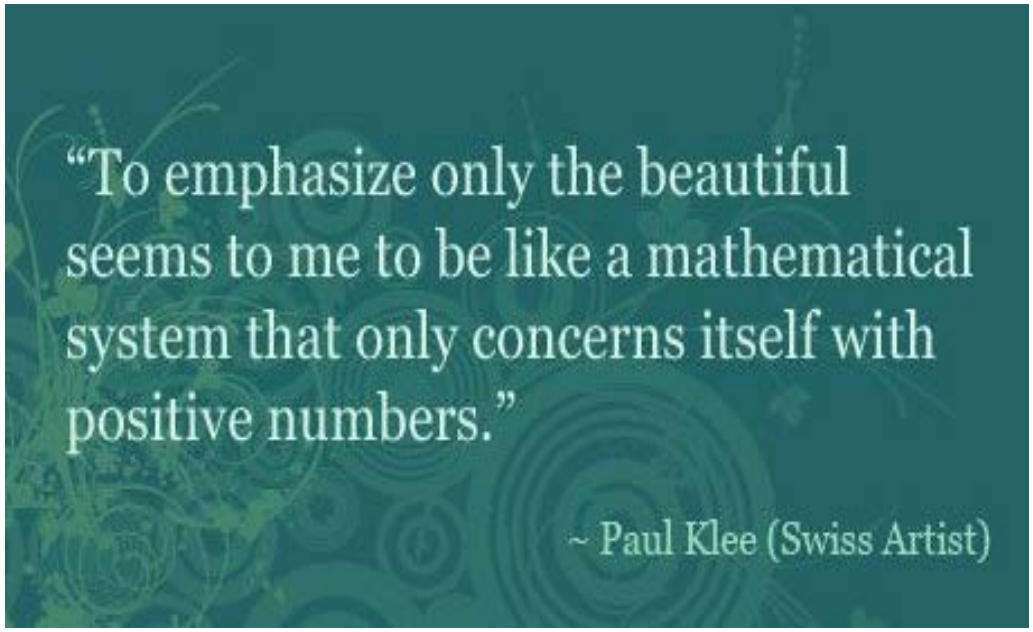
Managing Brain Metastases
Reality vs Optimism



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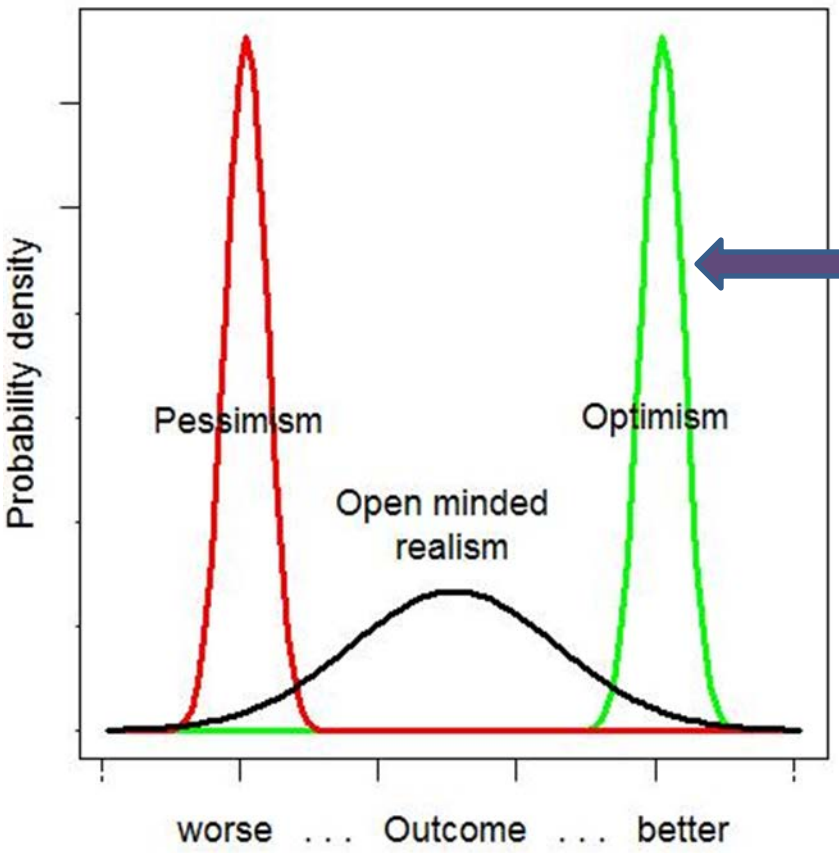
Optimism:

Hopefulness and confidence

Reality:

