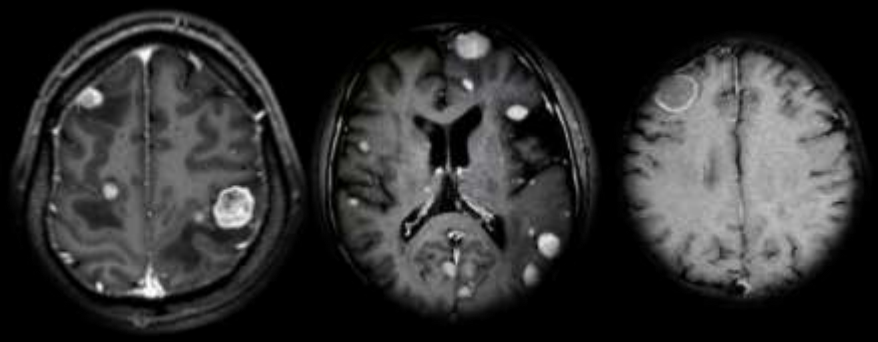
Landmark Trials in Brain Metastasis



Dr Tanweer Shahid
Apollo Hospital,
Kolkata

ELSEVIER

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

0360-3016/97 $17.00 + .00

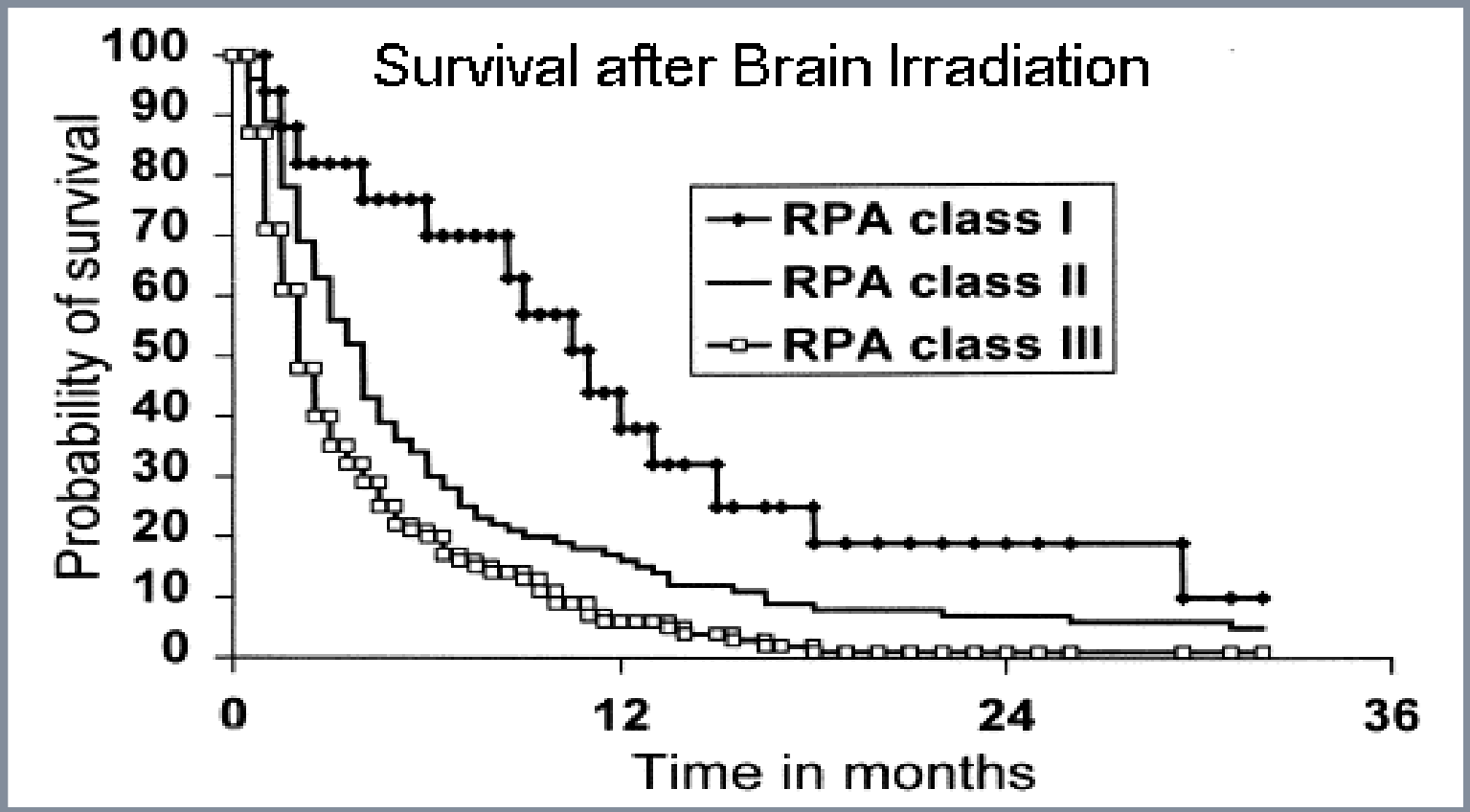
PII S0360-3016(96)00619-0

● *Clinical Investigation*

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

LAURIE GASPAR, M.D.,* CHARLES SCOTT, M.S.,† MARVIN ROTMAN, M.D.,‡

RTOG devised 3 prognostic groups using RPA based on 1200 patients treated on prospective clinical trials.



MEDIAN SURVIVAL
7.1 MONTHS
4.2 MONTHS
2.3 MONTHS

VOLUME 30 · NUMBER 4 · FEBRUARY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Era of Graded Prognostic Assessment

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,

Purpose of GPA is to identify significant diagnosis-specific prognostic factors in an updated era (1985-2007) as compared with the RTOG RPA

CRITERIA

- **Age**
- **KPS**
- **Number of brain metastasis**
- **Presence or absence of extracranial metastasis**

SCORE

- **Each criteria given a score of 0,0.5 and 1**

	GPA score†		
	0	0.5	1
Age, yr	≥60	50~59	<50
KPS	<70	70~80	90~100
Number of lesions	>3	2~3	1
Extracranial metastases	Present	-	None

Median survivals stratified by diagnosis and DS-GPA score for patients with newly diagnosed brain metastases.

