

The biological rationale and potential role of radiation dose escalation in patients with brain metastases

Frank J. Lagerwaard MD PhD
Dept of Radiation Oncology
VU University medical center Amsterdam



Disclosure slide

- The Dept of Radiation Oncology of the VUmc has research agreements with Varian Medical Systems and BrainLAB AG.



	Pro's	Con's
Whole brain radiotherapy (WBRT)	Treatment of micromets	Limited local efficacy Multiple sessions Neurocognitive dysfunction Alopecia
Radiosurgery (RS)	High local control Single fraction treatment	Outgrowth of micromets
Combination (WBRT + RS)	High local control Treatment of micromet	Multiple sessions Neurocognitive dysfunction Alopecia



	% neurological death
Surgery +/- WBRT	
Hashimoto 2011	36%
Kocher 2011	28%
Muacevic 2008	29%
Patchell 1998	14%

After aggressive local treatment of BM only a minority dies of intracranial PD



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After aggressive local treatment of BM only a minority dies of intracranial PD

	% neurological death
WBRT	
Knisely 2008	27-34%
Kocher 2005	36%
Andrews 2004	27-36%
Lagerwaard 1999	44%
Mandell 1984	50%



Dose-escalation ~ Who could benefit?

Only a minority of BM pts could benefit from radiation dose-escalation

How to select these patients.....??

Prognostic classification systems.....??

	RPA	R'dam	SIR	BSBM	GPA	DS-GPA	Rades	GGs
Primary tumor control								
Extracranial metastases								
Performance status								
Age								
Interval primary-BM								
Volume BM								
Number BM								
Steroid response								
Primary tumor site								

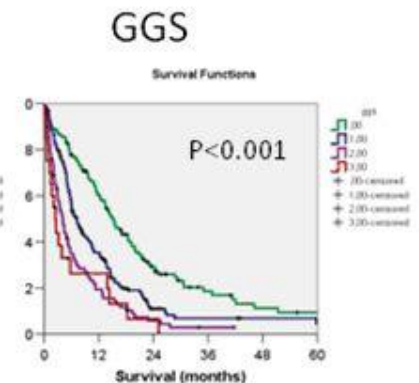
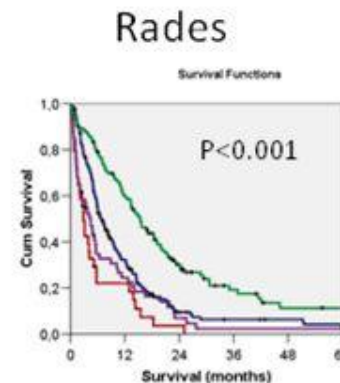
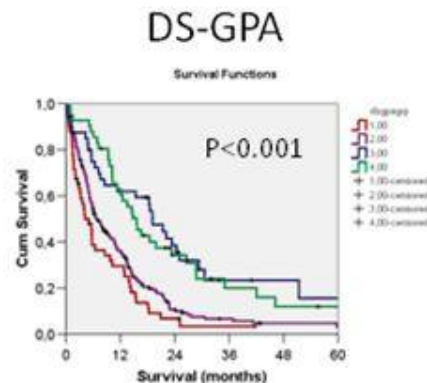
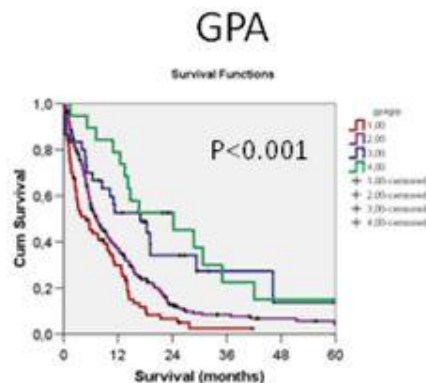
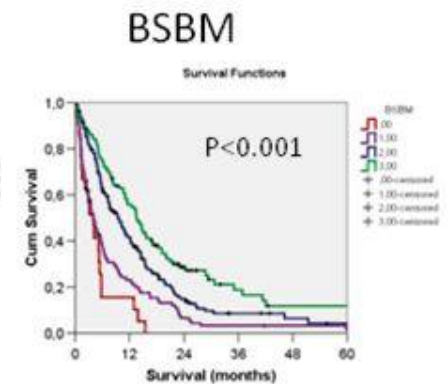
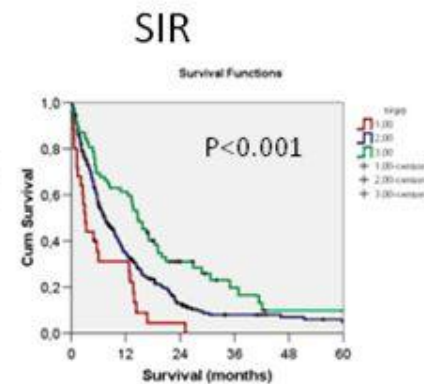
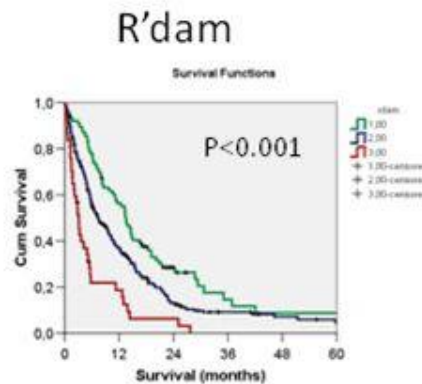
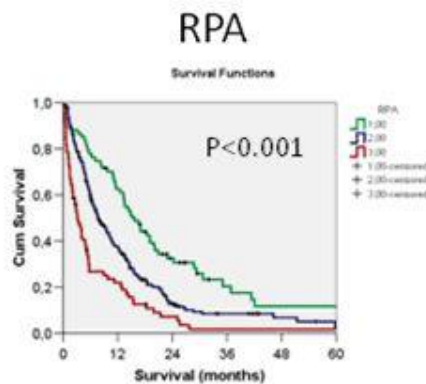


Dose-escalation ~ Who could benefit?

Only a minority of BM pts could benefit from radiation dose-escalation

How to select these patients.....??

Prognostic classification systems.....?? Only validated for OS!! Not predictive factors!!