The state of things as they actually exist

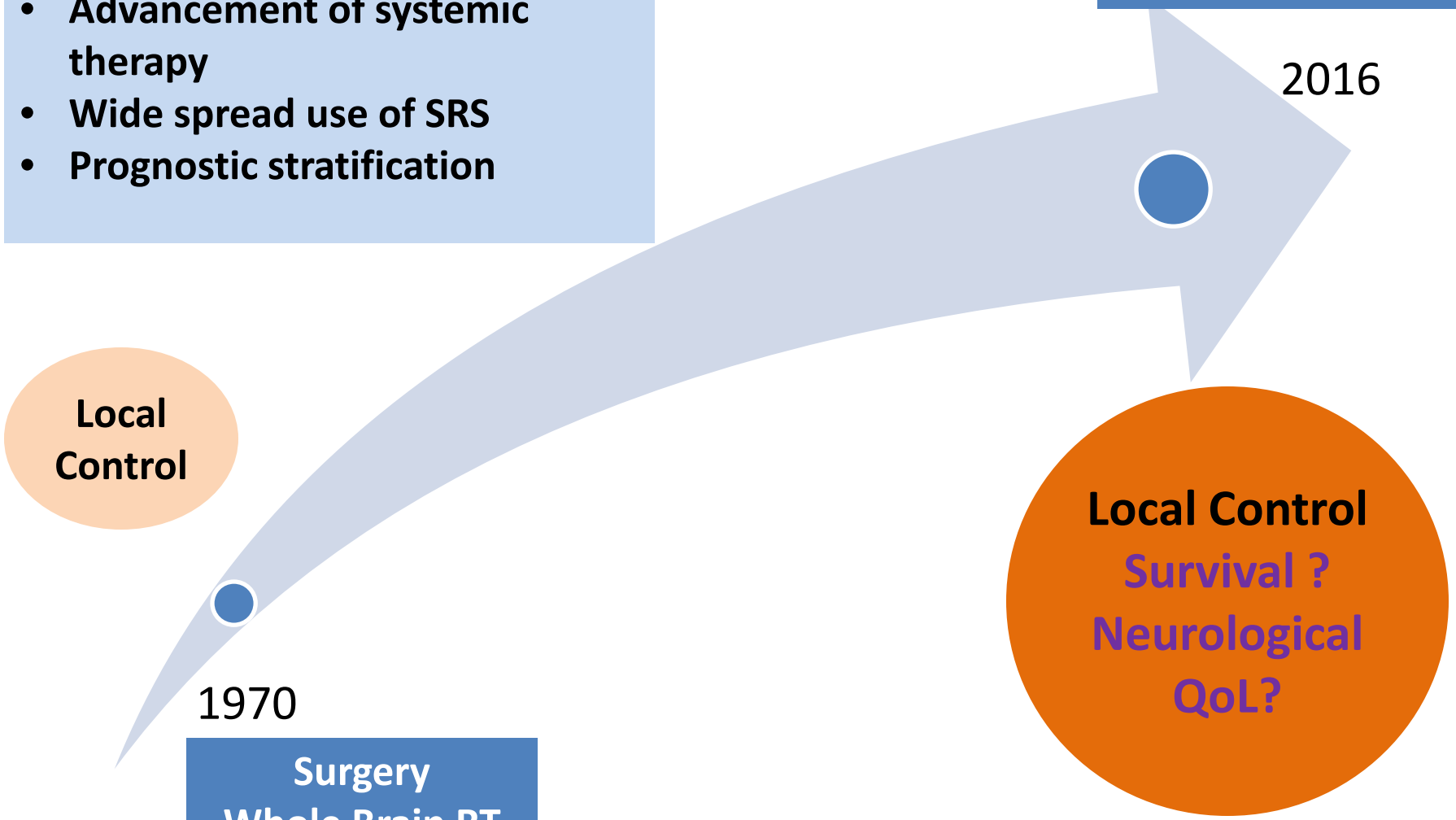


Shadows & caveats

- **The Optimism Bias:**
- **Denying the reality?**
- **Radical Optimism**

Brain mets Tt : The paradigm shift

- Early detection of asymptomatic metastasis
- Advancement of systemic therapy
- Wide spread use of SRS
- Prognostic stratification



Survival statistics

Table 4 Median survivals stratified by diagnosis and diagnosis-specific GPA score for patients with newly diagnosed brain metastases[15,20,21]

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.

Tsao MN et al. Practical Radiation Oncology 2012

The Major optimism

1. Stereotactic Radiosurgery alone for oligo-metastasis of brain replacing Whole Brain RT.

2. Elephant in the room is neurological QoL no local Control.

1-3 metastasis(es)

- **SRS +/- WBRT**
- **1990-2015**
- **16 studies**
- **5 Major RCTs**

- **No overall survival differences**
- **Improved Local control and distant brain control in WBRT+SRS arm**
- **More Neurological death in SRS alone arm**
- **Improved neurocognitive dysfunction in SRS alone arm**

Ayoama H et al. JAMA. 2006 Jun 7;295(21):2483-91
Chang EL et al. Lancet 10(11) 2009
Kocher M et al. J Clin Oncol 10(2) 2011
Soffietti R.J Clin Oncol 31(1) 2013
Brown PD et al. J Clin Oncol 33, 2015 (suppl; abstr LBA4)

Single brain metastasis

Table 3. Recent Studies Investigating Different Treatment Modalities for Single Brain Metastasis

