



Surgery for recurrent brain metastases

Pr Philippe METELLUS

Neurosurgeon, Clairval Hospital Center, Marseille

8th Annual Brain Metastases Research and Emerging Therapy
Conference

September 21st, 2018

Conflict of Interest Declaration

Herewith I confirm that I do NOT have any relevant financial relationships with commercial interests.

Recurrent brain metastatic disease

- Recurrence after which first line treatment? (Surgery, SRS, WBRT, systemic treatment, ...)
- Actual incidence of recurrent brain metastasis (BM)
- Definition of a recurrent BM
- Place of surgery in patients with recurrent BM
 - ✓ Diagnostic issues
 - ✓ Prognostic issues
 - ✓ Strategic issues

Recurrent brain metastatic disease

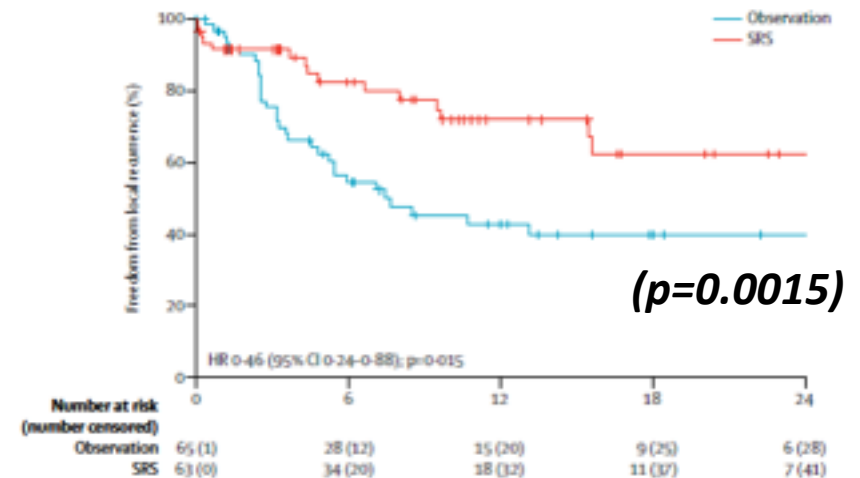
- Recurrence after which first line treatment? (Surgery, SRS, WBRT, systemic treatment, ...)
- Actual incidence of recurrent brain metastasis (BM)
- Definition of a recurrent BM
- Place of surgery in patients with recurrent BM
 - ✓ Diagnostic issues
 - ✓ Prognostic issues
 - ✓ Strategic issues

Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

Anita Mahajan, Salmaan Ahmed, Mary Frances McAleer, Jeffrey S Weinberg, Jing Li, Paul D Brown, Stephen Settle, Sujit S Prabhu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Sulman, Ian E McCutcheon, Syed Azeem, Daniel Cahill, Claudio Tatsui, Amy B Heimberger, Sherise Ferguson, Amol Ghia, Franco Demonte, Shaan Raza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, Kenneth R H Ganesh Rao

Lancet Oncol 2017; 18: 1040-48

- Phase III study – 1 to 3 complete resected BM
- Randomized : 128 patients included
 - SRS group : surgery + SRS (63 patients)
vs
 - Observation group : Surgery (65 patients)
- Primary endpoint:
 - Time to local recurrence
- Secondary endpoint
 - OS
 - Time to distant brain recurrence



12-month freedom from local recurrence

- 43% in the OBSV group
- 72% in the SRS group

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial

Paul D Brown, Karla V Ballman, Jane H Cerhan, S Keith Anderson, Xiomara W Carrero, Anthony C Whitton, Jeffrey Greenspoon, Ian F Parney, Nadia N I Laack, Jonathan B Ashman, Jean-Paul Bahary, Costas G Hadjipanayis, James J Urbanic, Fred G Barker II, Elana Farace, Deepak Khuntia, Caterina Giannini, Jan C Buckner, Evanthia Galanis, David Roberge

