


Place of surgery in diagnostic and therapeutic strategies: New challenges



**2nd Annual Brain Metastases Research
and Emerging Therapy Conference**

Philippe Métellus M.D., Ph.D.
Department of Neurosurgery, CHU Timone, Marseille, France

Place of surgery in diagnostic and therapeutic strategies: New challenges

Increasing incidence of cancer and the improvement of systemic treatment led to an increased incidence of brain metastases

Brain metastases has become a major public health problem

Evolving indication of surgical resection in BM

WBRT vs. Surgery + WBRT

	Study design/ Evidence based class	Intervention	Population	Median survival	Patients with rec./prog.	Time to rec./prog.
Patchell, 1990	RCT Class 1	G1 : WBRT (n=23) G2 : surgery +WBRT (n=25)	Unique BM	G1 : 15 sem. G2 :40 sem. OS curves Log rank P<0.01	Local G1 :12/23(52%) G2 :5/25(20%) P<0.02 At distance G1 :3/23(13%) G2 :5/25(20%) P=NS	Local G1 :21 we G2 :>59 we Local rec. curves Log rank P<0.0001
Vecht, 1993	RCT Class 1	G1 : WBRT (n=31) G2 : surgery +WBRT (n=32)	Unique BM	G1 : 3 mo G2 : 15 mo OS curves Log rank P=0.04	NR	NR
Mintz, 1996	RCT Class 1	G1 : WBRT (n=43) G2 : surgery +WBRT (n=41)	Unique BM	G1 : 6.3 mo G2 : 5.6 mo Os curves Log rank P=NS	NR	NR

Populations characteristics

	N patients	b Age (années)	KPS<70	Controlled extracranial disease	Preop MRI
Patchell, 1990	48	59.5 +/- 9.7	9/48 (18.8%)	30/48 (62.5%)*	48/48 (100%)*
Vecht, 1993	63	59.2 +/- 10.3	17/63 (27.0%)	43/63 (68.3%)*	NR
Mintz, 1996	84	58.9 +/- 9.3	20/84 (23.8%)	18/84 (21.4%)*	0/84 (0%)*

Selecting patients for surgical resection

Clinical status and patient characteristics

- Age
- pre-operative KPS score
- Interval between primary tumor occurrence and BM

Status of the systemic disease

- Active vs. Controlled
- Extracranial metastases
- Expected time of survival

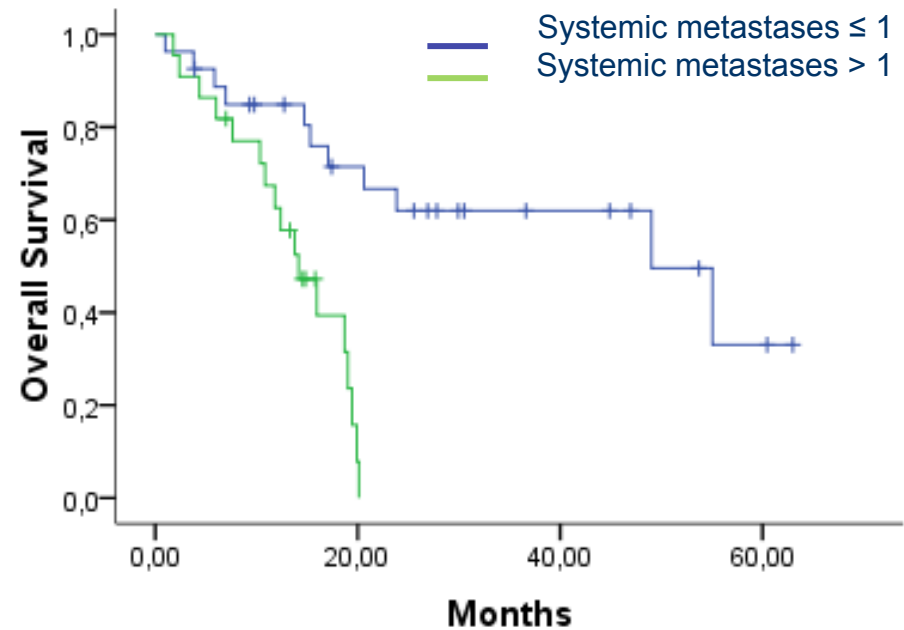
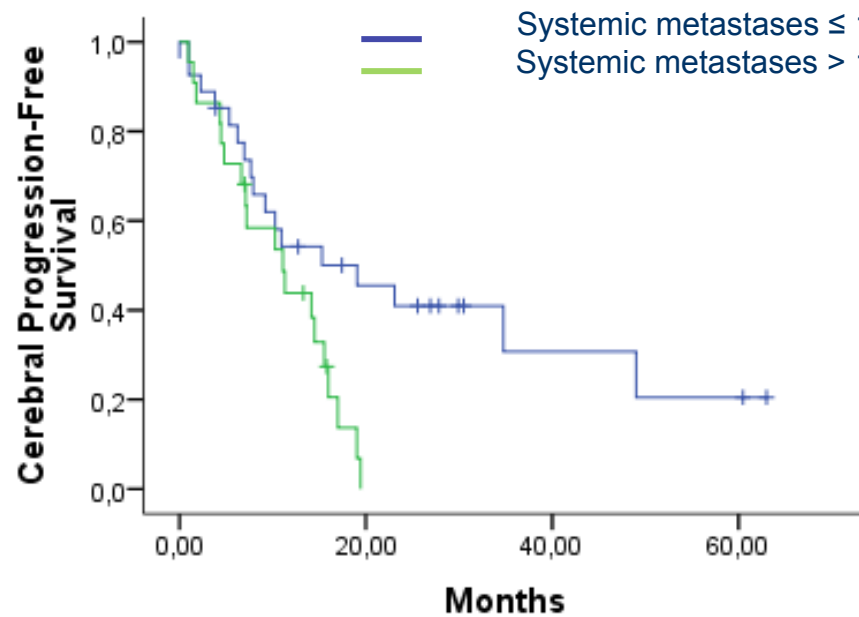
Intracranial features of the tumor