Diagnosis	Overall median survival (mo)	Diagnosis-specific GPA			
		GPA: 0-1 Median survival (mo)	GPA: 1.5-2.0 Median survival (mo)	GPA: 2.5-3.0 Median survival (mo)	GPA: 3.5-4.0 Median survival (mo)
NSCLC	7.0	3.0	5.5	9.4	14.8
SCLC	4.9	2.8	4.9	7.7	17.1
Melanoma	6.7	3.4	4.7	8.8	13.2
Renal cell	9.6	3.3	7.3	11.3	14.8
GI	5.4	3.1	4.4	6.9	13.5
Breast	13.8	3.4	7.7	15.1	25.3
Total	7.2	3.1	5.4	9.6	16.7

GI, gastrointestinal; GPA, graded prognostic assessment; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

LESSONs from HISTORY
When you find them SINGLE..

Single Metastases

WBRT with or w/o Surgery

- 1.Patchell RA, NEJM, 1990
- 2. Vecht CJ et al;
- 3. Mintz et al.

Surgery with or w/o WBRT

- 1. Patchell RA, JAMA 1998
- EORTC Kocher et al, JCO, 2011
- Christopher et al, Neuro Onco, 2010

SURGERY FOLLOWED BY WBRT
Vs
WBRT ALONE

ORIGINAL ARTICLE

A Randomized Trial of Surgery in the Treatment of Single Metastases to the Brain

Roy A. Patchell, M.D., Phillip A. Tibbs, M.D., John W. Walsh, M.D., Robert J. Dempsey, M.D., Yosh Maruyama, M.D., Richard J. Kryscio, Ph.D., William R. Markesbery, M.D., John S. Macdonald, M.D., and Byron Young, M.D.

Article Figures/Media

39 References 1849 Citing Articles Letters

February 22, 1990

N Engl J Med 1990; 322:494-

DOI: 10.1056/NEJM1990022

NEJM 1990

Annals of NEUROLOGY

An Official Journal of the American Neurological Association and the Child Neurology Society

ANA AMERICAN NEUROLOGICAL ASSOCIATION

Original Article

Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery

Dr., MD, PhD Charles J. Vecht, MD, PhD Hanny Haaxma-Reiche, MD, PhD Evert M. Noordijk, MD, PhD George W. Padberg, MD Joan H. C. Voormolen, MD Foppe H. Hoekstra, MD, PhD Joseph Th. J. Tans, MD Nanno Lamboolj, MD Jan A. L. Metsaars, MD, PhD A. Rolf W Hermans ... See fewer authors

First published: June 1993 | https://doi.org/10.1002/ana.4

ANNALS OF NEUROLOGY 1993

SURGERY + WBRT

is better than

WBRT alone

Cancer

Original Article | Free Access

A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis

Arlan H. Mintz M.D., M.Sc., John Kestle M.D., M.Sc., F.R.C.S.(C), Michel P. Rathbone M.B., Ch.B., Ph.D., F.R.C.P., Laurie Gaspar M.D., F.R.C.P.(C), Herman Hugenholtz M.D., F.R.C.S.(C), Barbara Fisher M.D., F.R.C.P.(C), Graeme Duncan M.D., F.R.C.P.(C), Peter Skingley, Gary Foster Ph.D., Mark Levine M.D., M.Sc., F.R.C.P.(C) ... See fewer authors

First published: 1 October 1996 |

https://doi.org/10.1002/(SICI)1097-0142(19961001)78:7<1470::AID-CNCR14>3.0.

CANCER 1996

SURGERY FOLLOWED BY WBRT
Vs
SURGERY ALONE

Original Contribution

FREE

November 4, 1998

Postoperative Radiotherapy in the Treatment of Single Metastases to the Brain

A Randomized Trial

Roy A. Patchell, MD; Phillip A. Tibbs, MD; William F. Regine, MD; et al

Author Affiliations

JAMA. 1998;280(17):1485-1489. doi:10.1001/jama.280.17.1485

JAMA 1998

VOLUME 29 · NUMBER 2 · JANUARY 10 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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, [illegible], Laura Fariselli, Tzahala Tzuk-Shina, Rolf-Dieter Kortmann, Christian Carrie, Mohan [illegible], Mauri Kouri, Egils Valeinis, Dirk van den Berge, Sandra Collette, Laurence Collette, and Rolf-Peter Mueller

JCO 2011

NEURO-ONCOLOGY

About

Author Guidelines

Editorial Board

Neuro Oncol. 2010 Jul; 12(7): 711–719.

Published online 2010 Feb 14. doi: 10.1093/neuonc/noq005

PMCID: PMC2940658

PMID: 20156806

Adjuvant whole-brain radiation therapy after surgical resection of single brain metastases

Christopher M. McPherson, Dima Suki, Iman Feiz-Erfan, Anita Mahajan, Eric Cha[illegible], Frederick F. Lang

NEURO ONCO 2010

SURGERY + WBRT

is better than

SURGERY alone

Guidelines

162 Neuro-Oncology
19(2), 162–174, 2017 | doi:10.1093/neuonc/now241

Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)

EANO

Clinical Practice Guideline

Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

Vinai Gondi, MD,[a,*] Glenn Bauman, MD,[b] Lisa Bradfield, BA,[c]

ASTRO

Neuro-Oncology
24(3), 331–357, 2022 | https://doi.org/10.1093/neuonc/noab262 | Advance Access date 21 December 2021

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

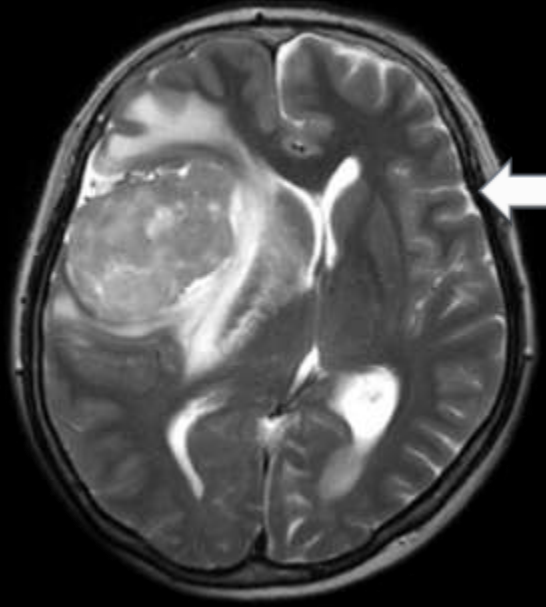
ASCO-SNO-ASTRO

Neuro-Oncology
24(10), 1613–1646, 2022 | https://doi.org/10.1093/neuonc/noac118 | Advance Access date 28 June 2022

Brain metastases: A Society for Neuro-Oncology (SNO) consensus review on current management and future directions

