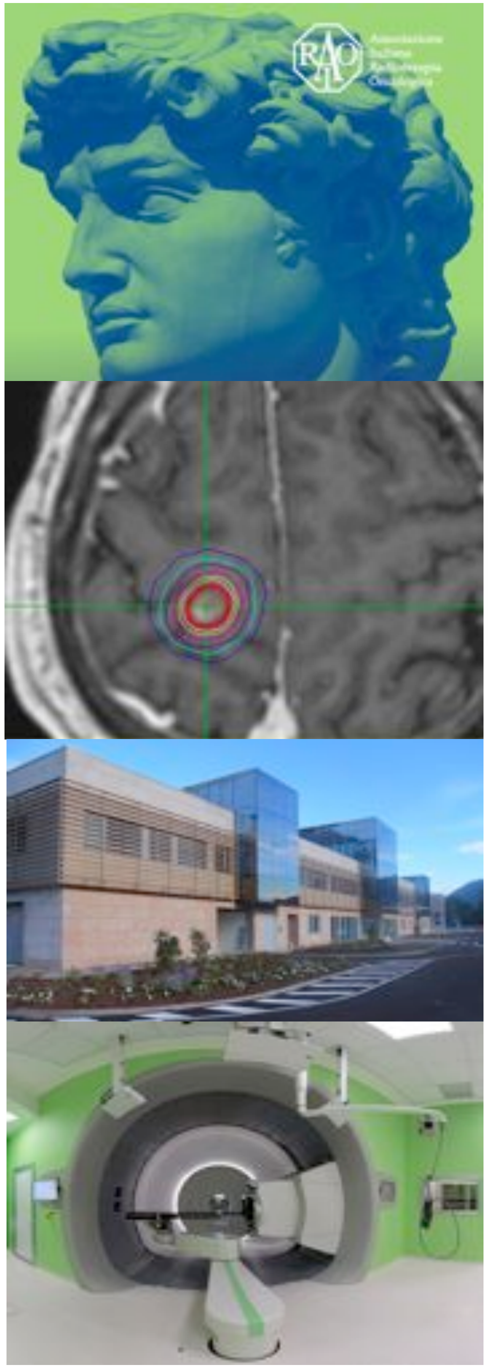

VII Congresso Nazionale AIRO Giovani

Firenze 14 Giugno 2014

La radioterapia stereotassica ablativa
LE METASTASI ENCEFALICHE

Dante Amelio

U.O. Protonterapia

Struttura Ospedaliera di Trento

Azienda Provinciale per i Servizi Sanitari (APSS), Trento

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

OUTLINE

- Introduction

- To review current indications, modalities, outcomes and toxicities of stereotactic radiosurgery (SRS) for brain metastases

- To highlight (some) current issues of interest

INTRODUCTION

- Most frequent malignant brain tumor
- 20-30% of patients with cancer may have brain metastases at autopsy

Table 1
Percentage of brain metastases caused by different primary tumors

	Baker [3]	Globus [4]	Tom [5]	Chason et al [7]	Hunter and Rewcastle [8]	Posner and Chernik [9]	Zimm et al [10]	Lagerwaard et al [11]	Nussbaum et al [12]
N=	114	41	82	200	393	572	191	1291	729
Lung	21	46	22	61	34	18	64	56	39
Breast	21	2	16	16	19	17	14	16	17
Colorectal	7	12	11	4	6	2	3		
Melanoma	8 ("skin")	7	9	5	6	16	4		11
Kidney	8	2	1	4	4	2	2	4	6
Thyroid	1	10	1	<1	2				
Leukemia						12			
Lymphoma						10			
Unknown primary	4	2	18	1	4		8	8	5
% with brain mets.	18	14		18	6	24			

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Lassman AB, et al. *Neurol Clin* 2003;21:1-23

INTRODUCTION

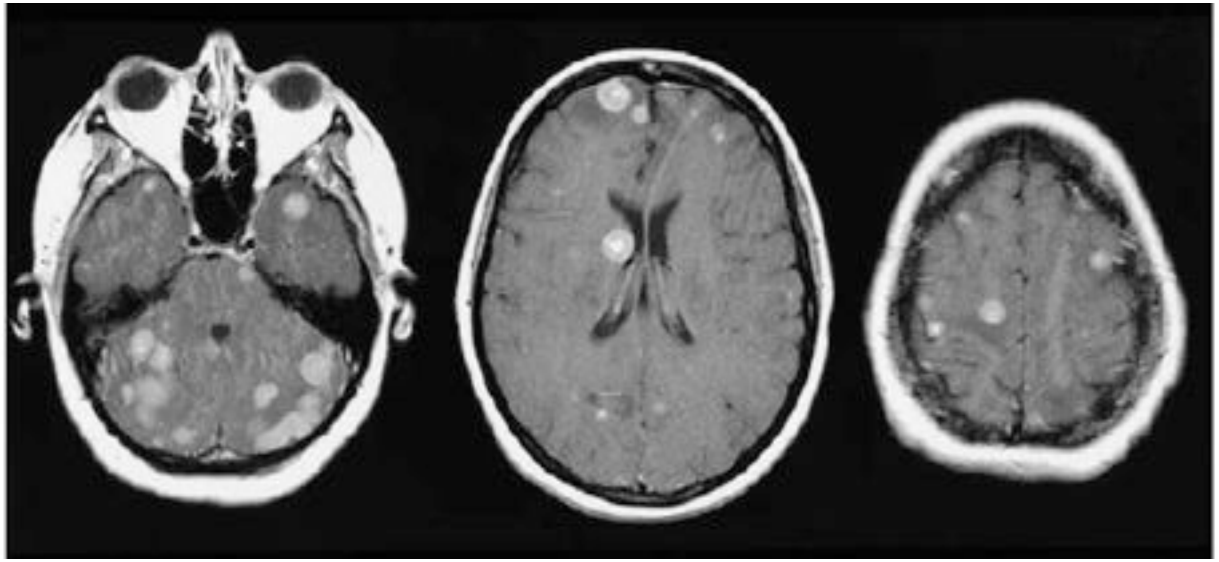
Brain metastases by histology

Histology	% of all Brain Metastases
Lung	50%
Breast	15-20%
Melanoma	10-15%
Colorectal	2-12%
Kidney	1-8%
Thyroid	1-10%

INTRODUCTION

Brain metastases by location

Location	% of all Brain Metastases
Brain	50%
Cerebellum	15-20%
Basal ganglia	10-15%



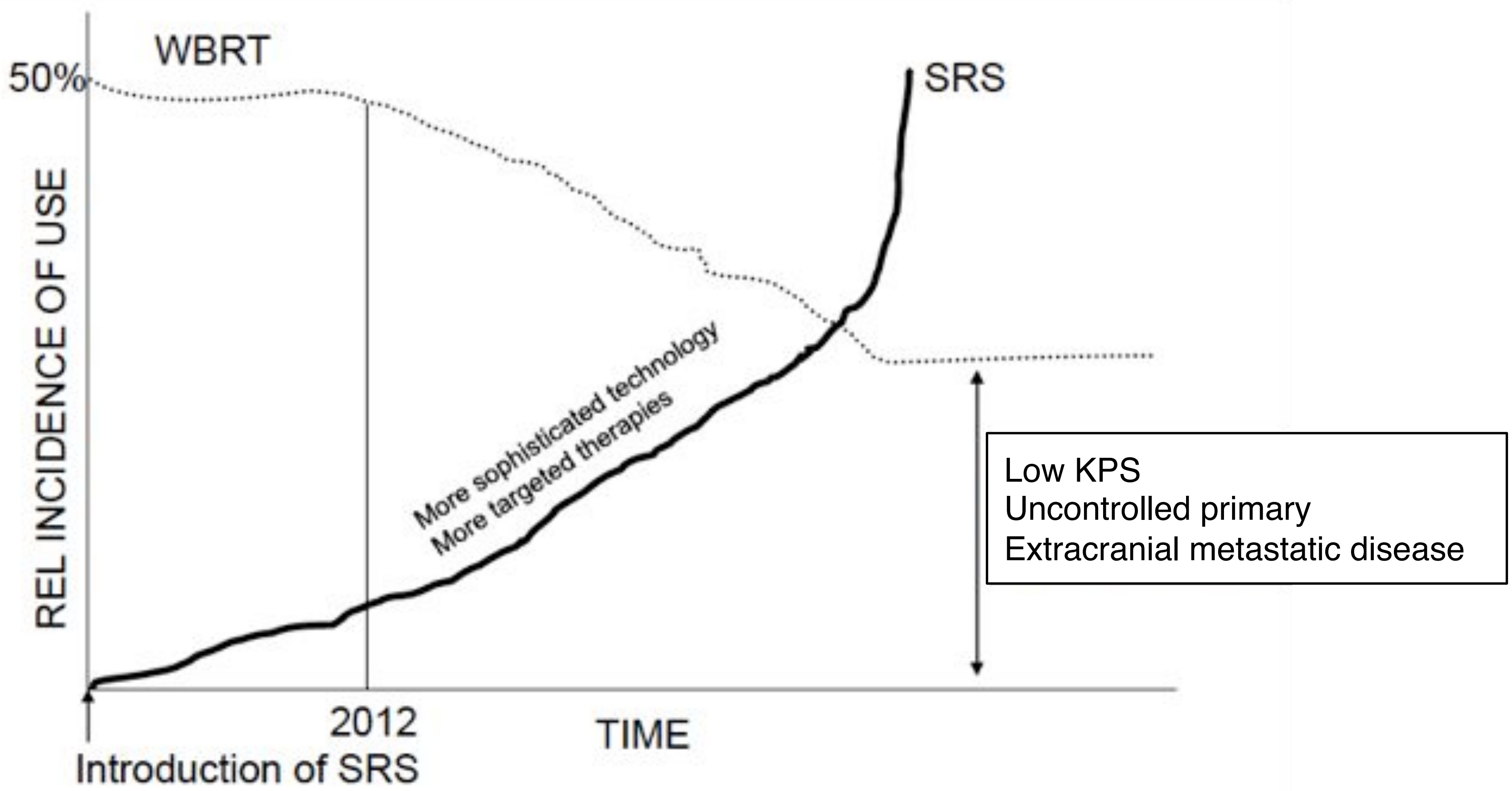
INTRODUCTION

Therapeutic options

- Surgery
- Radiotherapy (RT):
    1. Whole-brain RT (WBRT)
    2. Stereotactic radiosurgery (SRS) (single/multisession)
    3. Combination of both
- Chemotherapy
- Supportive care
- Combination of them

WHY ARE WE DISCUSSING ABOUT BRAIN METS TODAY?