- Single vs. multiple brain lesions
- Cystic or necrotic aspect
- Mass effect
- Location / eloquent areas

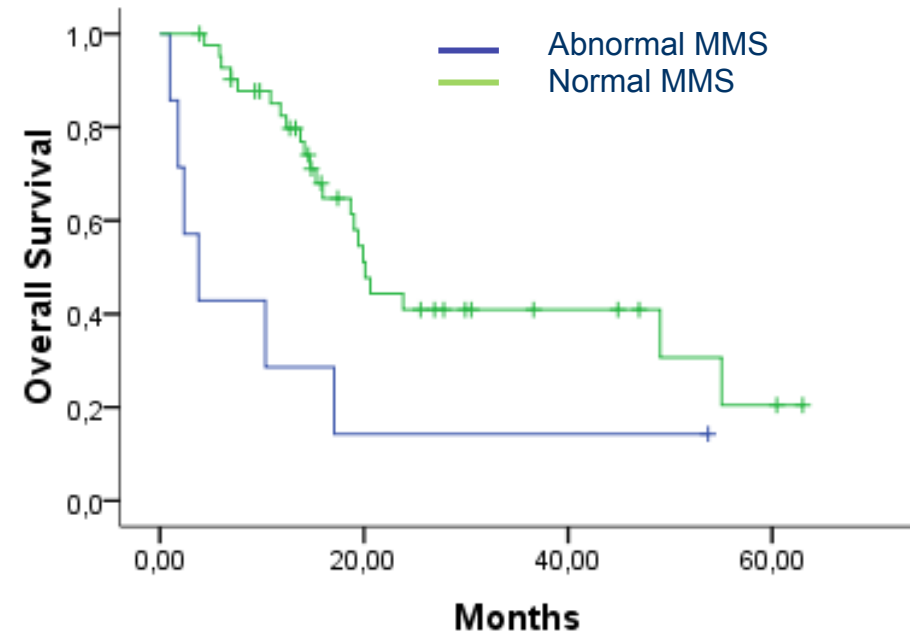
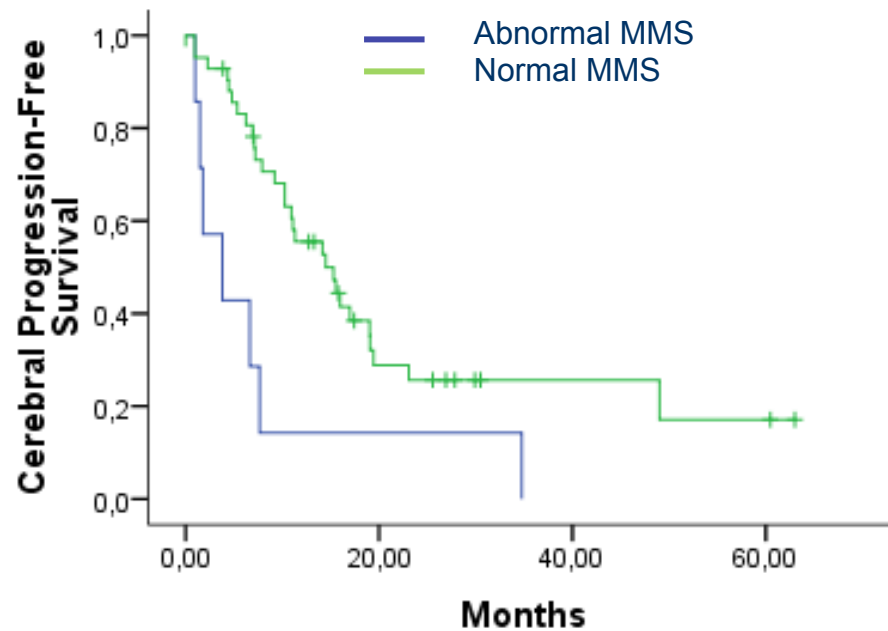
Retrospective study on BM from BC surgically treated at our institution

Characteristics	Data	%
<u>Patient-related</u>	49	
Age (range)	54 years (28 – 75)	
Gender (Men/women)	1 / 48	
KPS median	80 (50 - 90)	
≥ 70	34	69
< 70	15	31
2	14	28.6
≥ 3	10	20.4
<u>BM-related</u>		
Interval primary - BM diagnosis	43 months (0 - 214)	
Interval primary – first metastases diagnoses	34 months (0 - 214)	
Number of BM		
1	24	51.1
2	8	17

