTZ trial in clinical practice)
- WBRT with SIB not yet shown to improve outcomes but has potential

Individualise treatment and MDT evaluation!!!!

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