Brain metastases

Whole brain radiation therapy is indicated for most patients

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Disclosure

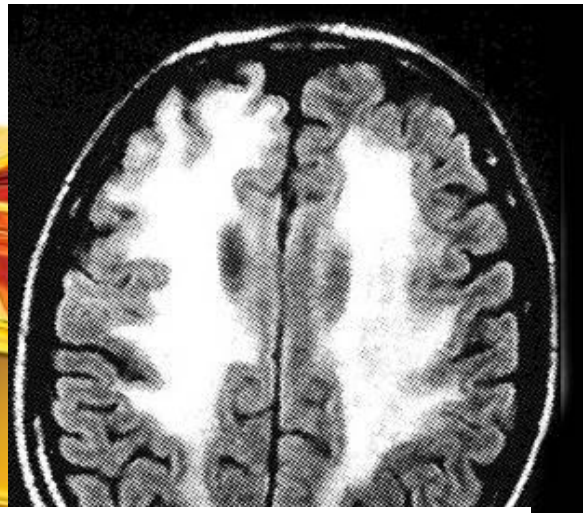
- Sanofi (Research funding)

DISCLOSURE PART 2

- Advocate for Stereotactic Radiosurgery for brain metastases

- I treat most patients with brain metastases with single modality Stereotactic Radiosurgery

Pandora's box



THE WALL STREET JOURNAL.

LIFE | HEALTH | HEALTH & WELLNESS

New Study Questions Use of Whole-Brain Radiation to Treat Cancer

By RON WINSLOW

Researchers say technique results in more memory loss, doesn't extend survival

May 31, 2015 5:18 p.m. ET

Side effects of Whole Brain RT

AE
Ear and labyrinth disorders
Other
Ear pain
External ear inflammation
Hearing impairment
Tinnitus
Vertigo
Eye disorders
Blurred vision
Other
GI disorders
Constipation
Diarrhea
Dry mouth
Esophagitis
Mucositis oral
Nausea
Vomiting
General disorders and administrative site conditions
Edema face
Fatigue
Gait disturbance
Injury, poisoning, and procedural complications
Radiation dermatitis
Investigations
Weight loss
Metabolism and nutrition disorders
Anorexia
Dehydration
Musculoskeletal and connective tissue disorders
Chest wall pain
Generalized muscle weakness
Nervous system disorders
Concentration impairment
Dizziness
Dysgeusia
Dysphasia
Headache
Memory impairment
Other
Paresthesia
Peripheral motor neuropathy
Peripheral sensory neuropathy
Seizure
Somnolence
Tremor
Psychiatric disorders
Insomnia
Respiratory, thoracic, and mediastinal disorders
Dyspnea
Sore throat
Skin and subcutaneous tissue disorders
Alopecia
Dry skin
Pruritus
Skin hyperpigmentation
Vascular disorders
Hypotension

Brain metastases

Whole brain radiation therapy is indicated for most patients

The devil is in the details…..

Are the side effects of WBRT *THAT BAD???*

Alopecia

- Commonest primary tumours associated with brain metastases
  - Breast
  - Lung
  - Skin (Melanoma)
  - Gastrointestinal

Alopecia

- Commonest primary tumours associated with brain metastases
  - Breast (Alopecia-inducing agents – Anthracyclines, Taxol etc…)
  - Lung (Alopecia-inducing agents – Taxol etc…)
  - Skin
  - Gastrointestinal

Alopecia

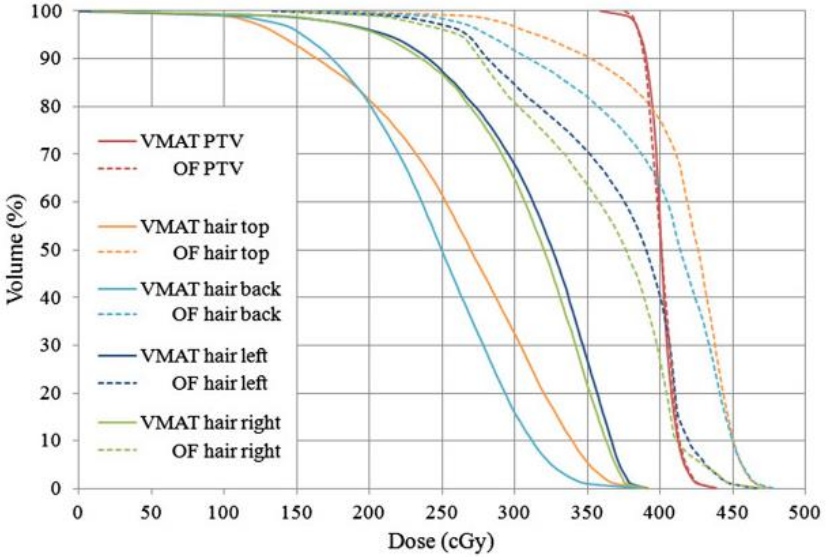
RESEARCH

Hair-sparing whole brain radiotherapy with volumetric arc therapy in patients treated for brain metastases: dosimetric and clinical results of a phase II trial