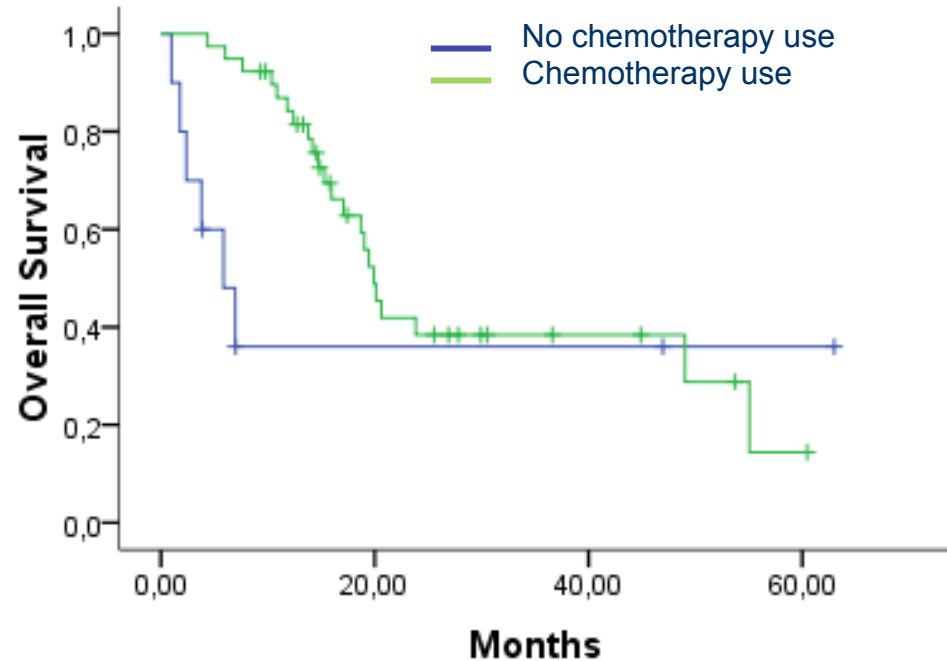
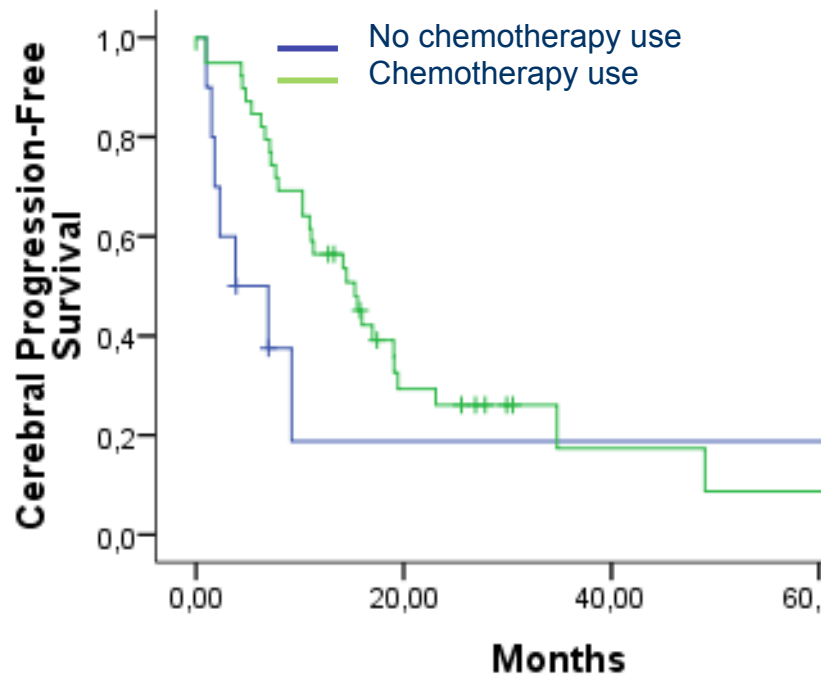
Number of systemic metastases is associated with cerebral progression-free and overall survival



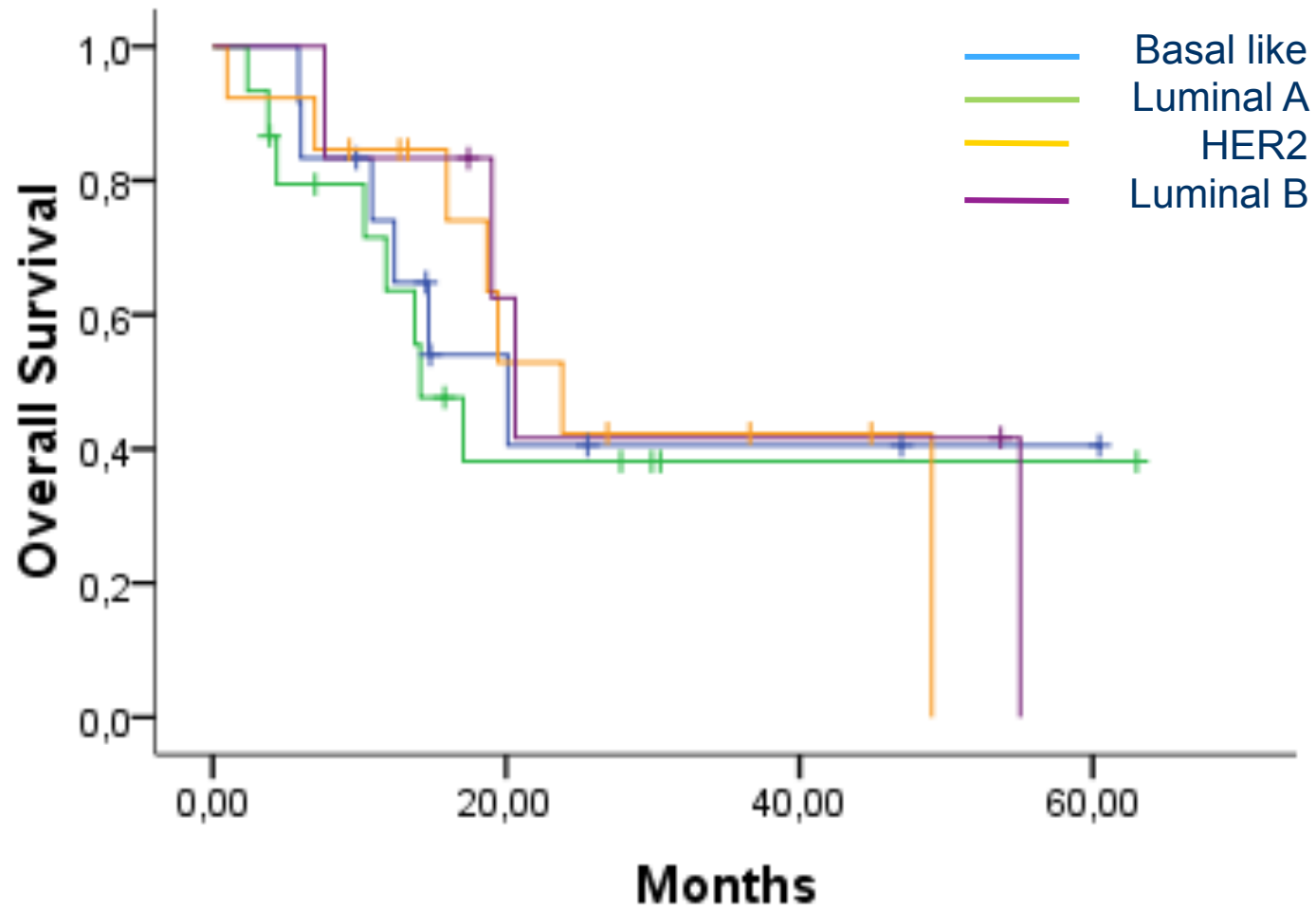
MMS score is associated with cerebral progression-free and overall survival