SNO

Single Lesion

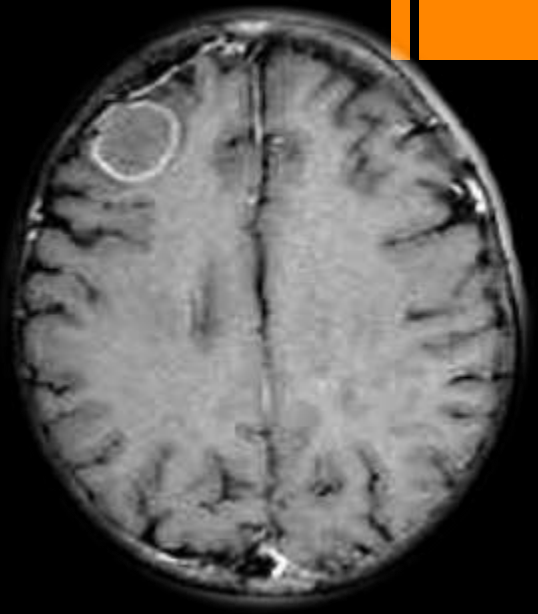


Surgery

- Lesion > 4cm
- Mass effect

SRS

- No mass effect
- Eloquent areas
- Lesion <4cm
- Unwilling for Sx
- Medically inoperable/unfit



Surgery Vs SRS

- **No high quality RCT comparing Surgery Vs SRS in single mets.**
- **Most studies comparing Surgery Vs SRS report similar outcomes.**
- **They are Non-RCT & may be affected by selection bias (class IIIb).**

After Surgical Resection for single mets…
What to give???
WBRT or
SRS to surgical cavity…

- WBRT is the standard of care to improve intracranial control following resection.
- SRS to the surgical cavity : Used to reduce cognitive toxicity.
- High-level comparative data lacking.
- SRS on survival and cognitive outcomes compared with WBRT in patients with resected brain metastasis.

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

LANCET 2017

Paul D Brown, Karla V Ballman, Jane H Cerhan, S Keith Anderson, Xiomara W Carrero, Anthony C Whitton, Jeffrey Greenspoon, Ian F Parney, Nadia N I Laack, Jonathan B Ashman, Jean-Paul Bahary, Costas G Hadjipanayis, James J Urbanic, Fred G Barker II, Elana Farace, Deepak Khuntia, Caterina Giannini, Jan C Buckner, Evanthia Galanis, David Roberge

SURGERY FOLLOWED BY SRS Vs SURGERY FOLLOWED BY WBRT

- **No difference in overall survival.**
- **Shorter time to intracranial failure: SRS 6.4 mos vs. WBRT 27.5 mos**
- **Improved overall QOL at 3 months with SRS**
- **Worse surgical bed control, LC and distant brain control with SRS**

Conclusion:

After resection of a brain metastasis, SRS should be considered one of the standards of care as a less toxic alternative to WBRT.

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

Anita Mahajan, Salmaan Ahmed, Mary Frances McAleer, Jeffrey S Weinberg, Jing Li, Paul D Brown, Stephen Settle, Sujit S Prabhu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Sulman, Ian E McCutcheon, Syed Azeem, Daniel Cahill, Claudio Tatsui, Amy B Heimberger, Sherise Ferguson, Amol Ghia, Franco Demonte, Shaan Raza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, K Ganesh Rao

LANCET 2017

SURGERY FOLLOWED BY SRS Vs SURGERY ALONE

- **SRS of the surgical cavity for 1, 2, or 3 metastases lowers local recurrence compared to observation.**
- **SRS after brain metastasis resection could be an alternative to WBRT.**

What do we learn from these 2 trials? (Brown et al & Mahajan et al)

- **Surgery alone is inadequate t/t.**
- **Surgery + WBRT is probably too much given the toxicities.**
- **SRS is a balance between preservation of neurocognition / QOL and improved intracranial tumor control.**
- **SRS is a reasonable postoperative t/t for resected brain metastases and a good trade-off between surgery alone and surgery + WBRT.**

- **The local control rates were lower than expected.**
- **Possible reasons:**
  1. **Low BED delivered, especially for larger cavities**
  2. **Surgical tract not included**
  3. **Radiation necrosis vs. progression**

Dose recommendations –RTOG 90-05 ; IJROBP 2000

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.,§

Size of lesion	Maximum Tolerated Dose (MTD)
≤ 2cm	24 Gy
2.1 – 3 cm	18 Gy
3.1 – 4 cm	15 Gy

- Radiation Necrosis (RN) is the dose limiting toxicity.
- V10 and V12 are the predictive factors for RN.

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

Paul D Brown, Karla V Ballman, Jane H Cerhan, S Keith Anderson, Xiomara W Carrero, Anthony C Whitton, Jeffrey Greenspoon, Ian F Parney, Nadia N I Laack, Jonathan B Ashman, Jean-Paul Bahary, Costas G Hadjipanayis, James J Urbanic, Fred G Barker II, Elana Farace, Deepak Khuntia, Caterina Giannini, Jan C Buckner, Evanthia Galanis, David Rober

BROWN et al. LANCET 2017

(SURGICAL CAVITY + 2 mm) VOLUME	SRS Dose
< 4.2 cc	20 Gy
4·2–7·9 cc	18 Gy
8·0–14·3 cc	17 Gy
14·4–19·9 cc	15 Gy
20·0–29·9 cc	14 Gy
≥30 cc	12 Gy

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

Anita Mahajan, Salmaan Ahmed, Mary Frances McAleer, Jeffrey S Weinberg, Jing Li, Paul Brown, Stephen Settle, Sujit S Prabhu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Sulman, Ian E McCutcheon, Syed Azeem, Daniel Cahill, Claudio Tatsui, Amy B Heimberger, Sherise Ferguson, Amol Ghia, Franco Demonte, Shaan Raza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, Kenneth R Hess, Ganesh Rao

MAHAJAN et al. LANCET 2017

Volume of target (Surgical cavity + 1 mm)	SRS Dose
≤ 10 cc	16 Gy
10.1 – 15 cc	14 Gy
> 15 cc	12 Gy