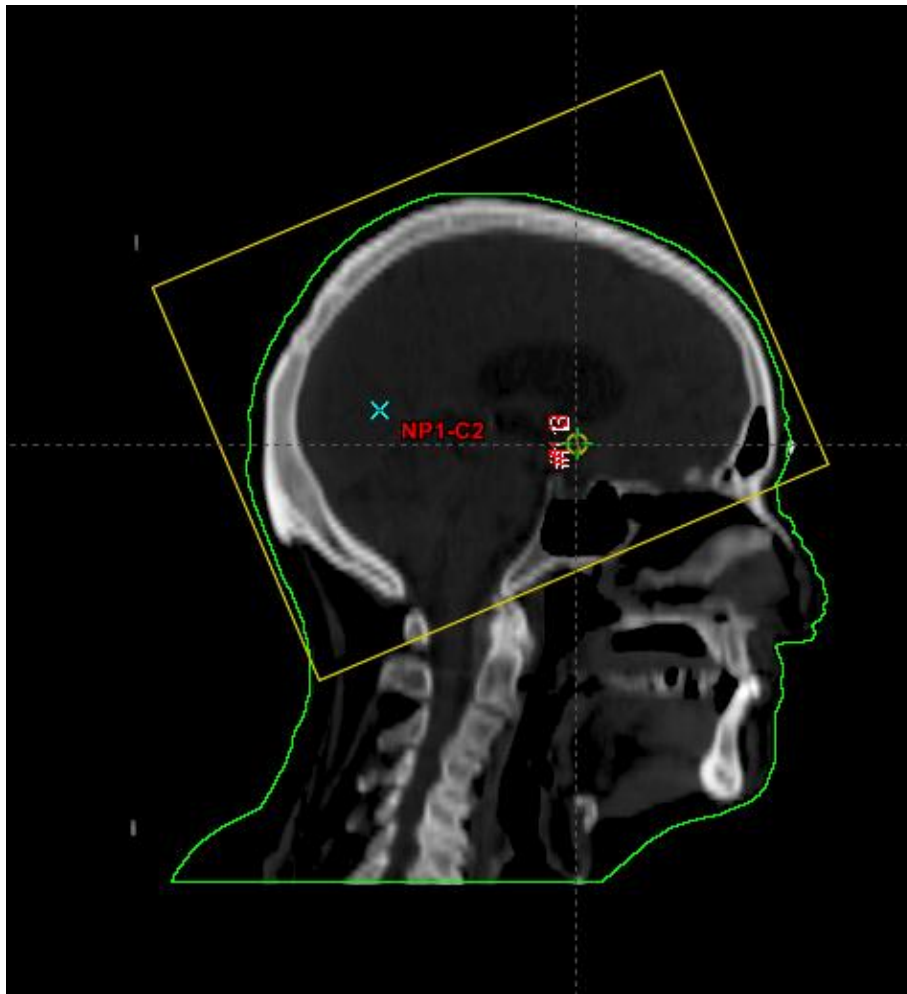


Despite lacking evidence.....

Who could at least theoretically benefit from radiation dose-escalation

- **Patients with relatively longer-term survival**
 - Performance status 0-1
 - No progressive extracranial disease
 - Limited number and size of brain metastases





Altered WBRT fractionation schemes have been attempted during past 30 years (e.g. Borgelt 1980; Borgelt 1981; Chatani 1985; Chatani 1994; Haie-Meder 1993; Harwood 1977; Kurtz 1981; Murray 1997; Priestman 1996)

- Adds to treatment duration
- Adds to toxicity
- Does it alter outcome?



Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

2012

Tsao MN, Lloyd N, Wong RKS, Chow E, Rakovitch E, Laperriere N, Xu W, Sahgal A



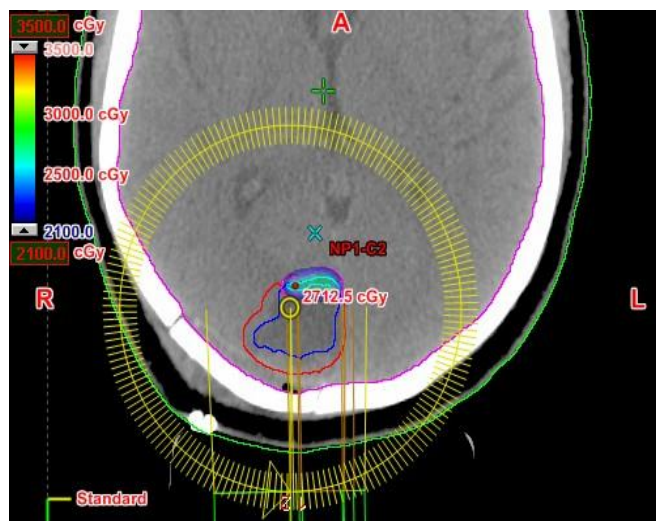
“In summary, none of the randomized controlled trials have found a benefit (in terms of overall survival or neurologic function) with altered dose-fractionation schedules as compared to standard (3000 cGy/10 or 2000 cGy/5 daily fractions).”



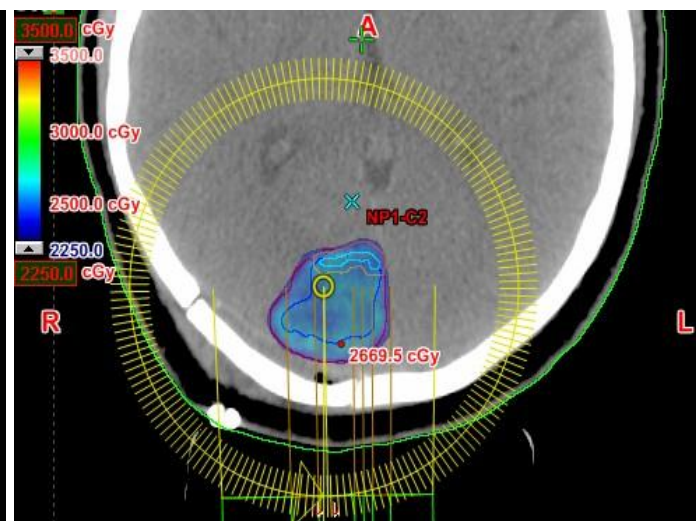
e.g. focal RS or fractionated RS after resection of brain metastasis....

Standard treatment used to be whole brain radiotherapy (20 Gy/5, or 30 Gy/10)

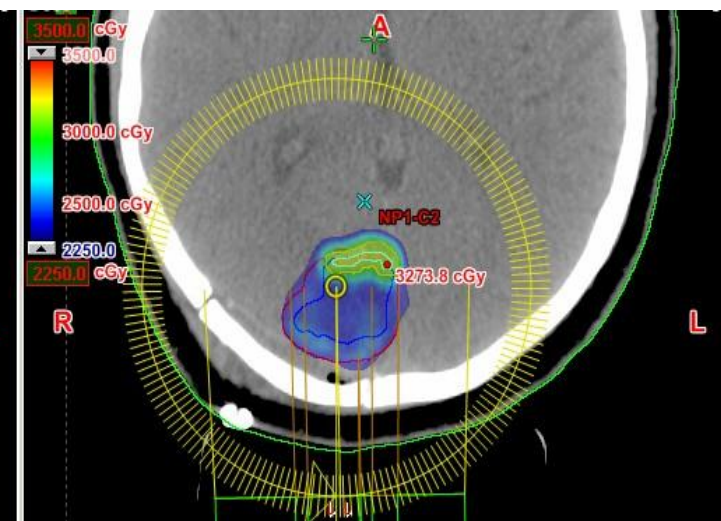
To increase radiation dose locally AND/OR prevent unwanted effects of WBRT,
more and more centers deliver focal RS following (ir)radical surgery. Dose escalation
to the macroscopic residual tumor after incomplete resection