Author	Year	Treatment(s)	*n*	Median Survival	Local/Distant Recurrence		Side Effects
Surgery							
McPherson (26)	2010	Surgery	216	11.7 months	Local 21%	Distant 53%	NS
O'Neill (32)	2003	Surgery	74	1-year FU 62% 2-year FU >30%	Local 14.9%	Distant 10.8%	NS
Patchell (34)	1998	Surgery	46	43 weeks	Local 46%	Distant 37%	NS
Mean				*46.8 weeks*	*27.3%*	*33.6%*	
SRS							
Ma (28)	2012	SRS	29	15 months	Tumor control at 12 months: 48.2%		Grade 3+ toxicity—1.9%
Rades (37)	2012	SRS	63	1-year survival 57%	Local 51%	Distant 30%	Grade 2+ toxicity acute/Late 5%/6%
Clarke (7)	2010	SRS	22	1-year FU 23.5% 18-month FU 11.7%	Local 22.7%	Distant 68.2%	Worsening of neuro sx (6)
O'Neill (32)	2003	SRS	23	1-year FU 56% 2-year FU <10%	Local 0% (−0.02)	Distant 26.1%	NS
Li (25)	1999	SRS	23	9.3 months	Median time to Local 6.9 months		No serious late complications in any patients
Muacevic (30)	1999	SRS	56	35 weeks	Local 83%	Distant 19.6%	Perioperative morbidity/ mortality 8.9% (seizure, nausea, H/A)/ 1.8%
Flickinger (9)	1994	SRS	116	11 months	15%		NS
Mean				*47.0 weeks*	*34.3%*	*36%*	
WBRT							
Rades (40)	2012	WBRT	86	15 months	Local 65%		Early toxicity (grade ≥ 2)—16% Late toxicity—20%
Rades (36)	2008	WBRT	96	6 months	Local 65%	Distant 54%	Grade 3+ Toxicity acute/Late 7%/5%
Andrews (1)	2004	WBRT	94	4.9 months	43% > with WBRT vs. WBRT+SRS		N/V Skin Neuro (Central/ Peripheral) 15% 45.8% 12.0%/3.0%
Li (25)	1999	WBRT	29	5.7 months	Median time to Local 4.0 months		No serious late complications in any patients
Mintz (29)	1996	WBRT	43	6.3 months	NS		NS
Noordijk (31)	1994	WBRT	63	6 months	NS		NS
Vecht (53)	1993	WBRT	31	6 months	NS		NS
Patchell (35)	1990	WBRT	23	15 weeks	Local 52.2%		30-day mortality/morbidity 4%/17%
Mean				*28.9 weeks*	*60.7%*	*54%*	
Surgery + WBRT							
Rades (41)	2012	Surgery + WBRT	111	13 months	Local 44%		Grade 2+ Toxicity acute/Late 15%/ 5%
Rades (39)	2012	Surgery + WBRT	46	19 months	Local 22%	Distant 32%	Grade 3+ Toxicity acute/Late 7%/9%

Kimmel KT et al. World Neurosurg.2015 Nov;84(5):1316-32.

1-3 Metastasis(es) : Results

Study	arm	Survival	Local relapse	Nuro QoL
JROSG99-1 **Aoyama et al 2006 (1993-2003)** N= 132	1-4 mets/<3cm SRS+ WBRT SRS MMSE Scale	8month Vs 7.5monts NS	1yr 46.8% vs 78.4%	Functional perseveration similar
MDAC NCT00548756 **Chang et al . 2009** 2001-2002 N =58	1-3mets SRS+WBRT SRS Hopkins Verbal Learning Test–Revised	Death 29% vs 13% OS?	1yr 27% vs 73%	Mean probability of decline at 4month 62% vs 24%
EORTC 22952 26001 Kocher et al. **2011** **N= 199(RS+/-WBRT)**	1-3mets SRS/SX + WBRT/OBS WHO PS Progression	WBRT vs Obs 10.9m vs 10.7 NS Neurological death 28% vs 44%	2yr 19% vs 31%	Survival with functional Independence 10m vs 9.5m (NS)
NCCTG N0574 **Brown PD et al.** **2015** N = 213	1-3mets <3cm SRS+WBRT vs SRS ?	OS 7.4m vs 10.4m (NS)	6months 11.6% vs 35.4%	3m neurocognitive decline 91.7% vs 63.5%

The caveats: JROSG99-1 trial (Aoyama et al.)

- MMSE is a poor measure of neuro-cognition as it lacks adequate sensitivity[1].
- Non significant (p =0.21)difference in drop in MMSE score (39% WBRT+ RS versus 26% RS alone arm).
- No difference in actuarial curves of freedom-from drop in MMSE (P = .73)
- Longer duration until deterioration of the MMSE in WBRT arm (16.5 m vs 7.6m,P = .05)
- No of single brain metastasis small (n=64) for subset analysis

1: Meyers CA, Wefel JS.J Clin Oncol. 2003;21:3557-3558

ds GPA based reanalysis

Groups of ds GPA	n (NSCLC)	WBRT versus SRS alone
Favorable (2.5 to 4)	n= 47	Median survival benefit 16m vs 10m in WBRT arm
Un favorable (0.5 to 2)	n=41	No difference

Better brain control translating in better OS in EBRT arm in favorable group.

Ayoma H et al. JASTRO annual meeting 2014

The caveats : MDAC NCT00548756 trial (Chang et al.)