Organ	Dose constraint
Brainstem	1 cc < 12 Gy
Optic Nv & Tract	Max <9 Gy

Journey Continues…

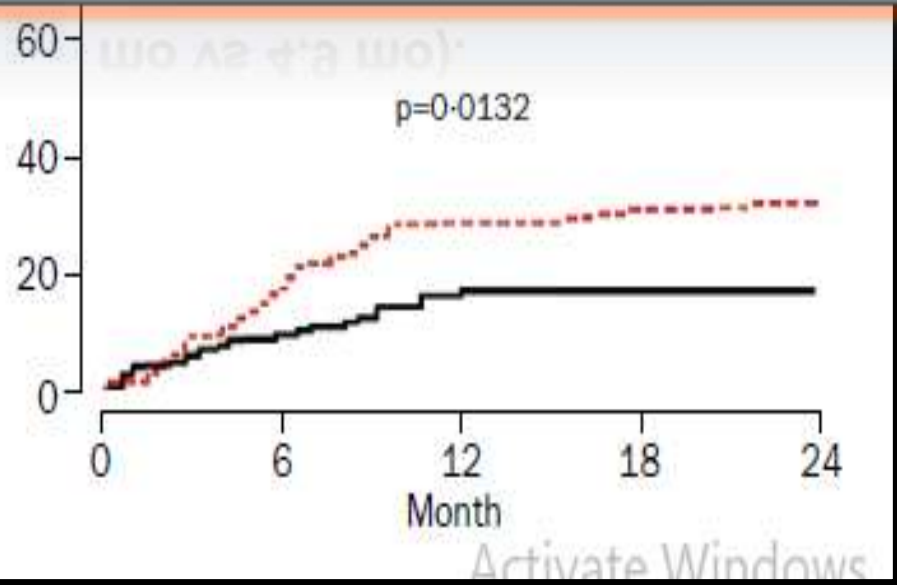
1-3 brain mets… WBRT + SRS vs WBRT alone (Lessons from RTOG 9508…)

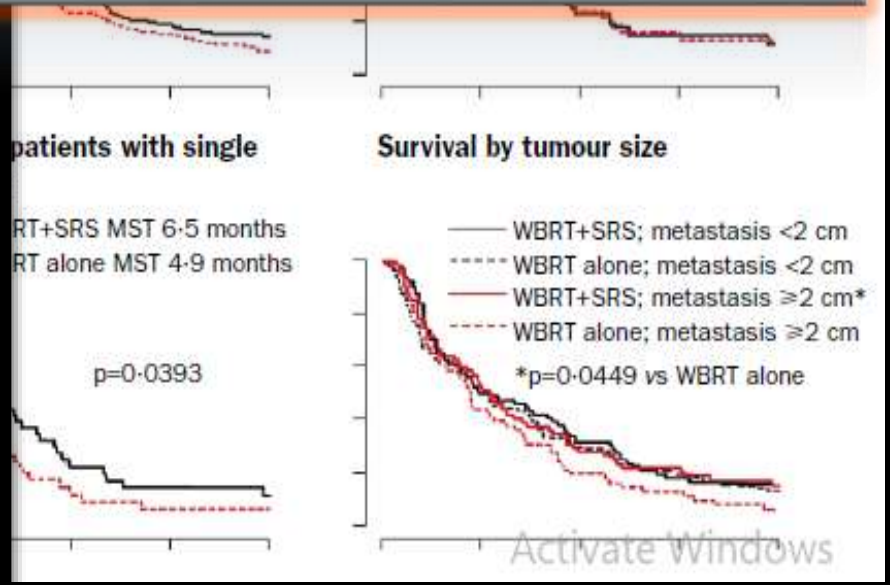
Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

LANCET 2004

WBRT + SRS

- **Better local control and performance status** (i.e. functional autonomy, KPS) at 6 months
- **Survival advantage** only in patients with **single metastasis** (6.5 mo vs 4.9 mo).