RS to residual tumor

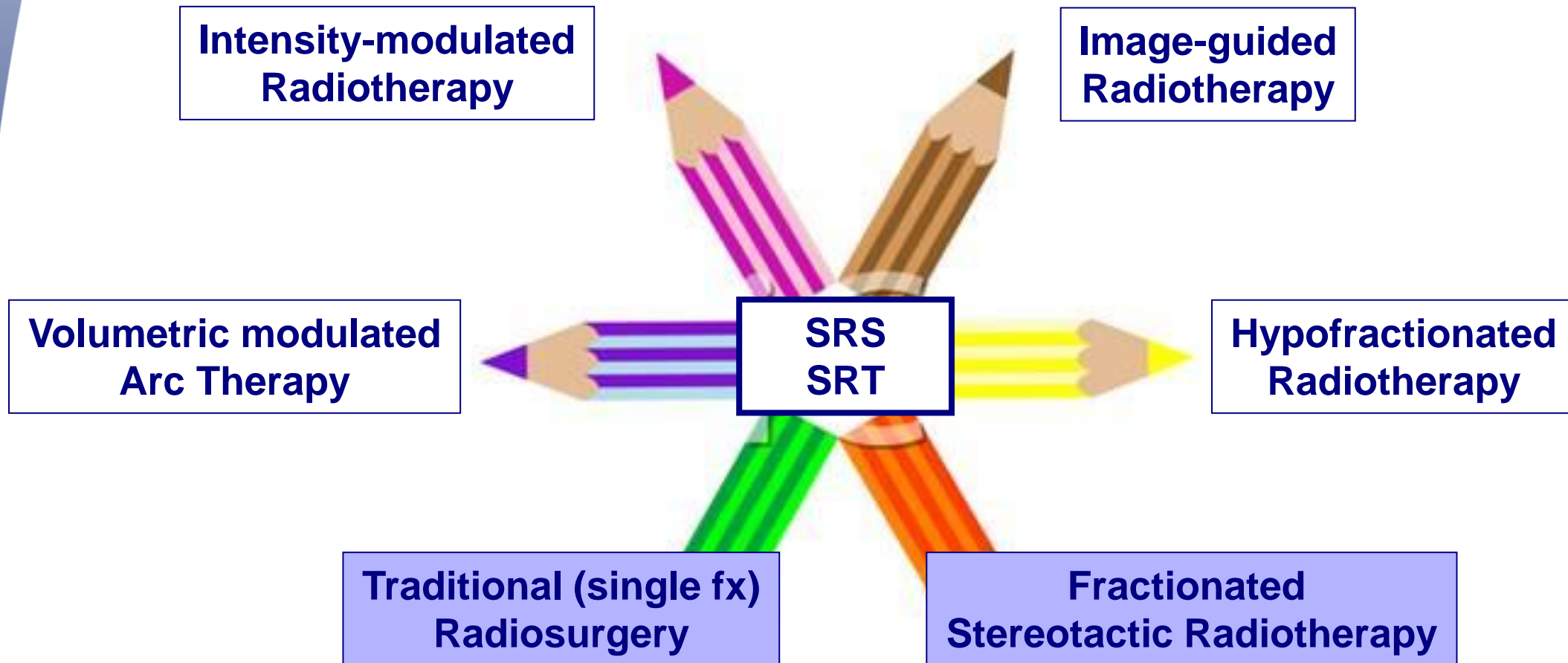


RS to resection cavity



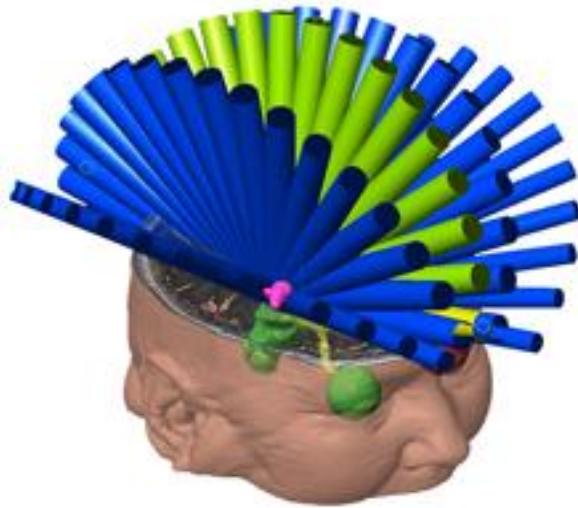
RS to resection cavity + SIB





= a form of high-precision radiotherapy, using a combination of accurate target definition, high-precision patient (or tumor) positioning, and multiple beams or arcs to deliver treatment.