Adjuvant chemotherapy is associated with cerebral progression-free and overall survival



Molecular subtype does not affect overall survival



Prognostic factors in surgical series

RPA, Nieder, Niwinska and Sperduto classifications did not impact C-PFS and OS

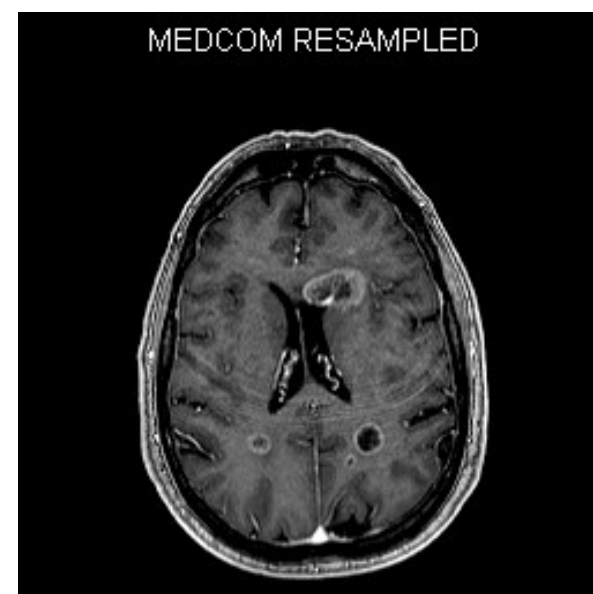
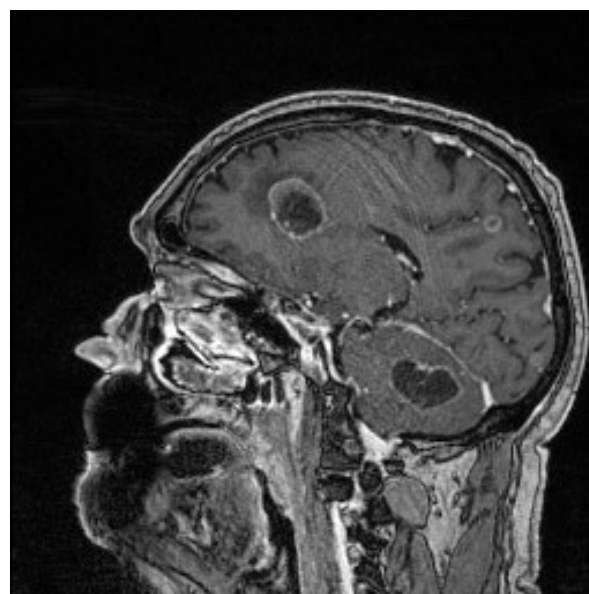
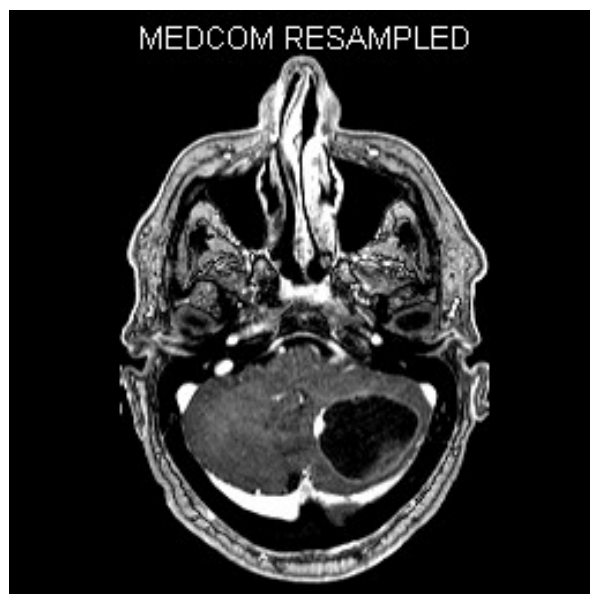
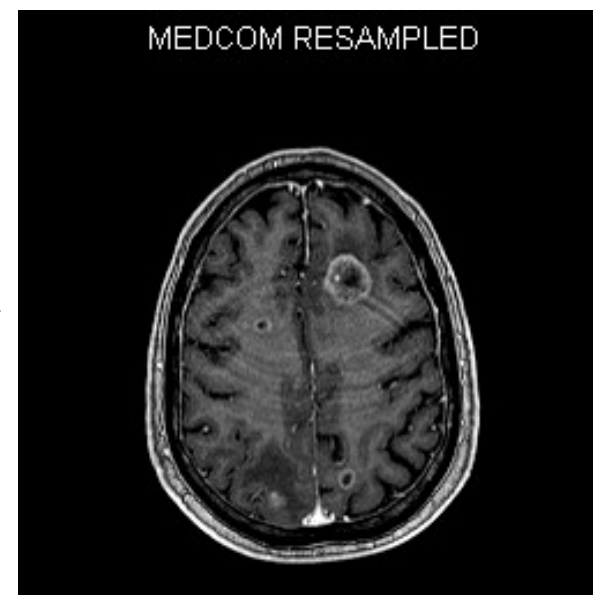
Pre-operative KPS score did not impact C-PFS and OS

Interval between primary tumor diagnosis and BM occurrence did not impact survival

Number of BM did not impact C-PFS and OS



64 year-old man
BM synchronous of a
lung cancer
KPS<70
Multiple brain lesions



Molecular status between primary and metastatic disease

10.3 % of patients presented a modification of Her2 status between primary and BM tumor

- 1 patient with primary Her 2 + tumor had a Her2- BM
- 2 patients with primary Her2- tumor had a Her2+ BM

22% of patients had a modification of their HR status between primary and recurrent tumor