Forecasting the evolving relative role of WBRT and SRS



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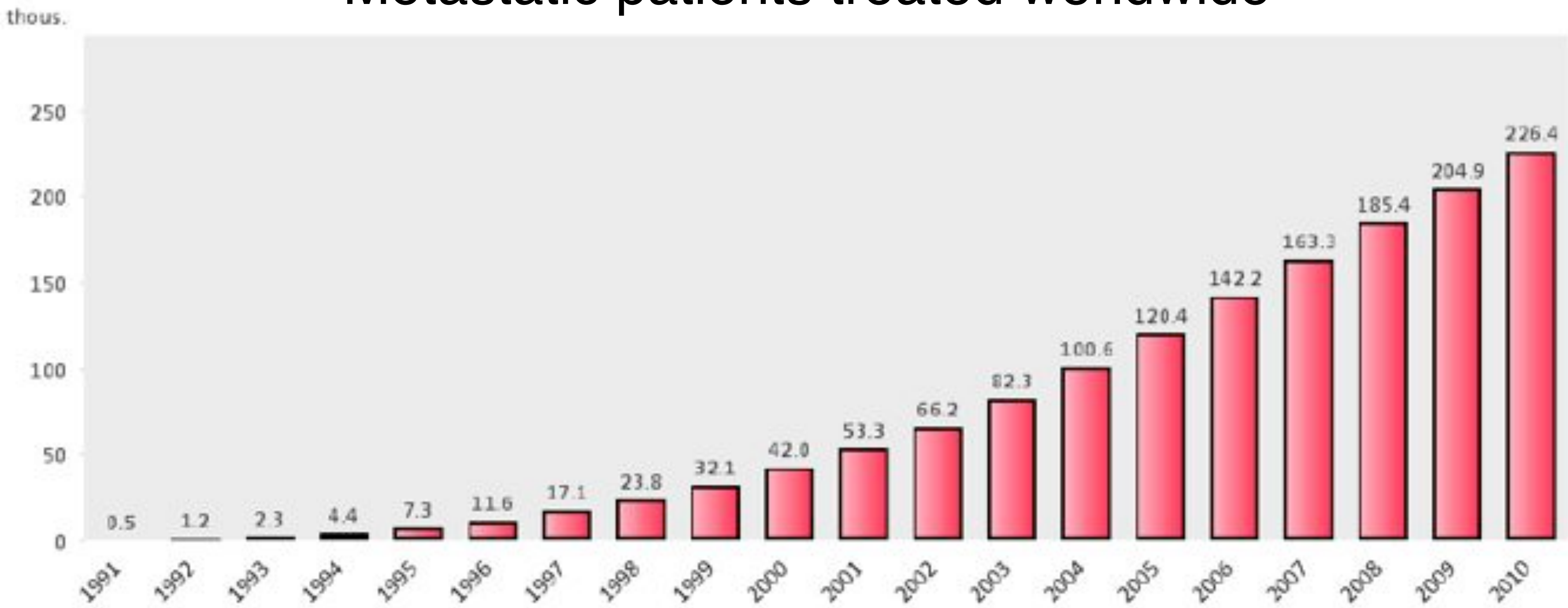
Leksell Gamma Knife Society

Metastatic patients treated worldwide



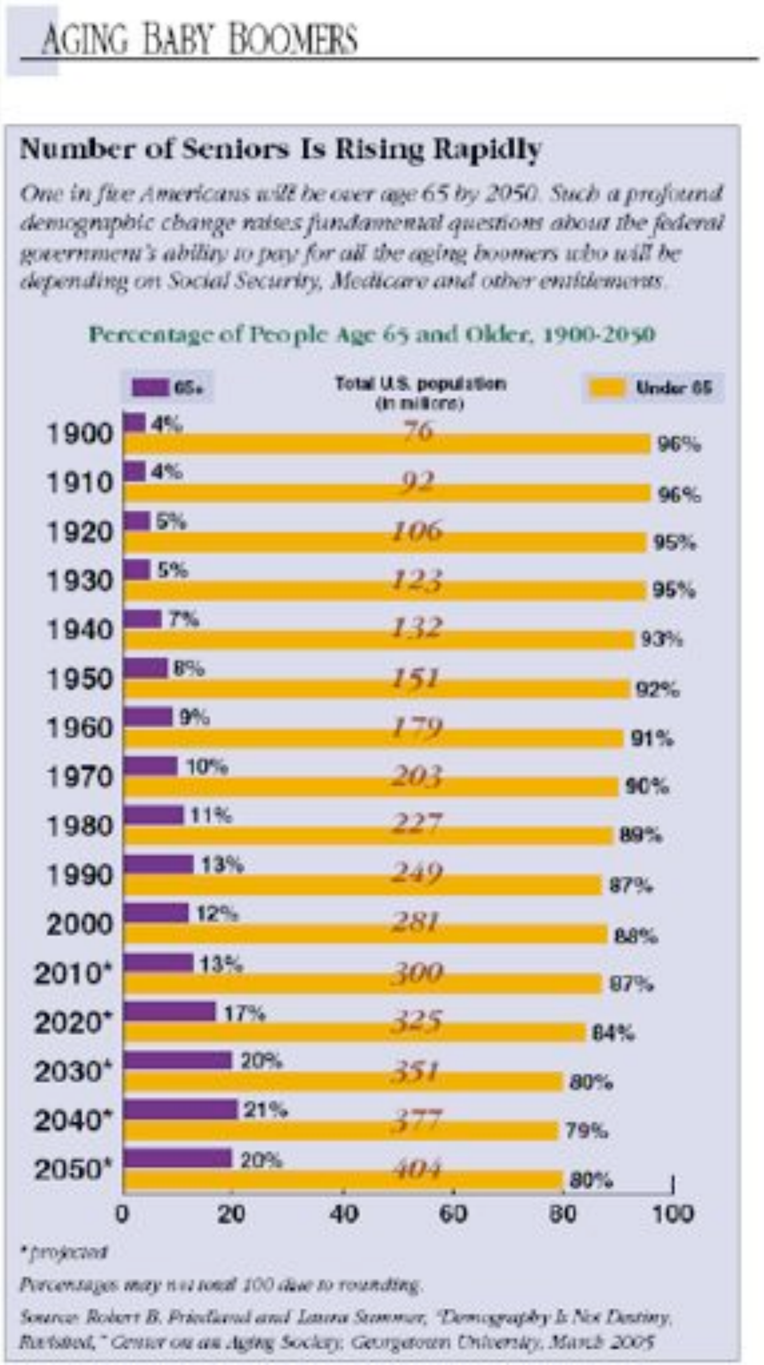
(Cumulative numbers)

WHY ARE WE DISCUSSING ABOUT BRAIN METS TODAY?

Population aging

Should we take it into account?

- QoL
- Neurocognitive status



WHY ARE WE DISCUSSING ABOUT BRAIN METS TODAY?

More effective systemic therapies may translate into CNS metastases increase

- In women with HER-2+ breast cancer, the widespread use of HER-2 target therapy with trastuzumab has unmasked a population in whom CNS progression is a significant source of morbidity and mortality since trastuzumab does not penetrate the CNS but is effective outside the CNS.

Bardell JC, et al. *Cancer* 2003;97:2972-2977

Lin NU, et al. *Clin Can Res* 2007;13:1648-1655

More effective systemic therapies may translate into OS lengthening

Should we take it into account?

- QoL
- Neurocognitive status

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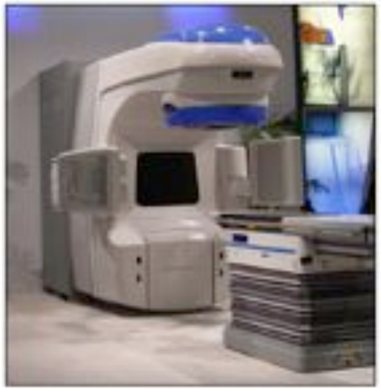
WHY ARE WE DISCUSSING ABOUT BRAIN METS TODAY?

Sophisticated platforms increase access and efficiency of SRS treatments.