1. SRS alone group have high RPA-class I , breast primary,single metastasis patients.
2. Higher volume of Intracranial disease in WBRT arm correlating (lower baseline neurocognitive)
3. More aggressive surgical salvage in SRS arm
4. % patients received chemotherapy was more in SRS arm.

Weiss SE et al. Lancet Oncol 2010 Mar;11(3):220-1
Li J et al.J Clin Oncol 2007 Apr 1;25(10):1260-6
Meyers CA, Smith JA, Bezjak A, et al. J Clin Oncol 2004; 22: 157–65.

5. No analysis >4month [Median F/U 9months]

6. Imbalance in the arms of the trial with respect to anti-seizure medications and benzodiazepines

Cranmer LD et al. Lancet Oncol.2010 Jan;11(1):13
Knisley JP Lancet Oncol 2009 Nov;10(11):1024
Tsao MN et al. IJROBP 2012
Mahmood U et al. Lancet Oncol 2010 Mar;11(3):221-2

The caveats : EORTC 22952-26001 trial (Kocher et al.)

- **Non blinded trial design**
- **WHO PS progression (Functional independence tool) is a rudimentary tool with inter/intra observer bias.[1]**

1: Mehta M J Clin Oncol.2011 Jan 10;29(2):121-4

International Journal of Radiation Oncology biology • physics

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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

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**,††

Received May 27, 2014, and in revised form Sep 28, 2014. Accepted for publication Oct 10, 2014.

Individual Patient Data Meta-Analysis

Included Trials:

1. JROSG99-1 Aoyama et al 2006
2. MDAC NCT00548756 Chang et al 2009
3. EORTC 22952 26001 Kocher et al

Table 2 Hazard ratio estimates for SRS alone versus SRS plus WBRT at different ages for overall survival and distant brain failure

Age*	HR (95% CI) for†	
	Overall survival	Distant brain failure
35	**0.46 (0.24-0.9)**	0.90 (0.42-1.94)
40	**0.52 (0.29-0.92)**	1.05 (0.56-1.98)
45	**0.58 (0.35-0.95)**	1.23 (0.73-2.05)
50	**0.64 (0.42-0.99)**	1.43 (0.95-2.15)
55	0.72 (0.49-1.05)	**1.67 (1.19-2.35)**
60	0.80 (0.56-1.14)	**1.95 (1.40-2.71)**
65	0.90 (0.62-1.29)	**2.27 (1.55-3.33)**
70	1.0 (0.67-1.49)	**2.65 (1.64-4.27)**
75	1.12 (0.71-1.76)	**3.09 (1.70-5.61)**
80	1.24 (0.73-2.11)	**3.60 (1.75-7.44)**

Abbreviations: CI = confidence interval; HR = hazard ratio.

* Because treatment effect depends on the patient's age (as it was a significant effect modifier), estimates of effects (HRs and corresponding 95% CIs) are presented at patients' ages from 35 to 80 years at intervals of 5 years.

† Estimates were obtained from adjusted analysis for important confounders and prognostic factors. Significant estimates (boldface) with HR < 1 and HR > 1 suggest protective and harmful effects, respectively, of SRS alone at the corresponding age on the respective outcome.

Conclusions: For patients ≤50 years of age, SRS alone favored survival, in addition, the initial omission of WBRT did not impact distant brain relapse rates. SRS alone may be the preferred treatment for this age group.

ASTRO
TARGETING CANCER CARE

American Society for Radiation Oncology

View all recommendations from this society

Released September 15, 2014

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

Choosing Wisely®
An initiative of the ABIM Foundation

The caveats

1. Inclusion of trials with statistical flaws and contradictory (neurological outcome) results.
2. Imbalance in primary cancer type in <50 years group (eg. Kidney cancer).SRS act better on Kidney cancer?[1]
3. Histology based separate analysis not done.
4. More local and distant relapses in SRS alone arm.

Cengiz Gemici C, Yaprak G Int J Radiat Oncol Biol Physics ;92(4) 2015
1: De Meerleer G, Khoo V, Escudier B, et al.Lancet Oncol 2014;15:e170-e177

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 WBRT age ≤50 yr (n=37)
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%)

7. Disparity in sex (more females in the SRS-alone group)
8. Presence of extra-cranial metastasis (higher in the SRS + WBRT group)
9. Discordance between systemic control and local outcome?
10. Survival benefit in <50 yr is based on post hoc analysis(n=35)

Lowrey GC ,Marcus B Int J Radiat Oncol Biol Physics ;92(4) 2015
Minesh P et al. 2015 ASCO Educational Book

Other reality check issues

- What should be the primary end point?
- What are the consequences of withholding WBRT?
- What is time-course of neurocognitive changes in WBRT?
- Change of scenario in radio-resistant tumors?
- What is cost benefit aspect?