Lancet Oncol 2017; 18:1-12

- Median time to Intracranial tumor progression : (**$p=0.001$**)
 - 6.4 mo in the SRS group
 - 27.5 mo in the WBRT group
- 12-months surgical bed control (**$p=0.00068$**)
 - 60.5% in the SRS group
 - 80.6% in the WBRT group

		Control Estimates (95%CI)		Gray's K-sample p-value
		SRS	WBRT	
Surgical Bed Control				p = 0.00068
at 3 months	95.9% (92.0, 99.9)	93.5% (88.7, 98.7)		
at 6 months	80.4% (72.8, 88.7)	87.1% (80.5, 94.2)		
at 12 months	60.5% (51.3, 71.3)	80.6% (73.0, 89.1)		
Local Control				p = 0.00016
at 3 months	84.7% (77.9, 92.1)	96.7% (93.2, 100)		
at 6 months	69.4% (60.8, 79.1)	92.5% (87.3, 98.0)		
at 12 months	61.8% (52.8, 72.3)	87.1% (80.5, 94.2)		
Distant Brain Control				p = 0.00045
at 3 months	88.7% (82.6, 95.2)	96.8% (93.3, 100)		
at 6 months	72.1% (63.7, 81.6)	94.6% (90.1, 99.3)		
at 12 months	64.7% (55.8, 75.0)	89.2% (83.1, 95.8)		
Leptomeningeal Disease Control				p = 0.62
at 3 months	98.0% (95.2, 100)	97.9% (95.0, 100)		
at 6 months	93.9% (89.2, 98.7)	96.8% (93.3, 100)		
at 12 months	92.8% (87.8, 98.1)	94.6% (90.1, 99.3)		
Total Intracranial Brain Control (based on time to first recurrence of any type)				p < 0.0001
at 3 months	79.6% (72.0, 88.0)	90.4% (84.7, 96.6)		
at 6 months	55.1% (46.1, 65.9)	80.8% (73.1, 89.2)		
at 12 months	36.6% (28.1, 47.8)	72.1% (63.6, 81.8)		

Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues

Arjun Sahgal, Mark Ruschin, Lijun Ma, Wilko Verbakel, David Larson, and Paul D. Brown

RCT	Patient Inclusion Criteria	% Single Brain Metastases	Primary Endpoint	Local Control	Distant Control	Overall Survival
Aoyama et al ¹³ SRS (N = 67) vs WBRT+SRS (N = 65)	1 to 4 metastases, KPS ≥ 70, maximum diameter ≤ 3 cm	49% vs 48%	Brain tumor recurrence	72.5% vs 88.7% @ 1 y (P = .002)	36.3% vs 58.5% @ 1 y (P = .003)	28.4% vs 38.5% @ 1 y (P = .42)
Chang et al ¹² SRS (N = 30) vs WBRT + SRS (N = 28)	1 to 3 metastases, RPA 1 or 2, KPS ≥ 70, maximum diameter ≤ 4 cm	60% vs 54%	Neurocognition: HVLT-R total recall @ 4 mo	67% vs 100% @ 1 y (P = .012)	45% vs 73% @ 1 y (P = .02)	63% vs 21% @ 1 y (P = .003)
Kocher et al ¹⁴ SRS (N = 100) vs WBRT+SRS (N = 99)	1 to 3 metastases WHO ≤ 2, stable disease or symptomatic synchronous primary tumor	68% vs 66%	Duration of functional independence based on a WHO ≥ 2	69% vs 81% @ 2 y (P = .04)	52% vs 67% @ 2 y (P = .023)	Median OS (including surgical patients): 10.9 mo vs 10.7 mo (P = .89)
Brown et al ¹¹ SRS (N = 102) vs WBRT + SRS (N = 111)	1 to 3 metastases, diameter ≤ 3 cm	55% vs 56%	Decline >1 SD from baseline on at least 1 of the 7 cognitive tests @ 3 mo	72.8% vs 90.1% @ 1 y (P = .003)	69.9% vs 92.3% @ 1 y (P < 0.001)	Median OS: 10.7 mo vs 7.5 mo (P = .92)