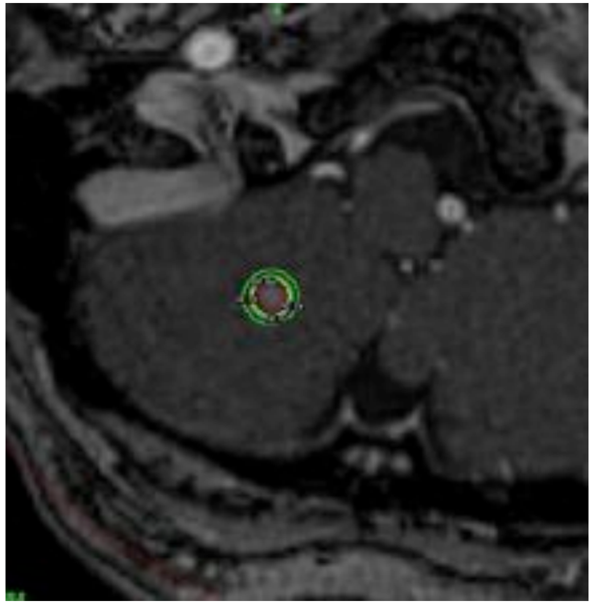
Moreover, they allow treatment of a larger number (> 4) of brain metastases than before and with greater efficiency.


Should we take it into account?

CURRENT INDICATIONS

(General) Radiosurgery rationale for brain metastases

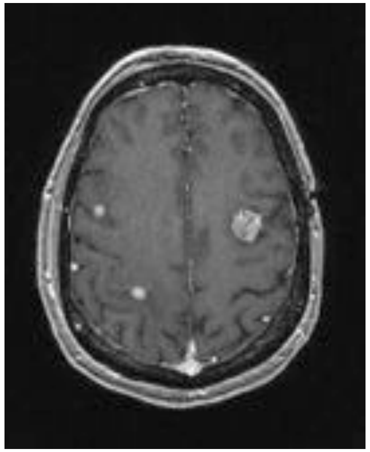


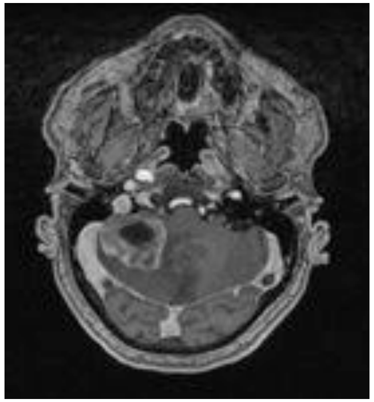
- Spherical/pseudospherical
- Most less than 3-4 cm diameter
- Typically grey-white matter location (non-eloquent)
- Generally well-circumscribed, non-infiltrative
- Improved LC of single lesions may leads to better survival
- Need for higher dose than achieved with WBRT for LC

INTRODUCTION

Factors used to assess therapy

- Number of metastases
- Size of lesion(s)/mass effect
- Location
- Neurologic deficit
- Age/KPS
- Primary tumor/stage
- Extracranial disease
- Patient's choice





INTRODUCTION

Prognostic factors and patient selection

RTOG Recursive Partioning Analysis (RPA) Classification

	Median Survival	**% in Analysis**
Class I **<65 (age) KPS ≥70** **Controlled primary** **No extracranial mets**	7.1 months	20
Class II – all others	4.2 months	65
Class III – KPS <70	2.3 months	15

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Gaspar L, et al. *Int J Radiat Oncol Biol Phys* 2000;47:1001-1006
Gaspar L, et al. *Int J Radiat Oncol Biol Phys* 1997;37:745-751

INTRODUCTION

Prognostic factors and patient selection

Graded Prognostic Assessment (GPA) Classification

Score	0	0.5	1.0
Age	>60	50-59	<50
KPS	<70	70-80	90-100
Number of CNS metastases	>3	2-3	1
Extracranial metastases	Present	-	None

Score	Median Survival (months)
3.5-4	16.7
2.5-3	9.6
1.5-2	5.4
0-1	3.1

Sperduto P, et al. *Int J Radiat Oncol Biol Phys* 2008;70:510-514

CURRENT INDICATIONS

Single brain metastases

Prognostic category	Other features	Treatment options
Good prognosis MST>3mos	Complete resection possible	<4cm • S + WBRT (L1) • SRS + WBRT (L1) • SRS alone (L1) • Surgery + boost to resection cavity (+/- WBRT) (L3)
		>4cm • S + WBRT (L1) • S + radiation boost to cavity (+/- WBRT) (L3)
	Not resectable	<4cm • SRS + WBRT (L1) • SRS alone (L1)
		>4cm • WBRT (L3)
Poor prognosis MST<3mos		• WBRT (L3) • Palliative care without WBRT (L3)

Tsao MN, et al. *Practical Radiation Oncology* 2012;2:210-225

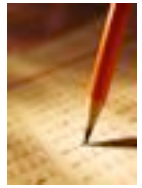
CURRENT INDICATIONS

Multiple brain metastases

Prognostic category	Other features	Treatment options
Good prognosis **MST>3mos**	<4cm	• SRS (L1) • SRS + WBRT (L1) • WBRT alone (L1)
	Significant mass effect	• S + WBRT (L3) • WBRT alone (L3)
Poor prognosis **MST<3mos**		• WBRT (L3) • Palliative care without WBRT (L3)

Tsao MN, et al. *Practical Radiation Oncology* 2012;2:210-225

CURRENT INDICATIONS



SRS dose prescription: RTOG 90-05

CLINICAL INVESTIGATION Brain

SINGLE DOSE RADIOSURGICAL TREATMENT OF RECURRENT PREVIOUSLY IRRADIATED PRIMARY BRAIN TUMORS AND BRAIN METASTASES: FINAL REPORT OF RTOG PROTOCOL 90-05

Edward Shaw, M.D.,* Charles Scott, Ph.D.,† Luis Souhami, M.D.,‡ Robert Dinapoli, M.D.,§ Robert Kline, Ph.D.,‖ Jay Loeffler, M.D.,¶ and Nancy Farnan, B.S.†

- Type of study: phase I, dose escalation
- Population: recurrent, previously irradiated primary brain tumors/brain mets.
- Endpoint: max tolerated dose

Accrual by arm and dose:

Tumor diameter	Treatment arm/dose/accrual			
≤ 20 mm	Arm 1—> 18 Gy $n = 12$	Arm 4—> 21 Gy $n = 18$	Arm 7 24 Gy $n = 10$	
21–30 mm	Arm 2 —> 15 Gy $n = 15$	Arm 5 —> 18 Gy $n = 15$	Arm 8 —> 21 Gy $n = 13$	Arm II 24 Gy $n = 12$
31–40 mm	Arm 3 —> 12 Gy $n = 21$	Arm 6—> 15 Gy $n = 22$	Arm 9 18 Gy $n = 18$	

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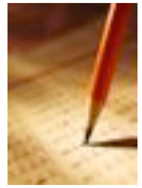
Shaw E, et al. *Int J Radiat Oncol Biol Phys* 2000;47:291-298

CURRENT INDICATIONS



RTOG 90-05: results

Incidence of Grade 3, 4, and 5 CNS Toxicity

Tumor size*	Arm	Dose	No. of patients	% of Patients With Toxicity: Acute	Chronic	Total
≤ 20 mm						
	1	18 Gy	12	0	8	8
	4	21 Gy	18	0	11	11
	7	24 Gy	10	0	10	10
21–30 mm						
	2	15 Gy	15	7	7	13
	5	18 Gy	15	0	20	20
	8	21 Gy	13	8	31	38
	11	24 Gy	12	33	25	58
31–40 mm						
	3	12 Gy	21	5	5	10
	6	15 Gy	22	0	14	14
	9	18 Gy	18	17	33	50

* Maximum tumor diameter.

Lesion Size	Max. Tolerated Dose
≤ 20 mm	24 Gy
21-30 mm	18 Gy
31-40 mm	15 Gy

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Shaw E, et al. *Int J Radiat Oncol Biol Phys* 2000;47:291-298

CURRENT INDICATIONS

SRS/WBRT Toxicity

- Radiation-related necrosis (≅ 5-10%; **strong correlation with V10-V16**)
- Visual damage (≅ 1-3%)
- Seizure (≅ 3-5%; **more frequent over 18 Gy single dose**)
- Endocrine deficit
- Hearing deficit
- Hair loss
- Scalp irritation
- Nausea
- Fatigue
- Worsened neurological function
- Dementia-like neurocognitive changes

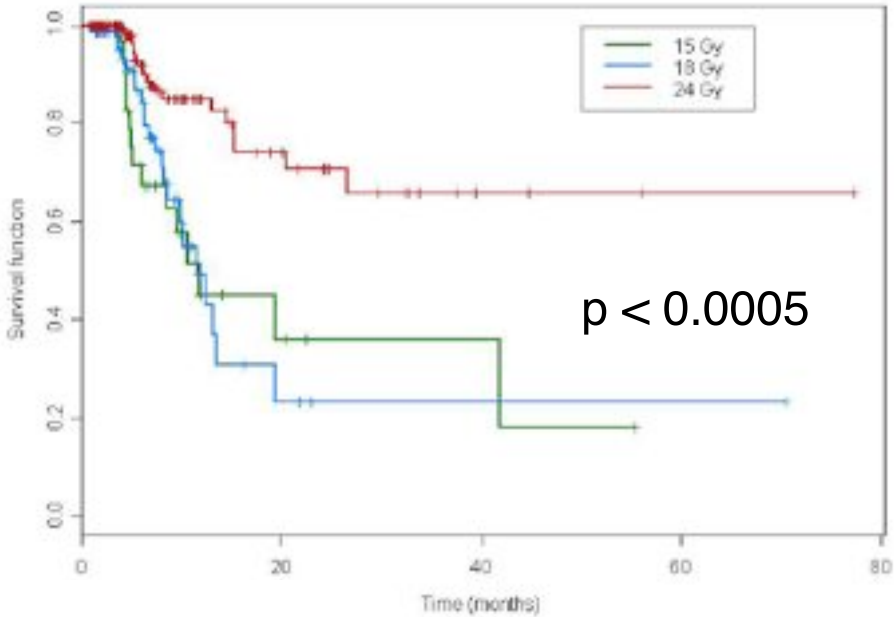
(that can be seen subacutely and chronically)

