Stereotactic Radiosurgery (SRS) for brain metastases -NO more WBRT please!

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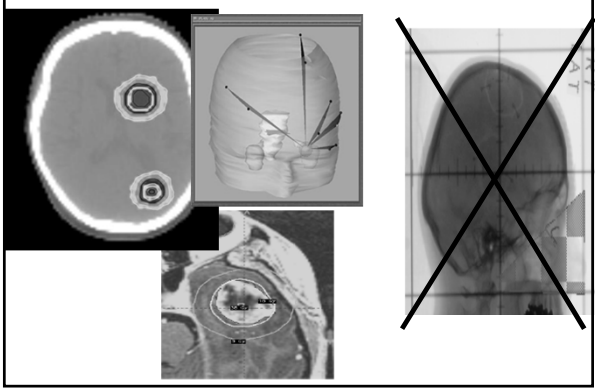
Disclosures:

Medtronic Kyphon: Honorarium for educational seminars
Elekta: Honorarium for educational seminars

SRS vs. WBRT

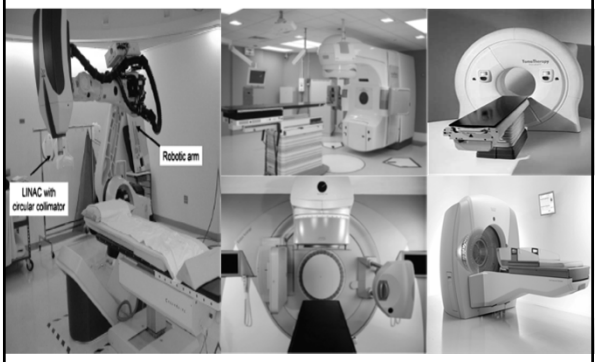


Brain SRS

- High dose of "ablative" radiation delivered to a target localized in three-dimensions with an overall end-to-end precision in the order of 1-2 mm delivered over 1 to 5 fractions

- Technical principles
  - Localize the tumor in three dimensions
    - Invasive head frame provides the reference 3D co-ordinates
      - MRI for tumor delineation
    - Immobilize the head
      - Invasive stereotactic head frame now frameless solutions
  - Radiotherapy system such that accuracy of delivery is <2 mm
    - Dedicated Linac-based systems or Gamma Knife

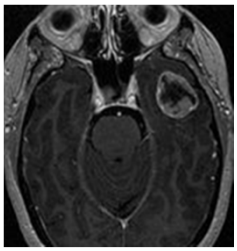
SRS Technologies

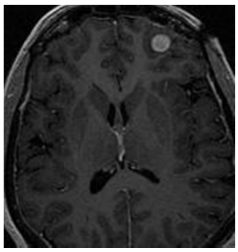


Case

- 50 year old male with known melanoma
  - 6 years later seizure
  - CT/MRI 2 brain mets
  - Staging 2 lung metastases
  - Excellent performance status
    - KPS <70 MS 3 months
    - KPS and up to 3 metastases MS 13 months
  - BRAF V600 +ve

Case





Case

- Management:
  - WBRT
  - SRS alone
  - WBRT+SRS boost
  - Surgery +WBRT
  - Surgery alone
  - Chemo/Targeted agent alone

  - Most debate between SRS alone vs. WBRT+SRS
  - Do we need the WBRT?

What do we know about the toxicities of WBRT?

Toxicity of WBRT vs. no WBRT: NSCLC PCI- RCT

VOLUME 29 · NUMBER 3 · JANUARY 20 2011
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Trial of Prophylactic Cranial Irradiation Compared With Observation in Patients With Locally Advanced Non–Small-Cell Lung Cancer: Neurocognitive and Quality-of-Life Analysis

Alexander Sun, Kyounghwa Bae, Elizabeth M. Gore, Benjamin Movsas, Stuart J. Wong, Christina A. Meyers, James A. Bonner, Steven E. Schild, Laurie E. Gaspar, Jeffery A. Bogart, Maria Werner-Wasik, and Hak Choy

