LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
Klinik und Poliklinik für Strahlentherapie und Radioonkologie
Campus Innenstadt und Campus Großhadern
Direktor: Prof. Claus Belka

Does IMRT, IMAT, tomotherapy reduce the neurotoxicity of whole brain radiotherapy?

Prof. Dr. med. Claus Belka

Whole Brain irradiation

- Multiple brain metastasis
- Adjunct to radiosurgery for limited brain metastasis
- Prophylactic irradiation (PCI-SCLC, ALL)

Most critical issue → Prophylatic irradiation

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PCI SCLC

Incidence of Brain metastasis

Analysis 01.02. Comparison 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 02 Brain metastasis

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

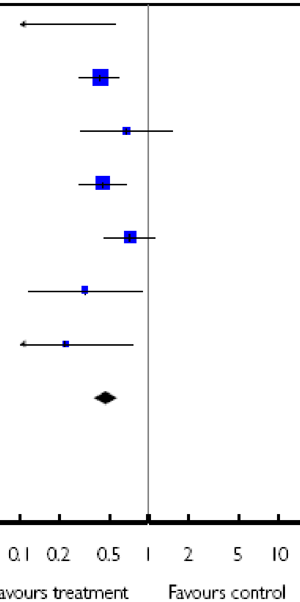
Comparison: 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 02 Brain metastasis

Study	PCI n/N	No PCI n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Aroney 1983	0/14	5/12		1.4	0.10 [0.02, 0.56]
Arriagada 1995	46/149	87/151		37.1	0.41 [0.29, 0.58]
Danish/NCI	10/27	13/25		6.5	0.67 [0.30, 1.53]
Gregor 1997	46/194	54/120		26.0	0.44 [0.29, 0.66]
Laplanche 1998	32/100	44/111		21.6	0.71 [0.45, 1.12]
Ohonoshi 1993	5/23	11/23		4.4	0.32 [0.12, 0.87]
Wagner 1996	4/17	8/15		3.0	0.23 [0.07, 0.76]
Total (95% CI)				**100.0**	**0.46 [0.38, 0.57]**

Test for heterogeneity chi-square=9.71 df=6 p=0.14 I^2 =38.2%

Test for overall effect z=7.18 p<0.00001



PCI SCLC

Overall survival

Analysis 01.01. Comparison 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 01 Survival

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

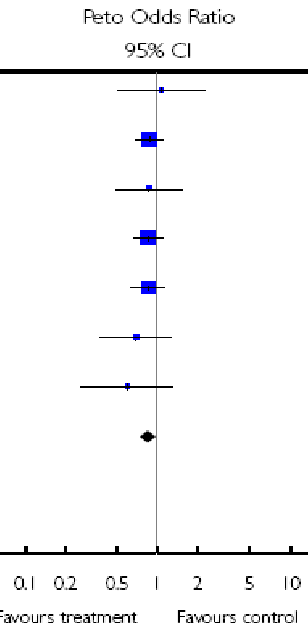
Comparison: 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 01 Survival

Study	PCI n/N	No PCI n/N	Weight (%)	Peto Odds Ratio 95% CI
Aroney 1983	14/15	13/14	3.3	1.06 [0.50, 2.26]
Arriagada 1995	133/149	135/151	32.5	0.87 [0.69, 1.11]
Danish/NCI	24/28	24/27	5.8	0.86 [0.49, 1.52]
Gregor 1997	154/194	106/120	29.5	0.85 [0.66, 1.09]
Laplanche 1998	80/100	94/111	21.1	0.84 [0.62, 1.13]
Ohonoshi 1993	21/23	21/23	4.9	0.69 [0.37, 1.27]
Wagner 1996	14/17	13/15	3.0	0.59 [0.27, 1.31]
Total (95% CI)			**100.0**	**0.84 [0.73, 0.97]**

Test for heterogeneity chi-square=1.64 df=6 p=0.95 I^2 =0.0%

Test for overall effect z=2.45 p=0.01



Effekt also in ED-SCLC (ZNS Metas.)

Analysis 01.11. Comparison 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 11 Brain metastasis by extend of initial disease

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 11 Brain metastasis by extend of initial disease

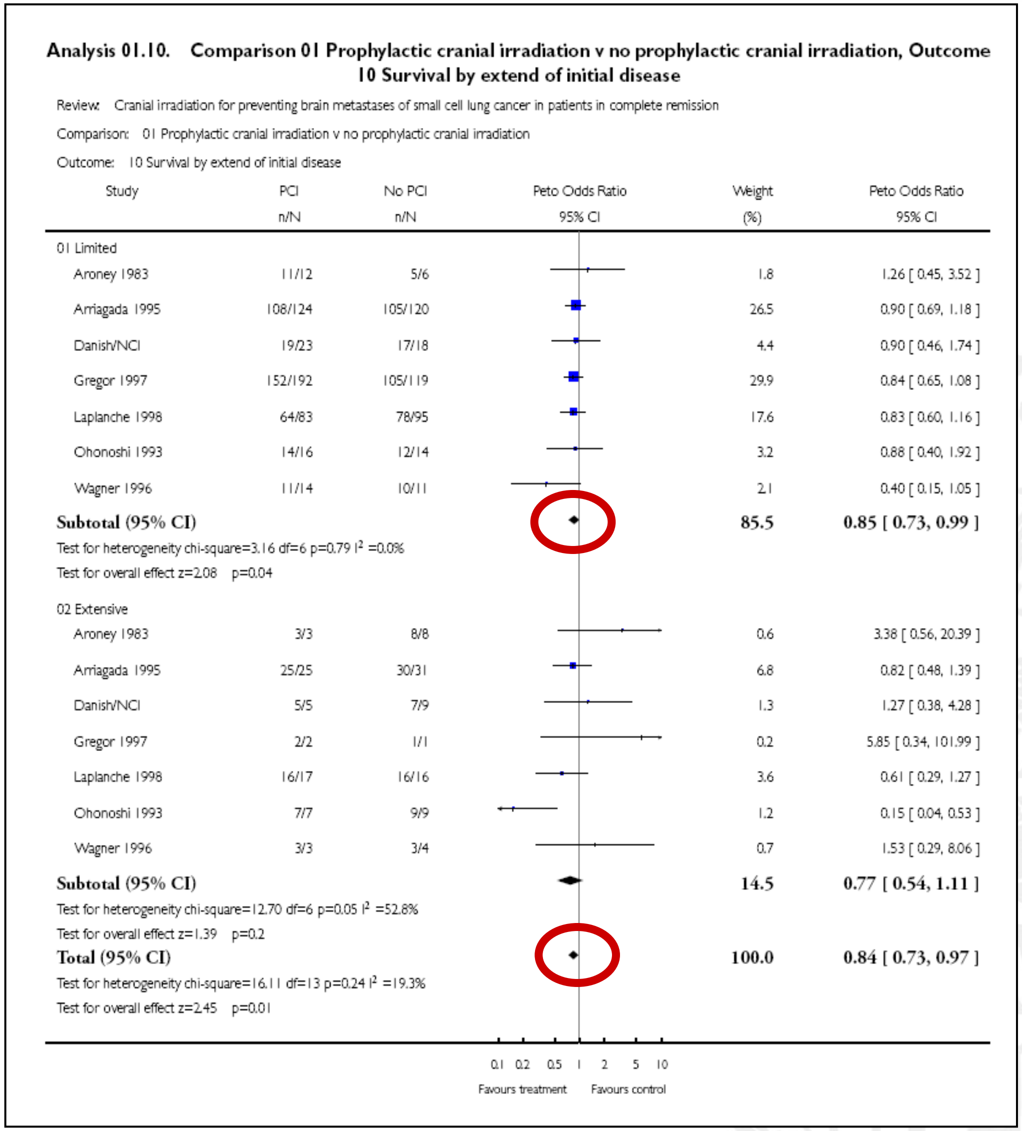
Study	PCI n/N	No PCI n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 limited					
Aroney 1983	0/11	2/5		0.5	0.04 [0.00, 0.80]
Arriagada 1995	39/124	65/120		29.2	0.45 [0.31, 0.67]
Danish/NCI	7/22	9/18		4.6	0.65 [0.24, 1.75]
Gregor 1997	45/192	54/119		25.8	0.42 [0.28, 0.64]
Laplanche 1998	27/83	37/95		18.3	0.74 [0.46, 1.22]
Ohonoshi 1993	3/16	6/14		2.5	0.35 [0.09, 1.34]
Wagner 1996	4/14	6/11		2.2	0.19 [0.05, 0.78]
Subtotal (95% CI)				**83.1**	**0.48 [0.38, 0.61]**
Test for heterogeneity chi-square=8.40 df=6 p=0.21 I^2 =28.6%					
Test for overall effect z=6.19 p<0.00001					
02 Extensive					
Aroney 1983	0/3	3/7		0.8	0.22 [0.02, 2.43]
Arriagada 1995	7/25	22/31		8.1	0.31 [0.15, 0.64]
Danish/NCI	3/5	4/7		2.0	0.92 [0.20, 4.10]
Gregor 1997	1/2	0/1		0.3	7.39 [0.15, 372.38]
Laplanche 1998	5/17	7/16		3.3	0.47 [0.15, 1.50]
Ohonoshi 1993	2/7	5/9		1.9	0.31 [0.07, 1.39]
Wagner 1996	0/3	2/4		0.6	0.15 [0.01, 2.46]
Subtotal (95% CI)				**16.9**	**0.38 [0.23, 0.64]**
Test for heterogeneity chi-square=4.68 df=6 p=0.59 I^2 =0.0%					
Test for overall effect z=3.67 p=0.0002					
Total (95% CI)				**100.0**	**0.46 [0.38, 0.57]**
Test for heterogeneity chi-square=13.73 df=13 p=0.39 I^2 =5.3%					
Test for overall effect z=7.15 p<0.00001					