The endpoint controversy

- Delay in PFS versus improvement of QoL or both:

- A few studies
- **Investigators found that lack of progression is independently associated with improved symptom control and QOL.**

Booth CM et al. ;JCO 30(4),2012
Siena S et al. Br J Cancer **97**:1469–1474

Consequence of Intracranial failure withholding WBRT

- **Patchel et al.**

  Neurological death high

  Salv te
- **Ayor**

  Cons to IC failure
- **Chang et al.**

  Upto 4month F/U no difference
- **Kocher et al.**

  Neurological death rate high

  Poor PFS/Local control/Distant Brain control

High Neurological death rate

Neurocognitive changes in WBRT

VOLUME 25 · NUMBER 10 · APRIL 1 2007

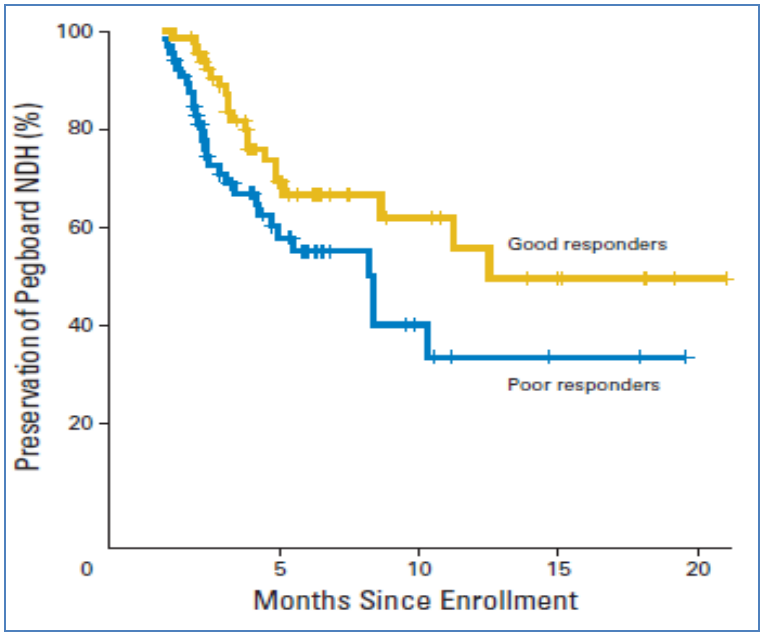
JOURNAL OF CLINICAL ONCOLOGY

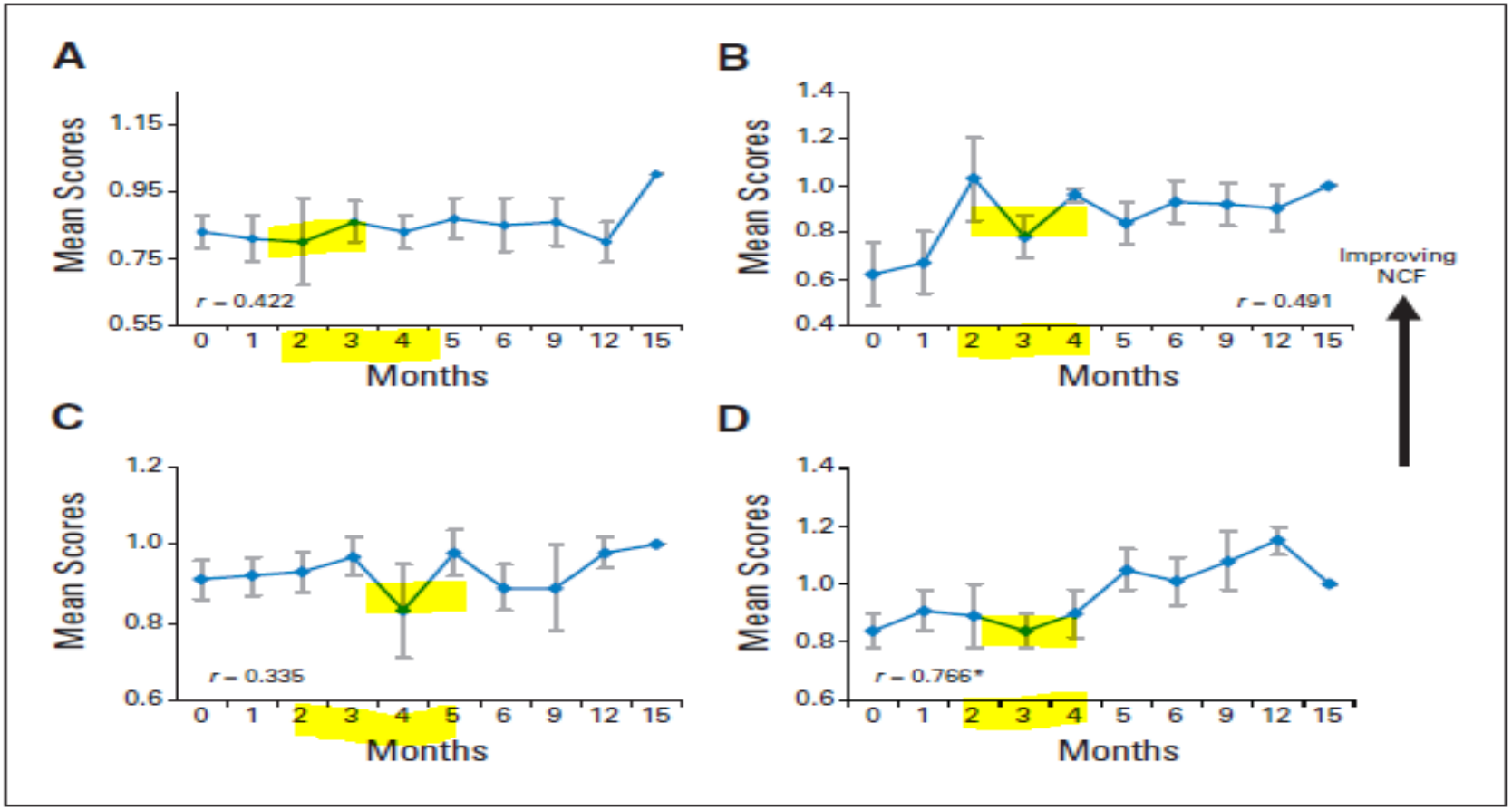
ORIGINAL REPORT

Regression After Whole-Brain Radiation Therapy for Brain Metastases Correlates With Survival and Improved Neurocognitive Function