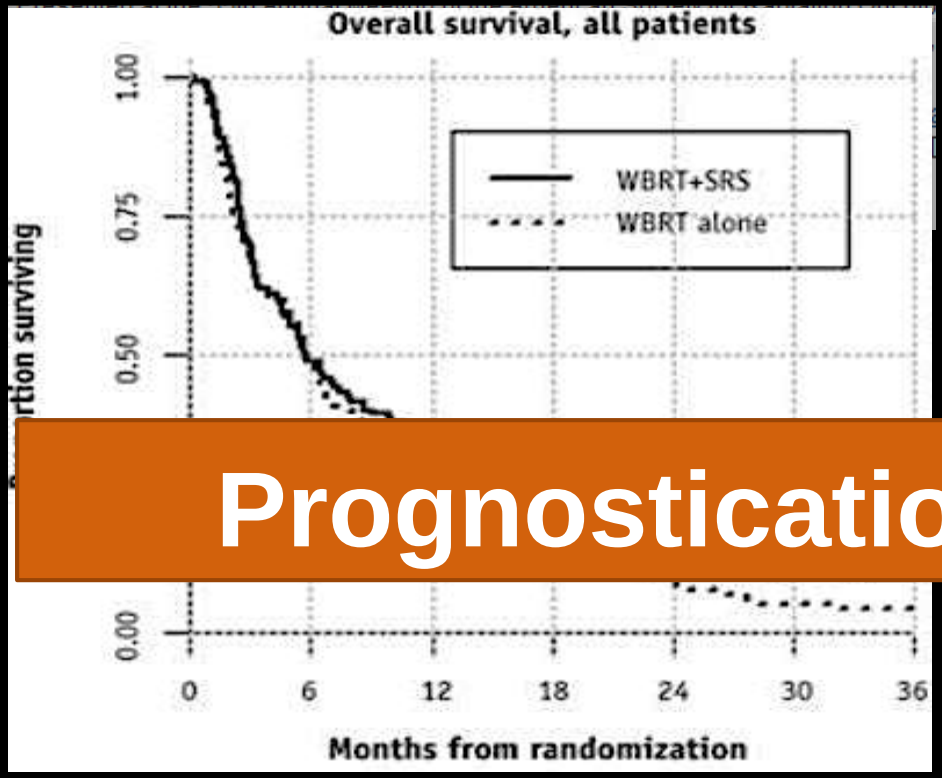


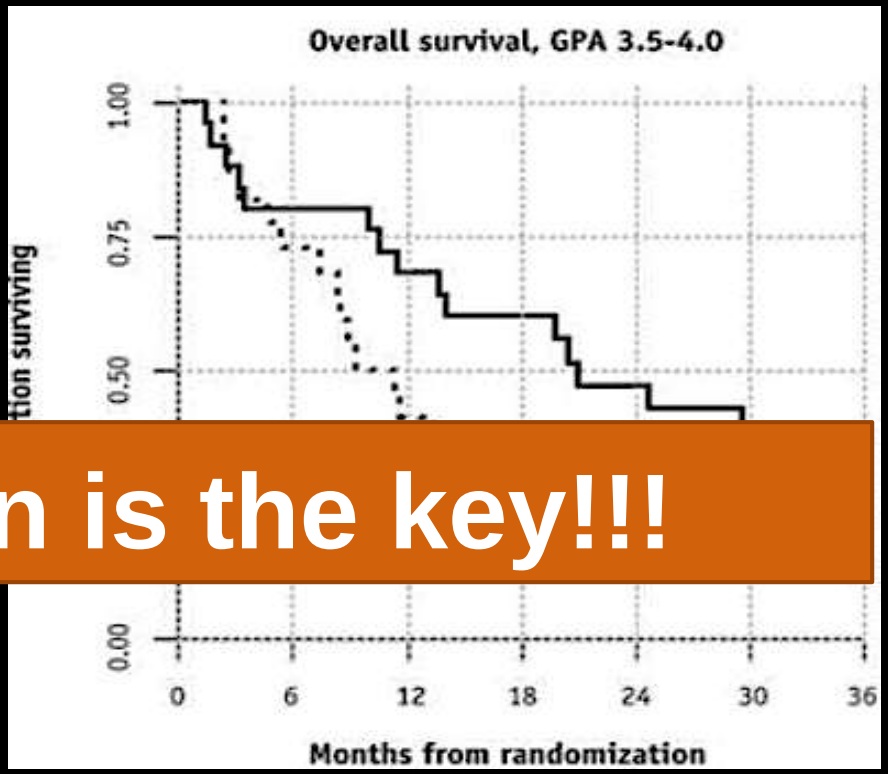
International Journal of
Radiation Oncology
biology • physics
Official Journal of the American Society for Radiation Oncology
ASTRO

10 YEARS LATER….

2014

Secondary Analysis of RTOG 9508, a Phase 3 Randomized Trial of Whole-Brain Radiation Therapy Versus WBRT Plus Stereotactic Radiosurgery in Patients With 1-3 Brain Metastases; Poststratified by the Graded Prognostic Assessment (GPA)





Prognostication is the key!!!

Can we do away with WBRT for limited Brain metastasis?

Better LC with SRS+WBRT

No OS benefit with addition of WBRT

Poor cognition with WBRT

	LC at 1 yr (%)		OS (months)		CLINICAL OUTCOMES
	SRS	SRS+WBRT	SRS	SRS + WBRT	
JROSG – 99-1 Aoyama et al **(JAMA 2006)**	72.5	88.7 (p =0.002)	8.0	7.5 (p=0.42)	
MDAC Chang et al **(Lancet 2009)**	67	100 (p =0.012)	15.2 (use of systemic therapy)	5.7 (p=0.03)	SRS+ [illegible] arm
EORTC 22952-26001 Kocher et al **(JCO 2011)**	69	81 (p =0.04)	10.7	10.9 (p=0.80)	Higher HRQOL in SRS alone arm
ALLIANCE – NCCTG – N0574 Brown et al **(JAMA 2016)**	72.8	90.1	10.4	7.4 (p=0.92)	Decline in immediate & delayed recall, verbal fluency, executive functioning in WBRT arm

What kills earlier??

1 – 4 Brain metastasis : Meta Analysis
SRS with WBRT Vs SRS ALONE

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

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

Arjun Sahgal, MD,* Hidefumi Aoyama, MD, PhD,† Martin Kocher, MD,‡ Binod Neupane, PhD,§ Sandra Collette, PhD,|| Masao Tago, MD,¶ Prakesh Shah, MD,# Joseph Beyene, PhD,§ and Eric L. Chang, MD**,††

2014

< 50 years age:

- **Survival advantage for SRS alone**
- **Distant brain relapse rates *not affected by SRS alone***

- **>50 years age:**
  - **No difference in survival**
  - **Distant Brain failure: *Risk decreased in WBRT***


The Startup Journey
Continues

SRS FOR MULTIPLE BRAIN METS… (UP TO 10 METS!!!)

LANCET 2014
N=1194 pt.

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*

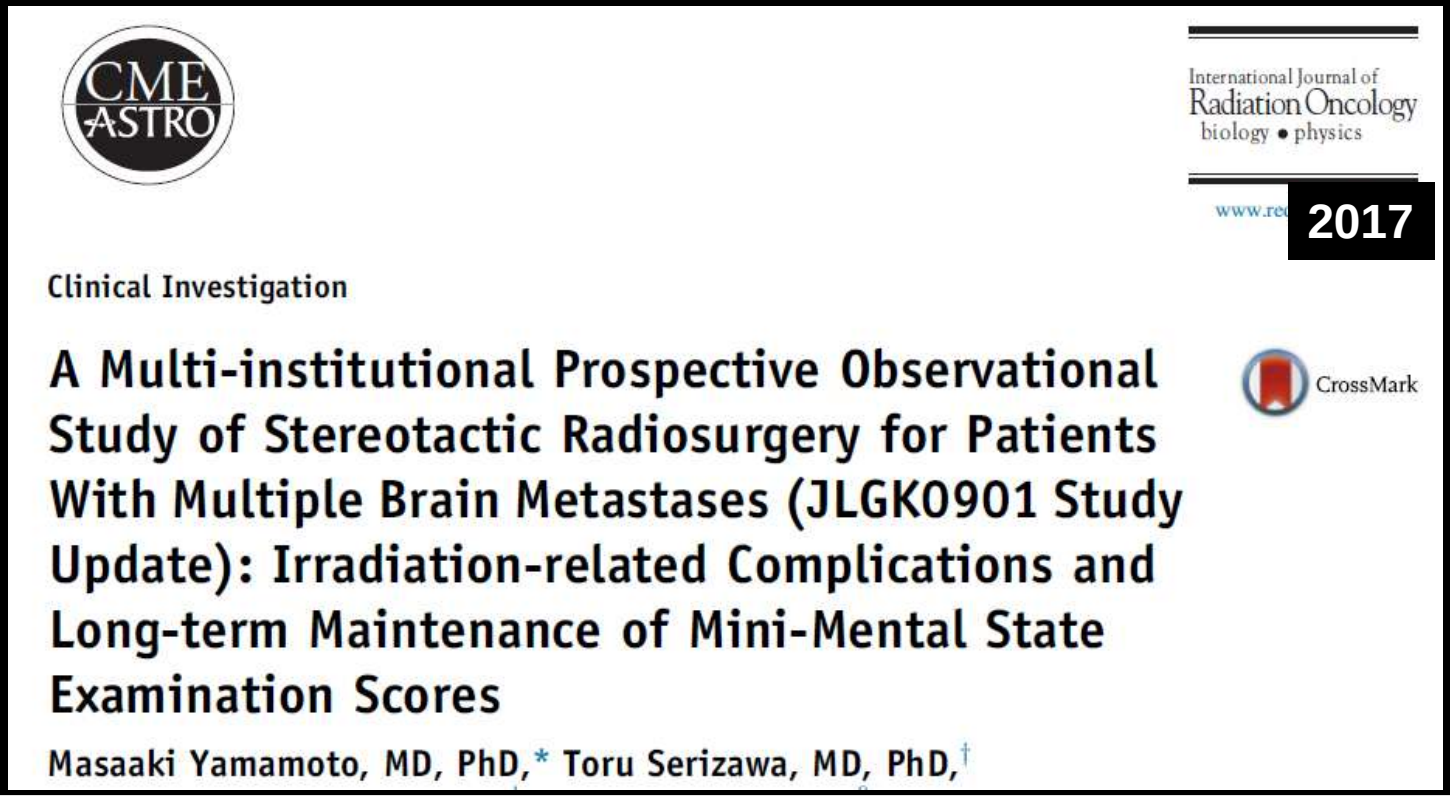
- **Use of SRS: (3 Groups)**
  - **With 1,**
  - **2 to 4 or**
  - **5 to 10 brain metastases.**

