

3D-Radiation Therapy Boost Improves Outcome of Whole Brain Radiation Therapy Treated RPA II Patients with One or Two Brain Metastases

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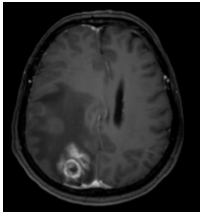
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Brain metastases (BM)

- First cause of intracerebral malign tumor
- Frequent cause of morbidity and mortality in patients suffering from a variety of solid tumors (20 to 40%)
- Lung (40 - 60%), breast (12 - 17%), melanoma (5 - 9%), gastrointestinal (8 - 13%), renal cell cancer (5 - 11%)
- Overall survival :1 month without treatment, 7 months with treatment , 1 to 2 months if corticosteroids alone

Nieder, C., et al. *Cancer*.

Sundstrom, J.T., et al. *Ann Med*, 1998.

Chao, J.H., R. Phillips, and J.J. Nickson *Cancer*, 1954.

Weissman, D.E. *J Clin Oncol*, 1988.

Sperduto, P.W., et al. *Int J Radiat Oncol Biol Phys*, 2010.

Antoni, D, et al. *Int J Radiat Oncol Biol Phys*, 2013.

Management of BM



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graph TD; A[Management of BM] --> B[Symptomatic therapy]; A --> C[Brain directed therapy]; C --> D[Either alone or in various combinations depending on the site, size and number of BM]; D --> E[Systemic treatments chemotherapy, radio-sensitizers, targeted therapies];
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Symptomatic therapy

- Corticosteroids treatment
- Anticonvulsivants
- Palliative care

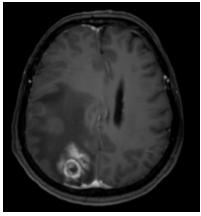
Brain directed therapy

- Whole brain radiotherapy: standard of care for years
- Radiosurgery (SRS)
- Neurosurgery

Either alone or in various combinations depending on the site, size and number of BM

Systemic treatments

chemotherapy, radio-sensitizers, targeted therapies

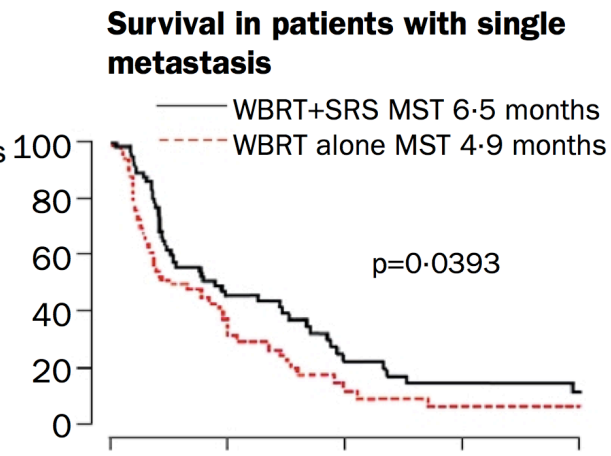
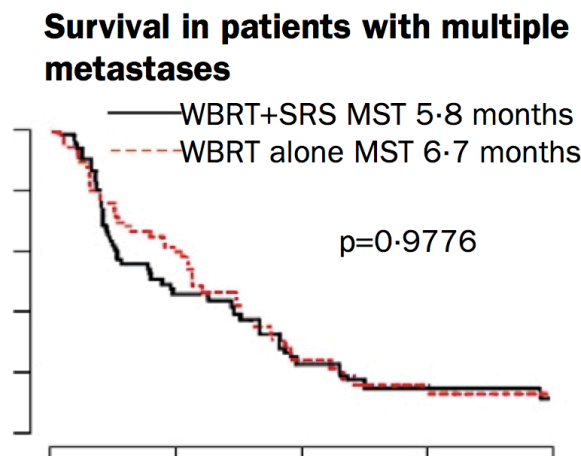
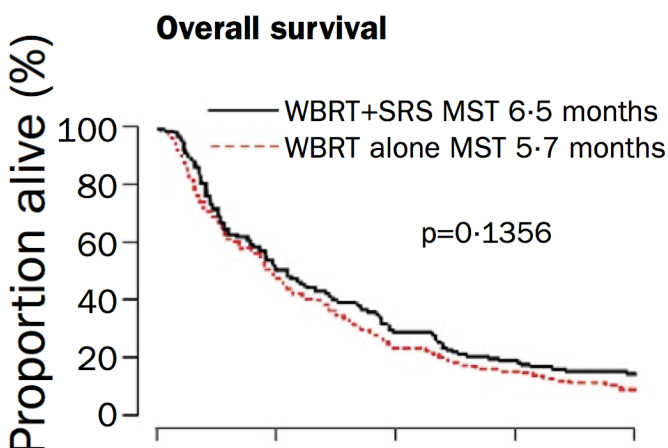