Lessons from a retrospective surgical series

Limitations

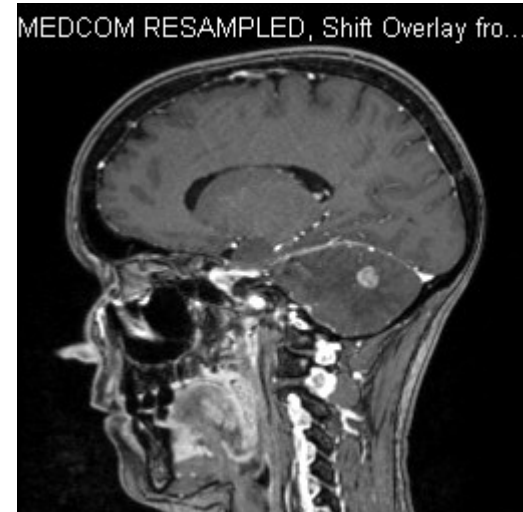
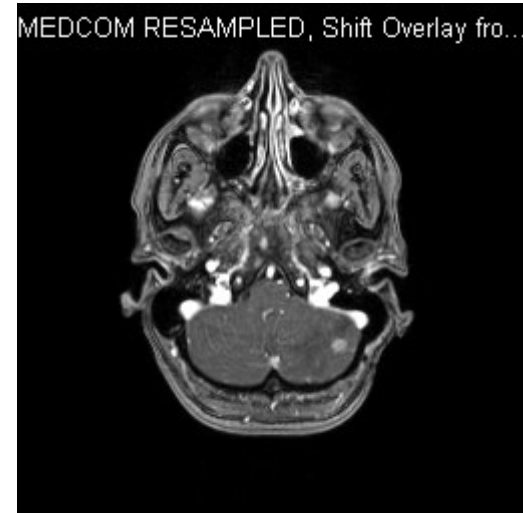
- Small and retrospective series
- Only breast cancer patients

Emerging questions

- Does KPS score and RPA classification are relevant in these surgical patients?
- Do we have to take into account molecular subtypes of the primary tumor in the decision process?
- When do we have to document biologically the metastatic brain disease or any metastatic localization?

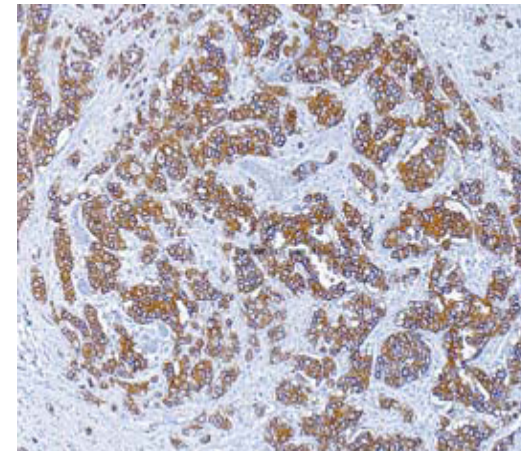
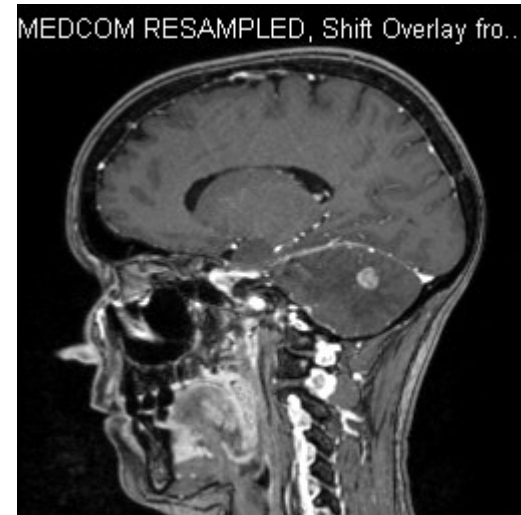
Her2 differential expression in primary tumor and breast cancer BM :Case report

- Woman 49 year-old
- Diagnosis of BC Her2- in 2008
- Trt: 3 FEC 100/3 Taxotere
- 2010 lymph node relapse
- Trt Taxol /Avastin
- 2012 cerebral progression
 - Gamma Knife radiosurgery?
 - Surgery?



Her2 differential expression in primary tumor and breast cancer BM :Case report

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- 2011 cerebral progression
 - **Surgery + WBRT**
- Introduction of Herceptin
- 2012 local and systemic control



Surgical resection or stereotactic radiosurgery for BM ?

Size < 3 cm

No/few mass effect

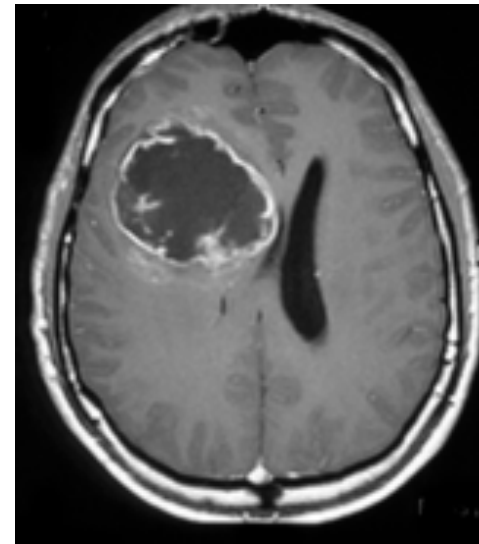
Asymptomatic

Location: deep seated

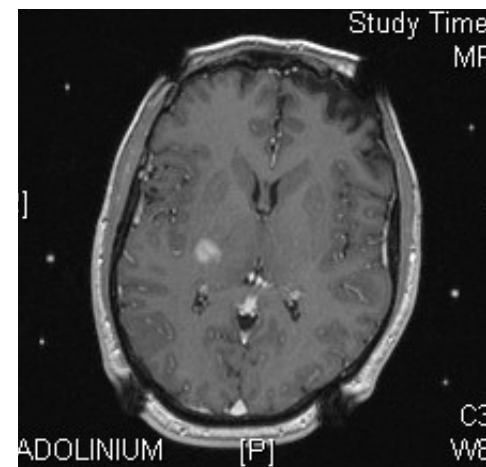
No/few edema

No/few cystic/necrotic features

Confirmation histol. not needed



**Surgery
candidate**



**SRS
candidate**

Surgical resection or stereotactic radiosurgery for BM ?