Sun A, Bae K, Gore E et al. JCO 29(3);279-286.2010

Toxicity of WBRT vs. no WBRT: NSCLC PCI RCT

- Closed early due to accrual-Primary endpoint was OS
- 340 patients evaluated with Stage III NSCLC
  - 163 treated with WBRT vs. 177 Observed
- Hopkins verbal learning test (HVLT)
  - Validated and reliable assessment of memory
- Results:
  - OS/DFS not different
  - PCI recurrence rate of 8% vs. 18% in observation arm at 1 year
  - HVLT outcomes:

Toxicity of WBRT vs. no WBRT: NSCLC PCI- RCT

Table 4. Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index

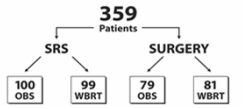
Component by Time Point	PCI				Observation					
	Deterioration		No Deterioration		Deterioration		No Deterioration			
	No.	%	No.	%	No.	%	No.	%	*P**	Adjusted *Pt*
3 months										
Recall	28	45	34	55	10	13	66	87	< .001	< .001
Delayed recall	25	44	32	56	7	10	64	90	< .001	< .001
6 months										
Recall	11	19	46	81	3	5	58	95	.02	.045
Delayed recall	8	15	44	85	8	14	50	86	.81	.81
12 months										
Recall	10	26	28	74	3	7	42	93	.01	.03
Delayed recall	10	32	21	68	2	5	38	95	.003	.008

8% recurrence rate **18% recurrence rate**

Sun A, Bae K, Gore E et al. JCO 29(3);279-286.2010

QOL: WBRT vs no WBRT

- QOL analysis (EORTC QLQC30) from the EORTC study randomizing following SRS or Surgery to WBRT vs. observation



  - Patients receiving WBRT had significantly worst QOL scores overall
  - Despite lower risk of brain relapse

Soffietti et al. JCO, 2013.

Memantine: Neuroprotective Drug

Neuro-Oncology 15(10):1429–1437, 2013.
doi:10.1093/neuonc/not114
Advance Access publication August 16, 2013

NEURO-ONCOLOGY

Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial

Paul D. Brown, Stephanie Pugh, Nadia N. Laack, Jeffrey S. Wefel, Deepak Khuntia, Christina Meyers, Ali Choucair, Sherry Fox, John H. Suh, David Roberge, Vivek Kavadi, Soren M. Bentzen, Minesh P. Mehta, and Deborah Watkins-Bruner for the Radiation Therapy Oncology Group (RTOG)

Brown et al. Neuro-Oncology, Oct 2013, 1429-1437.

Memantine

- RCT: Memantine for 6 months vs placebo (508 patients) in patients receiving WBRT

- Standardized neurocognitive testing with HVLT:
  - Significant benefits to memantine
    - Time to neurocognitive decline prolonged (p=0.01)
    - At 6 months probability of cognitive function failure 53.8% vs. 64.9% in placebo arm
    - Therefore one can conclude that WBRT adversely affects neurocognition!

Neurocognitive outcomes for SRS vs. WBRT + SRS

24%

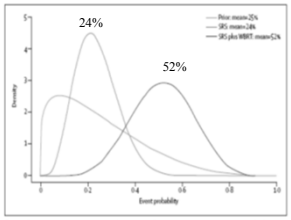
Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

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

www.thelancet.com/oncology Vol 10 November 2009

Multiple Brain Mets: SRS vs. WBRT + SRS

- Chang RCT:
- 58 patients with 1-3BM:
  - SRS alone vs. SRS+ WBRT
  - Primary endpoint:
    - Neurocognitive changes
    - HVLT:
      - Total recall @ 4months
    - 5 point drop is a failure



- 18% absolute difference in the 2 arms favoring SRS alone

Potential benefits of SRS alone

- Tolerate treatment better with less fatigue, appetite loss, less steroid dependence
- Chemotherapy delays were minimized
- Patients with SRS alone tolerated more chemo cycles

Summary

- If you radiate a normal brain then you cause memory damage
- It is the WBRT and not recurrent disease that impairs function
- WBRT impacts QOL negatively
- Strategies using drugs or hippocampal avoidance have been shown to lessen the damage induced by WBRT
  - Proof of principle that WBRT is toxic
- SRS vs. WBRT plus SRS
  - SRS better strategy to preserve neurocognitive function

Best way to spare the brain from radiation toxicity is not to treat normal brain at all and treat with SRS Alone!

Impact of tumor control/survival with WBRT?