Local control at 1 year

	S+OBSV	S+SRS	S+WBRT	SRS	SRS+WBRT
Mahajan et al <i>Lancet Oncol 2017</i>	43%	72%		-	-
Brown et al <i>Lancet Oncol 2017</i>		60.5%	80.6%	-	-
Aoyama et al <i>JAMA 2006</i>	-	-	-	72.5%	88.7%
Brown et al <i>JAMA 2016</i>	-	-	-	72.8%	90.1%
Chang et al <i>Lancet Oncol 2009</i>	-	-	-	67%	100%

Recurrent brain metastatic disease

- Recurrence after which first line treatment? (Surgery, SRS, WBRT, systemic treatment, ...)
- Actual incidence of recurrent brain metastasis (BM)
- Definition of a recurrent BM
- Place of surgery in patients with recurrent BM
 - ✓ Diagnostic issues
 - ✓ Prognostic issues
 - ✓ Strategic issues

Basic Original Report

Local recurrence patterns after postoperative stereotactic radiation surgery to resected brain metastases: A quantitative analysis to guide target delineation

**Chengcheng Gui^a, Joseph Moore PhD^a, Jimm Grimm PhD^a,
Lawrence Kleinberg MD^a, Todd McNutt PhD^a, Colette Shen MD, PhD^a,
Linda Chen MD^a, Chetan Bettegowda MD, PhD^b, Michael Lim MD^b,
Kristin J. Redmond MD, MPH^{a,*}**

^a*Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University, Baltimore, Maryland*

^b*Department of Neurosurgery, Johns Hopkins University, Baltimore, Maryland*

« Local failure in the resection cavity was defined as the fulfillment of 1 of 2 criteria: (1) A lesion that overlaps the original resection cavity that was surgically resected and confirmed by pathology to be a recurrence of the original brain metastasis, or (2) a lesion that overlaps the original resection cavity that was not resected but judged by the patient's oncology team on the basis of serial MRI scans to be highly suspicious for recurrence, which resulted in a recommendation for a second course of radiation therapy.»

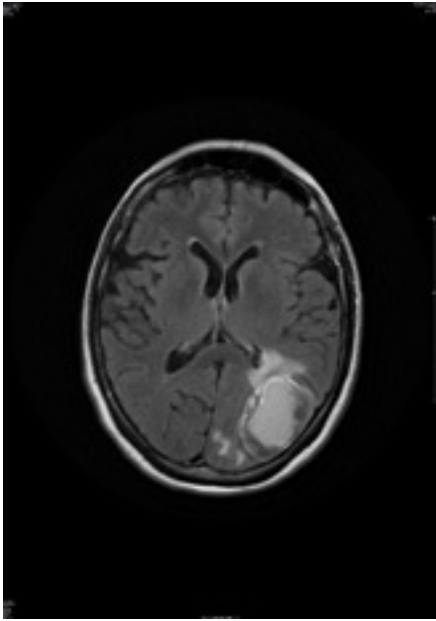
Recurrent brain metastatic disease

- Recurrence after which first line treatment? (Surgery, SRS, WBRT, systemic treatment, ...)
- Actual incidence of recurrent brain metastasis (BM)
- Definition of a recurrent BM
- Place of surgery in patients with recurrent BM
 - ✓ Diagnostic issues
 - ✓ Prognostic issues
 - ✓ Strategic issues