Annemieke De Puysseleyr, Joris Van De Velde, Bruno Speleers, Tom Vercauteren, Anneleen Goedgebeur, Tom Van Hoof, Tom Boterberg, Wilfried De Neve, Carlos De Wagter and Piet Ost

Radiation Oncology 2014 9:170 | DOI: 10.1186/1748-717X-9-170

Received: 15 April 2014 | **Accepted:** 18 July 2014 | **Published:** 29 July 2014



Neurological effects

Articles

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

Summary

Background It is unclear whether the benefit of adding whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) for the control of brain-tumours outweighs the potential neurocognitive risks. We proposed that the learning and memory functions of patients who undergo SRS plus WBRT are worse than those of patients who undergo SRS alone. We did a randomised controlled trial to test our prediction.

Lancet Oncol 2009; 10: 1037–44

Published Online October 5, 2009

DOI:10.1016/S1470-2045(09)70263-3

	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**

Supplementary information

	Stereotactic radiosurgery plus whole-brain radiotherapy (N=11)	Stereotactic radiosurgery alone (N=20)
Trail making test		
Part A	11%	12%
Part B	38%	18%
Digit span	0%	6%
Digit symbol	11%	18%
Multilingual aphasia examination controlled oral word-association test	22%	6%
Grooved pegboard dominant	33%	35%
Grooved pegboard non-dominant	50%	41%

Not all suffer from neurological decline

Original Investigation

Stereotactic Radiosurgery With or Without Whole-Brain Radiotherapy for Brain Metastases

Secondary Analysis of the JROSG 99-1 Randomized Clinical Trial

Hidefumi Aoyama, MD, PhD; Masao Tago, MD, PhD; Hiroki Shirato, MD, PhD; for the Japanese Radiation Oncology Study Group 99-1 (JROSG 99-1) Investigators

Neurocognitive Function

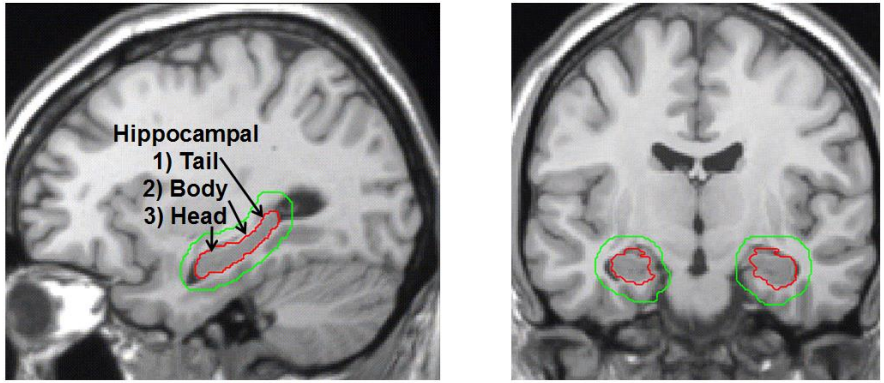
Neurocognitive function was assessed by the Japanese version of the Mini-Mental State Examination (MMSE), and the results are summarized in eTable 2 in the Supplement. Baseline data were available in 70 patients. At baseline, the MMSE score in the GPA 2.5-4.0 group was significantly better than that in the GPA 0.5-2.0 group (28.0 vs 27.0; $P = .01$). When the 2 prognostic groups (DS-GPA 0.5-2.0 and 2.5-4.0) were considered separately, there was no significant difference in baseline MMSE scores between the 2 treatment arms in either group. Follow-up MMSE data were available in 57 patients (81%). Among the 24 patients in the DS-GPA 0.5-2.0 group, the median duration until the last follow-up MMSE was 3.6 (range, 1.3-14.5) months in the SRS-alone arm and 3.6 (range, 1.3-49.5) months in the WBRT + SRS arm ($P = .86$). Among the 33 patients in the DS-GPA 2.5-4.0 group, these values were 8.5 (range, 1.4-49.8) months and 9.5 (1.8-58.7) months, respectively ($P = .81$). Regarding the score at the last follow-up, no significant difference between the treatment arms was observed in either the DS-GPA 0.5-2.0 group (SRS-alone arm, 27.5; and WBRT + SRS arm 28.0; $P = .77$) or DS-GPA 2.5-4.0 group (SRS-alone arm, 28.0; and WBRT + SRS arm, 26.5; $P = .40$).