Jing Li, Soren M. Bentzen, Markus Renschler, and Minesh P. Mehta

- **NCF is stable or improved in long-term survivors (>4months).**
- **Tumor progression adversely affects NCF more than WBRT does.**





(A) Recall, (B) delayed recall, (C) recognition, and (D) controlled oral word association (COWA).

Change of mean normalized NCF test scores stabilises/improves after 3-4 months in patients who were surviving at the 15th month.

Li J et al. J Clin Oncol 25(10) 2007

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

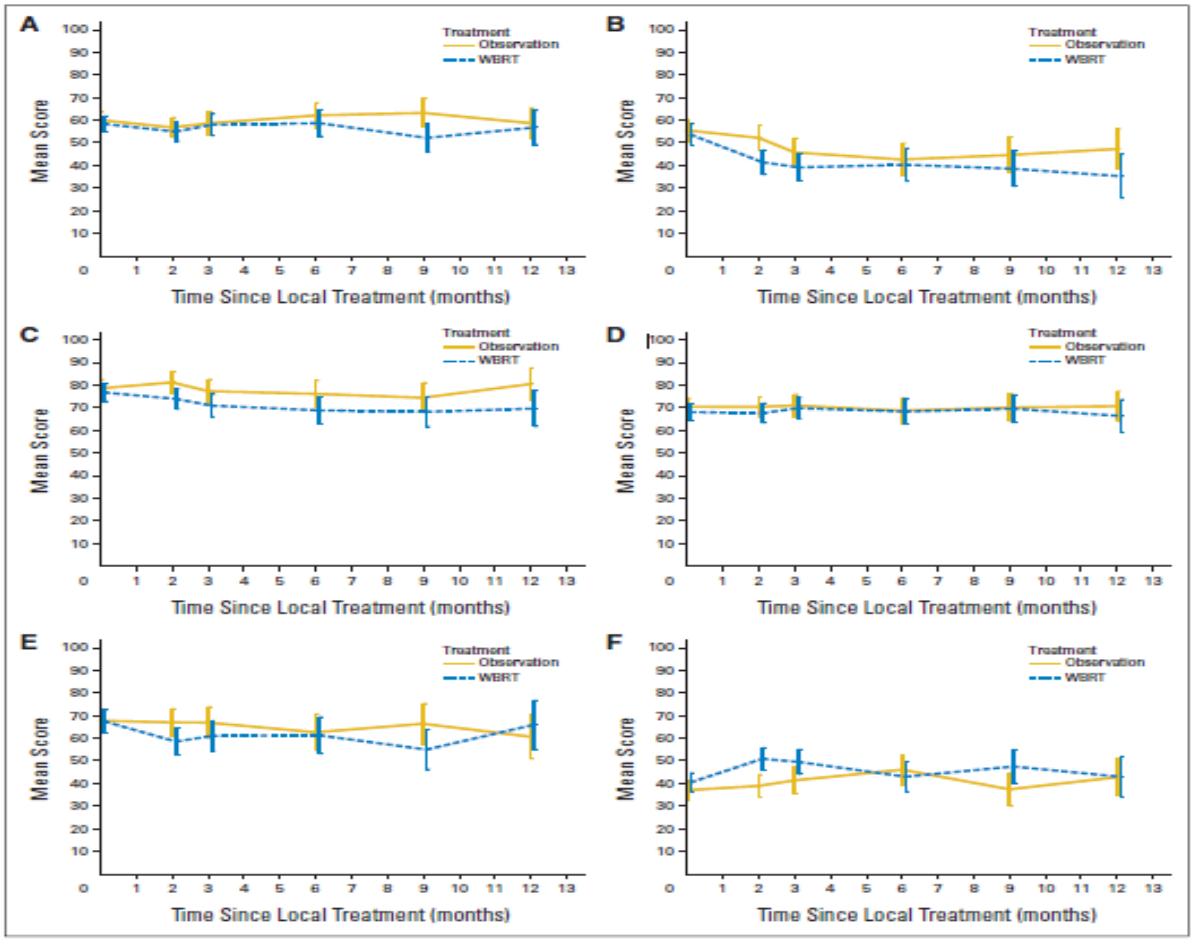


Fig 2. Changes over time in mean health-related quality of life scores: (A) global health status; (B) physical functioning; (C) cognitive functioning; (D) emotional functioning; (E) role functioning; and (F) fatigue. Data are adjusted means from linear mixed effects modal with their 95% CIs. WBRT, whole-brain radiotherapy.