Additional boost on the metastatic site

- Surgery combined with WBRT improved OS compared to WBRT alone or surgery alone (Patchell et al., Vecht et al.)
- **The benefit of an additional boost on the metastatic site is discussed**
- Two retrospective analysis
- Rades *et al.*: *retrospective analysis of 416* patients with BM treated with WBRT: no benefit in term of survival with a dose > 30Gy. (Cancer 2007)
- Rades *et al.* : surgical resection and WBRT +/- radiation boost to the metastatic site for patients with 1 to 2 BM. Improved 1-year OS for patients treated with WBRT and boost (66% vs. 41%; $p < 0.001$). (Cancer 2007)

WBRT +/- SRS: randomised trials

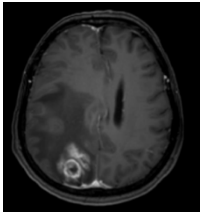
		n	# BM	Median survival (months)		LC at 1 year	
Chougule (2000)	SRS	36	1 - 3	7		87%	
	SRS + WBRT	37		5		91%	
	WBRT	31		9		62%	
Kondziolka (1999)	WBRT	14	2 - 4 (≤ 25 mm)	7.5	P=0.22	0%	P=0.0016
	SRS + WBRT	13		11		92%	
Andrews (2004)	WBRT	167	1 - 3 (20 - 40 mm)	5.7	P=0.1	71%	P=0.01
	SRS + WBRT	164		6.5		82%	



Andrews et al. Lancet 2004



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Patients and Methods

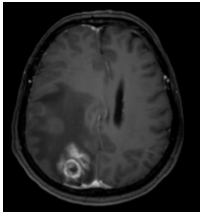
- **Single institutional retrospective analysis of a database of 208 patients treated for BM between September 2005 and December 2010**
- **Patients RPA II with 1 to 2 unresectable BM**
- **122 patients (58.7%): 1 BM**
- **86 patients (41.3%): 2 BM**
- **76 patients (36.5%): WBRT 30 Gy in 10 fractions of 3 Gy, 5 fractions a week, two weeks**
- **132 patients (63.5%): WBRT + 3D conformational radiation boost at the metastatic site: 9 Gy in 3 fractions of 3 Gy, 3 consecutive times per week**

Site of primary tumor	Entire series (n=208) N (%)	BOOST (n=132) 63.5% N (%)	NO BOOST (n=76) 36.5% N (%)
Lung	137 (65.9)	85 (64.4)	52 (68.4)
Breast	18 (8.6)	13 (9.8)	5 (6.6)
Melanoma	10 (4.8)	4 (3.0)	6 (7.9)
Gastro-intestinal	16 (7.7)	12 (9.2)	4 (5.3)
Renal cell carcinoma	7 (3.4)	5 (3.8)	2 (2.6)
Other	20 (9.6)	13 (9.8)	7 (9.2)

• Evaluation of seven potential prognostic factors:

- gender
- KPS
- primary tumor type
- presence of ECM (extracranial metastasis)
- number of ECM
- control of primary tumor
- interval between BM diagnosis and treatment