Aoyama, et al., JAMA Oncology, 2015

Hippocampal-avoidance WBRT

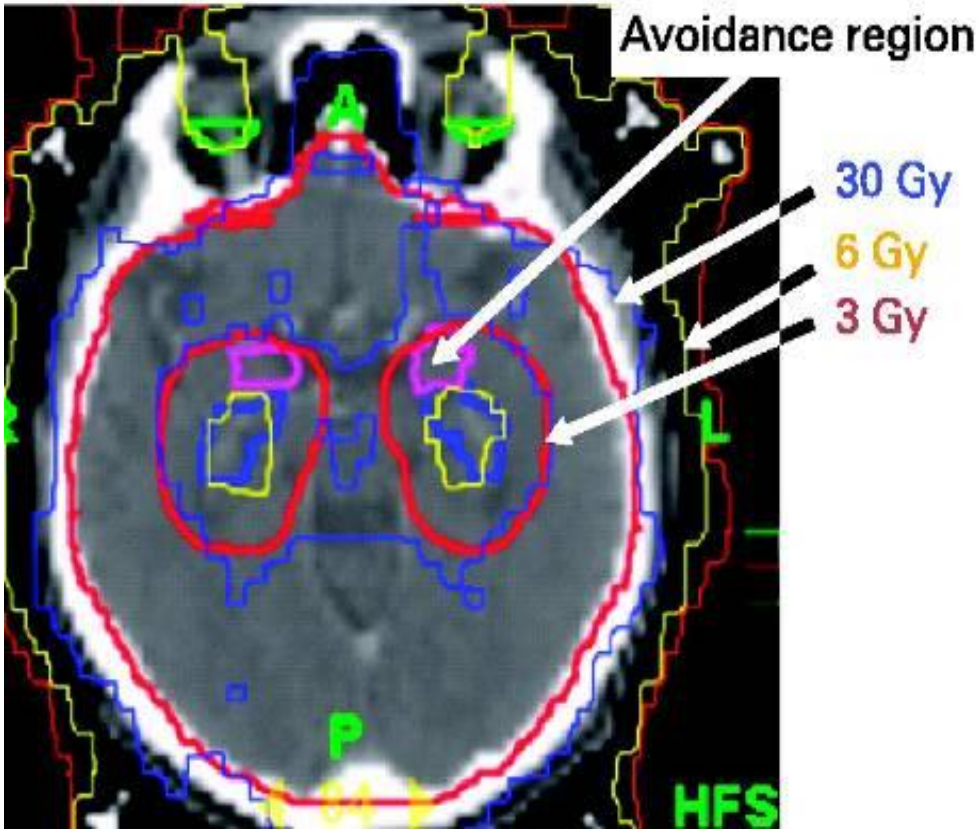
Possible answer to cognitive impairment??

Red: Hippocampus Green: Hippocampal Avoidance Zone



The hippocampus has three anatomic subdivisions: the head, body, and tail; note that the head is inferior or caudad, the body is superoposterior and the tail is most cephalad (superior) and posterior, and an overall "banana" shape emerges on sagittal images, located in the plane of the lateral ventricle.

Adapted from RTOG 0933 protocol



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

JCO Dec 1,32(34)

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

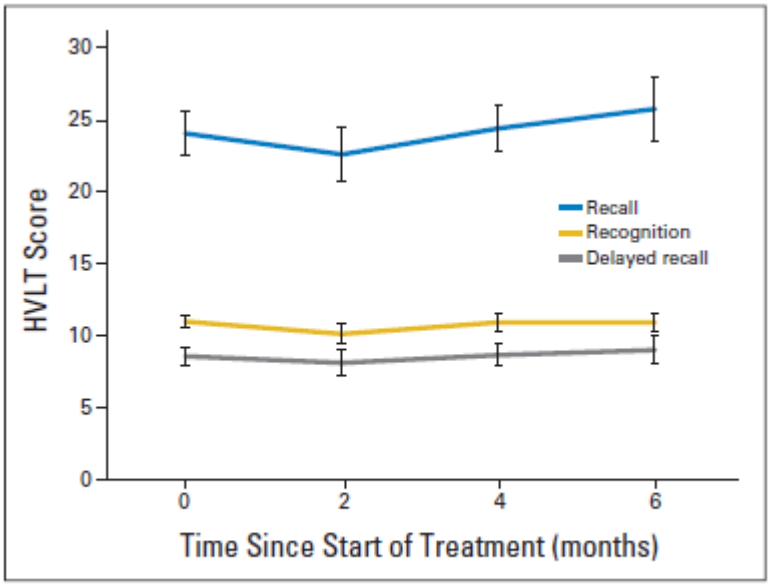


Fig 1. Hopkins Verbal Learning Test (HVLT) scores for 50 patients alive at 6 months.