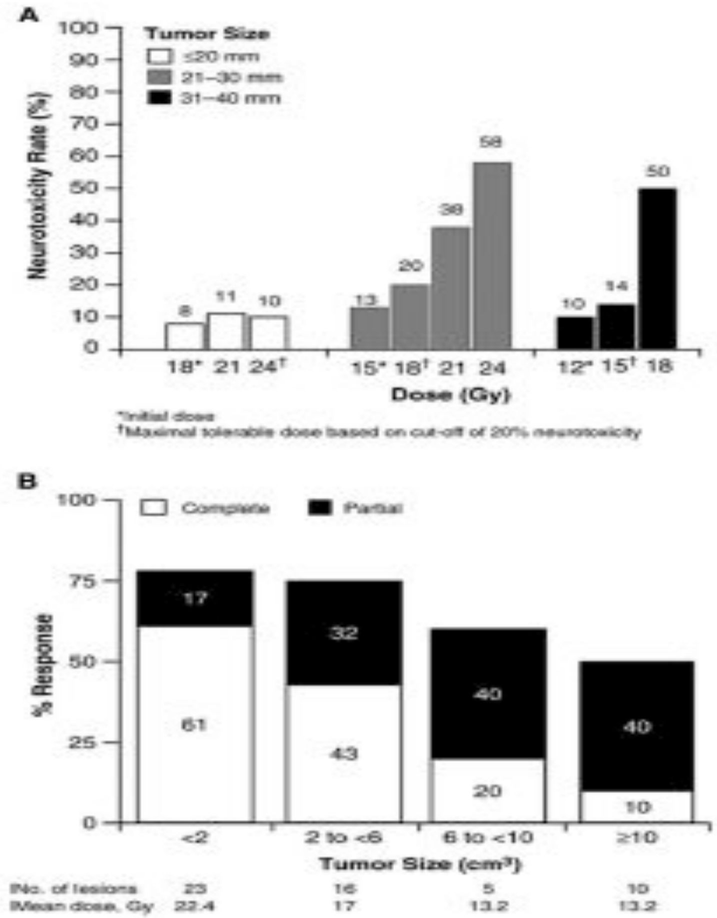
CURRENT INDICATIONS

Toxicity and efficacy are related to dose and tumor size

- 202 pts with 375 lesions
- 1-year LC rates by margin dose:
    1. 24Gy 85% (78-92)
    2. 18Gy 49% (30-68)
    3. 15Gy 45% (23-67)

Time to local failure by prescribed dose





Vogelbaum M, et al. *J Neurosurg* 2006;104:907-912

McDermott and Sneed, *Neurosurgery* 2005;47:S45-53

CURRENT INDICATIONS

WBRT vs WBRT with SRS boost: Pittsburgh Study

CLINICAL INVESTIGATION **Brain**

STEREOTACTIC RADIOSURGERY PLUS WHOLE BRAIN RADIOTHERAPY VERSUS RADIOTHERAPY ALONE FOR PATIENTS WITH MULTIPLE BRAIN METASTASES

DOUGLAS KONDZIOLKA, M.D., M.SC., FRCS(C),[*†‡] ATUL PATEL, M.D.,[*]
L. DADE LUNSFORD, M.D.,[*†‡] AMIN KASSAM, M.D., FRCS(C),[*] AND JOHN C. FLICKINGER, M.D.[*†‡]

- Type of study: single-inst. phase III, RCT
- Population: 2-4 brain mets. (≤ 25 mm ⌀)
- Primary endpoint: LC
- Interim analysis @ 60% accrual

RT regimen:

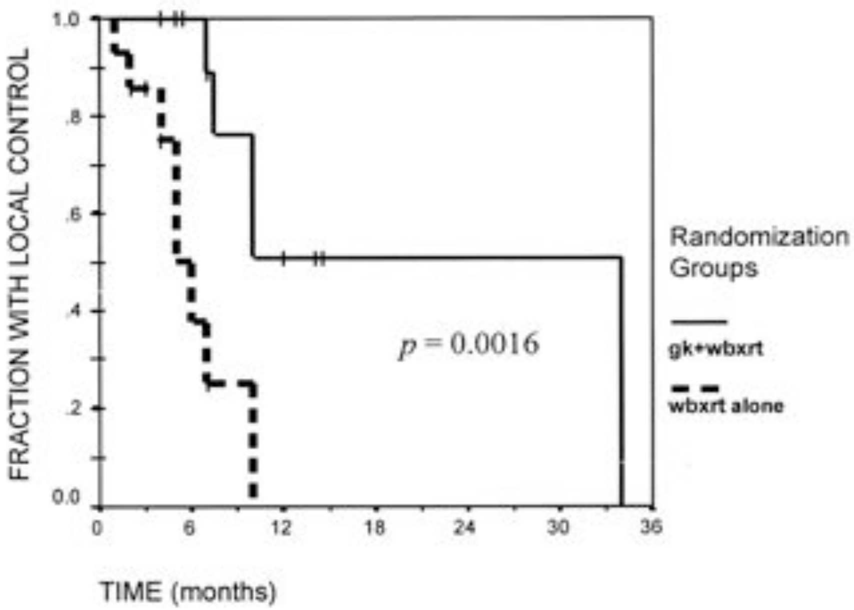
- WBRT: 30 Gy/12 fr (2.5 Gy/fr)
- SRS boost: 16 Gy
- Gamma Knife

Kondziolka D, et al. *Int J Radiat Oncol Biol Phys* 1999;45:427-434

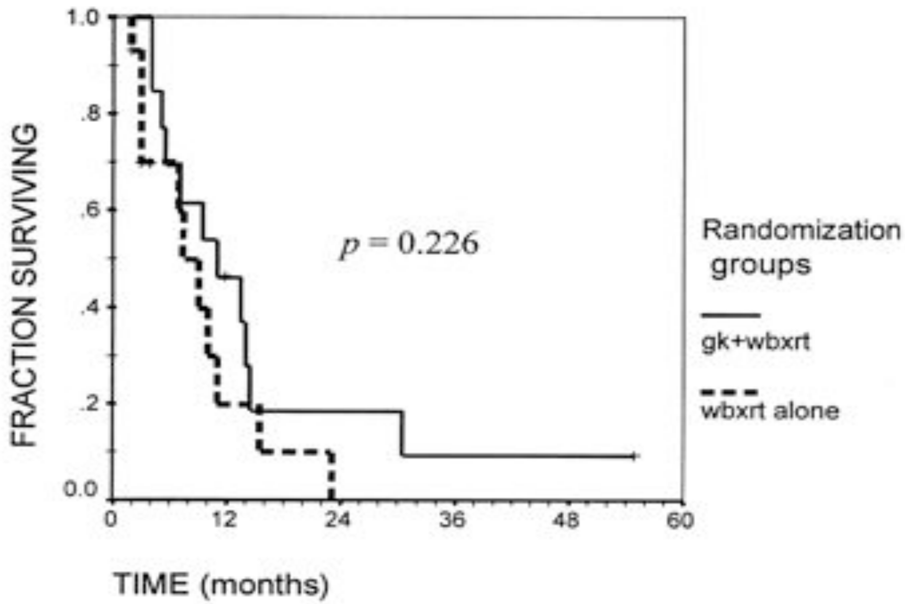
CURRENT INDICATIONS

WBRT vs WBRT with SRS boost: Pittsburgh Study (Interim Analysis) Results

Local control



Survival



No significant difference in toxicity

LC did not depend on:
- histology (p=0.85)
- N. of brain mets. (p=0.25)
- Extracranial disease (p=0.26)

OS did not depend on:
- histology (p=0.17)
- N. of brain mets. (p=0.42)

OS did depend on:
- Extracranial disease (p=0.02)

Kondziolka D, et al. *Int J Radiat Oncol Biol Phys* 1999;45:427-434

CURRENT INDICATIONS

WBRT vs WBRT with SRS boost: RTOG 95-08

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

David W Andrews, Charles B Scott, Paul W Sperduto, Adam E Flanders, Laurie E Gaspar, Michael C Schell, Maria Werner-Wasik, William Demas, Janice Ryu, Jean-Paul Bahary, Luis Souhami, Marvin Rotman, Minesh P Mehta, Walter J Curran Jr

- Type of study: multi-inst. phase III, RCT
- Population: 1-3 brain mets. no previous RT
- Primary endpoint: OS
- Secondary endpoints:
    - tumor response and LC
    - overall intracranial recurrence rate
    - cause of death
    - functional performance

WBRT regimen
37.5 Gy/15 fr (2.5 Gy/fr)