RCT: SRS alone vs WBRT+SRS

- 3 RCT evaluating SRS vs. WBRT+SRS for patients presenting with 1-4 brain metastases

RCT 1-4 BM

Table 1. Summary of the Phase III Randomized Controlled Studies Selected for this Meta Analysis

RCT	% Single Brain Mets	Performance Status	Tumor Size	Primary Endpoint	Local Control	Distant Control	OS
Aoyama:[7] SRS (n = 67) vs WBRT + SRS (n = 65)	49% vs. 48%	52% KPS 90-100 vs. 66% KPS 90-100	Median: 1.3 cm (0.2-3.0 cm) vs. 1.4 cm (0.2-3.0cm)	Brain tumor recurrence[b]	72.5% vs 88.7% at 1 y (P = .002)	36.3% vs 58.5% at 1 y (NSIG)	28.4% vs 38.5% at 1 y (NSIG)
Chang:[8] SRS (n = 30) vs WBRT + SRS (n = 28)	60% vs. 54%	100% KPS ≥70 (each arm)	Median TV: 1.4 cc (0.1- 20) vs. 2.3 cc (0.05-27)	Neuro-cognition: HVLT at 4 months	67% vs 100% at 1 y (P = .012)	45% vs 73% at 1 y (P = .02)	63% vs 21% at 1 y (P = .003)
Kocher:[9] SRS (n = 100) vs WBRT + SRS (n = 99)	68% vs. 66%	100% WHO status 0-2 (in each arm)	Median: 2.0 cm (0.4-4.0 cm) vs. 1.8 cm (0.5-3.4 cm)	Duration of functional independence	69% vs 81% at 2 y (P = .008)	52% vs 67% at 2 y (P = .023)	NSIG[a]

Tsao, Xu, Sahgal. Cancer. 2011.

Meta-Analysis

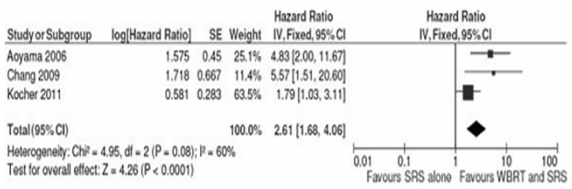
Original Article

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

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

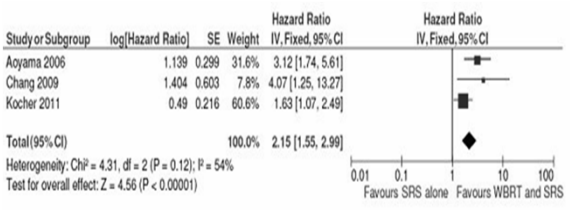
Tsao, Xu, Sahgal. Cancer. 2011. Best paper of 2011 in metastases by EANO

1-4 Brain Mets: Local Control



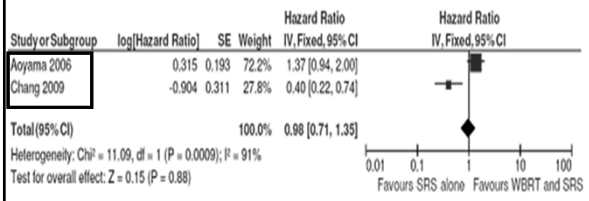
Tsao, Xu, Sahgal. Cancer. 2011. Best paper of 2011 in metastases by EANO

1-4 Brain Mets: Distant Brain Control



Tsao, Xu, Sahgal. Cancer. 2011. Best paper of 2011 in metastases by EANO

1-4 Brain Mets: Overall Survival



Tsao, Xu, Sahgal. Cancer. 2011. Best paper of 2011 in metastases by EANO

SRS vs. WBRT + SRS for 1 to 4 Brain Metastases Individual Patient Data (IPD) Meta-Analysis

Arjun Sahgal[1,2], Hidefumi Aoyama M.D. Ph.D.[3], Martin Kocher M.D.[4], Binod Neupane Ph.D.[5], Sandra Collette Ph.D.[6], Masao Tago M.D.[7], Prakesh Shah M.D.[8], Joseph Beyene Ph.D.[5], Eric Chang M.D.[10,11]