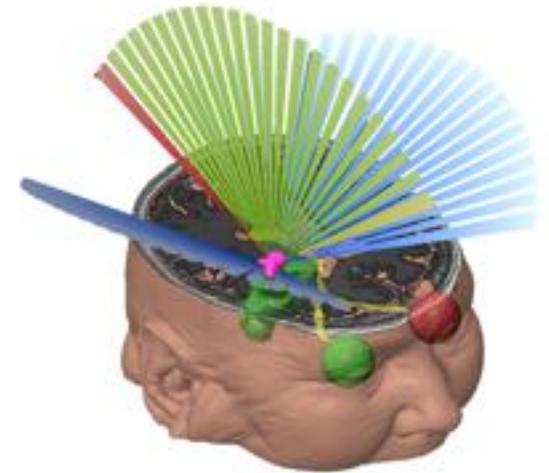




Circular Arc



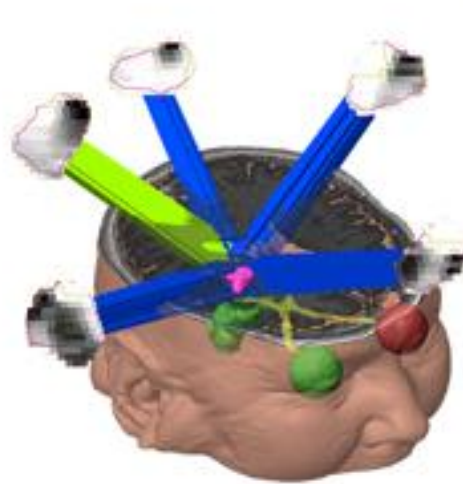
Conformal Beam



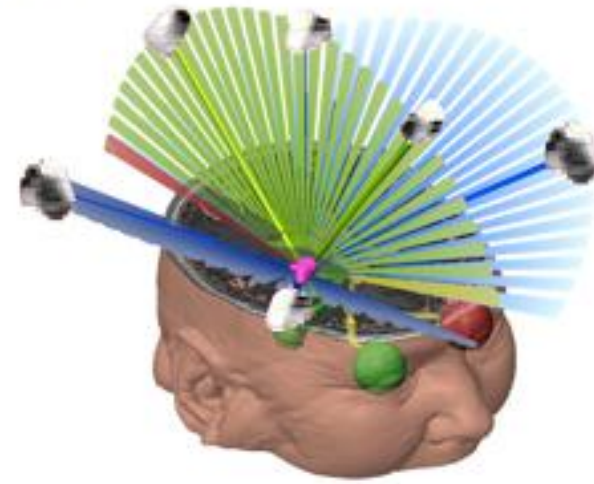
Dynamic Conformal Arc



Gamma Knife



IMRT



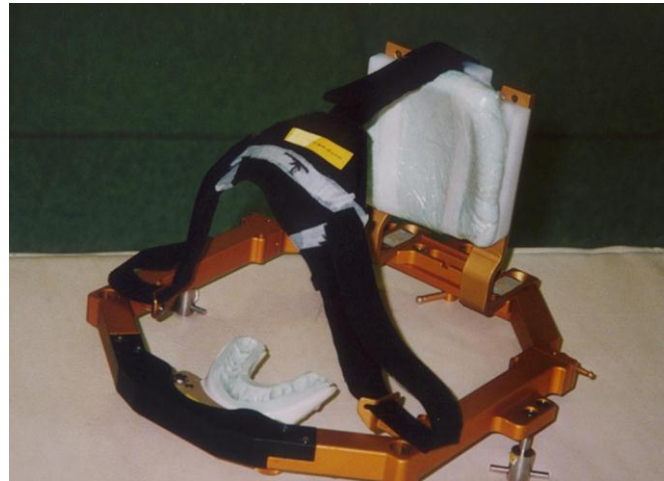
HybridArc



Frameless Radiosurgery



Invasive (BRW) frame
Accuracy 0.5-1 mm



Non-invasive GTC frame
Accuracy 1.0-1.5 mm



Frameless radiosurgery
Accuracy?

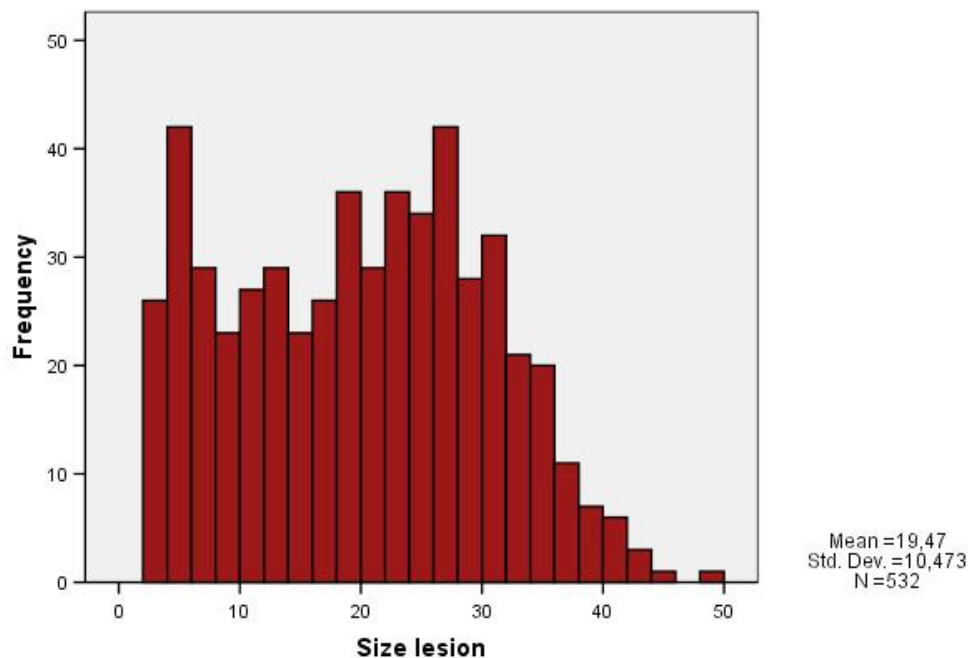
- Increasing patient tolerability (RS \approx WBRT)
- Logistical advantage: RS on full outpatient basis
- Threshold to perform RS lowered



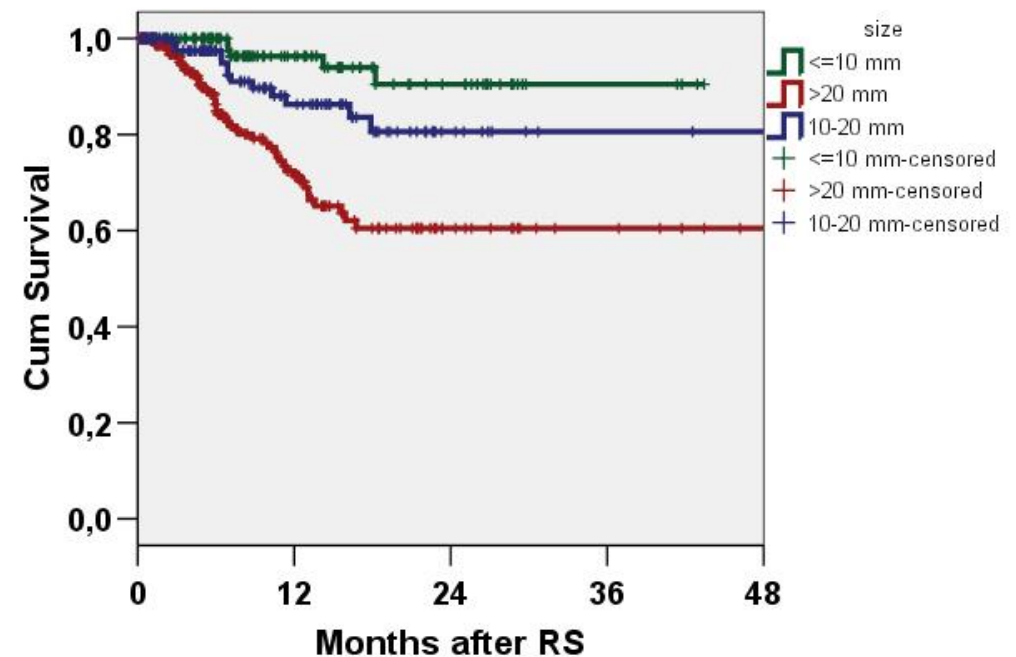
RS dose prescription generally “toxicity driven”

$<7\text{cm}^3$	(<2.5 cm)	1 x 21 Gy @80%
7-14 cm^3	(<3 cm)	1 x 18 Gy @80%
$>14\text{ cm}^3$	(>3cm)	1 x 15 Gy or 3 x 8 Gy @80%

Histogram



Local control (in-field)



Counter intuitive: Larger lesions, which should be given a higher dose, receive a lower dose for toxicity concerns...



Gamma Knife surgery as sole treatment for multiple brain metastases: 2-center retrospective review of 1508 cases meeting the inclusion criteria of the JLGK0901 multi-institutional prospective study

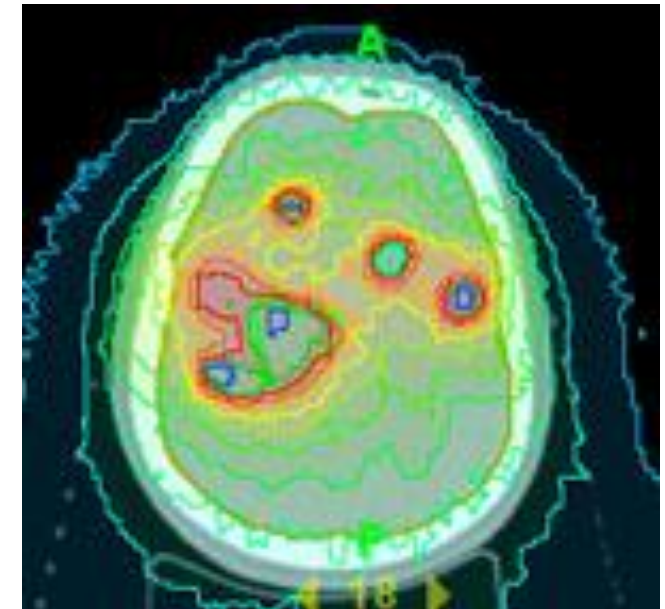
Clinical article

TORU SERIZAWA, M.D., PH.D.,¹ MASAOKI YAMAMOTO, M.D., PH.D.,² YASUNORI SATO, PH.D.,^{3,4} YOSHINORI HIGUCHI, M.D., PH.D.,⁵ OSAMU NAGANO, M.D., PH.D.,⁶ TAKUYA KAWABE, M.D.,² SHINJI MATSUDA, M.D., PH.D.,⁶ JUNICHI ONO, M.D., PH.D.,⁵ NAOKATSU SAEKI, M.D., PH.D.,^{3,4} MANABU HATANO, M.D., PH.D.,¹ AND TATSUO HIRAI, M.D. PH.D.¹

Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases?