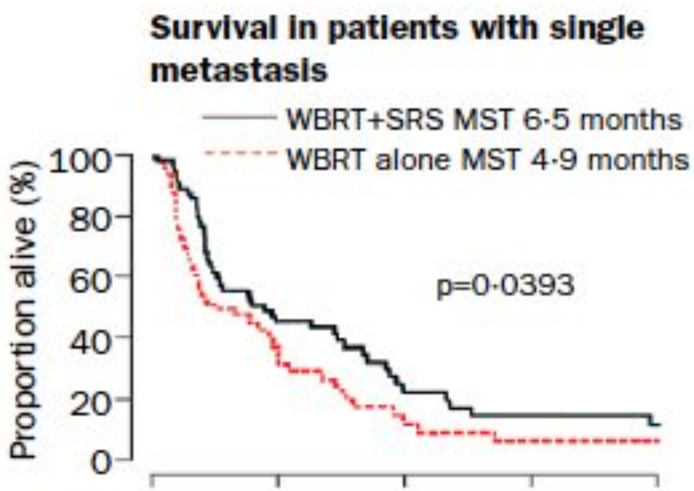
SRS boost
Within 1 wk of completing WBRT
Both Gamma Knife and LINAC

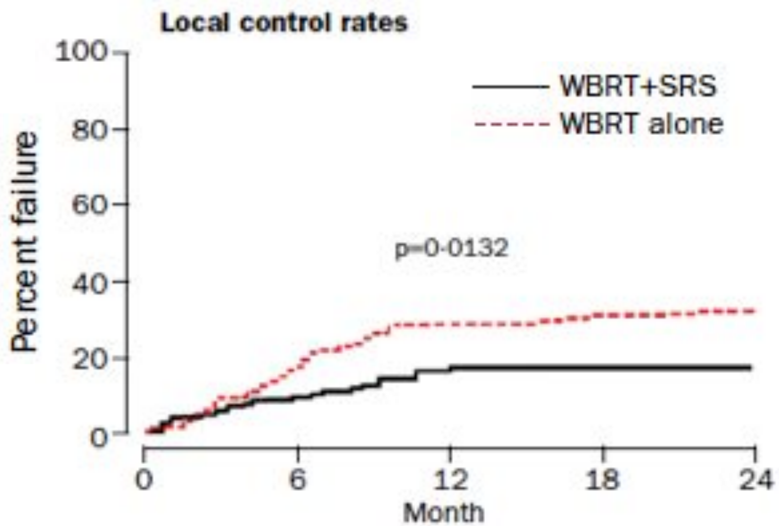
Dose (according to RTOG 90-05):
- < 2 cm = 24 Gy
- 2 – 3 cm = 18 Gy
- 3 – 4 cm = 15 Gy

Andrews DW, et al. *Lancet* 2004;363:1665-1672

CURRENT INDICATIONS

WBRT vs WBRT with SRS boost: RTOG 95-08 - Results





(Other) Results

- No significant difference in toxicity
- SRS reduces oedema (p=0.0017) and steroid dependence (p<0.0158)
- SRS improves performance status (p=0.0331)
- No difference by technique (Linac vs Gamma Knife)
- Post-hoc, unplanned subset analysis suggest survival benefit for patients with:
  - 1 to 3 mets with RPA Class 1 (p=0.0453)
  - 1 to 3 mets with NSCLC (p=0.0508)

Andrews DW, et al. *Lancet* 2004;363:1665-1672

CURRENT INDICATIONS

SRS vs WBRT and SRS: JRSOG-9901

Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases

A Randomized Controlled Trial

- Type of study: multi-inst. phase III, RCT
- Population: 1-4 brain mets. (≤ 3 cm ⌀)
- Primary endpoint: OS
- Secondary endpoints:
    - brain tumor control and LC
    - functional performance
    - toxicity
    - cause of death

WBRT regimen
30 Gy/10 fr (3 Gy/fr)

SRS
Within 1 wk of completing WBRT
Both Gamma Knife and LINAC

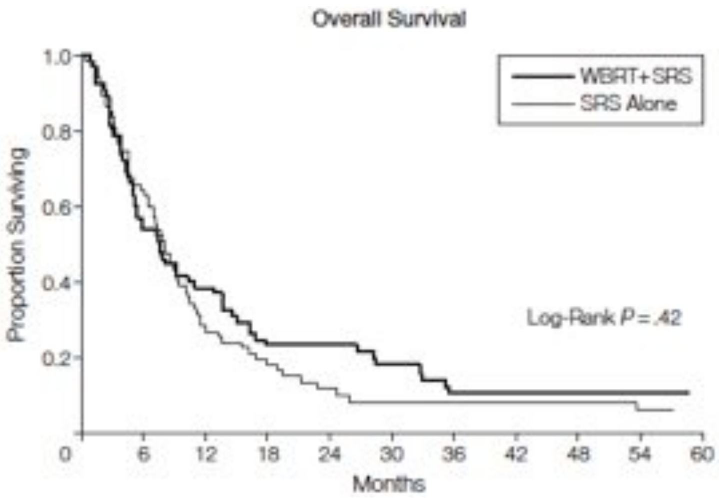
Dose:
- ≤ 2 cm = 22-25 Gy
- > 2 cm = 18-20 Gy

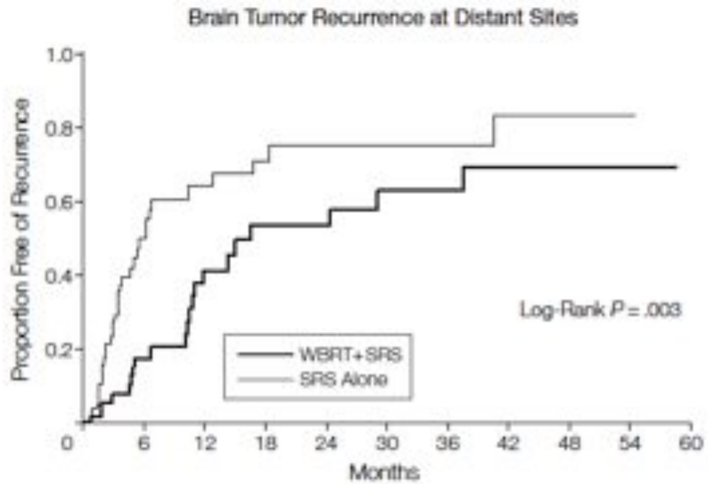
30% dose reduction for SRS+WBRT

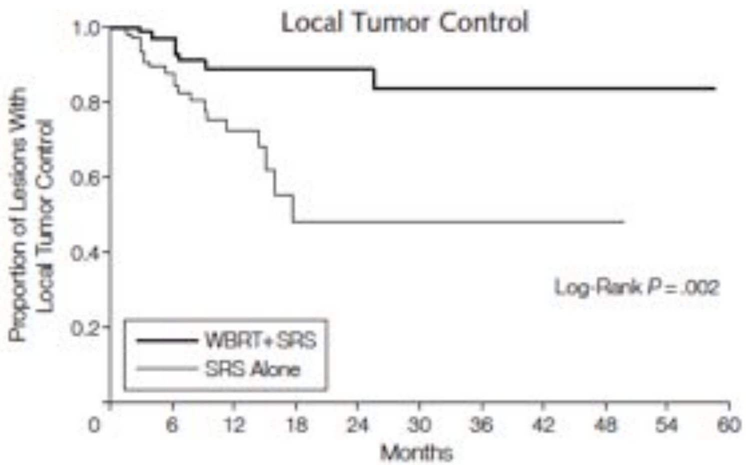
Aoyama H, et al. *JAMA* 2006;295:2483-2491

CURRENT INDICATIONS

SRS vs WBRT and SRS: JRSOG-9901 - Results







(Other) Results

- No significant difference in toxicity
- SRS alone needs more salvage treatment ($p<0.001$)
- No difference in neurologic preservation ($p=0.99$)
- No difference in death due to neurologic causes ($p=0.64$)

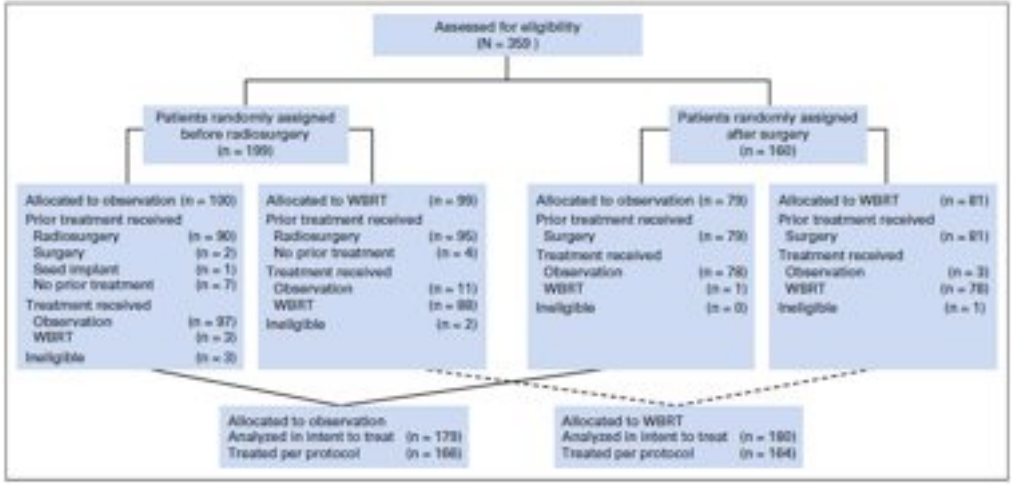
Aoyama H, et al. *JAMA* 2006;295:2483-2491

CURRENT INDICATIONS

SRS vs WBRT and SRS: EORTC 22952-26001

Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Results of the EORTC 22952-26001 Study