[1]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada
[2]Princess Margaret Cancer Centre, University of Toronto, Toronto, Canada
[3]Niigata University Graduate School of Medical and Dental Sciences, Nigita, Japan
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[7]Teikyo University, Mizonokuchi Hospital, Kanagawa, Japan
[8]Mount Sinai Hospital, University of Toronto, Canada
[10]University of Southern California, Los Angeles, California, USA
[11]MD Anderson Cancer Center, Houston, Texas, USA

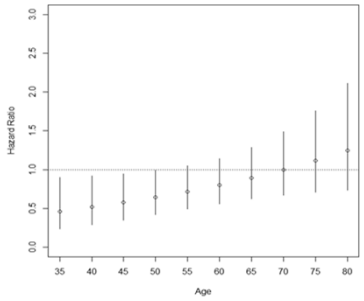
Methods

- IPD meta-analysis of the 3 RCTs (raw patient data obtained) to determine the effect of treatment (SRS vs. WBRT+SRS) on OS, DBC and LC
  - Adjusted *a priori* for co-variates:
    - Age, RPA and number of brain metastases (1 vs ≥2)
- Restricted inclusion to those with RPA 1 or 2 and KPS ≥70
  - Final cohort: 364 of 389 patients
  - Median follow-up 9.2 months
    - SRS alone 10.1 months, WBRT+SRS 8.6 months

Results: Baseline characteristics

Factor	Total N=364 patients	SRS alone cohort N=186	WBRT+SRS cohort N=178	P-value
SRS/WBRT+SRS	186/178 (51%/49%)	186 (100%)	178 (100%)	—
Female/Male	128/236 (35%/65%)	65/121 (35%/65%)	63/115 (35%/65%)	0.9999
Median Age, yr	62	62	61	0.3231
Age ≤50	68 (19%)	31 (17%)	37 (21%)	0.3823
RPA1/RPA2	149/215 (41%/59%)	73/113 (39%/61%)	76/102(43%/57%)	0.5738
KPS ≥70	364 (100%)	186 (100%)	178 (100%)	—
1 met/2-4 mets	217/147 (60%/40%)	111/75 (60/40)	106/72(60/40)	0.9999
Extra-cranial Mets	202 (56%)	100 (54%)	102 (58%)	0.5598
Cancer type				
Lung	214 (59%)	109 (59%)	105 (59%)	
Breast	43 (12%)	22 (12%)	21 (12%)	0.9422
Kidney	24 (7%)	11 (6%)	13 (7%)	
Other	83 (23%)	44 (24%)	39 (22%)	
Local Failure	72 (21%)	51 (28%)	21 (12%)	0.0004
Distant Brain Failure	156 (44%)	98 (54%)	58 (34%)	0.0001
Death by study completion	314 (86%)	157 (84%)	157 (88%)	0.3688

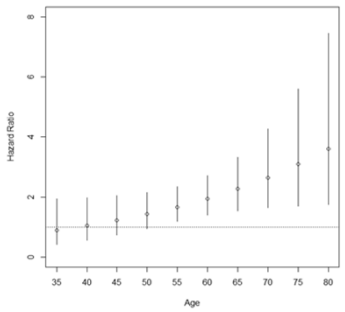
Hazard Ratios for SRS alone and Overall Survival



Age	HR (95% CI)
35	0.46 (0.24, 0.90)
40	0.52 (0.29, 0.92)
45	0.58 (0.35, 0.95)
50	0.64 (0.42, 0.99)
55	0.72 (0.49, 1.05)
60	0.80 (0.56, 1.14)
65	0.90 (0.62, 1.29)
70	1.00 (0.67, 1.49)
75	1.12 (0.71, 1.76)
80	1.24 (0.73, 2.11)

- Overall survival significantly increased with SRS alone in patients ages 35-50 relative to their age matched cohort treated with WBRT+ SRS

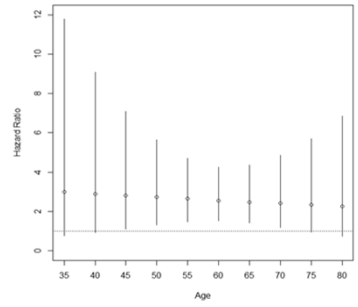
Hazard Ratios for SRS alone and Distant Brain Failure



