Place of tumor bed radiosurgery and focal radiotherapy following resection of brain metastases: A new paradigm

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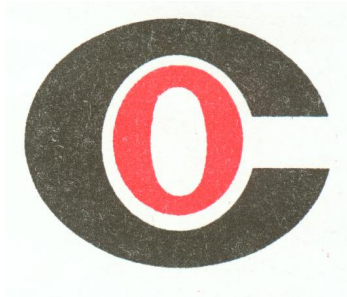


Outline of the presentation

1. Tumor bed radiotherapy in the context of the current standard – WBRT

- Survival
- Local control
- Neurocognitive function

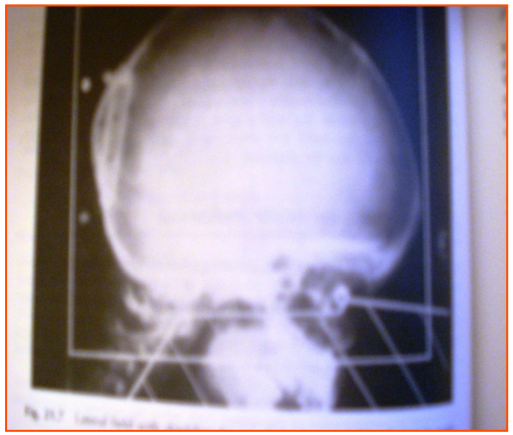
2. Techniques of tumor bed radiotherapy and clinical trials

Outline of the presentation

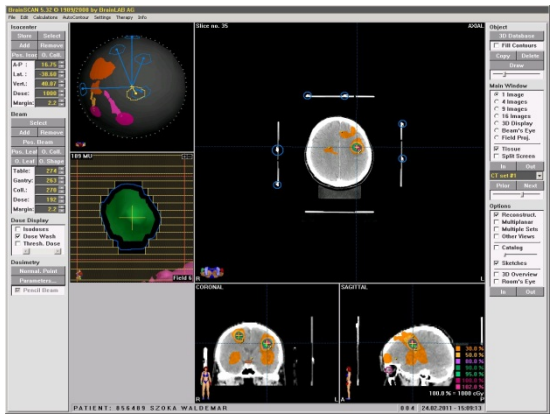
- **TUMOR BED RADIOSURGERY:**
- Alternative to WBRT
- Intensification of adjuvant WBRT
- After salvage craniotomy after failure to the previous WBRT

Treatment following resection of brain metastases

- Current standard: WBRT



- Emerging standard: Radiotherapy limited to tumor cavity without WBRT



Rationale for Tumor bed RT

- Randomized studies: – Local treatment vs. Local treatment + **WBRT**

- 1. Patchell (JAMA, 1998): 95 pts; Surgery vs. Surgery + WBRT; 10.2 m vs. 11.4 m; p=NS.
- 2. Aoyama (JAMA, 2006): 132 pts; Radiosurgery vs. Radiosurgery + WBRT; 8 m vs. 7.5 m; p=NS

- 3. Muacevic (J Neurooncol, 2008): 64 pts; Radiosurgery vs. Surgery+WBRT; 10.3 m vs. 9.5 m; p=NS

Rationale for Tumor bed RT

Randomized studies: – Local treatment vs. Local treatment + **WBRT**

•4. Chang (Lancet Oncol, 2009); 58 pts; Radiosurgery vs. Radiosurgery+WBRT; 15.2 m. vs. 5.7 m.; $p<0.05$

•5. Kocher (JCO, 2010); 359 pts; Radiosurgery or Surgery vs. Radiosurgery or Surgery + WBRT; 10.9 m. vs. 10.7 m.; p=NS

Rationale for Tumor bed RT

In conclusion:

No influence of WBRT on survival has been demonstrated.

WBRT after brain metastases surgery

In all randomized studies, WBRT was related to:

- **improvement of local control of locally treated brain metastases**
- **improvement of local control within whole brain**
- **reduction or trend to reduction of number of neurological deaths**

WBRT and neurocognitive functions

- Positive effect

via

improvement of local control within whole brain

- Negative effect

via

toxicity (subacute effect – *somnolence syndrome* and late effect - vascular damage and persistent brain damage)

WBRT: negative neurocognitive effect

- Recognized effect of the size of dose per fraction and irradiated volume

- Retrospective studies

- Chang (2009): prospective study: terminated after inclusion of 58 pts.