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours control

PCI SCLC

Effects also in ED –SCLC O-Survival



Analysis 01.10. Comparison 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation, Outcome 10 Survival by extend of initial disease

Review: Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission

Comparison: 01 Prophylactic cranial irradiation v no prophylactic cranial irradiation

Outcome: 10 Survival by extend of initial disease

Study	PCI n/N	No PCI n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Limited					
Aroney 1983	11/12	5/6		1.8	1.26 [0.45, 3.52]
Arriagada 1995	108/124	105/120		26.5	0.90 [0.69, 1.18]
Danish/NCI	19/23	17/18		4.4	0.90 [0.46, 1.74]
Gregor 1997	152/192	105/119		29.9	0.84 [0.65, 1.08]
Laplanche 1998	64/83	78/95		17.6	0.83 [0.60, 1.16]
Ohonoshi 1993	14/16	12/14		3.2	0.88 [0.40, 1.92]
Wagner 1996	11/14	10/11		2.1	0.40 [0.15, 1.05]
Subtotal (95% CI)				**85.5**	**0.85 [0.73, 0.99]**
Test for heterogeneity chi-square=3.16 df=6 p=0.79 I^2 =0.0%					
Test for overall effect z=2.08 p=0.04					
02 Extensive					
Aroney 1983	3/3	8/8		0.6	3.38 [0.56, 20.39]
Arriagada 1995	25/25	30/31		6.8	0.82 [0.48, 1.39]
Danish/NCI	5/5	7/9		1.3	1.27 [0.38, 4.28]
Gregor 1997	2/2	1/1		0.2	5.85 [0.34, 101.99]
Laplanche 1998	16/17	16/16		3.6	0.61 [0.29, 1.27]
Ohonoshi 1993	7/7	9/9		1.2	0.15 [0.04, 0.53]
Wagner 1996	3/3	3/4		0.7	1.53 [0.29, 8.06]
Subtotal (95% CI)				**14.5**	**0.77 [0.54, 1.11]**
Test for heterogeneity chi-square=12.70 df=6 p=0.05 I^2 =52.8%					
Test for overall effect z=1.39 p=0.2					
Total (95% CI)				**100.0**	**0.84 [0.73, 0.97]**
Test for heterogeneity chi-square=16.11 df=13 p=0.24 I^2 =19.3%					
Test for overall effect z=2.45 p=0.01					

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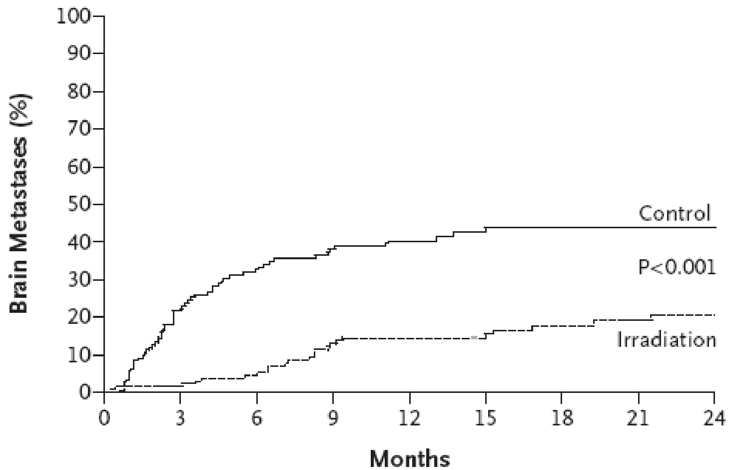
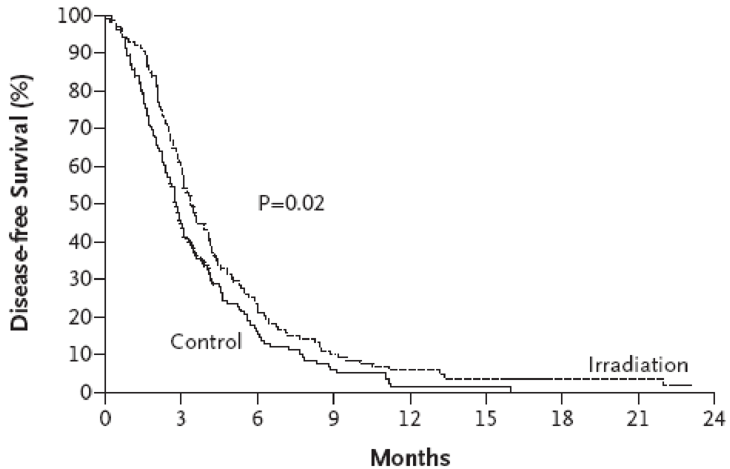
PCI SCLC



No. at Risk								
Control	143	94	48	29	11	2	1	1
Irradiation	143	119	66	38	24	16	10	5

Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.
The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).