	Age	HR.95CI
1	35	0.90 (0.42, 1.94)
2	40	1.05 (0.56, 1.98)
3	45	1.23 (0.73, 2.05)
4	50	1.43 (0.95, 2.15)
5	55	1.67 (1.19, 2.35)
6	60	1.95 (1.40, 2.71)
7	65	2.27 (1.55, 3.33)
8	70	2.65 (1.64, 4.27)
9	75	3.09 (1.70, 5.61)
10	80	3.60 (1.75, 7.44)

- Distant brain failure was no greater with SRS alone for age ≤50 relative to their age matched cohort treated with WBRT+ SRS

Hazard Ratios For SRS alone and Local Failure



Age	HR (95% CI)
35	2.99 (0.76, 11.79)
40	2.9 (0.93, 9.09)
45	2.81 (1.12, 7.08)
50	2.73 (1.32, 5.64)
55	2.64 (1.49, 4.7)
60	2.56 (1.54, 4.26)
65	2.48 (1.42, 4.35)
70	2.41 (1.19, 4.86)
75	2.33 (0.95, 5.7)
80	2.26 (0.75, 6.85)

- Age was not a treatment effect modifier and overall reduced risk of local failure

Summary of Results

Outcome	Aggregate meta-analysis*	IPD Meta-analysis
Overall survival	No survival benefit for WBRT+SRS	SRS alone favored for age ≤50
Local control	WBRT+SRS favored	WBRT+SRS favored
Distant brain control	WBRT+SRS favored	WBRT+SRS favored but not in patients age ≤50

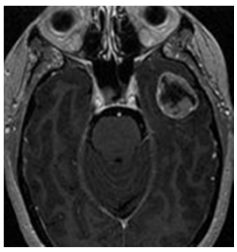
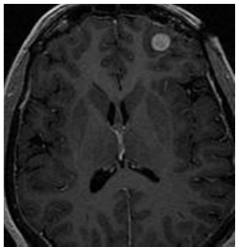
- Conclude: OS results support SRS alone and not WBRT + SRS for patients age ≤ 50

Hypothesis

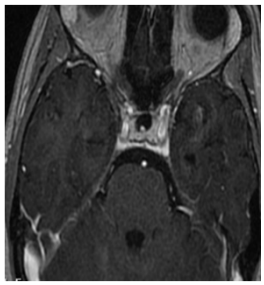
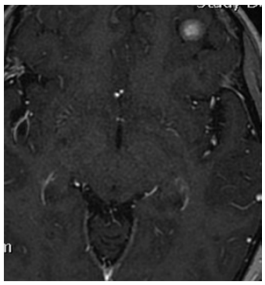
- Recent RCT's have confirmed the detrimental effects of WBRT on both neurocognition and quality of life (Chang et al., Sun et al, Soffietti et al.):
  - OS favoring SRS alone in younger patients (age ≤50) may be explained by the lack of benefit of WBRT with respect to distant brain control while exposing them to the toxicities of worse memory function and harming QOL which compromised survival

Chang et al. Lancet Oncology, Lancet Oncol. 2009 Nov;10(11):1037-44.
Sun et al. J Clin Oncol. 2011 Jan 20;29(3):279-86.
Soffietti et al. J Clin Oncol. 2013 Jan 1;31(1):65-72.

Case

5 years later: SRS alone

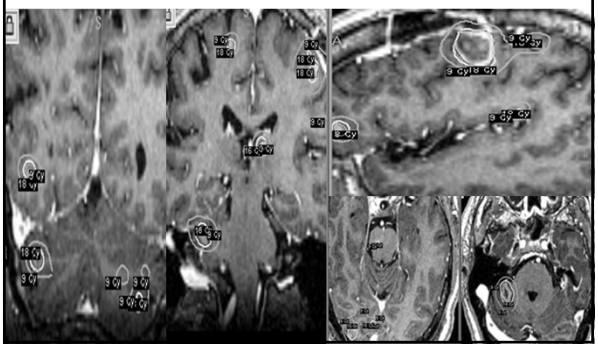
Multiple Metastases:

SRS alone for more than 4 mets

Multiple Metastases: Why now?