Characteristic		BOOST (n=132) N (%)	NO BOOST (n=76) N (%)	p
Age (y)	Median	63.4 (21.2-86.2)	65.2 (20.9-85.7)	0.33
Gender	Male	96 (72.7)	57 (75.0)	0.67
	Female	36 (27.3)	19 (25.0)	
KPS	70-80	91 (68.9)	52 (68.4)	0.79
	90-100	41 (31.1)	24 (31.6)	
BM	1	90 (68.2)	32 (42.1)	0.48
	2	42 (31.8)	44 (57.9)	
ECM	Yes	106 (80.3)	63 (82.9)	0.9
	No	26 (19.7)	13 (17.1)	
No of ECM	1	41 (38.7)	26 (41.3)	0.35
	≥2	65 (61.3)	37 (58.7)	
Control of primary tumor	Yes	56 (42.4)	17 (22.4)	0.04
	No	76 (57.6)	59 (77.6)	
Neurological symptoms	Yes	74 (56.1)	38 (50.0)	0.9
	No	58 (43.9)	38 (50.0)	



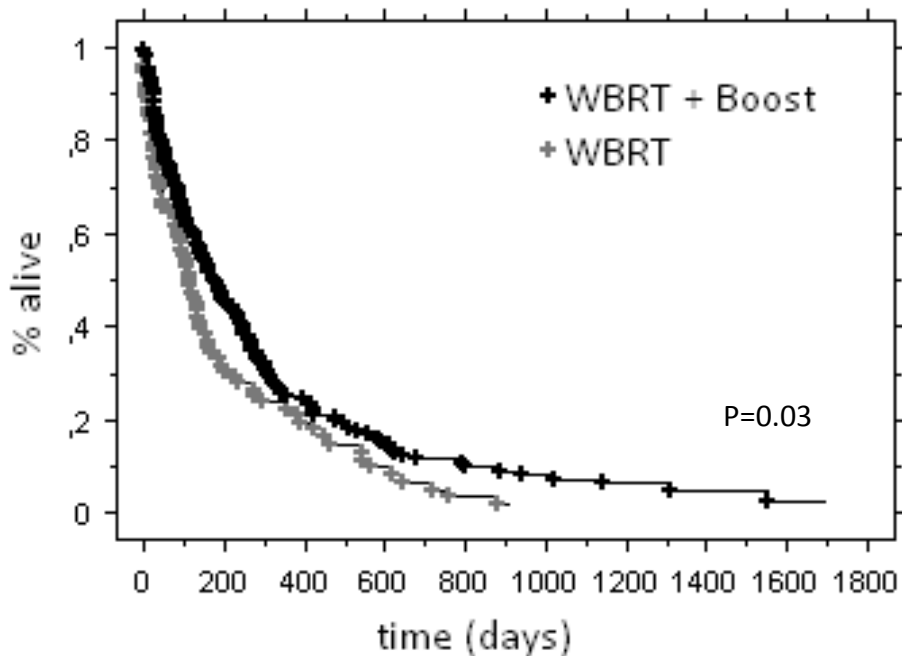
Results

- Overall median follow-up: 4.8 months (0-56.4 months)
- Median follow-up time of surviving patients: 30.3 months (12.4-56.4 months)
- 11 patients (5.3%) were alive at the time of analysis
- Comparable proportion in the two groups
- **Group WBRT + boost:** 125 patients (94.7%) deceased, 8% (n=10) of neurologic death
- **Group WBRT alone:** 72 patients (94.7%) deceased, 18% (n=13) of neurologic death

Median overall survival times:

1BM and 2BM: 4.6 months and 5.1 months ($p=0.4$)

Group WBRT + boost and **group WBRT alone**: 5.9 and 3.7 months ($p=0.03$)



Median survival	at 6 months (%)	at 12 months (%)	at 18 months (%)	at 24 months (%)	p
WBRT + Boost	48.5	25	17.4	10.6	0.03
WBRT alone	34	22.4	12	3.2	

Prognostic factors of overall survival:

	BOOST	NO BOOST
Univariate analysis	Gender (p<0.0001) Primary tumor type (p<0.0001) KPS>70 (p=0.02)	Primary tumor type (p=0.01) KPS >70 (p=0.05)
Multivariate analysis	Female gender (HR 0.54, CI95% 0.1-0.92, p=0.02) Primary tumor type: breast cancer vs other (HR 0.3, CI 95% 0.11-0.77, p=0.03) KPS>70 (HR 0.66, CI95% 0.44-0.98, p=0.04)	Primary tumor type (p=0.02) (breast cancer and RCC vs other) KPS > 70 (HR 0.55 Ci 95% 0.32-0.93, p=0.02)

Overall survival according to the primary type tumor (months):

	BOOST	NO BOOST	<i>p</i>
breast	26.6	9.1	0.01
lung	7.3	4.4	0.1
GI	2.9	1.3	0.06
RCC/melanoma	3.5	3	0.3

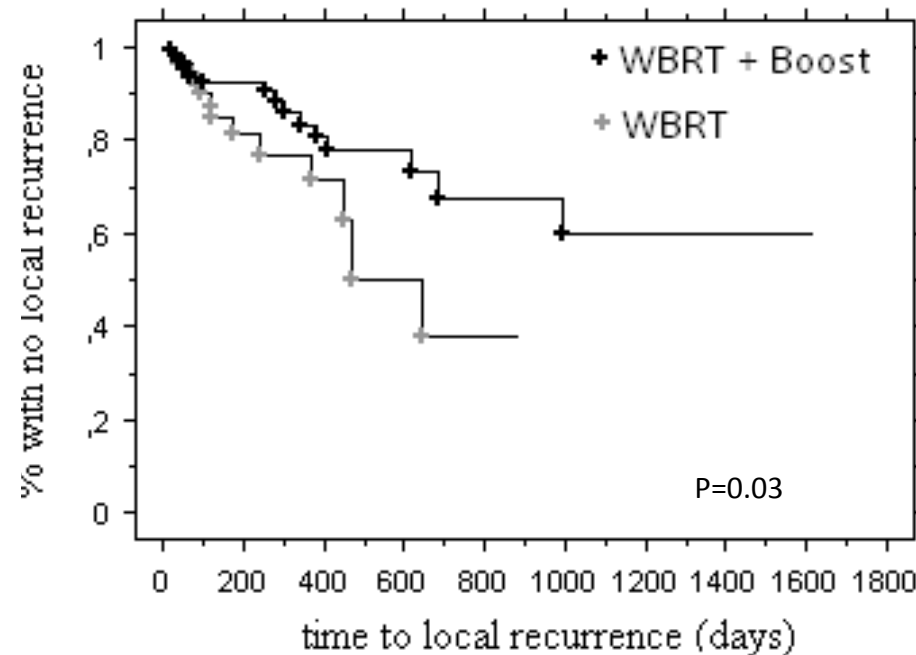
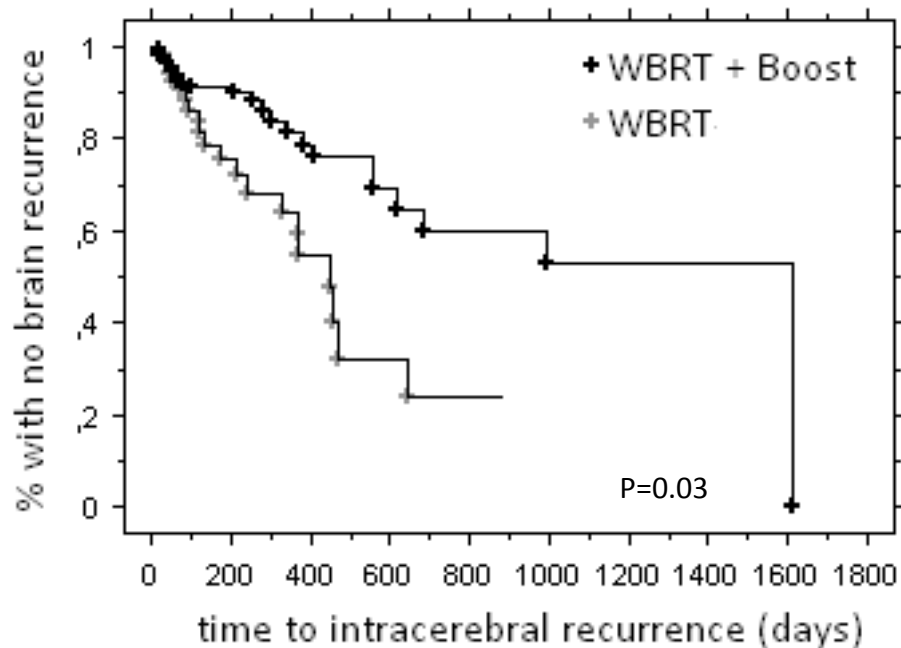
Local and brain controls:

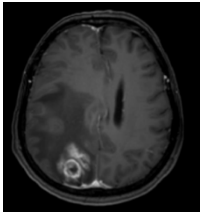
	Brain recurrence (n) (% of N)	Local recurrence n (% of N)	Regional Recurrence n (% of N)	Both n (% of N)	Unknown n (% of N)	Median delay of recurrence (months)
BOOST (N=132)	23 (17.4)	14 (10.6)	5 (3.8)	3 (2.3)	1 (0.75)	8.4 (1–54)
NO BOOST (N=76)	20 (26.3)	7 (9.2)	7 (9.2)	6 (7.9)	0	5.2 (1.2–21.5)
Total (N=208)	43 (20.6)	21 (48.8)	12 (27.9)	9 (20.9)	1 (2.3)	6.9 (1-54)

12.9% (**BOOST**) vs 17.1% (**NO BOOST**)
Local recurrence alone + local and regional recurrences

Local and brain controls:

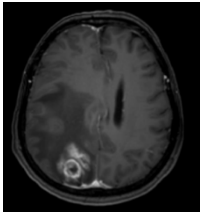
		at 6 months (%)	at 12 months (%)	at 18 months (%)	at 24 months (%)	<i>p</i>
Local control	BOOST	92	82	77.4	67	0.03
	NO BOOST	81.2	75	55	37.5	
Brain control	BOOST	88.7	75.8	69	62	0.03
	NO BOOST	78.5	59	44	37.7	





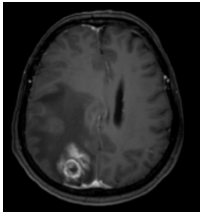
Discussion

- Overall survival comparable to those of Gaspar et al. (4.8 months and 4.5 months).
- Andrews *et al.* have compared WBRT vs WBRT+RS: patients treated with the combined therapeutic had an overall survival of 5.8 months (5.9 months in our study).
- EORTC 22952-26001 study: local and brain relapses at 2 years for patients treated by radiosurgery and adjuvant WBRT were 19% and 33% (33% and 38% in our study),
- but patients RPA I in the EORTC study and boost: radiosurgery



Discussion

- The difference in OS is probably not explained by cranial disease because there was no difference in terms of neurological death.
- Probably explained by extracranial disease (control of primary tumor)
- The control of primary tumor may be a prognostic factor of overall and distant free survival for these patients, this would confirm the conclusions of several retrospective studies before.
- Patients with breast cancer and good performance status would have a clinically and statistically significant benefit.



Conclusions

- For RPA II patients with 1 or 2 unresectable BM, WBRT and an additional radiation boost delivered with 3D conformal radiotherapy improves local and brain metastatic control rates significantly.
- Dose escalation may result in an improved outcome in selected patients even if not thought suitable for radiosurgery or surgery alone.
- A radiation boost delivered with 3D conformal radiotherapy could be applicable to all radiotherapy departments where radiosurgery is not available, increasing access of this treatment to a wider group of patients.