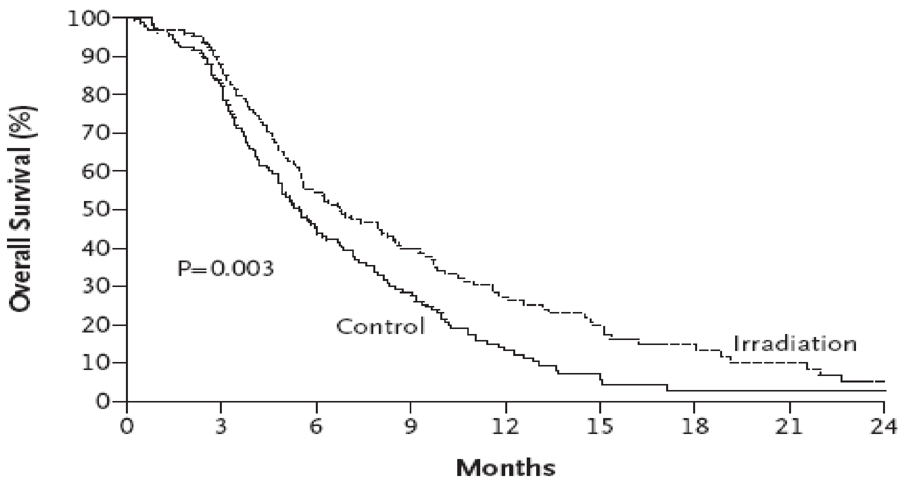
No. at Risk								
Control	143	62	20	8	1	1	0	0
Irradiation	143	79	30	13	6	3	3	2

Figure 2. Disease-free Survival.
Patients in the irradiation group had a longer median period of disease-free survival (14.7 weeks) than did those in the control group (12.0 weeks) (P=0.02 by log-rank test; hazard ratio, 0.76; 95% CI, 0.59 to 0.96).

20 Gy in 5 or 8 fractions, 24 Gy in 12 fractions,
25 Gy in 10 fractions, or 30 Gy in 10 or 12 fractions.

Slotman et al.

PCI SCLC



No. at Risk

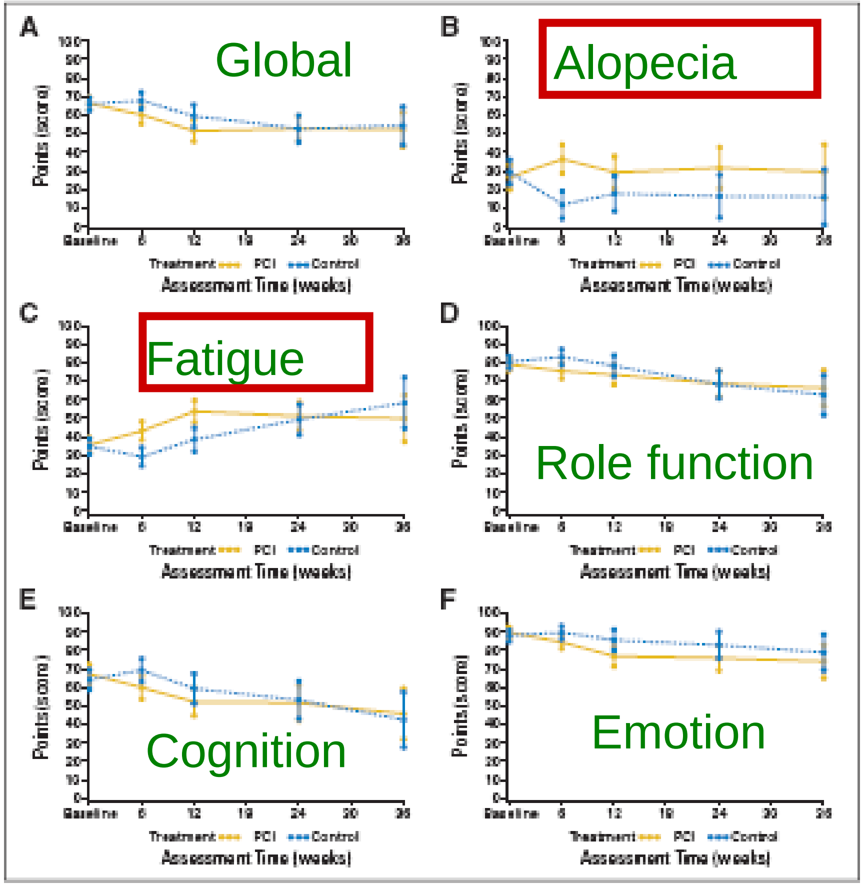
Control	143	115	58	36	15	3	2	1
Irradiation	143	119	67	44	26	17	11	6

Figure 3. Overall Survival.

Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Slotman et al.

LQ after PCI SCLC



Slotman et al.

Outline

- Anatomically and physiologically critical structures for neurotoxicity

British Journal of Cancer (2001) **85**(9), 1233–1239

doi: 10.1054/ bjoc.2001.2100, available online at http://www.idealibrary.com on IDEAL®
http://www.bjcancer.com

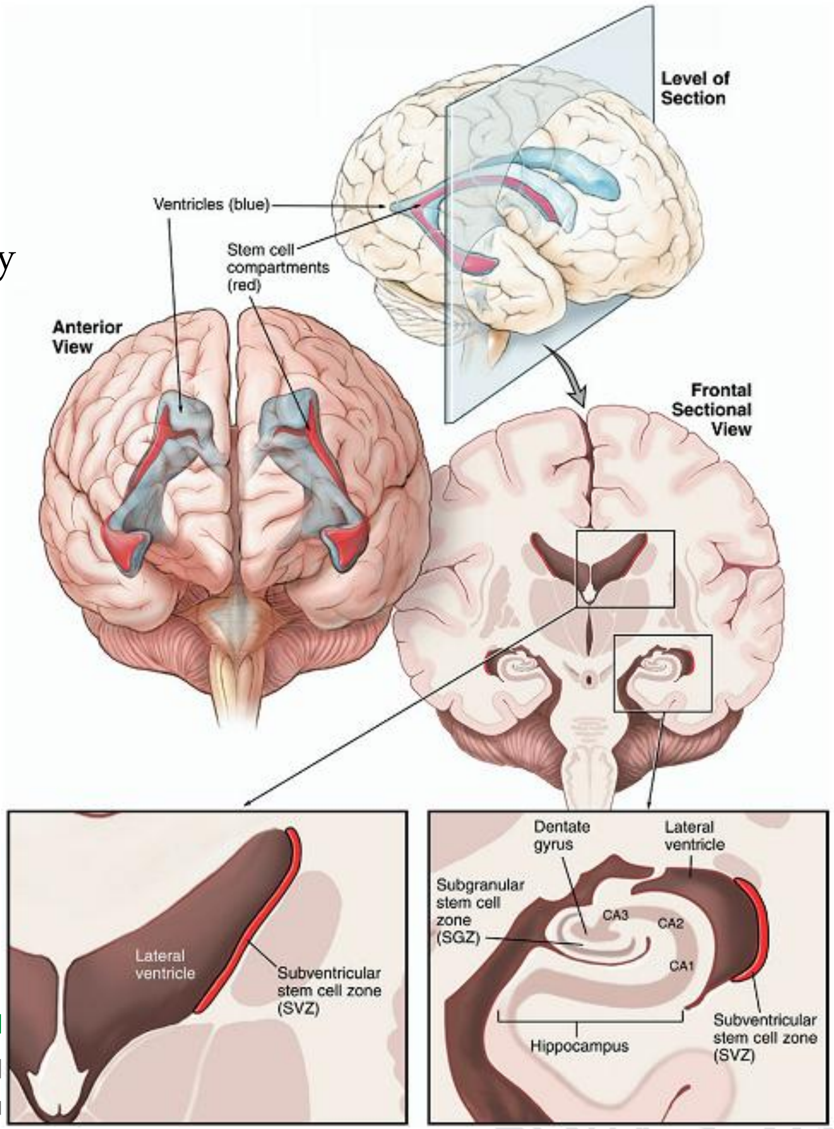
Review

Radiation induced CNS toxicity – molecular and cellular mechanisms

C Belka, W Budach, RD Kortmann and M Bamberg

Anatomically and physiologically critical structures for neurotoxicity

- Neurogenesis persists predominantly in subventricular and subgranular zone
- Neural stem cells contribute to intrinsic brain plasticity & repair
- Radiation can depopulate these regions & impair neurogenesis by inflammatory processes
- Radiation to SVZ eliminates proliferating neural precursor cells and migrating neuroblasts



Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 2, pp. 324–333, 2007
doi: 10.1002/stem.1214

Anatomically and physiologically critical structures for neurotoxicity

- Irradiation increases hippocampal apoptosis and decreases hippocampal proliferation
- Loss of hippocampal neurogenesis even at doses <2Gy

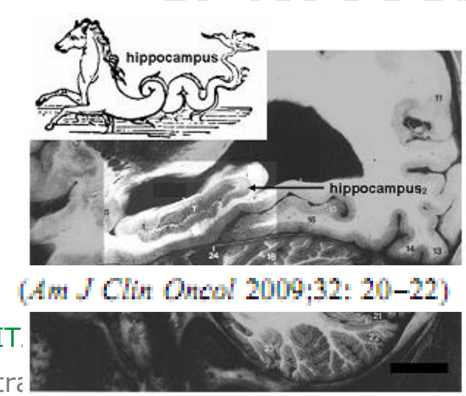
  (irradiation of murine embryonic brains)

POSSIBLE CONSEQUENCES →

- Responsible for short-term memory formation and recall
- Deficits in learning, memory, attention

  and spatial processing due to radiation

  induced hippocampal injury



(*Am J Clin Oncol* 2009;32: 20–22)

Radiotherapy and Oncology 97 (2010) 370–376

Neurotoxicity of whole brain radiotherapy

- Spectrum of different toxicities with variable time course
- Late toxicity: dementia in <11%: several months to years following RT
- Early toxicity: verbal and short-term memory recall: 1-4 months after RT
- No decline in neurocognitive function if fraction size <3Gy

Neurotoxicity of whole brain radiotherapy

Table 3 Randomized controlled trials assessing quality of life and impairment of neurocognitive function in patients with brain metastases

Author	Study type	Patients	Evaluable patients for cognitive outcome	Treatment arms	RS Dose	WBRT Total dose	WBRT Dose per fraction	Cognitive assessment or quality of life questionnaires	Cognitive outcome	Follow-up
Aoyama [34, 45]	Phase III randomized controlled trial	132	92	RS RS + WBRT	≤2 cm: 22–25 Gy; >2 cm: 18–20 (Dose reduction by 30% for patients treated with WBRT)	– 30 Gy	– 3 Gy	MMSE	RS alone: Shorter time to neurocognitive deterioration	Median 5.3 m (0.7–58.7 m)
Chang [35]	Phase III randomized controlled trial	58	58	RS RS + WBRT	<2 cm: 18 Gy; 2–3 cm: 15 Gy; 3–4 cm: 12 Gy	– 30 Gy	– 2.75 Gy	Standardized tests (Functional assessment of cancer therapy brain, Hopkins verbal learning test-revised, Wechsler adult intelligence scale III, Controlled oral word association)	RS + WBRT: significantly lower score in Hopkins verbal learning test-revised at 4 months assessment	Median 9.5 m
Soffietti [37] Kocher [43]	Phase III randomized controlled trial	359	317	RS or S RS or S + WBRT	20 Gy	– 30 Gy	– 3 Gy	EORTC QOL-C30 and BN20	RS or S + WBRT: deterioration in global HR-QoL at 9 m assessment, in Physical functioning at 2 m assessment and in cognitive function at 2 and 12 m evaluation for patients treated with the combined treatment	NA (The analysis focused on the first year after the treatment)
Roos [44]	Phase III randomized controlled trial	19	18	RS or S RS or S + WBRT	NA	– 36 or 30 Gy	– 2 or 3 Gy	EORTC QOL-C30 and BN20 MMSE	Not significant difference between the two treatment arms	Median 6.2 years

WBRT whole brain radiotherapy, *RS* radiosurgery, *S* surgery, *fr* fractions, *MMSE* mini mental state examination, *SQLI* spitzer quality of life index, *EORTC QOL-C30* EORTC quality of life 30-item questionnaire C30, *BN-20* brain cancer module 20, *HR-QOL* health-related quality of life, *m* months, *y* = years

J Neurooncol (2012) 108:291–308

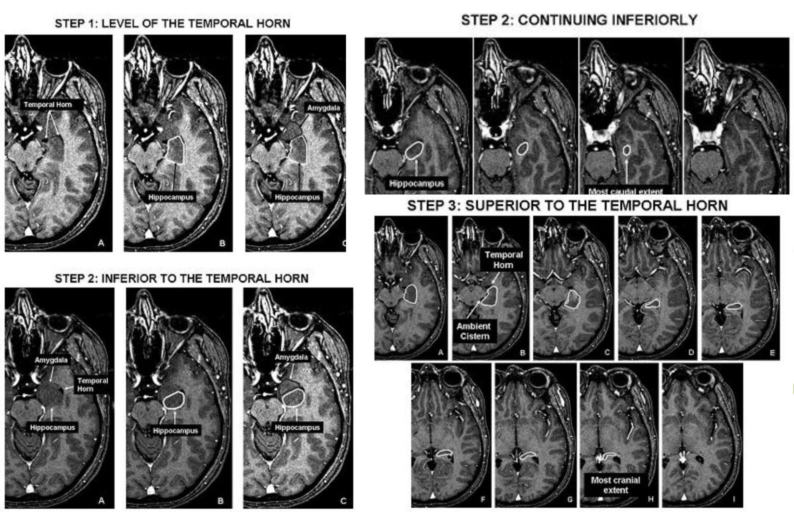
Anatomically and physiologically critical structures for neurotoxicity

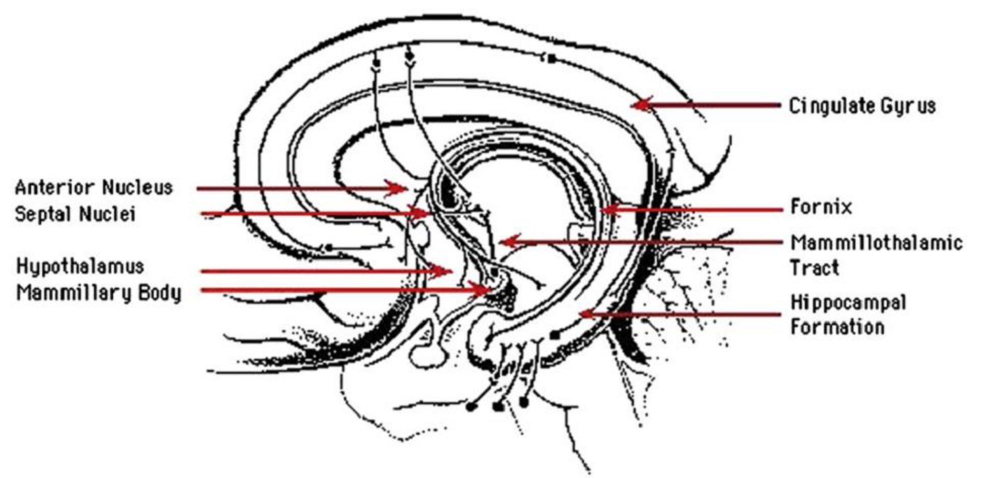
- OAR definition:

  - SVZ: strip of periventricular striatum (= lateral wall of lateral ventricles + 5mm)

  - SGZ: hippocampal formation + 5mm

- Estimated dose tolerance: 10-20Gy, notable fraction-size dependence





Distribution of brain metastases

- Intra

Cancer	Median no. of netastases per patient
Non-small- cel	5.2
Small-cell lung	13.2
Breast cancer	7.7
Other	5.7