Clinical article

WON SEOK CHANG, M.D.,¹ HAE YU KIM, M.D.,² JIN WOO CHANG, M.D., PH.D.,¹ YONG GOU PARK, M.D., PH.D.,¹ AND JONG HEE CHANG, M.D., PH.D.¹



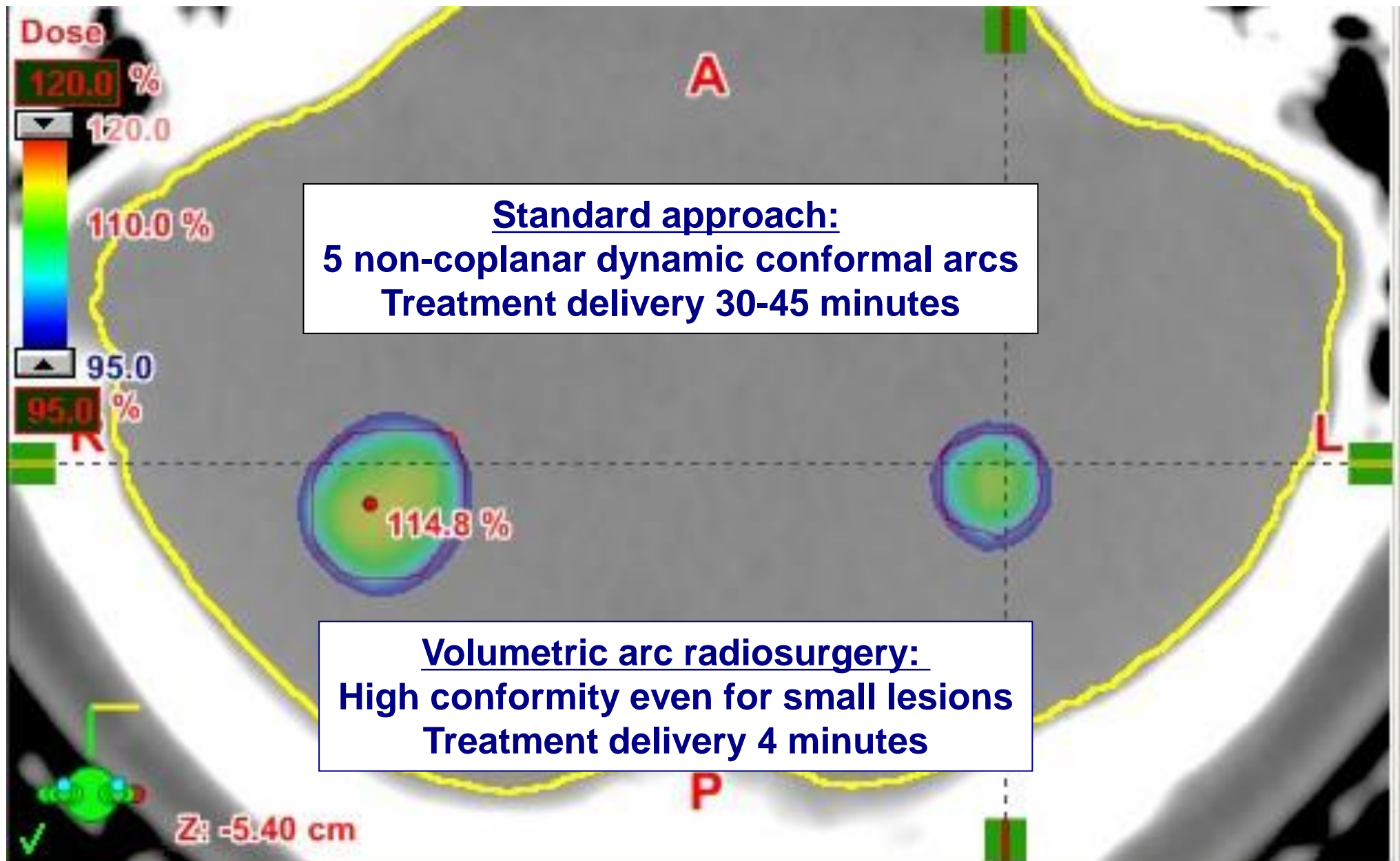
Clinical Study

Gamma knife radiosurgery for multiple brain metastases from lung cancer

Seong-Hyun Park *, Sung-Kyoo Hwang, Dong-Hun Kang, Sun-Ho Lee, Jaechan Park, Jeong-Hyun Hwang, In-Suk Hamm, Yeun-Mook Park

Department of Neurosurgery, BioMedical Research Institute, Kyungpook National University Hospital 50, Samduk-2-ga, Jung-gu, Daegu 700-721, South Korea







THE LANCET



Volume 363, Issue 9422, 22 May 2004, Page 1665

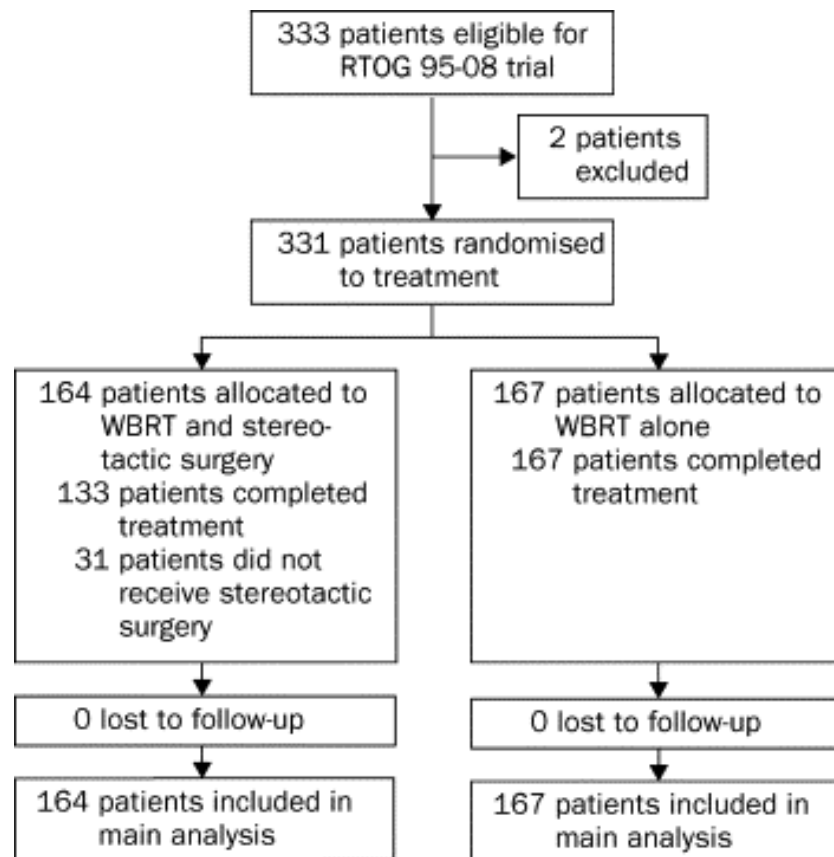
[doi:10.1016/S0140-6736\(04\)16250-8](https://doi.org/10.1016/S0140-6736(04)16250-8) | [How to Cite or Link Using DOI](#)