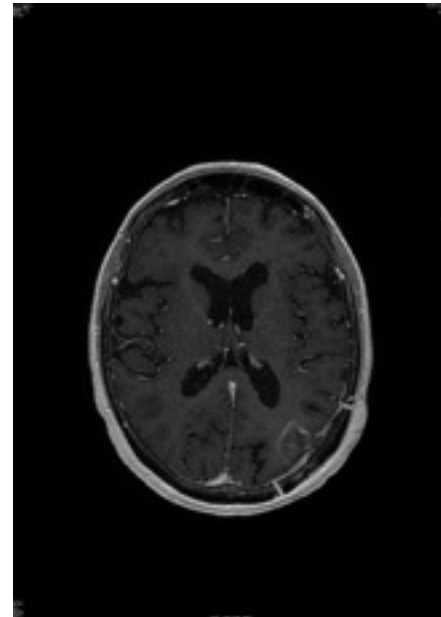
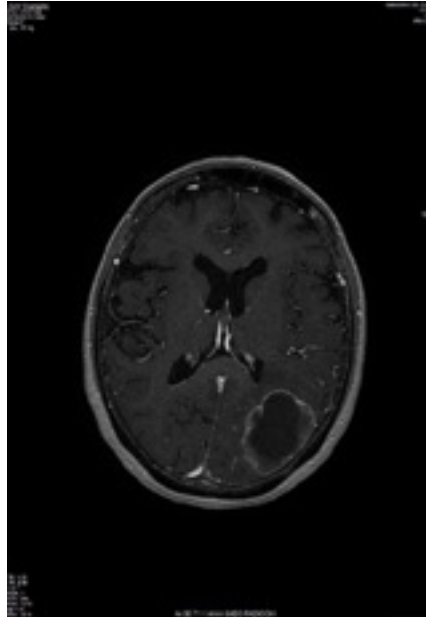
Diagnostic issues

- Optimal neuroradiological investigations (MRI, PET, TDM,)
- Peculiar radiological presentations in patients treated with targeted therapies or immuno checkpoint inhibitors
- Need for a thorough assessment of the systemic disease
- Timing of surgery: immediate or after steroids / bev treatment

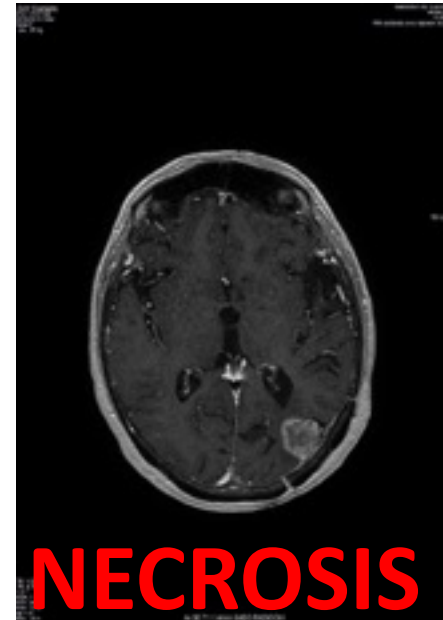
Progression after surgery plus adjuvant SRS