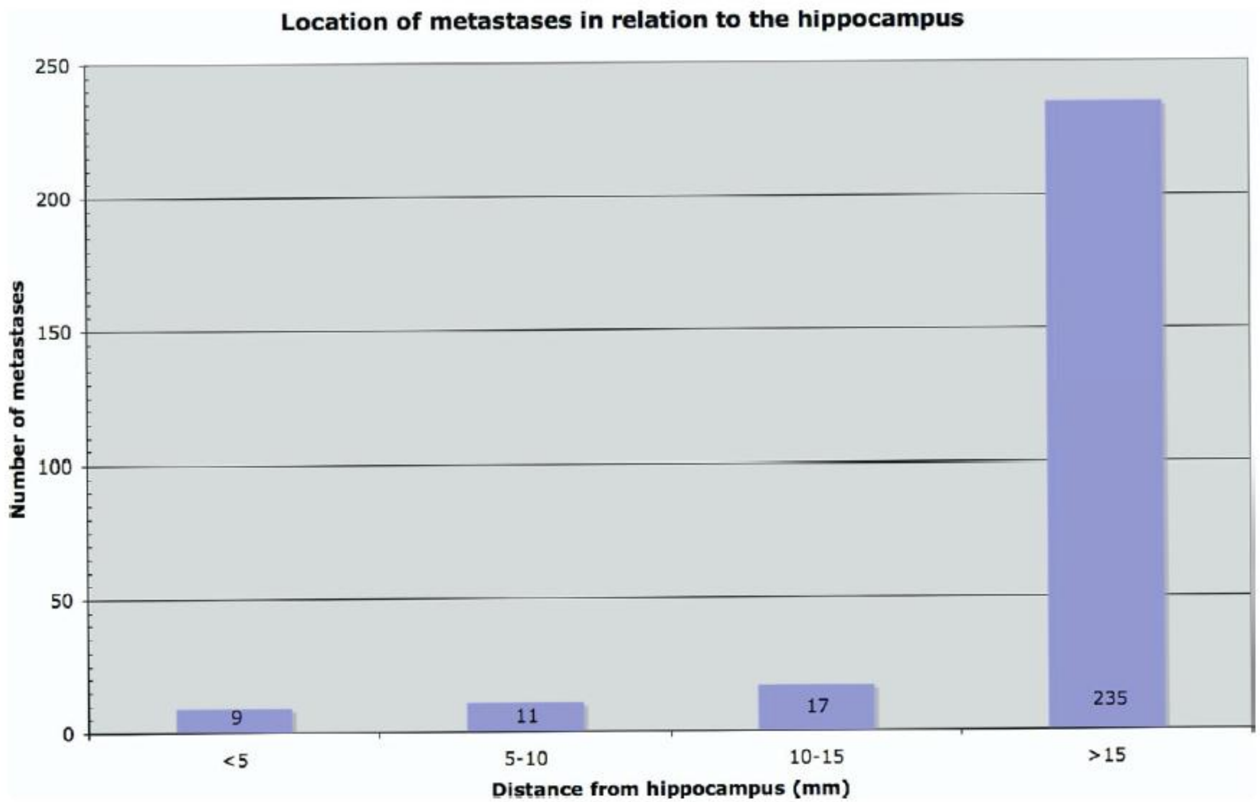
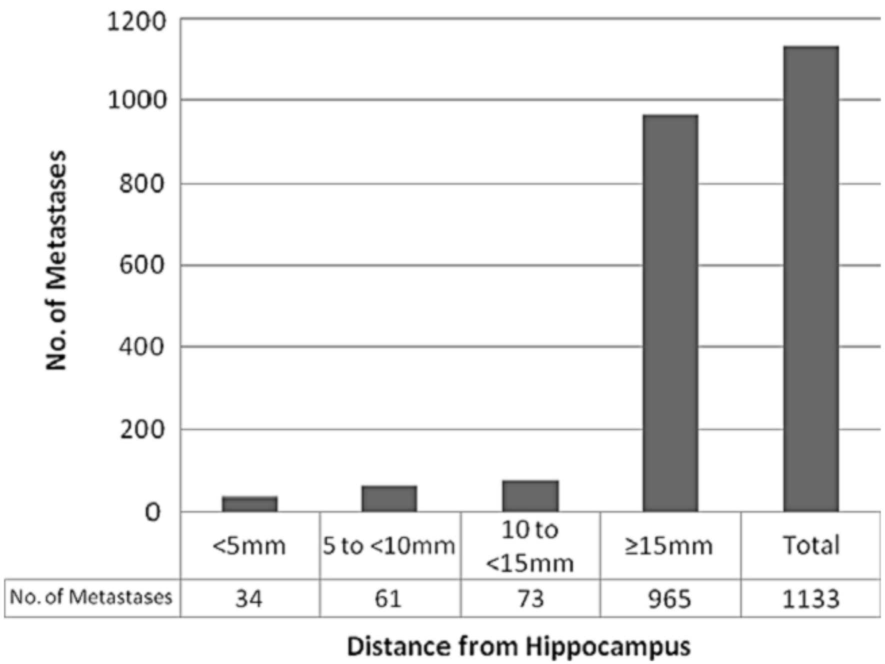


Fig. 1. Location of brain metastasis as a function of distance from the hippocampus.

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 4, pp. 971–977, 2007
Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 2, pp. 504–512, 2010

Distribution of brain metastases

- Within hippocampus + 5mm: in 8.6% of patients and in 3.0% of brain metastases



Patients according to distance from the hippocampus of the closest metastasis.

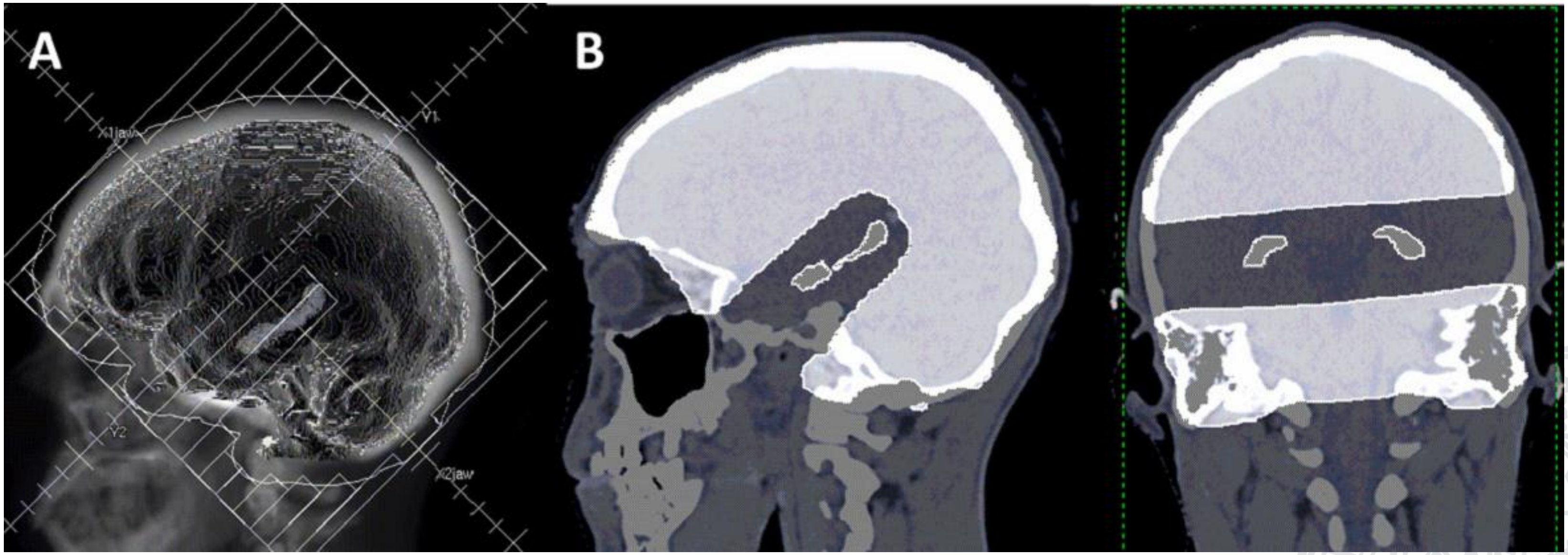
	<5 mm	5 to <10 mm	10 to <15 mm	⩾15 mm
Primary site				
NSCLC	14 (9.0%)	20 (12.9)	22 (14.2)	99 (63.9)
SCLC	4 (10.5)	5 (13.2)	10 (26.3)	19 (50)
Breast	4 (6.3)	9 (14.3)	11 (17.5)	39 (61.9)
Melanoma	7 (14.9)	5 (10.6)	3 (6.4)	32 (68.1)
Renal	0	0	2 (13.3)	13 (86.7)
Other	3 (5.7)	6 (11.3)	6 (11.3)	38 (71.7)
Aggregate number of metastases				
1	10 (6.7%)	10 (6.7)	11 (7.4)	118 (79.2)
2	7 (8.9)	9 (11.4)	14 (17.7)	49 (62.0)
3	7 (15.9)	5 (11.4)	7 (15.9)	25 (56.8)
⩾4	8 (8.1)	21 (21.2)	22 (22.2)	48 (48.5)
Aggregate volume of metastases				
⩽ Median[a]	9 (4.9%)	15 (8.1)	23 (12.4)	138 (74.6)
> Median[a]	23 (12.4)	30 (16.1)	31 (16.7)	102 (54.8)
Total	32 (8.6%)	45 (12.1)	54 (14.5)	240 (64.7)