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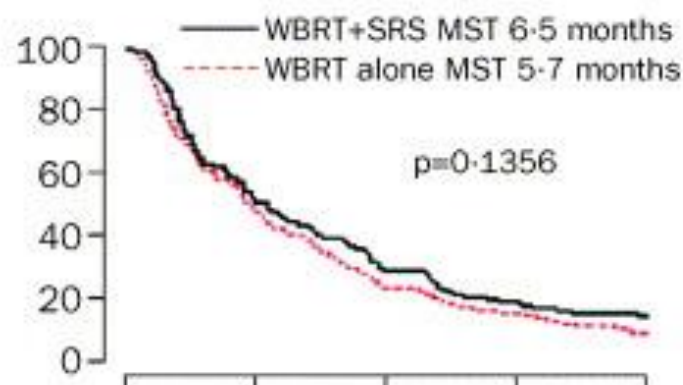
Articles

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

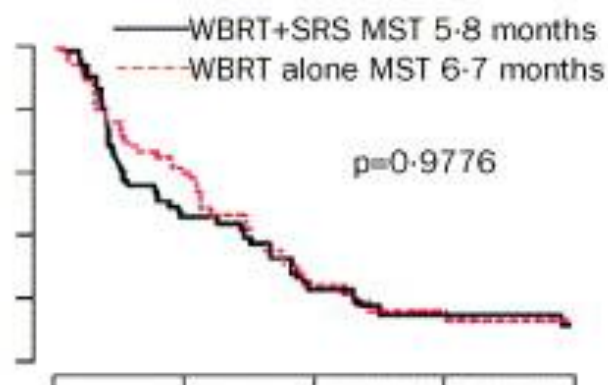
Professor David W Andrews MD^a, , , Charles B Scott PhD^d, Paul W Sperduto MD^e, Adam E Flanders MD^b, Laurie E Gaspar MDⁱ, Michael C Schell PhD^f, Maria Werner-Wasik MD^c, William Demas MD^g, Janice Ryu MD^h, Jean-Paul Bahary MD^j, Luis Souhami MD^k, Marvin Rotman MD^l, Minesh P Mehta MD^m and Walter J Curran, Jr MD^c



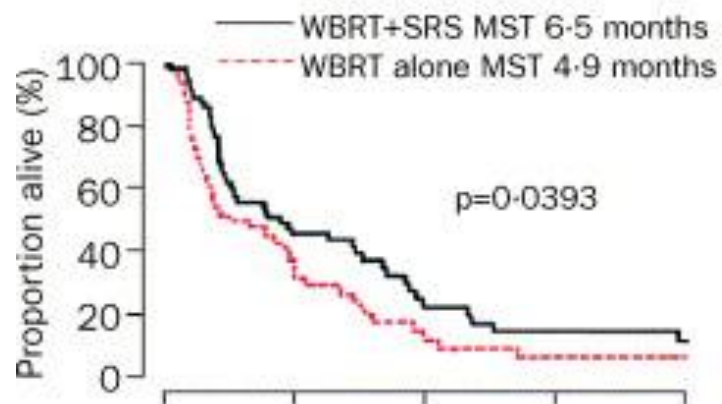
Overall survival



Survival in patients with multiple metastases



Survival in patients with single metastasis



	WBRT+stereotactic surgery	WBRT alone
KPS	(n=79)	(n=75)
Improved	10 [‡]	3
Worsened	43	50
Unchanged	23	16
Data missing	3	6
Steroids[†]	(n=76)	(n=75)
Increased	7	6
Decreased	41 [‡]	25
Unchanged	15	24
Data missing	13	20
Mental status	(n=79)	(n=75)
Improved	20	24
Worsened	21	24
Unchanged	9	12
Data missing	29	15

* $p=0.0331$.

[†] Most patients were not taking steroids by 3 months.

[‡] $p<0.0158$.

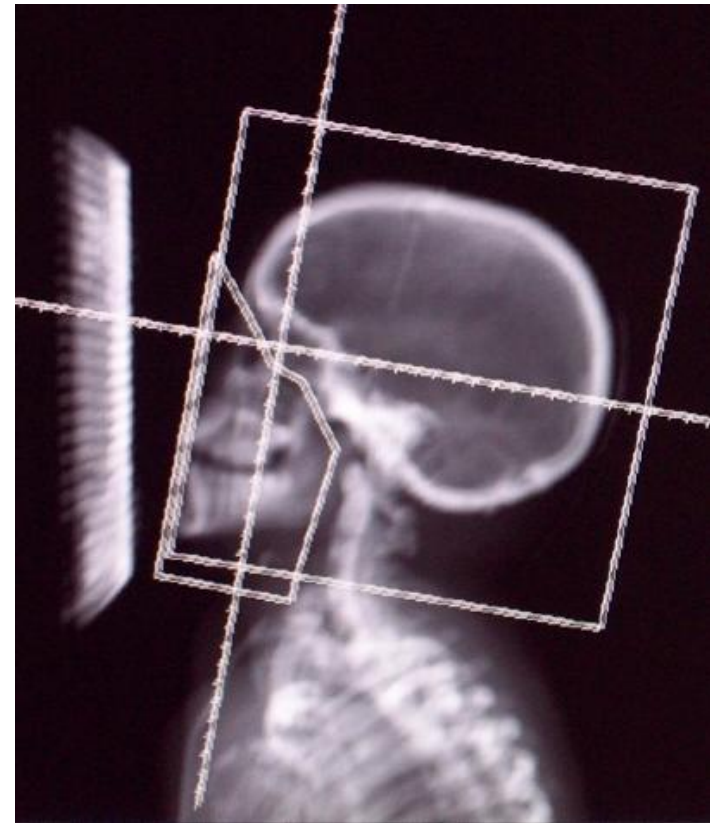


The risk of development of new BM increases with the number of treated lesions. For >2-3 lesions RS can be combined with WBRT