Martin Kocher, Riccardo Soffietti, Ufuk Abacioglu, Salvador Villà, Francois Fauchon, Brigitta G. Baumert, Laura Fariselli, Tzahala Tzuk-Shina, Rolf-Dieter Kortmann, Christian Carrie, Mohamed Ben Hassel, Mauri Kouri, Egils Valeinis, Dirk van den Berge, Sandra Collette, Laurence Collette, and Rolf-Peter Mueller



- Type of study: multi-inst. phase III, RCT
- Population: 1-3 brain mets. (≤ 2.5/3.5 cm ⃠)
- Primary endpoint: WHO PS deterioration to more than 2
- Secondary endpoints: brain tumor control and LC, PFS, OS, toxicity, QoL

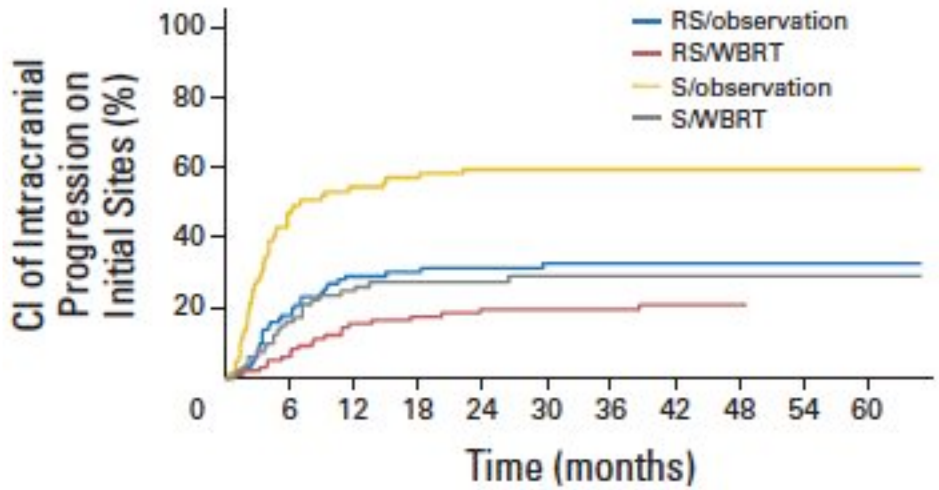
WBRT: 30 Gy/10 fr (3 Gy/fr)

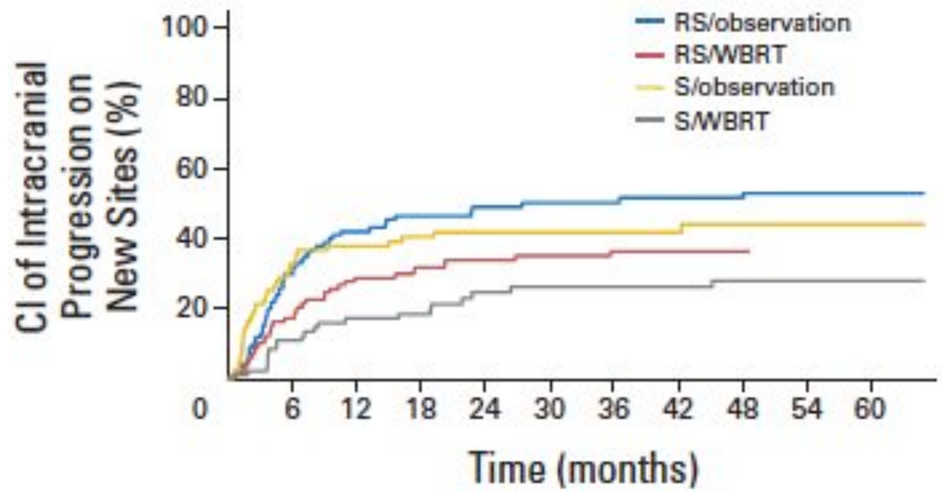
SRS: 25 Gy to isocenter

Kocher M, et al. *J Clin Oncol* 2011;29:134-141

CURRENT INDICATIONS

SRS vs SRS and WBRT: EORTC 22952-26001 - Results





No difference in WHO PS deterioration to more than 2 (p=0.71)

No difference in toxicity, PFS, OS

WBRT significantly reduced 2-year risk of both local (p=0.04) and intracranial relapse (p=0.023)

Kocher M, et al. *J Clin Oncol* 2011;29:134-141

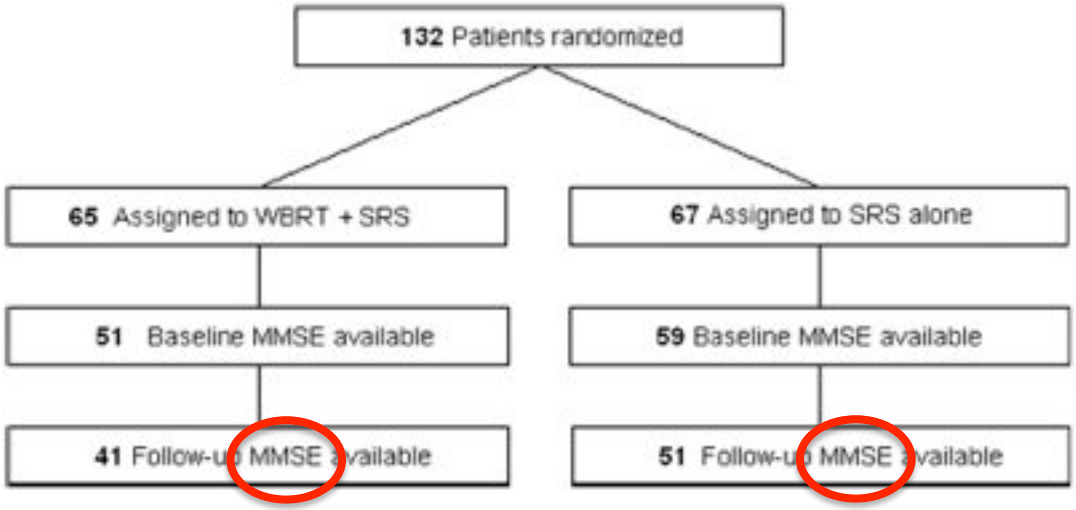
CURRENT INDICATIONS

SRS vs WBRT and SRS: JRSOG-9901
Neurocognitive Assessment

CLINICAL INVESTIGATION **Brain**

NEUROCOGNITIVE FUNCTION OF PATIENTS WITH BRAIN METASTASIS WHO RECEIVED EITHER WHOLE BRAIN RADIOTHERAPY PLUS STEREOTACTIC RADIOSURGERY OR RADIOSURGERY ALONE

Hidefumi Aoyama, M.D., Ph.D.,[a] Masao Tago, M.D., Ph.D.,[b] Norio Kato, M.D.,[a] Tatsuya Toyoda, M.D., Ph.D.,[c] Masahiro Kenjyo, M.D., Ph.D.,[d] Saeko Hirota, M.D., Ph.D.,[e] Hiroki Shioura, M.D., Ph.D.,[f] Taisuke Inomata, M.D., Ph.D.,[g] Etsuo Kunieda, M.D., Ph.D.,[h] Kazushige Hayakawa, M.D., Ph.D.,[i] Keiichi Nakagawa, M.D., Ph.D.,[b] Gen Kobashi, M.D., Ph.D.,[j] and Hiroki Shirato, M.D., Ph.D.[a]



Results

Deterioration in MMSE p=0.21

Freedom-from-3 point drop MMSE p=0.73

Aoyama H, et al. *Int J Radiat Oncol Biol Phys* 2007;68:1388-1395

CURRENT INDICATIONS

SRS vs WBRT and SRS: Neurocognitive outcomes

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers

- Type of study: single-inst. phase III, RCT
- Population: 1-3 brain mets. (≤ 3 cm ⌀)
- Primary endpoint: Neurocognitive function

Deterioration: 5-point drop compared to baseline in Hopkins Verbal Learning Test-Revised (HVLT-R) @ 4 months

- Secondary endpoints:

LC, distant brain control, OS

WBRT regimen
30 Gy/12 fr (2.5 Gy/fr)

SRS dose according to RTOG 90-05:
< 2 cm = 24 Gy
2 – 3 cm = 18 Gy
3 – 4 cm = 15 Gy

Pts assigned to SRS+WBRT received SRS first

Chang EL, et al. *Lancet Oncol* 2009;10:1037-1044

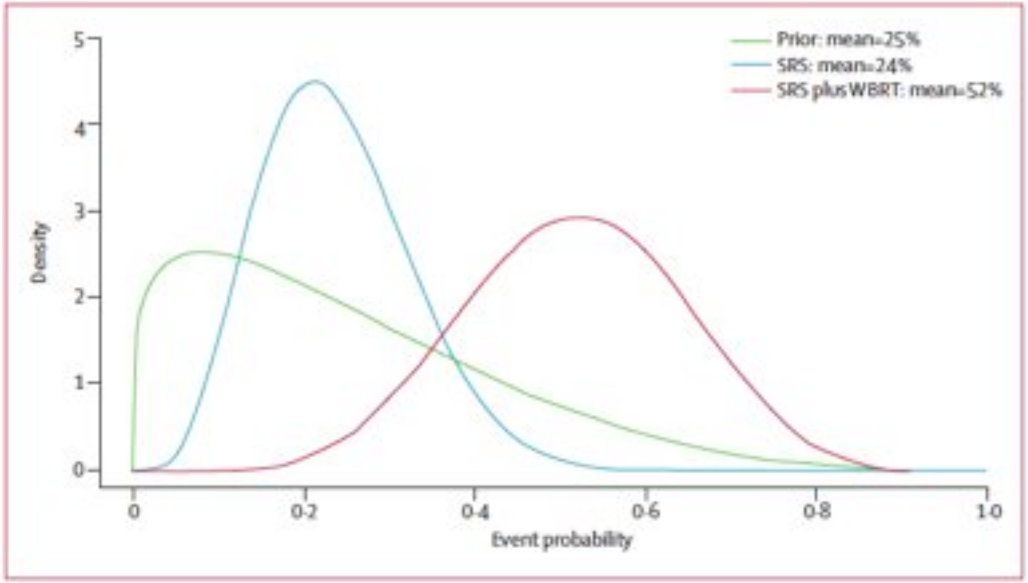
CURRENT INDICATIONS

SRS vs WBRT and SRS:
Neurocognitive outcomes after early stopping

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)	p (A>B)
Total recall	52%	24%	96%
Delayed recall	22%	6%	86%
Delayed recognition	11%	0%	86%

p (A>B)=Bayesian probability that the proportion with a significant neurocognitive worsening is higher in stereotactic radiosurgery plus whole-brain radiotherapy than stereotactic radiosurgery alone.