- Dogma of >4 metastases had to be treated WBRT
  - Thought risk of new mets developing 100%
  - Data emerging showing similar rates of new metastases as compared to patients with 1 to 4 mets (MRI era)
- Technical advances allowing several metastases treated with SRS alone in a single session are now available and practical
- Early on in this experience: data emerging (retrospective)
- Randomized trials for 5 or more mets ongoing

34 Mets including a brainstem lesion and a cavity all treated SRS one session:
No WBRT



Drug Therapy Alone for Melanoma Brain Metastases

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

www.thelancet.com/oncology Vol 13 May 2012

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

12 WEEKS POST

	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
CNS				
CR	0	0	1 (5%)	1 (5%)
PR	8 (16%)	8 (16%)	0	0
SD	4 (8%)	5 (10%)	1 (5%)	1 (5%)
PD†	39 (76%)	38 (75%)	19 (90%)	19 (90%)
Unknown	0	0	0	0

Asymptomatic no dexa **Symptomatic on dexa**

Interpretation Ipilimumab has activity in some patients with advanced melanoma and brain metastases, particularly when metastases are small and asymptomatic. The drug has no unexpected toxic effects in this population.

Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial

Georgina V Long, Uwe Trefzer, Michael A Davies, Richard F Kefford, Paolo A Ascierto, Paul B Chapman, Igor Puzanov, Axel Hauschild, Caroline Robert, Alain Algazi, Laurent Mortier, Hussein Tawbi, Tabea Wilhelm, Lisa Zimmer, Julie Switzky, Suzanne Swann, Anne-Marie Martin, Mary Guckert, Vicki Goodman, Michael Streit, John M Kirkwood*, Dirk Schadendorf*

www.thelancet.com/oncology Vol 13 November 2012

	Cohort A	Cohort B
Val600Glu BRAF mutant	**No prior XRT**	**Prior XRT**
Intracranial duration of response*	20·1 (12·1-NR)	28·1 (20·1-28·1)
Progression-free survival	16·1 (15·7-21·9)	16·6 (15·9-23·7)
Overall survival	33·1 (25·6-NR)	31·4 (25·7-NR)
Val600Lys BRAF mutant		
Intracranial duration of response*	12·4 (NR-NR)	16·6 (NR-NR)
Progression-free survival	8·1 (3·1-16·1)	15·9 (7·9-22·4)
Overall survival	16·3 (6·9-22·4)	21·9 (15·3-NR)

Data are median number of weeks (95% CI). NR=not reached. *Duration of response in those with an intracranial partial or complete response.

Table 3: Duration of response

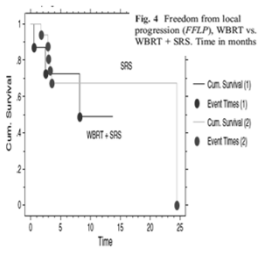
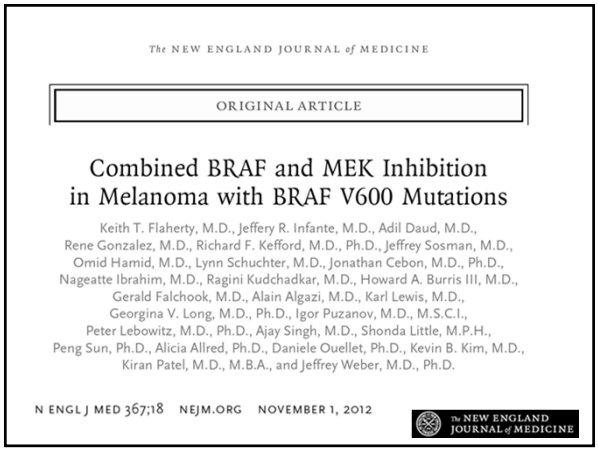


Fig. 4 Freedom from local progression (*FFLP*), WBRT vs. WBRT + SRS. Time in months

Lo et al. 2011, JRON

Logical NEXT Step:

SRS alone
plus
Dabrafenib
Combined with
Tramitinib



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations

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Conclusions

- Patients with brain metastases are living longer
- SRS alone will be the standard of care for all patients as we learn more and more that WBRT is toxic to memory and QOL
- New targeted melanoma agents can penetrate the BBB
  - Duration of response questionable
  - Treat gross disease with SRS and use the drug to enhance both the SRS effect and control micro-metastatic brain metastases to reduce the distant brain relapse