Radiosurgery

interval

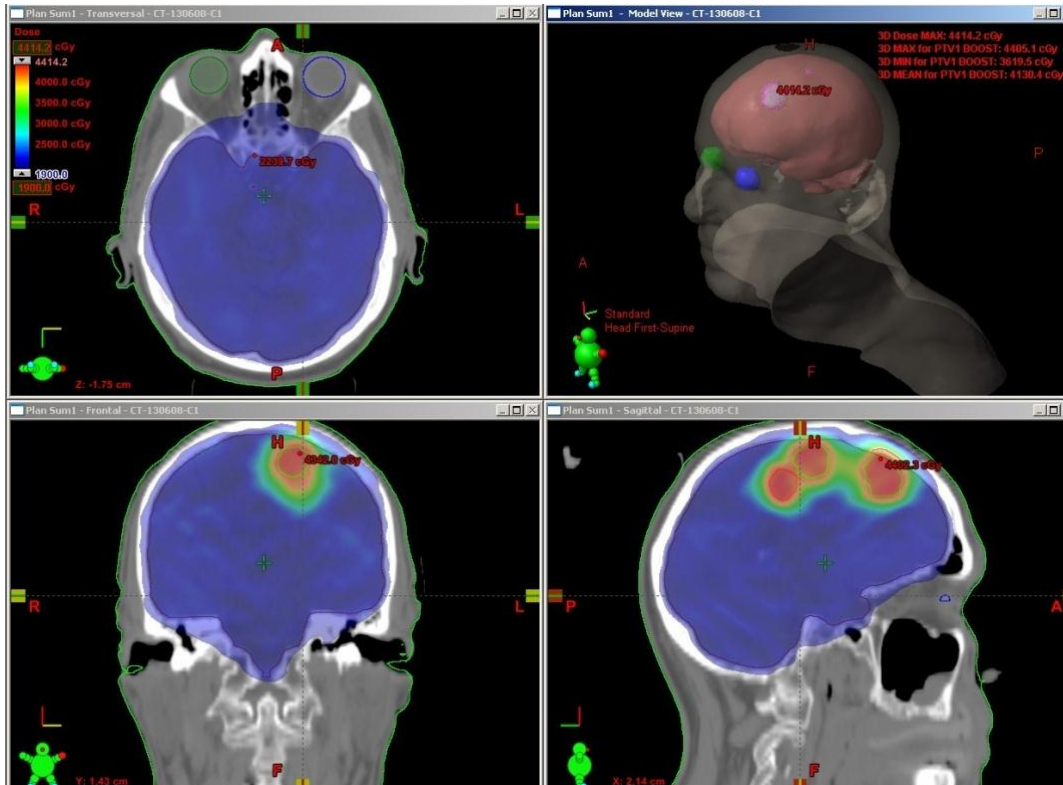


WBRT 5 x 4 Gy

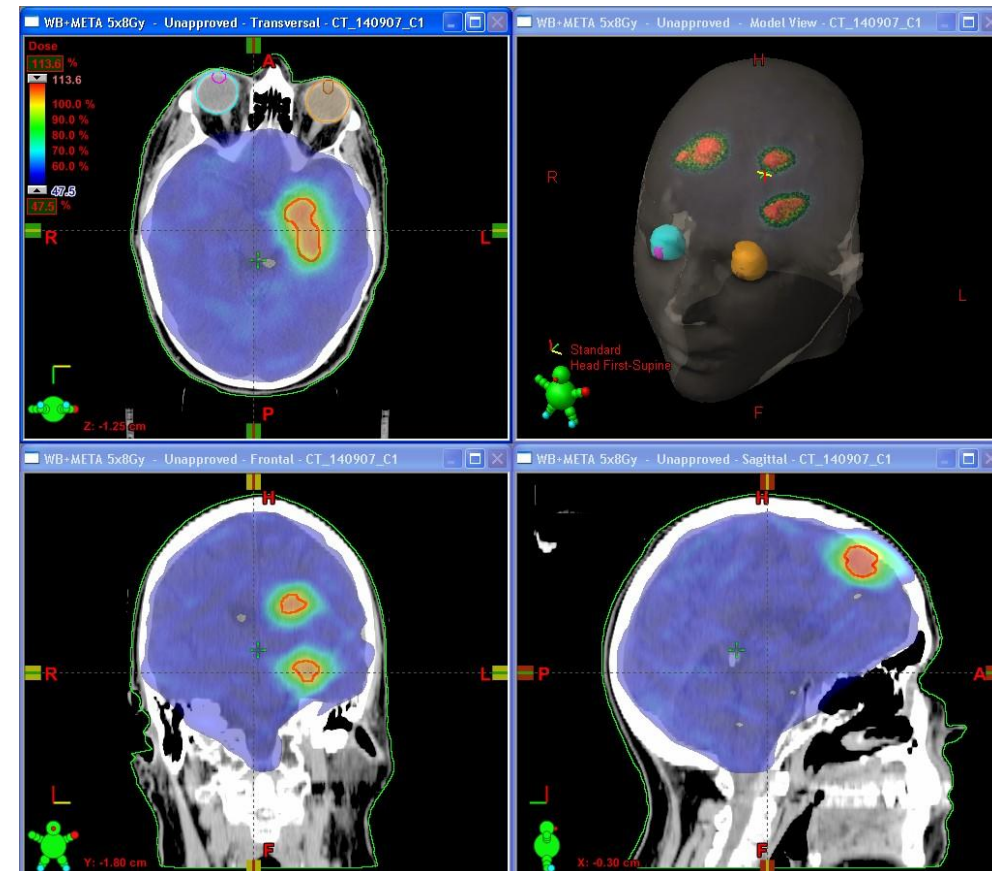


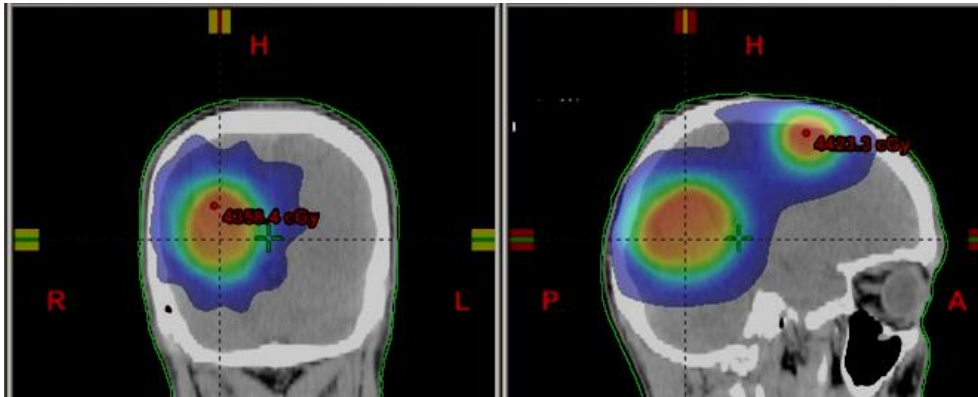
Volumetric modulated arc

Combining WBRT & radiosurgery boosts

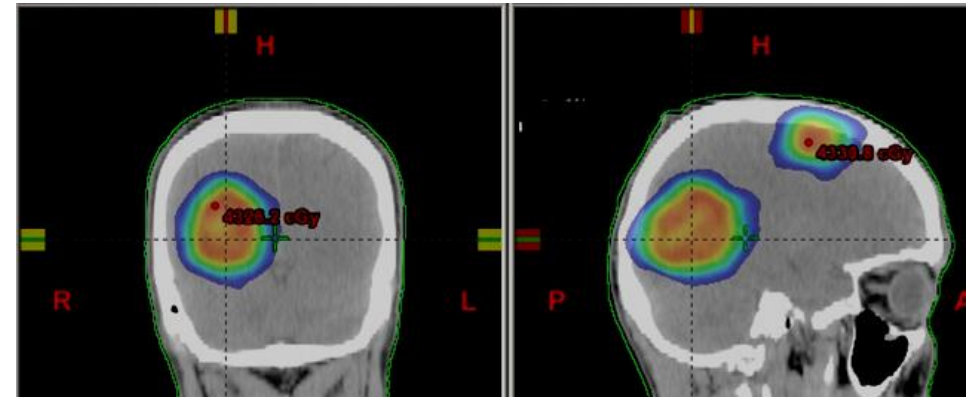


- Plans generated in 1-2 hours
- 5 x 4 Gy WBRT + 5 x 4 Gy boost @100%
- Patient setup with ExacTrac
- Treatment using 2 arcs
- Beam-on time approx 3 minutes (!)





WBRT + RS separate techniques

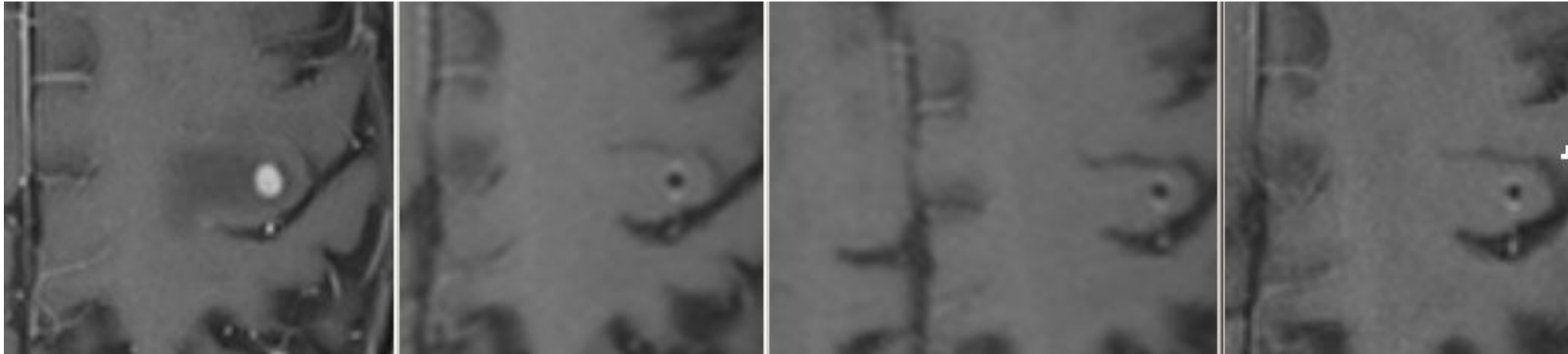


Integrated WBRT + boosts (VMAT)

New RTH delivery techniques allow for more complex tailored planning, including so called simultaneous integrated boosts (SIB).

- Dosimetric advantages (steeper dose gradients)
- Logistic advantages (no separate procedures)
- Patient tolerance advantages (outpatient, frameless, delivery ~5 minutes)

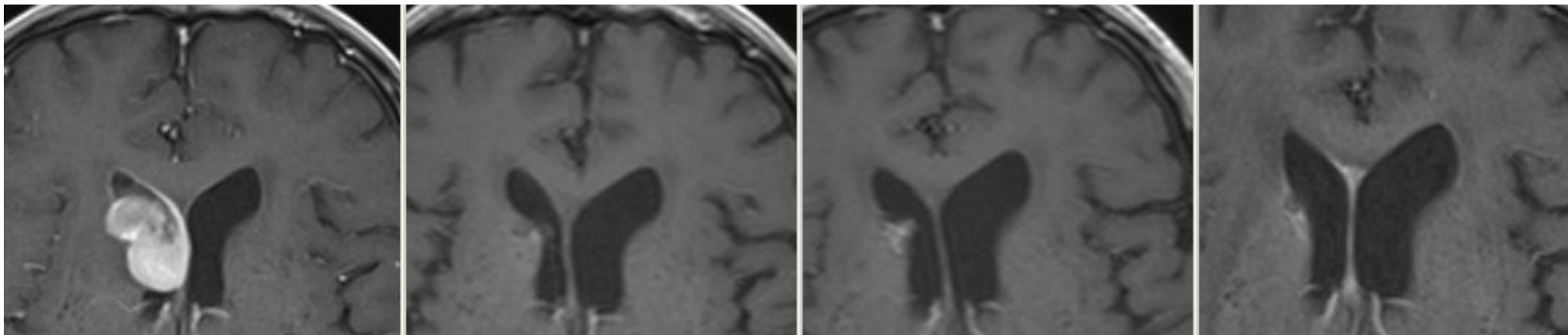




5 x 8 Gy @BM: biological dose for tumor effects 72 Gy₁₀

For comparison: 30 x 2 Gy (glioblastoma scheme) = 72 Gy₁₀

1 x 20 Gy (radiosurgery) = 60 Gy₁₀



Is radiation dose escalation clinically relevant in patients with multiple BM?

Toxicity? Efficacy?



EORTC 22111-26111

**Whole brain radiotherapy with or without synchronous integrated boost in patients with 2 to 5 brain metastases.
A randomized Phase III Study of the EORTC ROG and BTG**

PI: B. Baumert, S. Erridge, F. Lagerwaard
Initiating end of 2012



Study Design:

- Phase III RCT with safety stopping rules