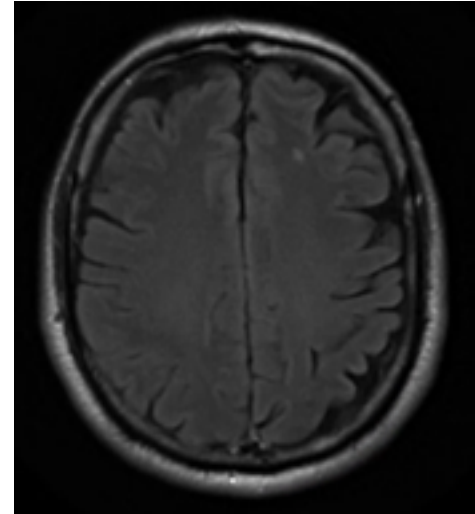
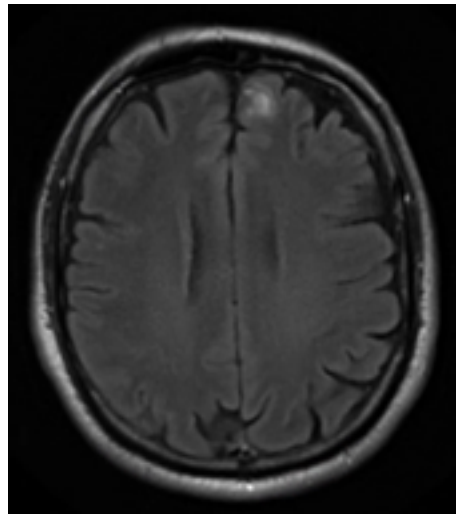
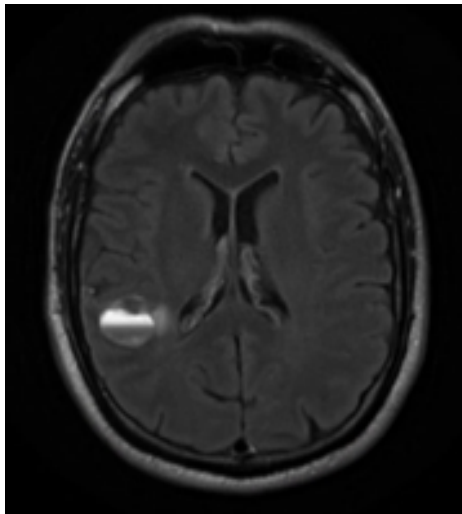
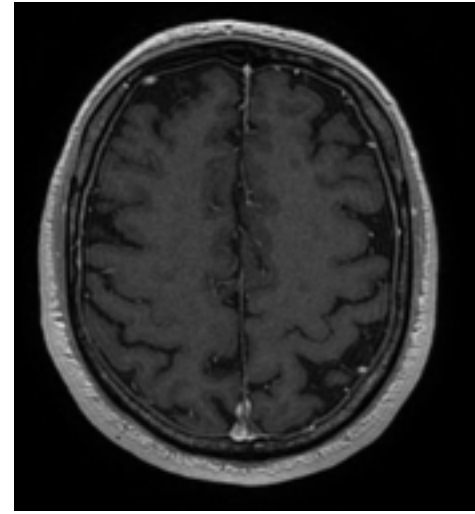
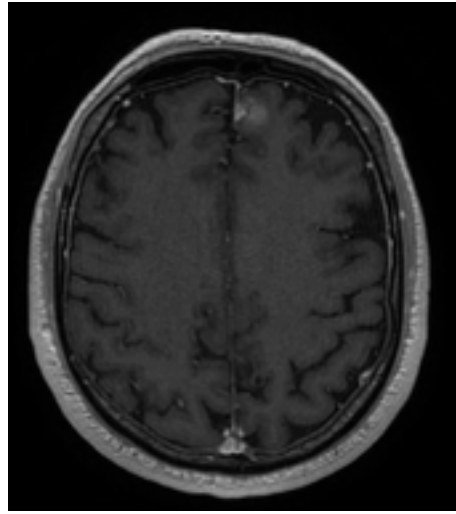
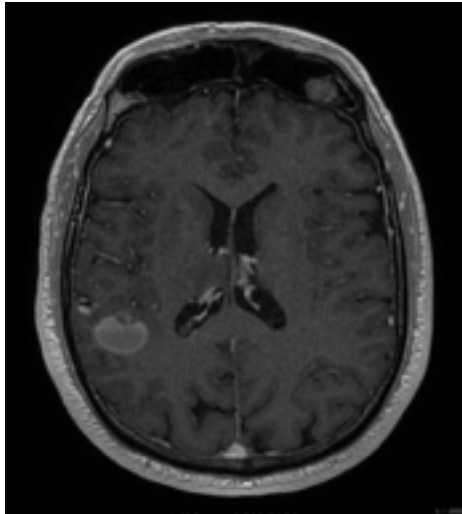
Pre op