Table 3: **Bayesian posterior mean probability of significant neurocognitive decline at 4 months by treatment group, by HopkinsVerbal Learning Test—Revised**



(Other) Results

- SRS+WBRT better LC (p=0.01)
- SRS+WBRT better distant brain control (p=0.02)
- SRS alone better OS (p=0.03)

Chang EL, et al. *Lancet Oncol* 2009;10:1037-1044

CURRENT ISSUES OF INTEREST

SRS BOOST RESECTION CAVITY

Reference	Study	Pts #	Lesion #	SRS dose/fr	1-y LC	DF	RN
Brennan '14	Phase II	49	1-2	15-22/1	85%	NR	17.5%
Choi '11	Retrosp.	112	1-3	15-30/1-5	90.5%	59%	7%
Do '09	Retrosp.	30	1-4	15-27.5/1-6	82%	63%	7%
Hatford '13	Retrosp.	47	1-3	12-20/1	85.5%	63%	NR
Hwang '10	Retrosp.	25	1+	15-20/1	100%	28%	NR
Jensen '11	Retrosp.	106	1+	11-23/1	80%	54%	3%
Ogiwara '12	Retrosp.	56	1	14-20/1	75%	37.5%	NR
Mathieu '08	Retrosp.	40	1-7	11-20/1	74%	54%	0%
Prabhu '12	Retrosp.	62	1-3	15-21/1	78%	51%	8%
Minniti '13	Retrosp.	101	1	27/3	93%	51%	9%
Steinmann '12	Retrosp.	33	1	30-40/5-10	71%	60%	0%
Wang '12	Retrosp.	37	1-3	24/3	80%	20%	3%

CURRENT ISSUES OF INTEREST

SRS alone in patients with more than four brain metastases

Role of stereotactic radiosurgery in patients with more than four brain metastases

Vikram Jairam[1,*], Veronica LS Chiang[2,3], James B Yu[1,2,4], and Jonathan PS Knisely[5]

Study (year)	Patients (n)	Metastases (n)	Median survival (weeks)	Major finding	Ref.
Serizawa *et al.* (2000)	96	1–10	SRS: 377 WBRT: 199	SRS group had a greater mean survival time, higher freedom from neurologic death and higher qualitative survival	[19]
Park *et al.* (2009)	33	2–20	SRS: 32 WBRT: 24	Median and overall survival were greater in the SRS than the WBRT group	[20]
Hunter *et al.* (2012)	64	≥5	SRS: 30	SRS can effectively treat five or more metastases at a time	[21]
Chang *et al.* (2010)	323	Group 1: 1–5 Group 2: 6–10 Group 3: 11–15 Group 4: >15	Group 1: 40 Group 2: 40 Group 3: 52 Group 4: 32 (not significant)	SRS is a recommended treatment option for all groups for both improved survival and local control	[22]
Raldow *et al.* (2012)	103	Group 1: 5–9 Group 2: 10+	Group 1: 7.6 Group 2: 8.3 (not significant)	KPS score was the only variable significantly affecting overall survival	[23]
Serizawa *et al.* (2010)	778	Group A: 1 Group B: 2 Group C: 3–4 Group D: 5–6 Group E: 7–10	Group A: 44.73 Group B: 35.9 Group C: 35.9 Group D: 30.7 Group E: 32.2 (not significant)	SRS without WBRT provides excellent survival in patients with one to ten brain metastases	[24]
Suzuki *et al.* (2000)	24	10–47	SRS: 11	SRS achieves acceptable tumor control, low morbidity and good quality of life	[25]
Kim *et al.* (2008)	26	10–37	SRS: 34	SRS can treat patients with ten or more metastases	[26]
Grandhi *et al.* (2012)	61	10–28	SRS: 16	SRS safely and effectively treats patients with ten or more metastases with good local control	[27]

KPS: Karnofsky performance status; SRS: Stereotactic radiosurgery; WBRT: Whole-brain radiation therapy.

Jairam V, et al. *CNS Oncol* 2013;2:1-18

CURRENT ISSUES OF INTEREST

SRS alone in patients with more than four brain metastases

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

- Type of study: single-inst., observational
- Population: 1-10 brain mets. (Cumulative volume ≤ 15 ml)
- Primary endpoint: OS
- Secondary endpoints:

LC, distant brain control, NCF (<u>MMSE</u>)

Results

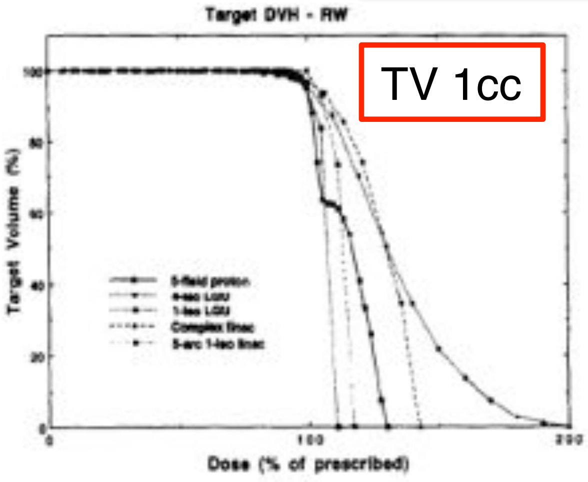
- Better OS for 1 lesion SR (p=0.0004)
- Comparable OS 2-4 vs 5-10 (p=0.02)
- Comparable LC 2-4 vs 1 vs 5-10
- Better DF 1 vs 2-4 vs 5-10 (p<0.0001)
- Comparable NCF 1 vs 2-4 vs 5-10

Interpretation Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases.

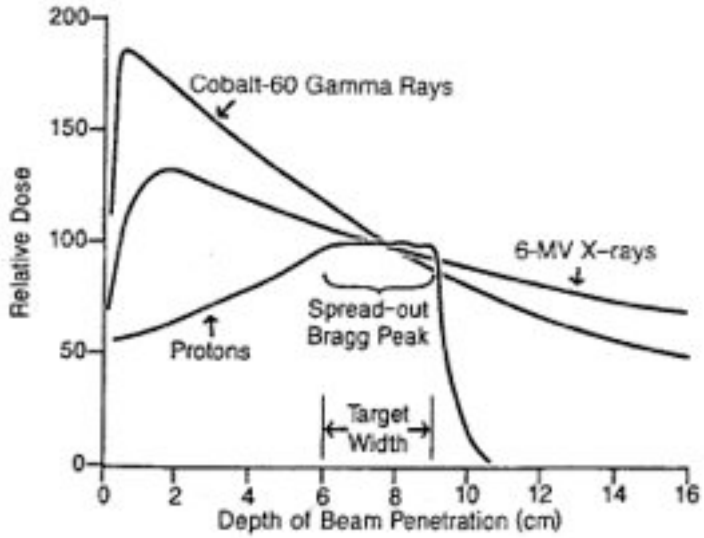
Yamamoto M, et al. *Lancet Oncol* 2014;15:387-395

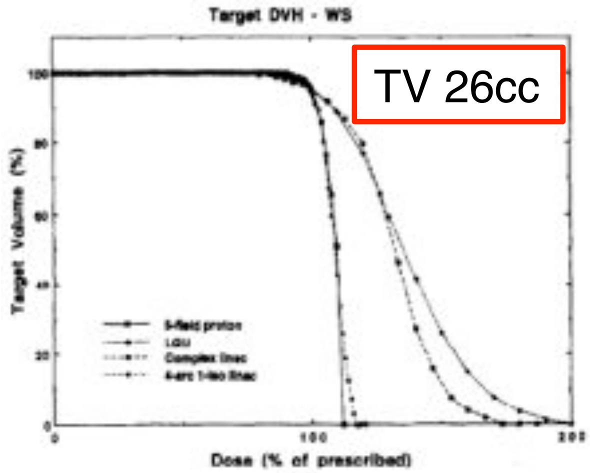
CURRENT ISSUES OF INTEREST

Potential role of PROTON SRS alone in patients with multiple brain metastases

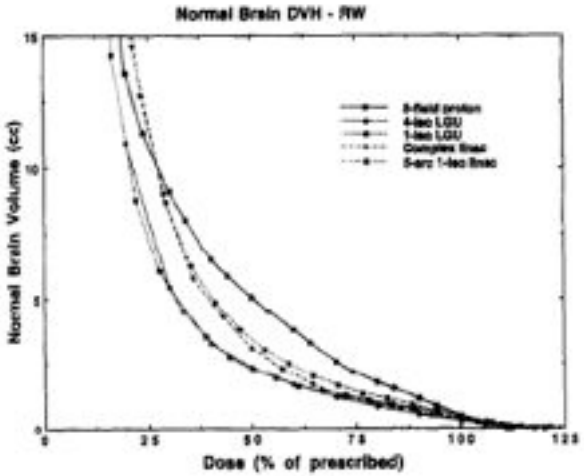


(a)