	Surgical resection	Stereotactic radiosurgery
Patient selection		
Tissue diagnosis	Confirms the lesion is a tumor	Can't confirm the lesion is a tumor
Lesion size	Large, $\geq 1.5 \text{ cm}^3$; especially if there is mass effect	Small, $\leq 3.0 \text{ cm}^3$; significant mass effect absent
Surgical candidate	Yes	No (or patient declines surgery)
Treatment outcome		
Tumor status	Removed ($\geq 94\%$ on average) ^b	Not removed
Local control	85% for >40 months (up to 5 years) ^c	85% at 12 months; 65% at 24 months ^d
Local recurrence rate	8 ^c to 12% ^b	30 ^e to 47% ^f
Median survival time	10 ^g to 16.4 ^c months	7.5 ^c to 14 ^h months
Complications		
Presentation	Usually immediate	Frequently delayed; necrosis may necessitate surgical resection
Major neurological	7% in eloquent brain; 6% overall ^b	25% in eloquent brain (RTOG ⁱ grade 3) ^j
Mortality (30-day) ^k	$<2\%$	1.8%

Surgical resection or stereotactic radiosurgery for BM ?

	Surgical resection	Stereotactic radiosurgery
Cost-effectiveness	Based on 3-day hospital stay	Based on 1-day outpatient stay; includes no costs of maintenance steroids, follow-up office visits, or follow-up MR images
Quality of life		
Relief from mass effect	Immediate	Delayed
Steroid use	Tapered off over 2–4 weeks	Can last for months; may cause dependence
Follow-up visits	Few	Many
Patient debilitation	Not debilitated at home	Debilitated at home

Chirurgie + IPE vs SRS seule

Interventions	Median survival	Recurrence/progression (1 yr control rate)		Median time to recurrence/progression	
		At original site	At distant brain site	At original site	At distant brain site
G1: SRS (n=31)	10.3 months	97%	26%	Median not reached	Median not reached
G2: Surgery+WBRT (n=33)	9.5 months	82%	3%	Median not reached	Median not reached
	(NS)	(NS)	(P<0.01)	(NS)	(P=0.04)

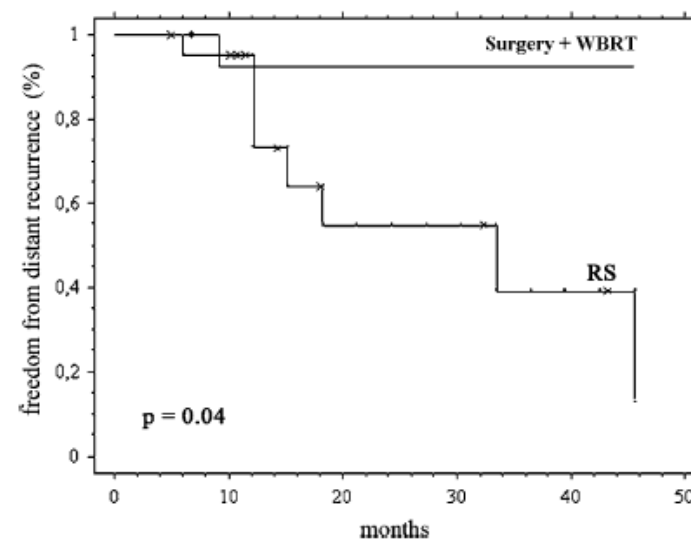
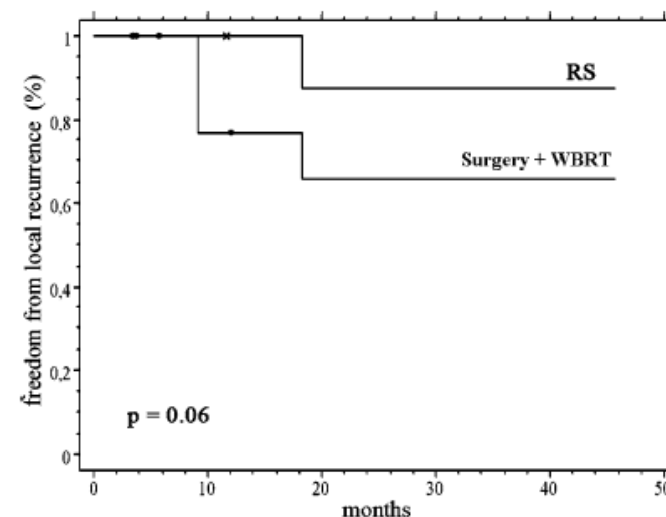
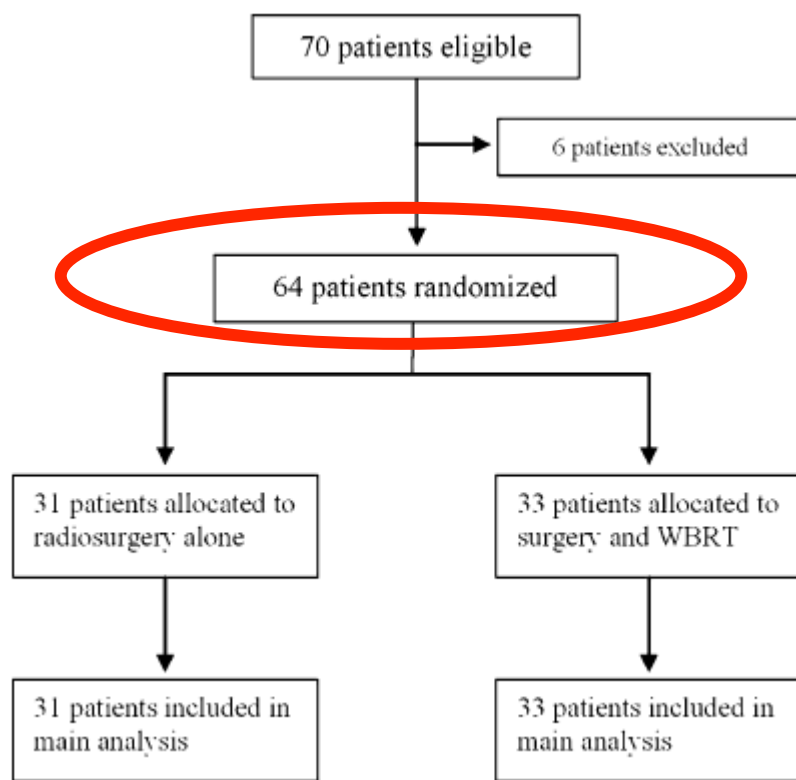
*Randomized Control Trial closed early with only ¼ of the proposed participants.