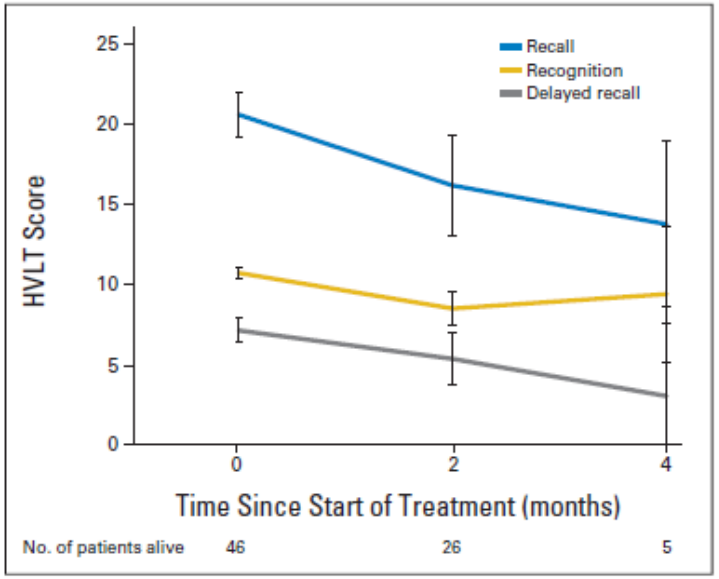


Fig 2. Hopkins Verbal Learning Test (HVLT) scores for 46 patients who had died by 6 months.

Quality of life decline post-WBRT: *Myth or truth??*

No difference in Global HRQOL between WBRT or Observation except at 9 mths

Table 2. Global Quality-of-Life Results With Cut Off at 12 Months

Time Point	WBRT Mean Score*	WBRT SD	Observation Mean Score*	Observation SD	*P* for Treatment Difference
Overall postbaseline test†					.1
Baseline	58.3	1.8	60.0	1.8	.5
8 weeks	54.9	2.1	56.8	2.2	.5
3 months	58.0	2.4	58.6	2.5	.9
6 months	58.7	2.9	62.1	2.9	.4
9 months	52.2	3.2	63.2	3.2	.01
12 months	56.8	3.9	58.7	3.5	.7

Abbreviations: SD, standard deviation; WBRT, whole-brain radiotherapy.
*Means are adjusted means from linear mixed model with time and treatment as covariates and AR(1) covariance matrix.
†This test is applied first, and differences by time point are interpreted only if this primary test is statistically significant.

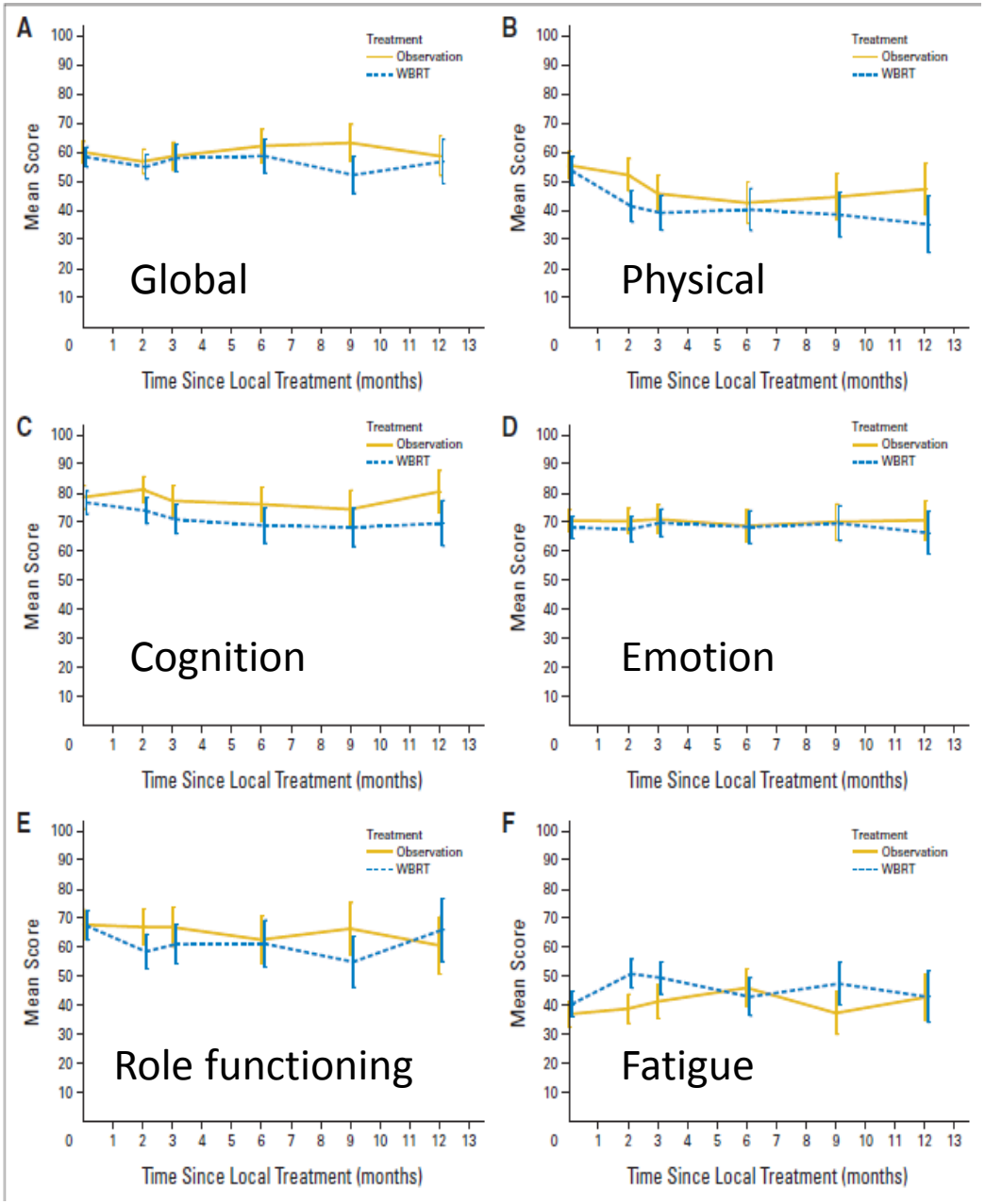
Soffietti R et al, JCO 31(1):65-72, 2013