- **Result:**
  - **Similar OS**
  - **Similar t/t related toxicity**

  } **Between groups with 2 to 4 & 5 to 10 mets.**

- **Cumulative volume of metastases, rather than the number is important.**
- **SRS is suitable alternative for patients up to 10 brain metastases.**

SRS for > 4 brain mets: An upcoming strategy



CME ASTRO

International Journal of Radiation Oncology biology • physics

www.re

2017

Clinical Investigation

A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores

CrossMark

Masaaki Yamamoto, MD, PhD,* Toru Serizawa, MD, PhD,†

Conclusion:

- **MMSE score maintenance comparable.**
- **Post-SRS complication comparable.**
- **SRS alone for patients with 5 to 10 mets. Vs 2 to 4 mets. is doable.**

Why FSRS?

- Toxicity
  - Single session SRS dose is limited by tumor size
  - Fractionation allows for repair/recovery of radiation effects in the normal tissue
  - Use stereotactic techniques to spare dose to normal tissue
  - Reirradiation
- Tumor control
  - Able to give a higher cumulative dose to larger tumors/target volumes
- ***Image guided frameless RT utilizing radiosurgical margins to minimize toxicity and maximize tumor control***

Josh Yamada MD FRCPC, Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center

FSRS – WHEN ? WHY ?

IJROBP 2016

	Single #	Multi #	P value
1 yr Local control	77 %	91 %	P =0.01
Recurrence	25	11	P = 0.03
Radionecrosis	20 %	8 %	P = 0.004
1 yr Radionecrosis	18 %	9 %	P = 0.01

CONCLUSIONS:

- **Multifraction SRS : Effective t/t modality for large brain metastases.**
- **Better local control & reduced risk of radiation-induced radionecrosis. (Compared with Single Fraction-SRS).**

DOSE FOR FSRS

Hypofractionated Stereotactic Radiation Therapy to the Surgical Bed for Patients With Brain Metastases Provides Effective Local Control for Bed ≥ 48

A.M.S. Kumar,[1] A.E. Sloan,[2] J. Miller,[2] Y. Zhang,[1] S.A. Hoffer,[2] D.B. Mansur,[3] M. Machtay,[1] and S.S. Lo[4]; [1]*Radiation Oncology,*

- **BED should be more than ≥ 48 Gy**
  - **30Gy in 5 fractions.**
  - **27Gy in 3 fractions.**

IJROBP, October 1, 2017 Volume 99, Issue 2, Supplement, Page E85

WBRT: What"s the indication???