One major drawback: remaining enhancing abnormality stable over time after SRS considered « local control » (questionable)

Muacevic, 2008, *J Neurooncol*

Surgery + WBRT vs WBRT

242 patients to include



Muacevic, 2008, *J Neurooncol*

Chirurgie + IPE vs SRS seule

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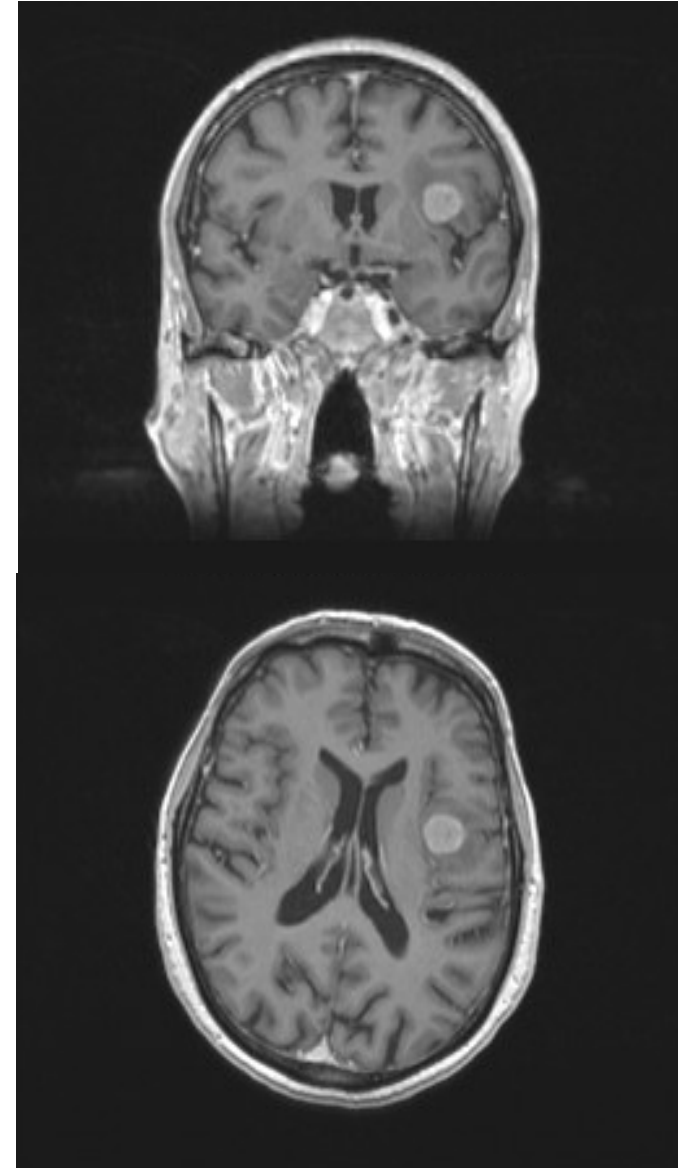
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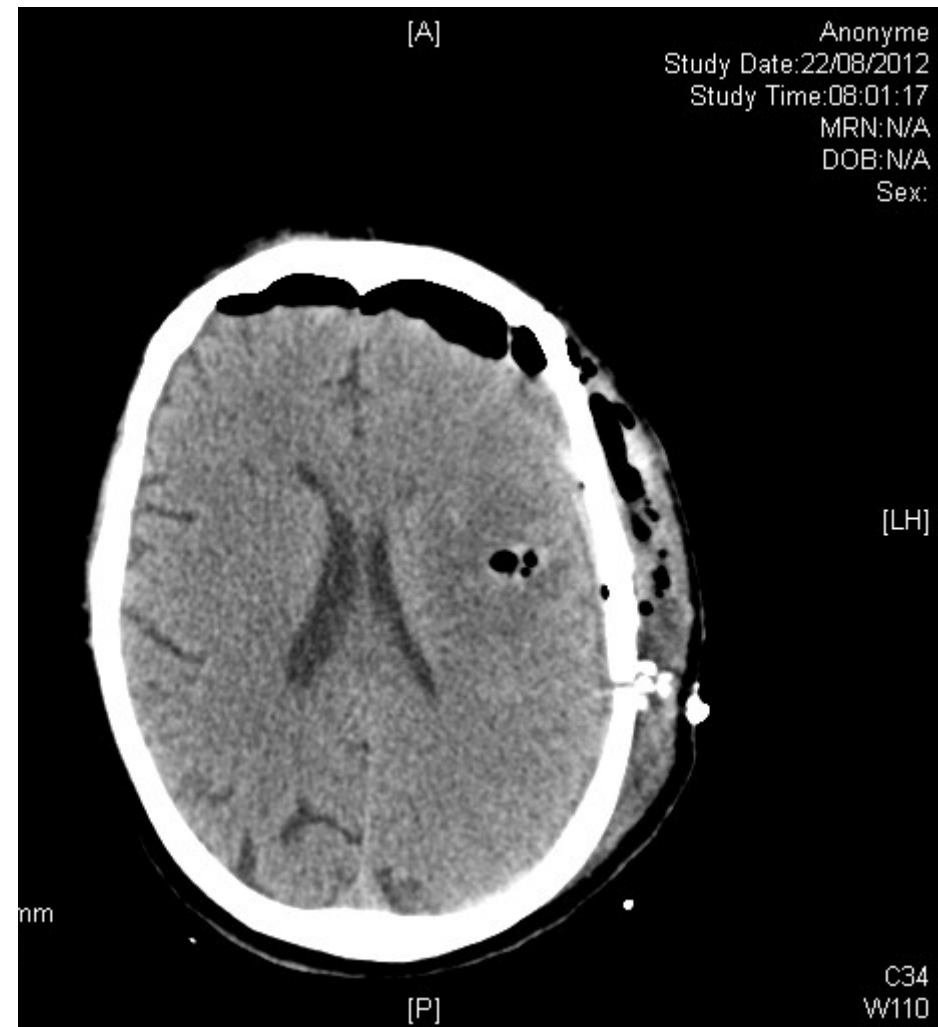
Surgical resection of BM in eloquent areas