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.
Percentage of patients within each row given parenthetically.
[a] Median aggregate volume of intra-cranial metastases = 4.9 cm^3.

Radiotherapy and Oncology 95 (2010) 327–331

Technical strategies for reduction of neurotoxicity in whole brain radiotherapy

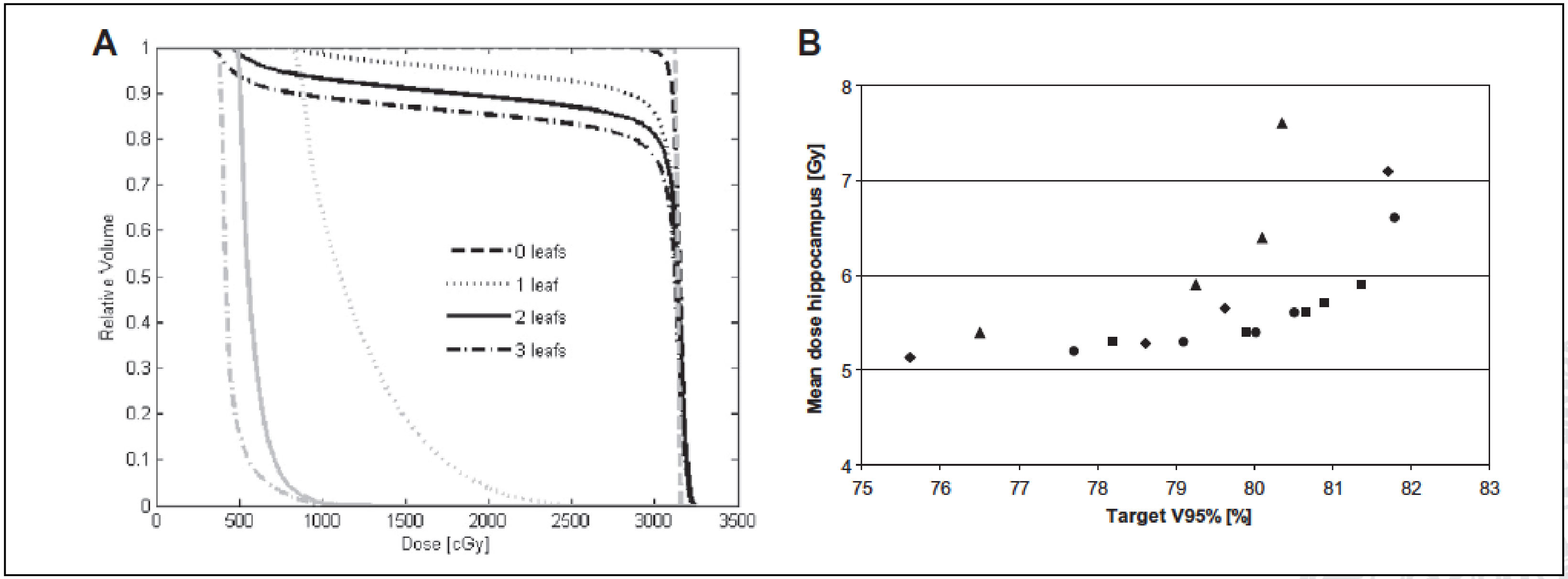
- 12x 2.5Gy: hippocampus mean 6.1Gy, max 13.5Gy; V95% brain 81.7% NON IMRT



Radiotherapy and Oncology 102 (2012) 225–227

Technical strategies for reduction of neurotoxicity in whole brain radiotherapy

- 12x 2.5Gy: hippocampus mean 6.1Gy, max 13.5Gy; V95% brain 81.7% NON IMRT



Radiotherapy and Oncology 102 (2012) 225–227

PHYSICS CONTRIBUTION

SPARING OF THE NEURAL STEM CELL COMPARTMENT DURING WHOLE-BRAIN RADIATION THERAPY: A DOSIMETRIC STUDY USING HELICAL TOMOTHERAPY

JAMES C. MARSH, M.D.,* ROHIT H. GODBOLE, B.S.,† ARNOLD M. HERSKOVIC, M.D.,*
BENJAMIN T. GIELDA, M.D.,* AND JULIUS V. TURIAN, PH.D.*

*Department of Radiation Oncology, Rush University Medical Center, Chicago, Illinois, and †Rush Medical College, Chicago, Illinois

PHYSICS CONTRIBUTION

HIPPOCAMPAL-SPARING WHOLE-BRAIN RADIOTHERAPY: A "HOW-TO" TECHNIQUE USING HELICAL TOMOTHERAPY AND LINEAR ACCELERATOR–BASED INTENSITY-MODULATED RADIOTHERAPY

VINAI GONDI, M.D.,* RANJINI TOLAKANAHALLI, M.S.,† MINESH P. MEHTA, M.D.,*
DINESH TEWATIA, M.S.,*† HOWARD ROWLEY, M.D.,‡ JOHN S. KUO, M.D., PH.D.,*§
DEEPAK KHUNTIA, M.D.,* AND WOLFGANG A. TOMÉ, PH.D.*†

PHYSICS CONTRIBUTION

WHOLE BRAIN RADIOTHERAPY WITH HIPPOCAMPAL AVOIDANCE AND SIMULTANEOUSLY INTEGRATED BRAIN METASTASES BOOST: A PLANNING STUDY

ALONSO N. GUTIÉRREZ, PH.D.,* DAVID C. WESTERLY, M.SC.,* WOLFGANG A. TOMÉ, PH.D.,*†
HAZIM A. JARADAT, PH.D.,† THOMAS R. MACKIE, PH.D.,*†‡ SØREN M. BENTZEN, PH.D., D.SC.,†
DEEPAK KHUNTIA, M.D.,† AND MINESH P. MEHTA, M.D.†