Negative impact of WBRT on neurocognitive function: prospective data

Lancet Oncol 2009; 10: 1037–44

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

Negative impact of WBRT on neurocognitive function: prospective data

(Chang's study)

	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**

Impairment of Total recall stable up to 6 mo.

Study terminated: predictable result.

Negative impact of WBRT on neurocognitive function: prospective data (Chang's study)

Negative impact of WBRT on neurocognitive function:

- Survival: RS: 15.2 m; RS+WBRT: 5.7 m; $p<0,05$
- Local control within one year: RS - 67%; RS+WBRT - 100%; $p<0,05$.
- Local control in the whole brain within one year: RS - 45%; RS+WBRT: 73%; $p<0,05$

Negative impact of WBRT on neurocognitive function: prospective data

- No impact of WBRT on survival in pts with NSCLC
- Impairment in memory tests after WBRT

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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

Negative impact of WBRT on neurocognitive function: prospective data

Neurocognitive and Quality-of-Life Analysis of RTOG 0214

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 *P*†
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

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.
†Adjusted using the Hommel's method; adjustment is made within time point.

Sun et al., JCO 2011

Positive impact of WBRT on the neurocognitive function

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 5, pp. 1388–1395, 2007

0360-3016/07/$–see front matter

doi:10.1016/j.ijrobp.2007.03.048

CLINICAL INVESTIGATION **Brain**

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

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Positive impact of WBRT on the neurocognitive function

Aoyama, 2007:

Mini Mental State Examination – MMSE 110/132 pts;

No worsening by 3 points and more after 12, 24, 36 months:

WBRT+RS: 76%, 69%, 15%

RS: 59%, 52%, 52%.

Mean time to the Worsening:

WBRT+RS: 16.5 months

RS: 7.6 months (p=0,05)

Influence of WBRT on patients' functioning (Performance Status - PS)

- **WBRT improves local control within brain w/out impact on survival**
- **At the price of worse neurocognitive function?**

- **It is possible with omission of WBRT after local treatment to avoid deterioration of the PS despite increased risk of brain relapse by the use of MRI to detect early, asymptomatic recurrence?**

Influence of WBRT on patients' functioning (Performance Status - PS)

- **EORTC study (Kocher, 2010): 359 pts randomized to local treatment (S or RS) vs. S or RS + WBRT;**

- **<u>WBRT omission did not increase a proportion of pts with worsening of PS of 2 points and more (loss of functional independence).</u>**

Influence of WBRT on patients' functioning (Performance Status - PS)

- **Conclusion (from EORTC study):**

- **<u>When using local treatment - RS or surgery, WBRT may be omitted under condition of strict MRI monitoring*</u>**

- **Every 2-3 months*

Other findings from EORTC study

- Main site of failure for patients treated with surgery only was surgical cavity (59%; 95% CI, 48% to 71%)

  WBRT reduced the probability of the relapse in surgical bed to 27% (95% CI, 31% to 53%), $p<0.001$.

- Failures at new sites in the brain reached with surgery alone 42% (95% CI, 31% to 53%)

  WBRT reduced these events to 23% (95% CI, 14% to 33%), $p=0.008$.

Surgery for brain metastases and radiotherapy of tumor bed

- New method (and increasing trend) in the treatment of brain metastases

- <u>Rationale for its use:</u>

1. High risk of the relapse in the surgical cavity (about 60%)
2. Data on the toxicity of WBRT
3. Lack of impact of WBRT on survival.
4. Probable succesful salvage of brain relapses with strict MRI monitoring.

Surgery for brain metastases and radiotherapy of tumor bed

- Eight retrospective studies (Kelly, IJROBP 2012):

1. About 80% of local control in tumor bed
2. About 45% of relapses in new sites in the brain
3. Monitoring with MRI: early detection allows reducing risk of neurological death