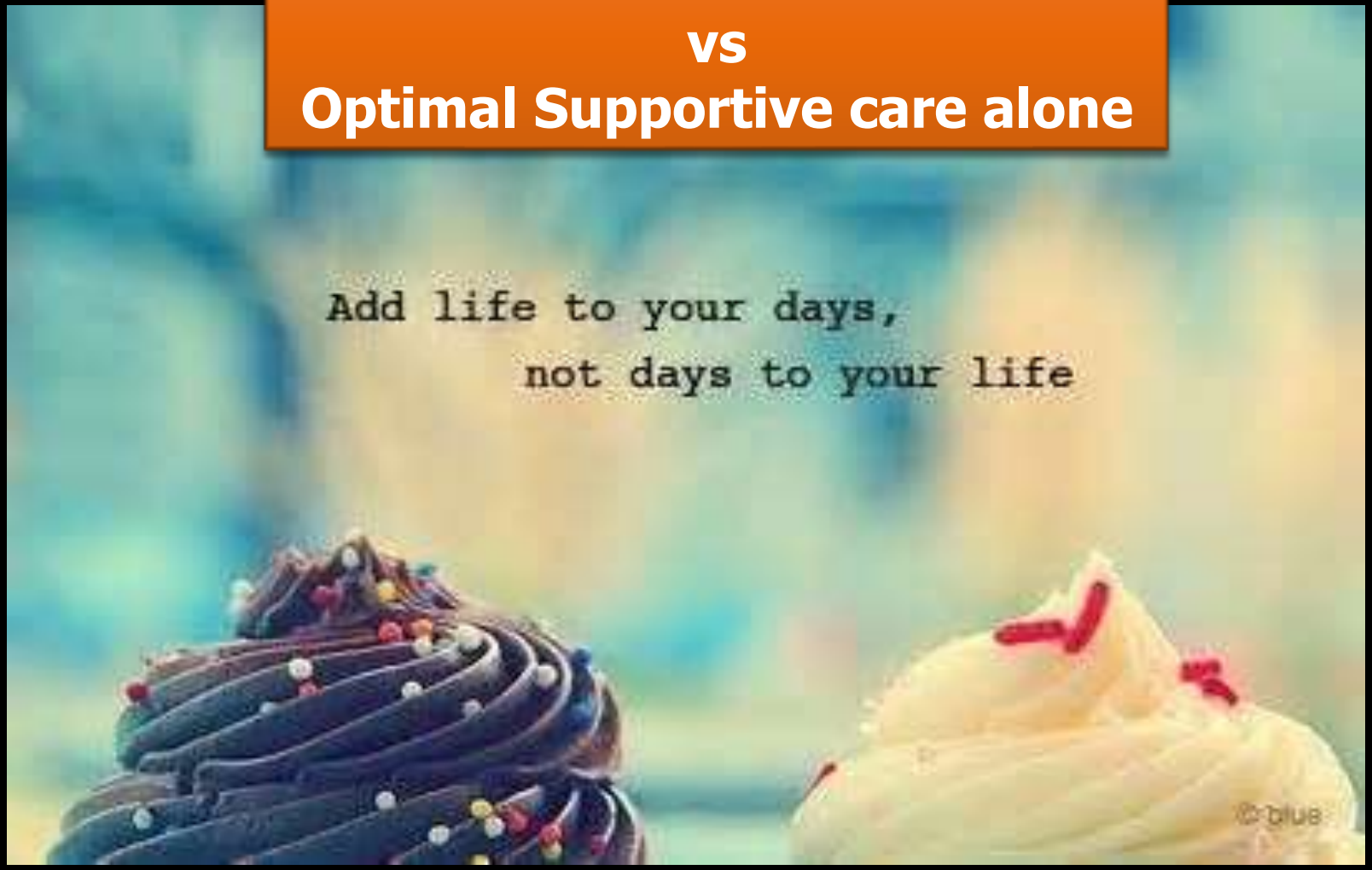
EANO

- **WBRT or best supportive care should be considered for patients with:**
  - **Short life expectancy**
  - **Low KPS score.**
  - **Progressive systemic disease.**
- **When employing initial WBRT, a monitoring of cognitive functions with specific batteries is recommended**

ASTRO

- **Poor life expectancy (less than 3 months).**
- **Use of WBRT may or may not significantly improve symptoms from brain metastases.**
- **Comfort measures only, or short course (20 Gy in 5 daily fractions) WBRT, is reasonable option.**

WBRT + optimal supportive care
vs
Optimal Supportive care alone



Acta Oncologica, 2010; 44: 382–388

informa

- **Does WBRT works in all???**
- **Can WBRT be avoided in some patients???**

ORIGINAL ARTICLE

Prospective evaluation of the palliative effect of whole-brain radiotherapy in patients with brain metastases and poor performance st

ACTA ONCOLOGICA 2010

Benefit of WBRT in RPA 3 patients is questionable…

LANCET 2016

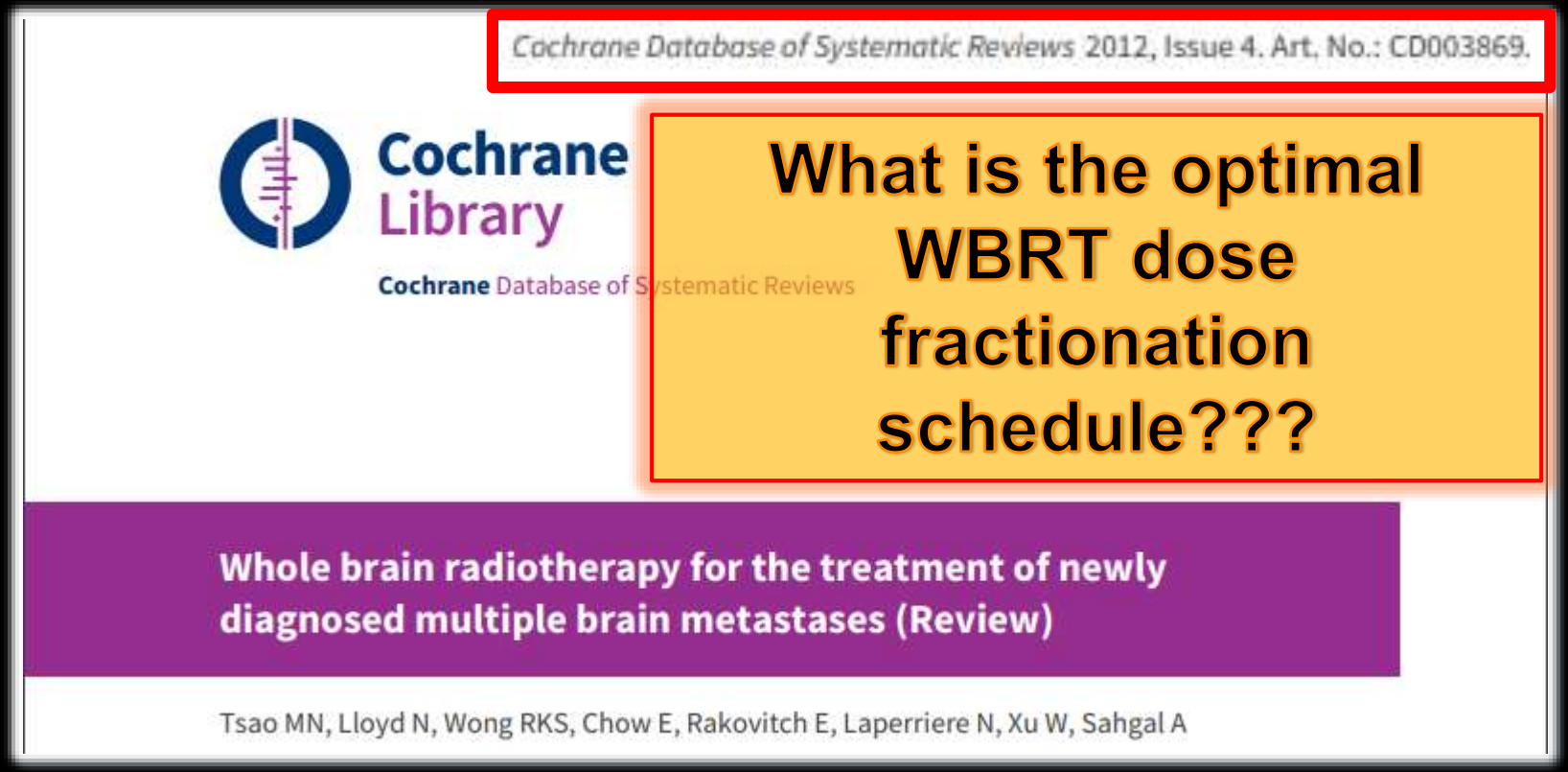
Dexa… without whole b… non-small cell … itable for resection or stereotact… …lts from a phase 3, non-inferio…, ran… sed