Differences in HR QoL disappear in majority of indices on 1Yr.

Soffietti R.J Clin Oncol 31(1) 2013

Radio-resistant Tumors

VOLUME 23 · NUMBER 34 · DECEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase II Trial of Radiosurgery for One to Three Newly Diagnosed Brain Metastases From Renal Cell Carcinoma, Melanoma, and Sarcoma: An Eastern Cooperative Oncology Group Study (E 6397)

Rafael Manon, Anne O'Neill, Jonathan Knisely, Maria Werner-Wasik, Hillard M. Lazarus, Henry Wagner, Mark Gilbert, and Minesh Mehta

Radiosurgery may act better in Renal cell Ca

Scope of stratification of patients for SRS alone tt

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< Previous Article | Volume 15, No. 4, e170–e177, April 2014

Radiotherapy for renal-cell carcinoma

Gert De Meerleer, Vincent Khoo, Bernard Escudier, Steven Joniau, Alberto Bossi, Piet Ost, Alberto Briganti, Valérie Fonteyne, Marco Van Vulpen, Nicolaas Lumen, Martin Spahn, Marc Mareel

Where do we stand now

1-3 metastasis(es)

SRS alone evidences:

Criticism on methodology and interpretation

Primary End point conflict

Lack of Histological stratification

Poor Local and distant brain control

But with SRS

Better neurological quality of life(Long term?)

Ability to salvage for additional lesions

Treat the Whole Lawn or Weed Selectively?

Grey areas

- Effect of histological/molecular stratification on local control
- Implication of systemic therapy as confounding factors
- The radio-resistant tumor issue
- Brain relapse and its effect on neurological QoL
- Basline neurocognitive status influencing survival
- The primary end point dilemma
- Prospective study using Radiosurgery vs WBRT alone
- Studies including single metastasis only

Mehta M J Clin Oncol.2011 Jan 10;29(2):121-4

Cost benefit dilemma

- **Hall MD et al. (Retrospective Review 2001-2007)**
- Treatment costs comparison SRS(GK) vs SRS + WBRT vs Sx+ SRS (n= 289)
- Cost of initial and all salvage therapies for brain metastases, hospitalizations, management of complications, and imaging.
- Average cost per month of median survival
  - $2412 per month for SRS alone
  - $3220 per month for SRS+WBRT
  - $4360 per month for S+SRS
- **SRS alone more cost effective.**
- **Initial management with SRS alone does not result in a higher average cost.**

J Neurosurg 2014 Dec;121 Suppl:84-90

Comparative Effectiveness Analysis of Treatment Options for Single Brain Metastasis.

- **Kimmel KT et al. (review)**
- Integrated analysis

Cost	SRS	SRS + WBRT
Clinical efficacy	SX	SX + SRS
QoL	WBRT	SX + WBRT

The choice of strategy must be individualized for patients with a single BM.

Developed ranking based choice table.

World Neurosurg.2015 Nov;84(5):1316-32.

Table 4. Efficacy of Treatments, Determined by Median Survival and Freedom from Local Recurrence

Treatment	Median Survival	Local Recurrence	Freedom from Local Recurrence
Surgery + SRS	62.8 weeks	20.0%	80.0%
SRS + WBRT	50.9 weeks	19.6%	80.4%
Surgery + WBRT	47.5 weeks	26.4%	73.6%
SRS	47.0 weeks	34.3%	65.7%
Surgery	46.8 weeks	27.3%	72.7%
WBRT	28.9 weeks	60.7%	39.3%

SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

Table 8. Method for Semiqualitative Evaluation of Treatments Based on Weight of Domains

Efficacy: Cost: QoL	1:1:1		3:1:1		1:1:3		1:3:1		3:1:3	
Description	Balanced		Preference for Efficacy		Preference for QoL		Preference for Low Cost		Efficacy and QoL Balanced & More Important Than Cost	
Most Preferable	SRS + WBRT	8	SRS + WBRT	11	SRS + WBRT	10	SRS	15	SRS + WBRT	13
	SRS	9	Surgery + SRS	15	SRS	13	WBRT	18	Surgery + SRS	18
	Surgery + SRS	11	SRS	16	Surgery + SRS	17	SRS + WBRT	18	SRS	20
	Surg + WBRT	13	Surg + WBRT	18	Surg + WBRT	20	Surgery	22	Surg + WBRT	26
	Surgery	14	Surgery	23	Surgery	23	Surgery + SRS	24	Surgery	33
Least Preferable	WBRT	14	WBRT	25	WBRT	25	Surg + WBRT	25	WBRT	37

The following equation, in conjunction with domain-specific weight factors, may be used to calculate a categorical rank coefficient (X) for each modality:

$$X = (R_{efficacy})(WF_{Efficacy}) + (R_{cost})(WF_{cost}) + (R_{QoL})(WF_{QoL})$$

where R = categorical rank (1 – 6)