- Man 61 year-old, right-handed
- Partial seizure august 2012/Aphasia
DO 80 (63/80)
- Right superior limb numbness
- Brain MRI: solitary lesion
- Body scan: lung cancer
- Treatment
 - **Radiosurgery ?**
 - **Surgery ?**



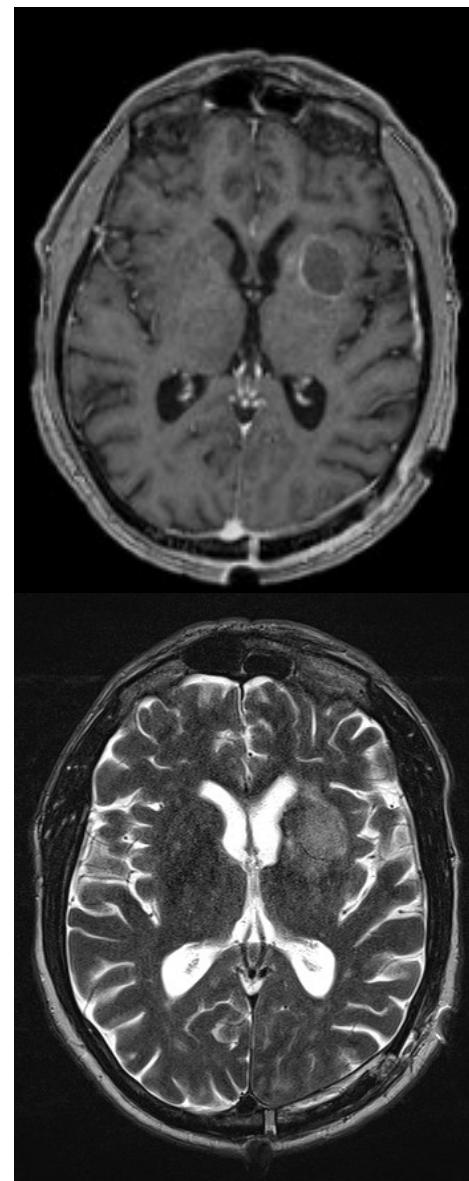
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- Body scan: lung cancer
- Treatment
 - **Surgery : awake craniotomy**
- Discharged at day 5 / DO 80 (74/80)
- WBRT planned



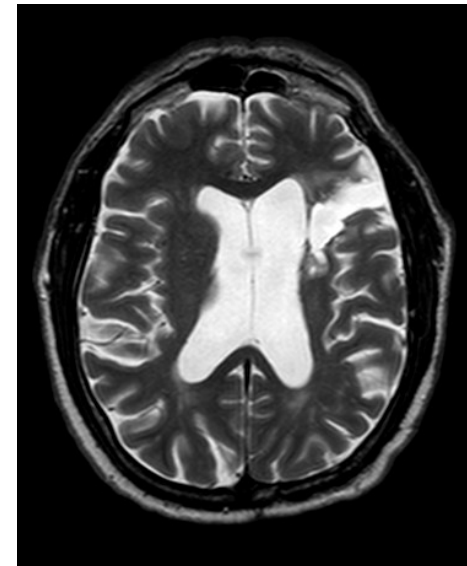
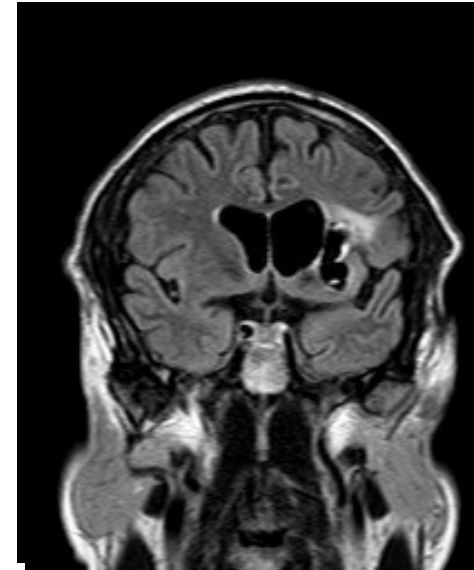
Surgical resection of BM in eloquent areas

- Man 53 year-old, right-handed
- Temporal secondarily generalized seizure
- Brain MRI: solitary lesion
- Body scan: normal
- Treatment
 - Biopsy ?
 - Surgery ?



Surgical resection of BM in eloquent areas

- Man 53 year-old, right-handed
- Temporal secondarily generalized seizure
- Brain MRI: solitary lesion
- Body scan: normal
- Treatment
 - **Surgery: awake craniotomy**
- Patient discharged at day 7
- Histology: lung ADK, K-ras mutated
- Inclusion in a RCT



Conclusion

In 2012 microsurgical removal of BM still represents an actual effective and efficient treatment option in the management of brain metastatic disease

BM located in eloquent must be discussed in neurosurgical staff to thoroughly assess their resecability

KPS score and RPA classification in presence of symptomatic BM are probably less relevant than in asymptomatic ones

Surgery must be considered in the treatment decision making process of BM when the biology of the metastatic disease could affect the therapeutic strategy:

MOLECULAR SURGICAL INDICATION