 - Exp arm: WBRT 30Gy/10 fractions + SIB 20Gy/10 fractions
 - Control arm: WBRT 30Gy in 10 fractions WBRT
- Stratified by institution, primary site, RPA, total boost volume
- 226 patients will be needed to detect, with 80% power, increased survival from 20% to 35% in WHO <3.

Key eligibility criteria

- Histologically confirmed cancer
- 2-5 brain metastases on MRI
- Max total volume of metastases <30cc
- RPA Class 1 or 2
- Stable extra-cranial disease for at least 3 months
- Stable neurological condition for at least one week
- Not HER2+ breast, SCLC, lymphoma, leukaemia, myeloma, germ cell



- Primary endpoint
 - Survival with WHO <3 (i.e. independent life)
- Secondary endpoints
 - Overall survival at 6, 12 and 24 months
 - Neurological function score*
 - Clinically defined progression-free survival* (!!)
 - Dose of steroids*
 - QoL (EPRTC Q30 + brain module) *
 - Neurocognitive assessment (baseline, 6 and 12 months)



- Although many prognostic classification systems are available for patients with BM, predictive systems are mostly lacking
- Dose-escalation using traditional irradiation fields is not effective and adds to toxicity
- Radiosurgery or alternative novel radiation planning and delivery techniques allow for focal tailored dose-escalation
- With the exception of (few) randomized radiosurgery data, the clinical benefit of dose-escalation remains to be defined



Thank you for your attention