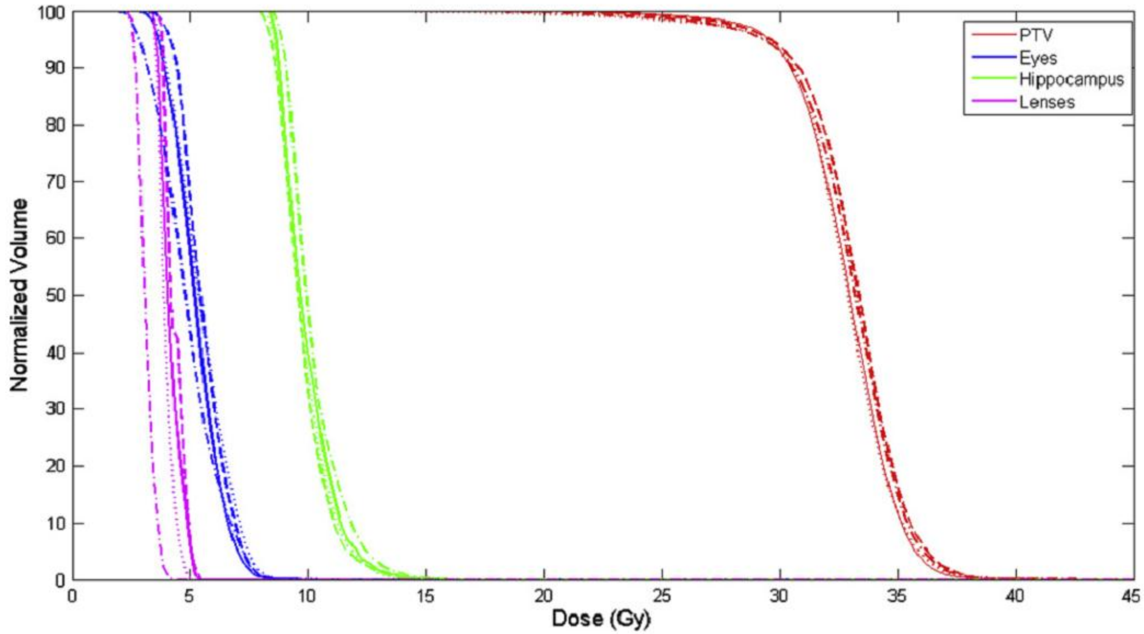
CLINICAL INVESTIGATION **Brain**

WHOLE BRAIN RADIOTHERAPY WITH HIPPOCAMPAL AVOIDANCE AND SIMULTANEOUS INTEGRATED BOOST FOR 1–3 BRAIN METASTASES: A FEASIBILITY STUDY USING VOLUMETRIC MODULATED ARC THERAPY

FRED HSU, M.D.,* HANNAH CAROLAN, M.D.,† ALAN NICHOL, M.D.,* FRED CAO, PH.D.,‡
NIMET NURANEY, R.T.T.,† RICHARD LEE, PH.D.,§ ERMIAS GETE, PH.D.,§ FRANCES WONG, M.D.,†
MOIRA SCHMULAND, M.SC.,§ MANRAJ HERAN, M.D.,¶ AND KARL OTTO, PH.D.§

Technical strategies for reduction of neurotoxicity in whole brain radiotherapy

- LINAC: 10x 3Gy: hippocampus median 7.8Gy, max 15.3Gy

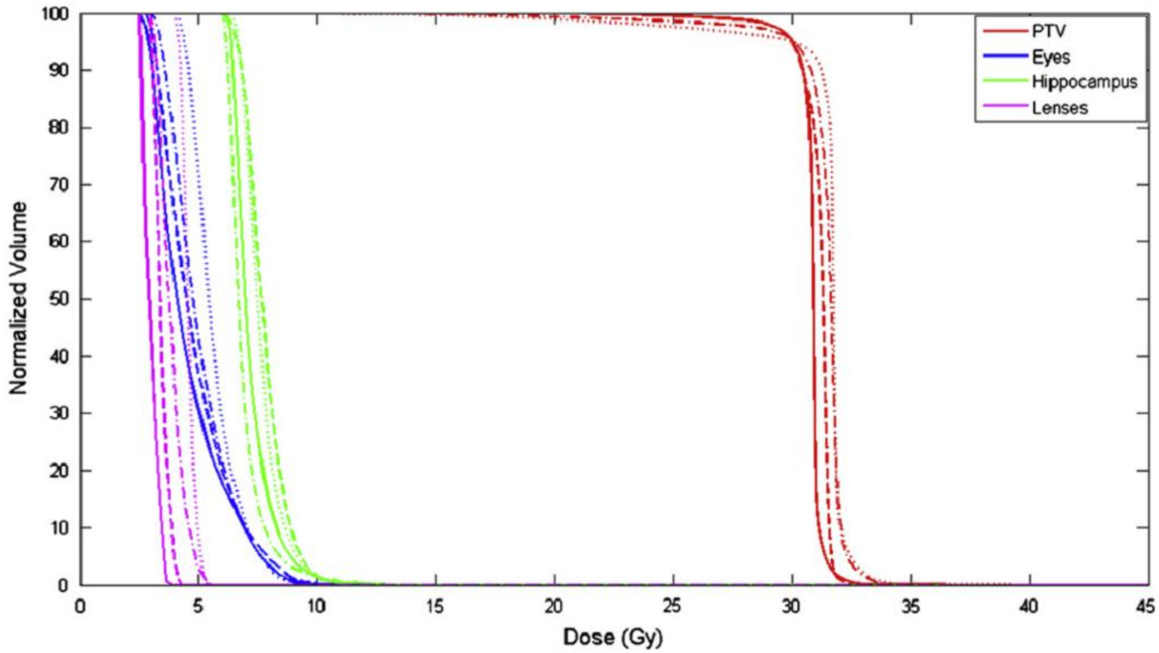


Dose–volume histogram for hippocampal avoidance during whole-brain radiotherapy using linear accelerator

Gondi et al.

Technical strategies for reduction of neurotoxicity in whole brain radiotherapy

- Tomo: 10x 3Gy: hippocampus median 5.5Gy, max12.8Gy



Dose–volume histogram for hippocampal avoidance during whole-brain radiotherapy using helical tomotherapy.

Gondi et al.

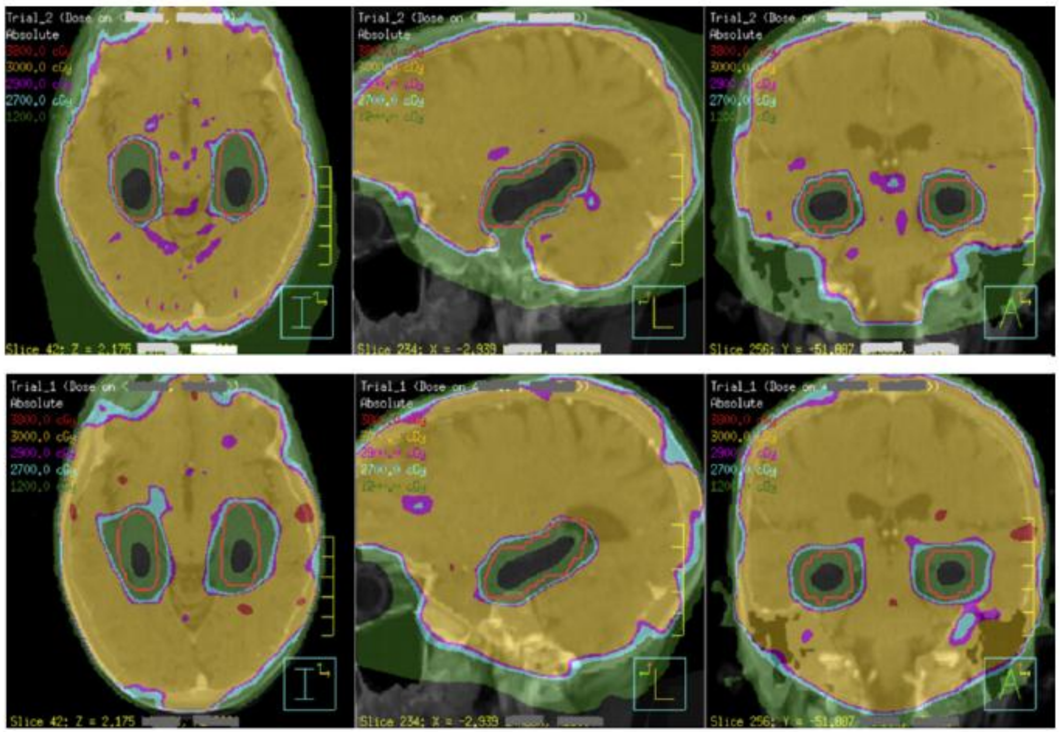
Technical strategies for reduction of neurotoxicity in whole brain radiotherapy