Paula Mulvenna, Matthew Nankivell, Rachae… Corinne Faivre-F… la Wilson, Elaine McColl, Barbara Moore, Iona Brisbane, David Ardron, Tanya Holt, Sally Morgan, Caro… Kathryn Waite, Nei… man, Cheryl Pugh, Benjamin Sydes, Richard Stephens, Mahesh K Parmar, Ruth E Langley

Lancet 2016; 388: 2004-14

Summary

Background Whole brain radiotherapy (WBRT) and dexamethasone are widely used to treat brain metastases from



- **Standard fractionation: (30 Gy in 10 fractions or 20 Gy in 5 fractions).**
- **No differences in OS or symptom control with 30 Gy in 10 daily fractions or 20 Gy in 5 daily fractions.**
- **Others: 37.5 Gy in 15 daily fractions and 40 Gy in 20 daily (or twice daily) fractions.**

Choosing Wisely®

An initiative of the ABIM Foundation

American Society for Radiation Oncology

ASTRO

TARGETING CANCER CARE

Five More Things Physicians and Patients Should Question

Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

Pros & Cons

Adjuvant WBRT + SRS:

- **No OS benefit (Especially in pt. with Good PS)**
- **Diminished cognitive function**

SRS alone:

- **Importance of Surveillance**
- **More risk of Distant brain failure**
- **Better QoL without OS compromise**

JOURNAL OF CLINICAL ONCOLOGY

2014

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,

PRESERVATION OF MEMORY WITH CONFORMAL AVOIDANCE OF HIPPOCAMPAL NEURAL STEM-CELL COMPARTMENT DURING WBRT FOR BRAIN METS - RTOG 0933

JCO, 2014
Gondi et al, USA
Ph II Trial

- Hippocampal neural stem-cell injury during WBRT → may play a role in memory decline.
- IMRT to avoid hippocampus → may yield clinically significant neurocognitive benefit.

TEST ARM

- Brain mets 5 mm away from Hippocampus
- Primary Solid tumors except SCLC/ GCT
- RTOG RPA class I or II

HISTORICAL CONTROL

- Matched eligibility criteria
- Control arm of the PCI-P-120-9801 phase III trial

OBJECTIVES

Cognitive Decline assessed by HVLT-R DR (Hopkins Verbal Learning Test– Revised, Delayed recall)

QOL assessment

Comparison with historical control

HA-WBRT

IMRT: 30 Gy/10 Fr

STANDARD WBRT

30 Gy/10 Fr

RESULTS

- HA-WBRT associated with significant memory preservation
- Mean relative decline in HVLT-R DR from baseline to 4 months: 7% for HA vs 30 % for standard, p= .001
- Cognitive decline greater with ↑age, ↑ D100% of Hippocampus, previous neurological symptoms
- QOL preserved with HA-WBRT
- Risk of developing brain mets in the HA region → low

CONCLUSION

- HA-WBRT can be safely delivered for brain mets
- Hippocampal neural stem-cell niche is central to RT-induced memory decline

NRG CC001

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

JCO ; Feb, 2020
P D Brown,
Phase III

Hippocampal avoidance (HA) – WBRT, to preserve cognition.

Jul, 2015 – Mar, 2018
N - 518

R

Baseline evaluation
=> MRI Brain, Cognitive tests, QoL, Symptom burden

- **WBRT + Mem (N- 257)**
- **WBRT: 30 Gy / 10 #**
- **HA-WBRT + Mem (N- 261)**

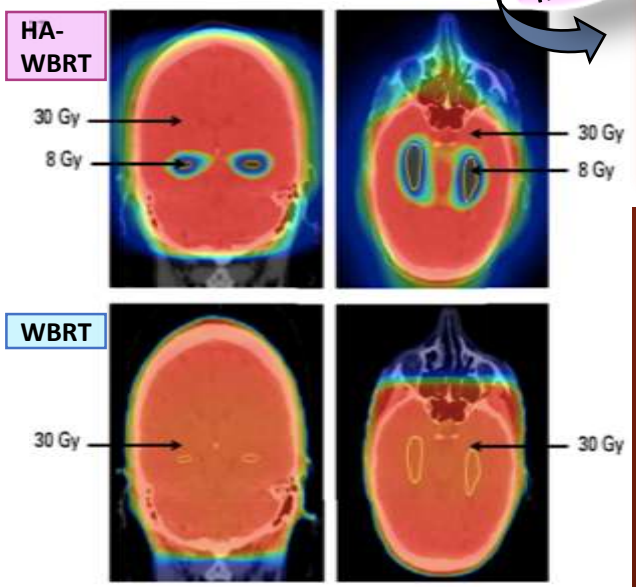
1° End Point:
Time to Cognitive Function Failure,

2° End Points:
OS, Intracranial PFS, Toxicity, & Patient-Reported Symptom Burden

Evaluated @ 2 m, 4 m, 6 m and 12 m

Med F.U. 7.9 m *(for alive pts)*

Results



Risk of cognitive failure => significantly lower

↓ deterioration in

- **executive function at 4 m**
- **Learning and memory at 6 m**

No significant difference in

- OS, intracranial PFS, or toxicity.

@ 6 m: Pt reported symptom burden
↓

CONCLUSION:

HA-WBRT + Memantine

- better preserves cognitive function and patient-reported symptoms,
- with no difference in intracranial PFS and OS

⇒Should be considered a **Standard of Care** for pts with

✓ good PS &

✓ no mets in the HA region

Let"s Summarise

Take Home Message:

- **Prognostication is the key.**
- **(Age, KPS, Extracranial control, Primary ds…) – *Choose wisely.***

Number of lesion:

- **Single:**
  - **Without mass effect: SRS alone no compromise in OS**
  - **With Mass effect: Sx -> SRS +/- WBRT; if not resectable SRS +/- WBRT**
  - **FSRS is another option if volume is big.**

Take Home Message:

- Oligo / Limited: 1 – 3 or 1 – 4 or 5 – 10…
- Multiple:
  - WBRT + SRS boost
  - WBRT Hippocampal sparing
  - WBRT alone
- Volume of Metastatic lesion(s).
- SRS Dose: Lesser the volume – Higher the dose

Take Home Message:

SRS alone:

- **Better Neurocognitive function / Better QOL**
- **Risk of distant brain failure is high**
- **Increased requirement of surveillance and salvage t/t**

- **FSRS: For Larger Volume disease to prevent RN**

- **WBRT: Poor KPS and poorly controlled disease,**

Future direction:

- **WBRT hippocampal sparing with SIB vs SRS alone**
- **WBRT with Memantine (To preserve neurocognition)**

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