Surgery + RS to tumor bed

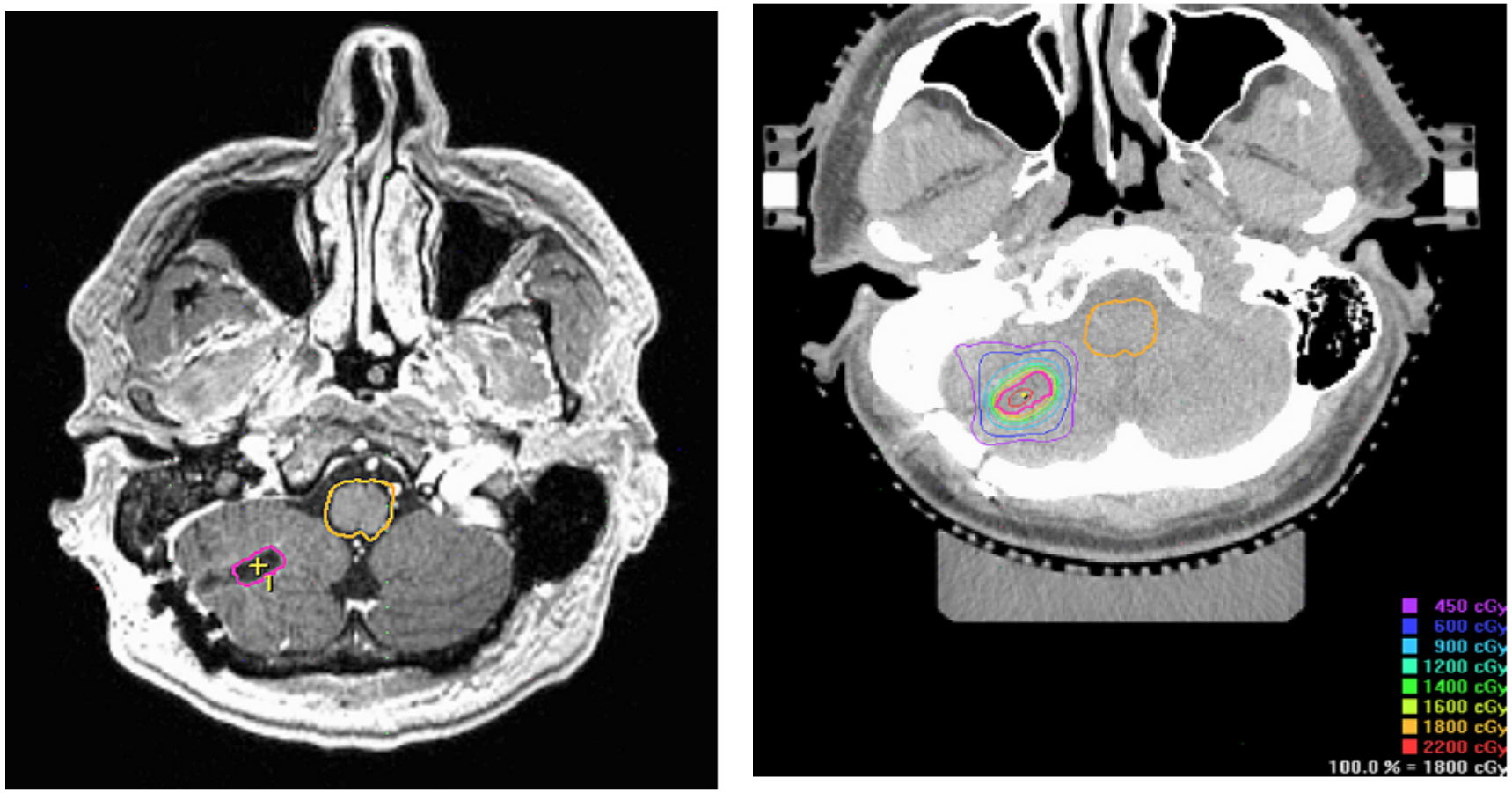
Table 1
Reported series of tumor bed radiosurgery.