VOLUME 31 · NUMBER 1 · JANUARY 1 2013

JOURNAL OF CLINICAL ONCOLOGY

A European Organisation for Research and Treatment of Cancer Phase III Trial of Adjuvant Whole-Brain Radiotherapy Versus Observation in Patients With One to Three Brain Metastases From Solid Tumors After Surgical Resection or Radiosurgery: Quality-of-Life Results

Riccardo Soffietti, Martin Kocher, Ufuk M. Abacioglu, Salvador Villa, François 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, Rolf-Peter Mueller, Gloria Tridello, Laurence Collette, and Andrew Bottomley



Role of Whole Brain Radiotherapy?

- ≤ 5 brain mets
  - Is WBRT indicated in patients who had received local treatment (Stereotactic Radiosurgery/Surgery) to the brain lesions?

- > 5 brain mets
  - Is SRS just as good as WBRT?

Argument against WBRT in few brain mets

Prevailing thought

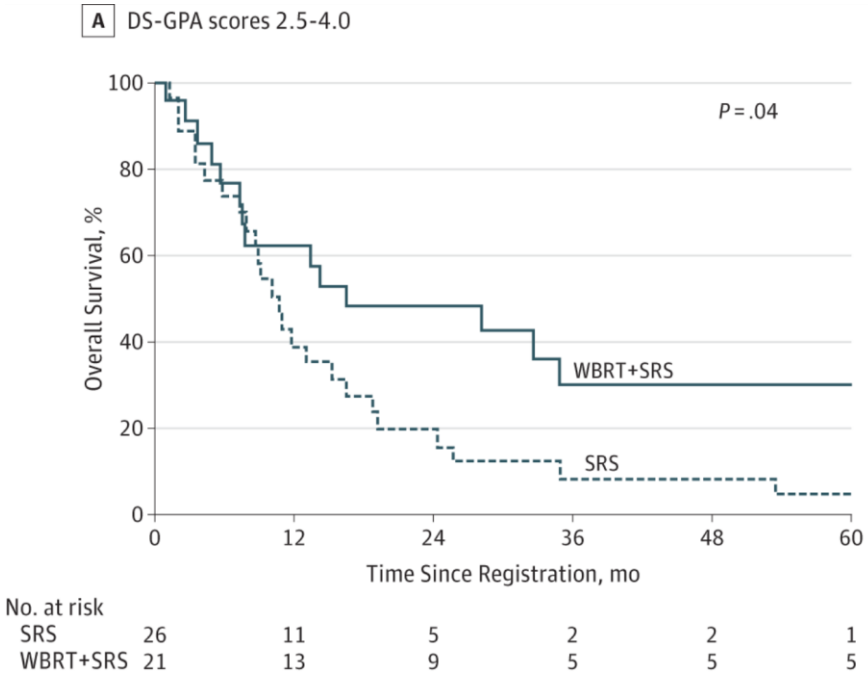
Additional WBRT does not offer survival advantage over and above outcomes following SRS in these patients.