WF = Weight Factor

Kimmel KT et al.World Neurosurg.2015 Nov;84(5):1316-32

The realism: Indian context

- Total no of centers having RTfacility:319

  [Latest AERB statistics 2012]

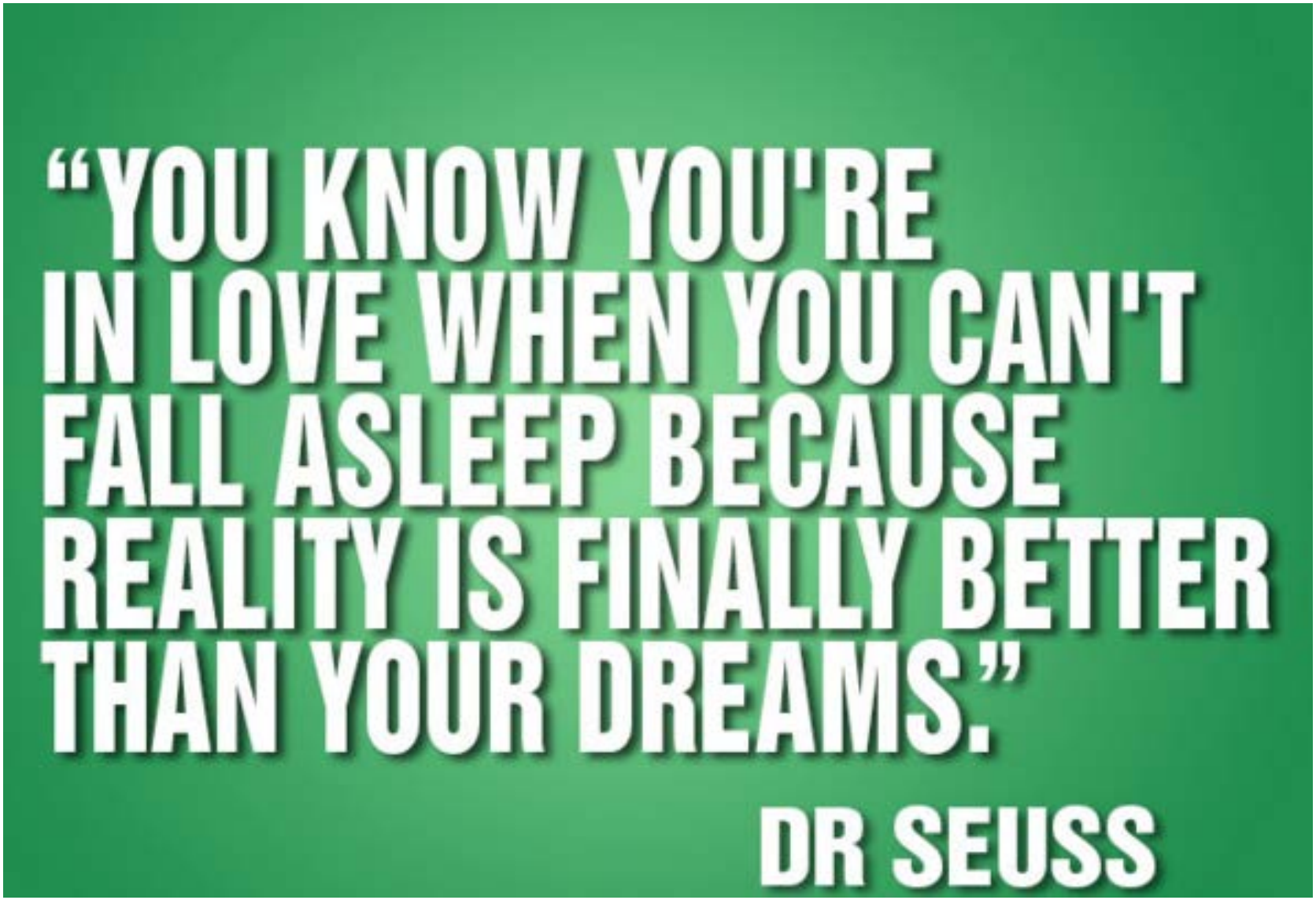
- Centers having SRS/SRT facilities:
- Varian 13(Total center 37)
- Eleckta 15(Total center 67)
- CyberKnife 5
- GammaKnife 7
- Tomotherapy 2

http://www.aerb.gov.in/
www.varian.com/en-in/oncology/treatment_locator
http://www.elektaindia.co.in/oncology/
http://cyberknifeindia.com/
http://gammaknife.in/
http://www.tomotherapy.com/centers/index

Summary

Optimism	Realism
SRS alone with close surveillance is the best treatment strategy.	Hypothesis generating Not a practice changing option yet. May consider in Oligo-metastasis setting with caution.
Neurological QoL is the key issue	Local control and distant brain control influences Neuro QoL
End of an era for WBRT.	Still a sound option

Comparative-effectiveness and cost-effectiveness data are important for future brain metastasis trials


"YOU KNOW YOU'RE
IN LOVE WHEN YOU CAN'T
FALL ASLEEP BECAUSE
REALITY IS FINALLY BETTER
THAN YOUR DREAMS."
DR SEUSS