Institution	Year	Patients	% GTR	% single metastases	Crude LC	1y LC	Median OS	% new metastases	CNS control	Complications
Series of tumor bed radiosurgery alone										
BNI/UCSF (25)	2003	61	52%	100%	70%	61%	14.9	34%	38% 1y	2% necrosis
Allegheny (18)	2006	17	NR	65%	NR	NR	19.6 for solitary	NR	NR	NR
MSKCC (16)	2006	25	NR	100%	84%	35%	12.0	24%	38% 1y	4% necrosis
Osaka (13)	2007	21	100%	76%	76%	82%	20	48%	NR	0%
Stanford (20)	2008	72	85%	65%	86% (per cavity)	79%	15.1	49%	NR	15% tumor associated edema, 4% necrosis
William Beaumont (17)	2008	35	NR	51%	94%	NR	65% at 1y	33% at 1y	NR	6% necrosis
UC Irvine (12)	2008	30	NR	43%	87%	82%	12	63%	22% 1y	26.6% grade 2
Pittsburgh/Sherbrooke (15)	2008	40	80%	68%	73%	74%	13	54%	NR	5% symptomatic T2 changes
Virginia (11)	2009	47	100%	28%	94%	NR	10	87%	4% crude	11% tumor associated edema
Washington University (14)	2009	15	80%	80%	73%	77%	20	60%	33% crude	NR
Total		363	80%	67%	79%	70%	14.2	52%		
Tumor bed radiosurgery and whole-brain radiotherapy										
McGill	2010	38	95%	100%	92%	90%	17.6	13%	89% crude, 86% 1y	5% necrosis
Tumor bed radiosurgery following surgical salvage of whole-brain radiotherapy failures										
Wake Forest (26)	2006	79	NR	NR	95%	NR	17	NR	NR	4% necrosis

GTR: gross total resection, LC: local control, NR: not reported, OS: overall survival.

Roberge & Souhami, TCRT 2010; courtesy of the Authors

Surgery + Radiosurgery of tumor bed



From Kelly, IJROBP 2012

Purpose of the Polish study: CAVITY

- *„Does omission of the WBRT after brain metastases surgery and irradiation of tumor bed only make the remaining life better?”*

- Purpose: Comparison of neurological and neurocognitive functions after surgery of brain metastases between WBRT and tumor bed RS arms .

CAVITY: end-points

Survival free of event defined as:

- Worsening of neurological status by one point or more in 5-point MRC scale

or

- Worsening of MMSE result by three or more points compared to the initial score

or

- Neurological death

CAVITY: secondary end-points

- QLQ: EORTC QLQ C-30 and brain model BN-20,
- Time to worsening of MiniMental by 3 points or more,
- KPS,
- Local control in the tumor bed,
- Local control in the brain outside tumor bed,
- Overall survival.

CAVITY: Inclusion criteria

- Pathological confirmation of malignancy in the resected brain metastasis
- Total or subtotal extent of resection in the opinion of neurosurgeon
- Single brain metastasis confirmed in the MRI
- KPS ≥70
- Life expectancy taking into account extracranial cancer extension > 6 months
- No previous brain radiotherapy
- Possible MRI monitoring
- No obstacle to start RT within 6 weeks after brain surgery
- Informed consent of patient

CAVITY: Exclusion criteria

- Dementia and CNS diseases related to the risk of the increased toxicity of WBRT
- SCLC or hematological malignancies in the resected brain metastasis
- Contraindications or no tolerance of the MRI

CAVITY: schema of the study

- Pts after brain metastasis surgery randomized to two arms:

1. Experimental arm: Stereotactic irradiation of the surgical cavity (15 Gy or 5 x 5 Gy if larger cavity or dose constraints due to the proximity of critical structures)
2. Control arm: WBRT – 30 Gy in 10 fractions

Stratification: center; KPS; presence of extracranial disease; „radioresistant" cancer (melanoma, kidney) vs. Other.

CAVITY: schema of examinations

- At baseline (before RT): EORTC QLQ-C30 and BN-20 + MiniMental test, KPS and neurologic status evaluation (MRC scale); dose of steroids.
- Eight weeks after RT and next every three months: as above + MRI of the brain.

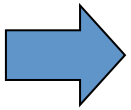
RTOG 1270/NCCTG N107C: another phase III trial comparing WBRT and stereotactic RT of the surgical cavity

1. To ascertain in patients with one to four brain metastases whether there is improved overall survival in patients who receive SRS (!) to the surgical bed compared to patients who WBRT

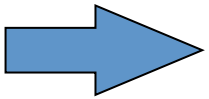
2. To ascertain whether there is less neurocognitive progression at 6 months post-radiation in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

Tumor bed radiosurgery

- Therapeutic concept which needs validation in phase III trial.

- Local control? 

Certainly worse outside tumor bed

- Survival? 

Difference hard to be demonstrated

- Neurocognitive function and Quality of Life improvement remains to be demonstrated.