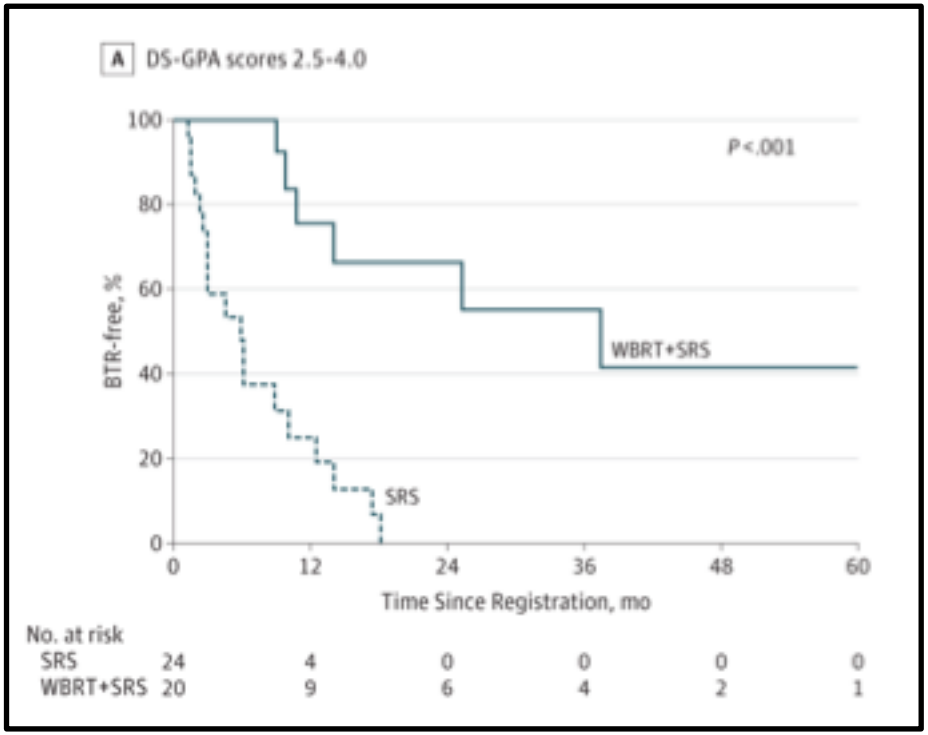
Moreover, WBRT is neurologically 'toxic'… (we know that is not wholly true)

RCTs of SRS *vs* SRS + WBRT for few brain mets

RCT (Primary endpoint)	% solitary met	Tumour size	Local Control	Distant control	OS
Aoyam *et al.* 2006 JROSG 99-1 N = 132 (OS)	49% *vs* 58%	Median 1.3-1.4 cm	**73% *vs* 89% (p=0.002)**	**36% *vs* 59% at 1y (p=0.003)**	28% *vs* 39% at 1y (NS)
Chang *et al.* 2009 MDACC N = 58 (Neurocognition)	60% *vs* 54%	1.4-2.3 cc	**67% *vs* 100% at 1y (p=0.012)**	**45% *vs* 73% at 1y (p=0.02)**	63% *vs* 21% at 1y (p=0.003)
Kocher *et al.* 2011 EORTC 22952 N = 199 (PS deterioration >2)	68% *vs* 66%	Median 1-2 cm	**69% *vs* 81 % at 2y (p=0.006)**	**52% *vs* 67% at 2y (p=0.023)**	NS
Brown *et al.* 2015 N0574 N = 213 (Cognitive worsening 3 months)				**50% *vs* 85% at 1y (p<0.001)**	10 *vs* 8 mths (p=0.92)

In fact, WBRT prolongs survival in 'some' lung cancer patients with few brain mets