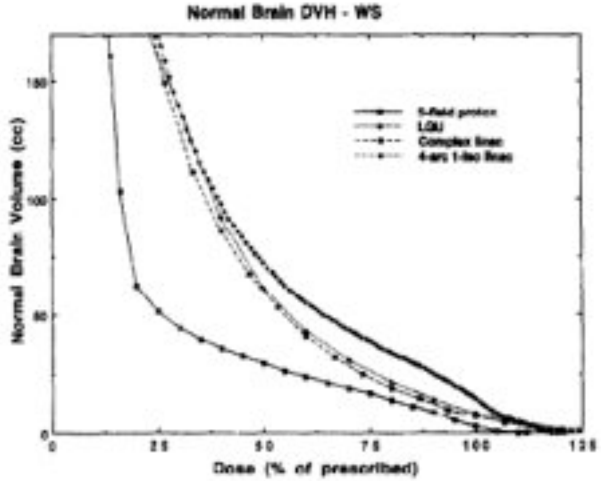


(a)



(b)

Case	Description	Volume	Dose	Central section
A	Approximate sphere	1.1 cm^3	20.0	
B	Perfect sphere	4.2 cm^3	17.0	
C	Irregular	6.0 cm^3	15.2	
D	Approximate sphere	24.2 cm^3	13.3	



(b)

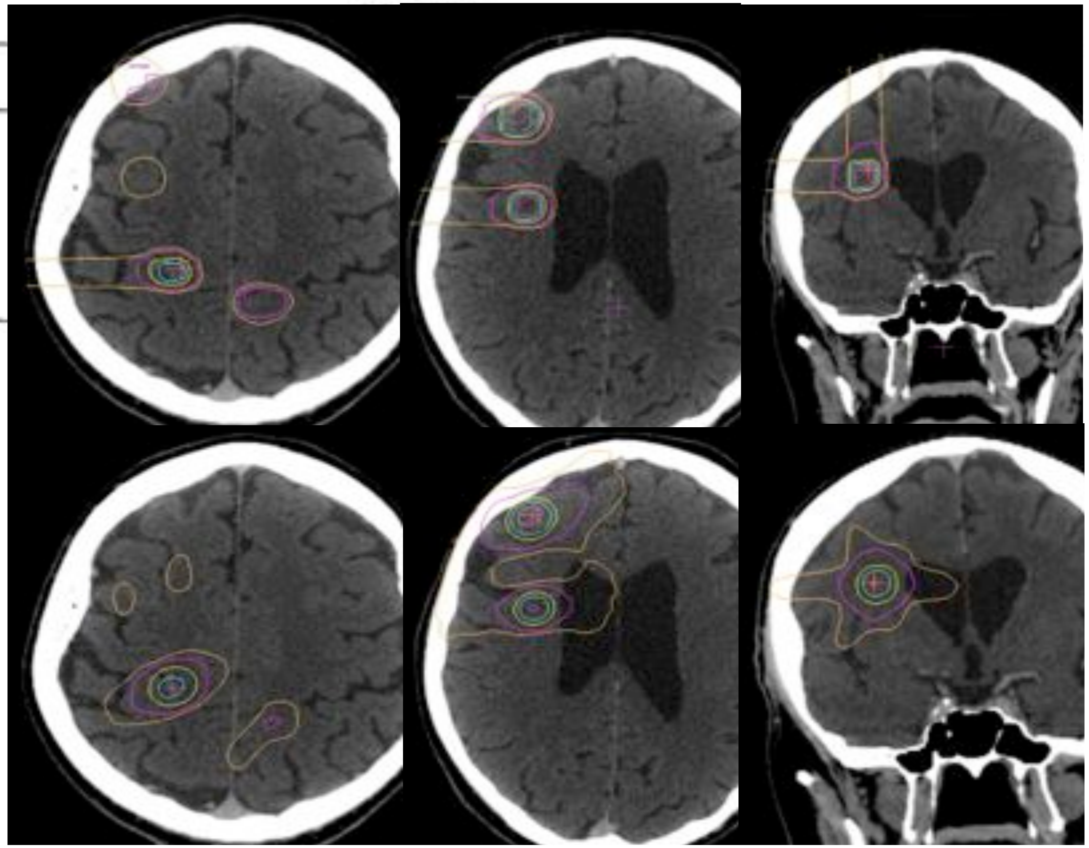
Verhey LJ, et al. *Int J Radiol Oncol Biol Phys 1998; 40:497-505*

CURRENT ISSUES OF INTEREST

Potential role of PROTON SRS alone
in patients with multiple brain metastases

Table 3. Normal tissue complication probabilities (%) calculated using a Poisson model based on the Emami *et al.* tolerance data (5), normalized to a dose in Gy (shown in parentheses) giving a tumor control probability of 50%

Target volume (cc)	Simple linac
1.0	0.95 (21.9)
6.0	15.3 (23.4)
6.5	19.4 (22.9)
14.5	39.6 (23.0)
26.0	36.4 (23.7)



Protons

X-Rays

Courtesy of
J. Loeffler & H. Shih
MGH

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

Smith V, et al. *Int J Radiat Oncol Biol Phys* 1998;40:507-513

CURRENT ISSUES OF INTEREST

Hippocampal-Sparing WBRT with SIB for brain metastases

PHYSICS CONTRIBUTION

WHOLE BRAIN RADIOTHERAPY WITH HIPPOCAMPAL AVOIDANCE AND SIMULTANEOUSLY INTEGRATED BRAIN METASTASES BOOST: A PLANNING STUDY

Alonso N. Gutiérrez, Ph.D.,* David C. Westerly, M.Sc.,* Wolfgang A. Tomé, Ph.D.,*† Hazim A. Jaradat, Ph.D.,† Thomas R. Mackie, Ph.D.,*†‡ Søren M. Bentzen, Ph.D., D.Sc.,† Deepak Khuntia, M.D.,† and Minesh P. Mehta, M.D.†

Conclusion: Composite tomotherapy plans achieved three objectives: homogeneous whole brain dose distribution equivalent to conventional whole brain radiotherapy; conformal hippocampal avoidance; and radiosurgically equivalent dose distributions to individual metastases. © 2007 Elsevier Inc.

Gutierrez AN, et al. *Int J Radiat Oncol Biol Phys* 2007;69:589-597

CLINICAL INVESTIGATION Brain

WHOLE BRAIN RADIOTHERAPY WITH HIPPOCAMPAL AVOIDANCE AND SIMULTANEOUS INTEGRATED BOOST FOR 1–3 BRAIN METASTASES: A FEASIBILITY STUDY USING VOLUMETRIC MODULATED ARC THERAPY

Fred Hsu, M.D.,* Hannah Carolan, M.D.,† Alan Nichol, M.D.,* Fred Cao, Ph.D.,‡ Nimet Nuraney, R.T.T.,† Richard Lee, Ph.D.,§ Ermias Gete, Ph.D.,§ Frances Wong, M.D.,† Moira Schmuland, M.Sc.,§ Manraj Heran, M.D.,¶ and Karl Otto, Ph.D.§

Conclusions: VMAT was able to achieve adequate whole brain coverage with conformal hippocampal avoidance and radiosurgical quality dose distributions for one to three brain metastases. The mean delivery time was under 4 min. Crown Copyright © 2010 Elsevier Inc.

Hsu F, et al. *Int J Radiat Oncol Biol Phys* 2010;76:1480-1485

CURRENT ISSUES OF INTEREST

Hippocampal-Sparing WBRT with SIB for brain metastases

RESEARCH **Open Access**

Hippocampal avoidance with volumetric modulated arc therapy in melanoma brain metastases – the first Australian experience

Raef Awad[1,2*], Gerald Fogarty[1,2], Angela Hong[3,4], Patricia Kelly[1,2], Diana Ng[1,2], Daniel Santos[1,2] and Lauren Haydu[3,5]

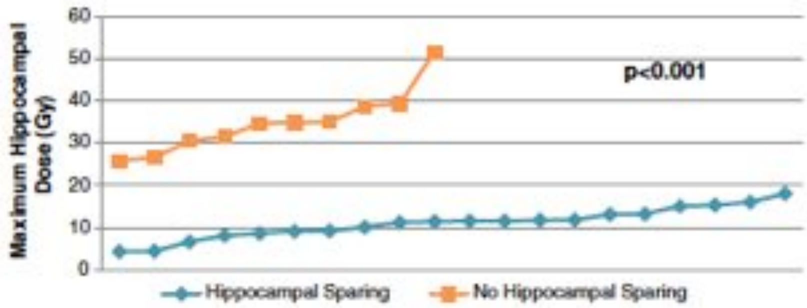


Figure 1 Maximum hippocampal dose for patients having HA versus no HA p<0.001.

Conclusions: VMAT for BMs is feasible, safe and associated with a similar survival times and toxicities to conventional SRT+/−WBRT. The advantage of VMAT is that WBRT and SRT can be delivered at the same time on one machine.

Awad R, et al. *Rad Oncol* 2013;8:62

…thank you for your attention…

Questions?