LINAC

A)

TOMO

B)



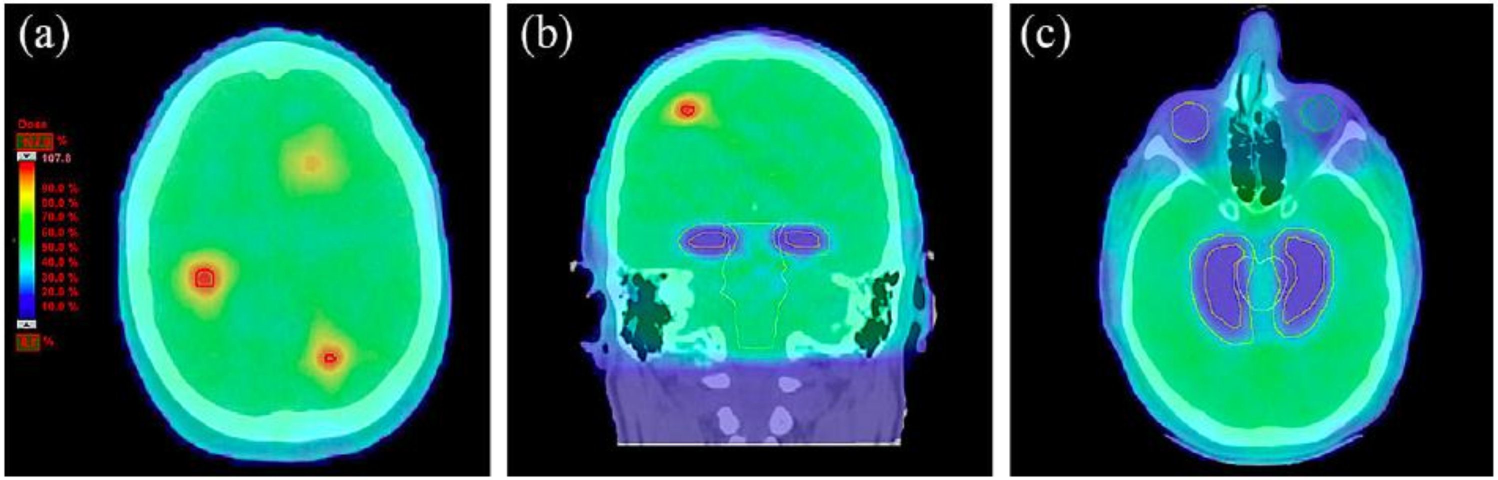
Gray shade: Hippocampus

Orange contour: Hippocampal avoidance region

Gondi et al.

Technical strategies for reduction of neurotoxicity in whole brain radiotherapy

- The prescription to the whole brain was 32.25 Gy in 15 fractions to 95% of the volume
- Dose to brain metastases was 63 Gy to 95% of the volume for lesions **>**2.0 cm in diameter and 70.8 Gy to 95% of the volume for lesions <2.0 cm in diameter



Hsu et al.

Technical strategies for reduction of neurotoxicity in whole brain radiotherapy

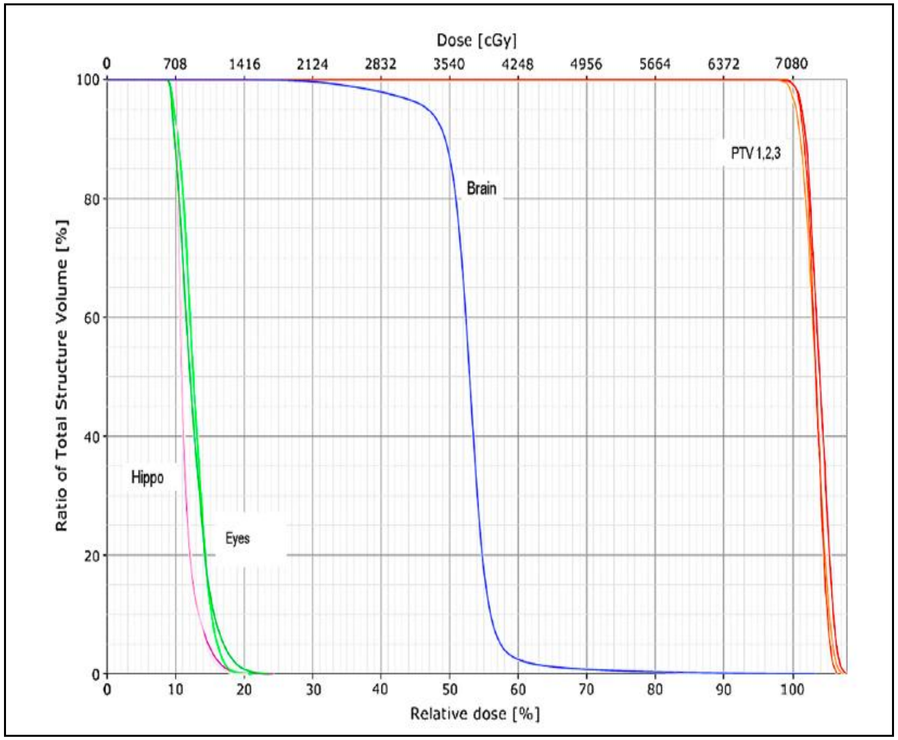


Table 1. Description of metastases and VMAT treatment time for the 10 patients

Patient	No. of metastases	PTV (cm^3)	Prescription dose (Gy)	Treatment time (min)
1	1	1.17	70.8	3.6
2	2	15.15	63.0	3.4
		1.19	70.8	
3	2	2.88	70.8	3.5
		0.61	70.8	
4	2	0.38	70.8	3.5
		0.16	70.8	
5	3	0.16	70.8	3.4
		0.13	70.8	
		0.17	70.8	
6	1	1.29	70.8	3.9
7	2	2.01	70.8	3.6
		3.11	63.0	
8	1	3.80	63.0	3.3
9	3	0.72	70.8	4.1
		0.87	70.8	
		0.82	70.8	
10	1	0.37	70.8	3.3
	Total = 18	Mean = 1.94 ± 3.47		Mean = 3.6 ± 0.3

Abbreviations: VMAT = volumetric modulated arc therapy; PTV = planning target volume. Data are presented as mean ± standard deviation.

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Conclusions

- Sparing of hippocampus structures is possible
- IMRT, VMAT, Tomo seem to be suitable
- No data on improved neurological outcomes available
- No data on tumour control outcomes available

Conclusions → Clinical trials

RTOG 0933 and others

THANK YOU FOR YOUR ATTENTION!