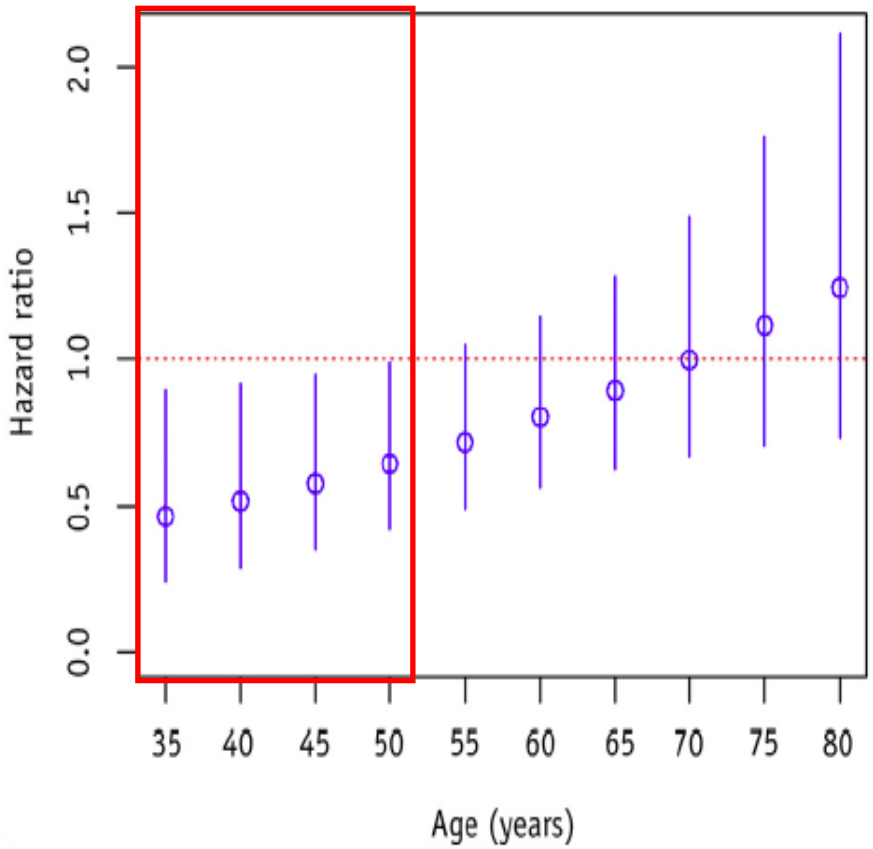




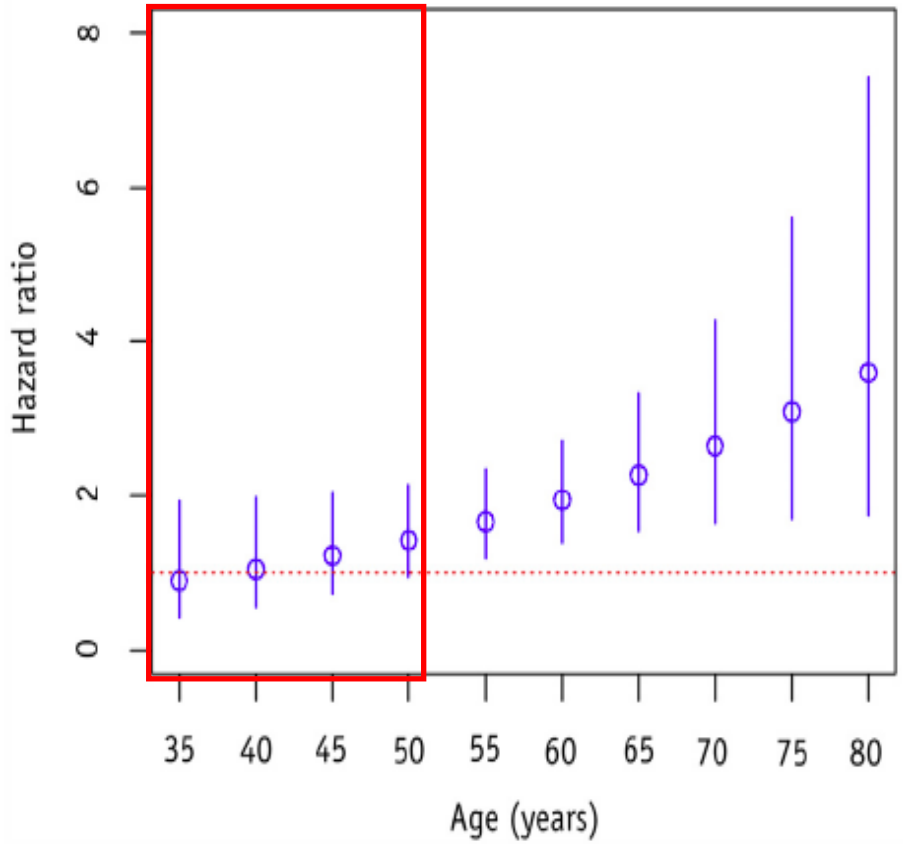
Aoyama, et al., JAMA Oncology, 2015

Saghal *et al.* Meta-analysis of 3 RCTs

Survival



Distant failure



Saghal, et al., IJROBP, 2015

Brain metastases

Whole brain radiation therapy is indicated for most patients

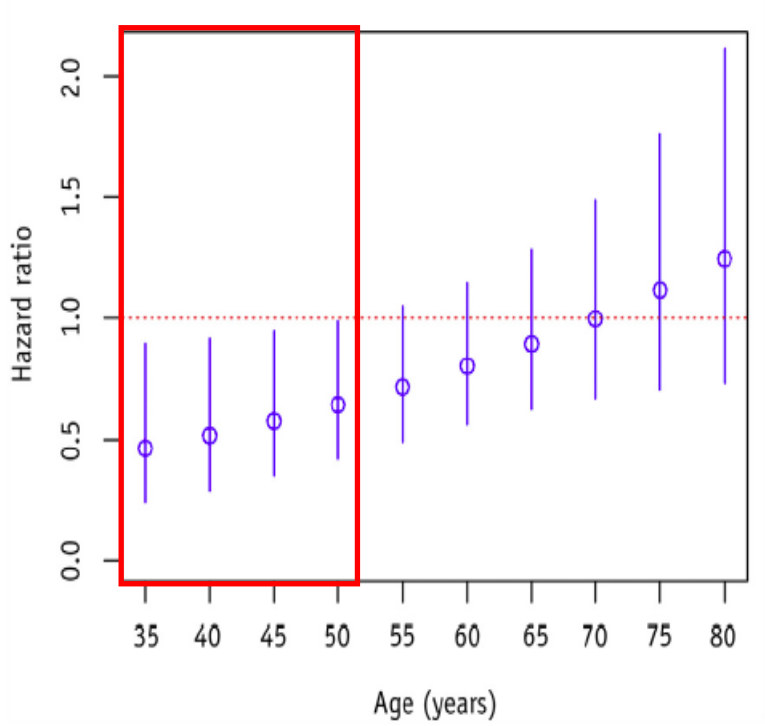


Table 1 Descriptive statistics for 364 patients and those stratified

Factor	Total no. of patients (n=364)	SRS alone (n=186)	SRS plus WBRT (n=178)
No. of females/ males (%/%)	128/236 (35/65)	65/121 (35/65)	63/115 (35/65)
Median age, yr (range)	62 (33-86)	62 (33-86)	61 (35-78)
Age ≤50 yr (%)	68 (19%)	31 (17%)	37 (21%)

Role of Whole Brain Radiotherapy?

- ≤ 5 brain mets
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- > 5 brain mets
  - Is SRS just as good as WBRT?

Multiple brain metastases: *Should SRS be preferred over WBRT?*

Hypothesis

SRS to multiple lesions is no ‘worse’ than WBRT

AND… WBRT is neurologically ‘toxic’

What we know…

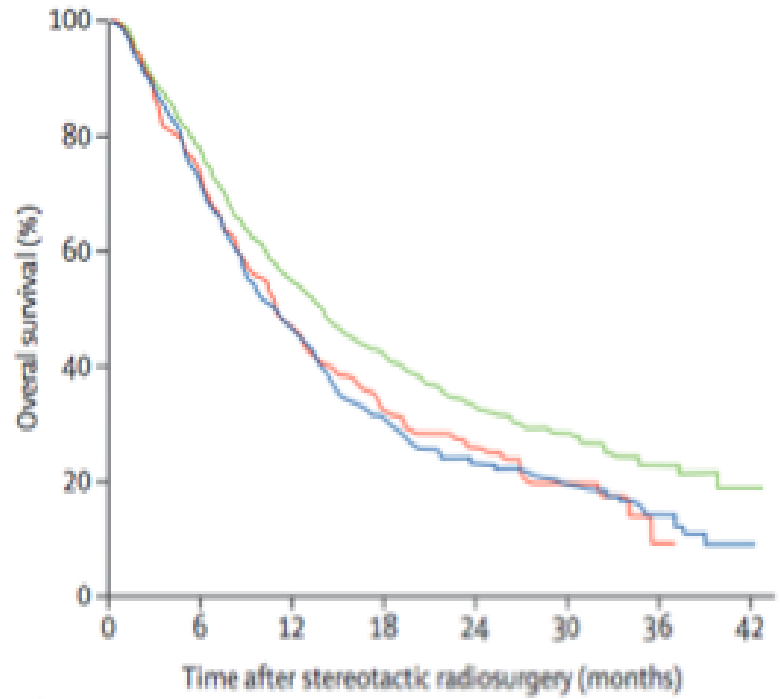
Patients with multiple mets who receive SRS do no worse than individuals with few mets

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

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

Yamamoto et al., Lancet Oncology, 2014



Powerful message by JLGK0901 but

are 2-4 tumours and 5-10 tumours really equal?

	Total (n=1194)	1 tumour (n=455)	2–4 tumours (n=531)	5–10 tumours (n=208)
Cumulative tumour volume, mL				
Mean (SD)	2·84 (2·91)	2·27 (2·38)	3·07 (3·08)	3·54 (3·25)
Range	0·01–14·96	0·01–9·90	0·02–14·96	0·02–13·90
≥1·9 mL	601 (50%)	195 (43%)	279 (53%)	127 (61%)
Maximum diameter of the largest tumour (cm)				
Mean (SD)	1·63 (0·68)	1·60 (0·69)	1·66 (0·68)	1·62 (0·64)
Range	0·08–2·99	0·11–2·98	0·11–2·99	0·08–2·97
≥1·6 cm	600 (50%)	221 (49%)	273 (51%)	106 (51%)

Yamamoto et al., Lancet Oncology, 2014

BUT……

- What about SRS *vs* WBRT for multiple mets?

Till then…. Stereotactic Radiosurgery ALONE *cannot* be considered standard therapy in patients with >5 brain metastases

- RCT = N.A. Gamma Knife Consortium WBRT vs SRS for multiple brain mets (NCT01731704)

Summary Arguments

- WBRT is NOT 'clinically unbearable' – *Scalp/Hippocampal sparing WBRT*

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- WBRT is NOT 'clinically unbearable' – *Scalp/Hippocampal sparing WBRT*
- WBRT improves tumour control in all patients, even after SRS

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Summary Arguments

- WBRT is NOT 'clinically unbearable' – *Scalp/Hippocampal sparing WBRT*
- WBRT improves tumour control in all patients, even after SRS
- WBRT can improve survival - *choosing the right patients*
- WBRT remains the only standard of care in >5 brain mets patients

Thank you!