Post op



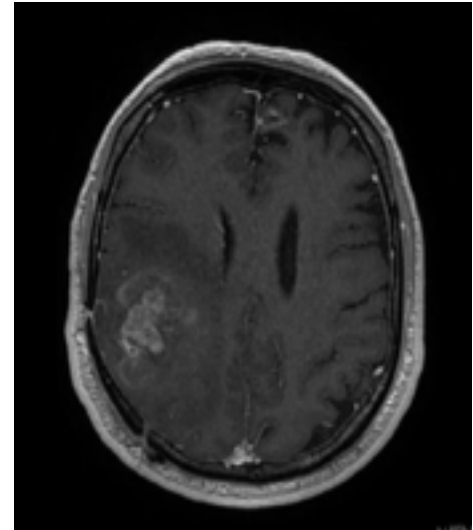
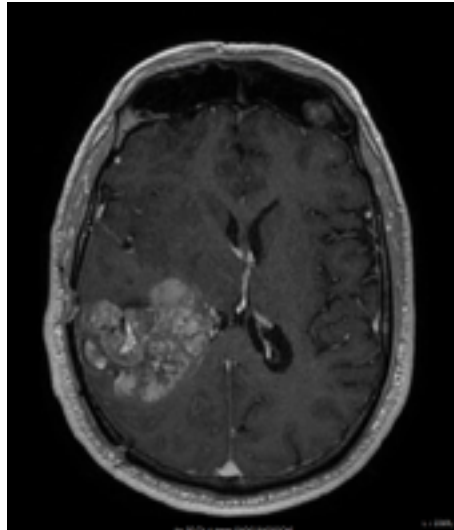
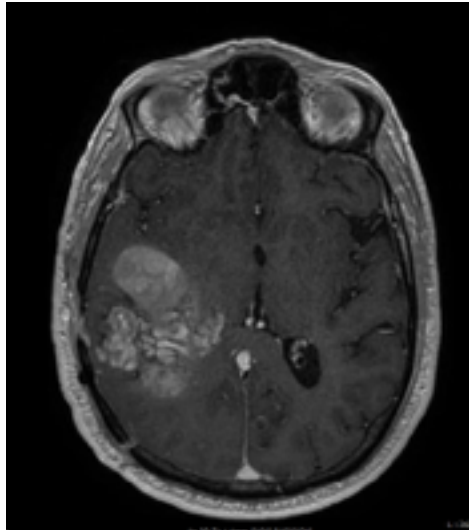
Progression after surgery plus adjuvant SRS



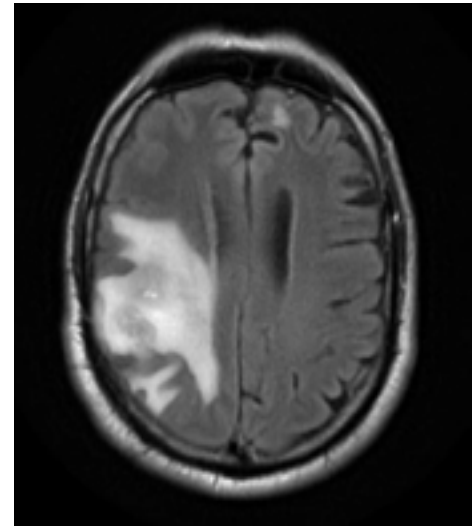
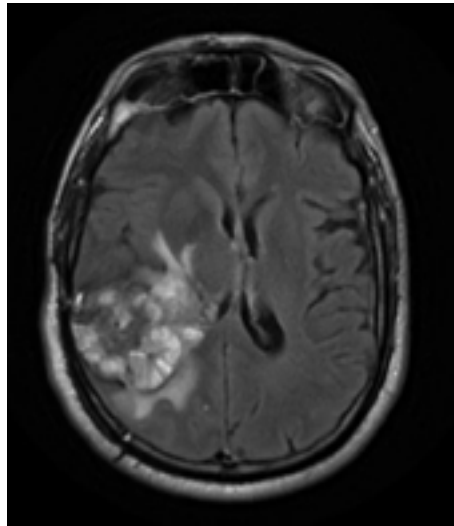
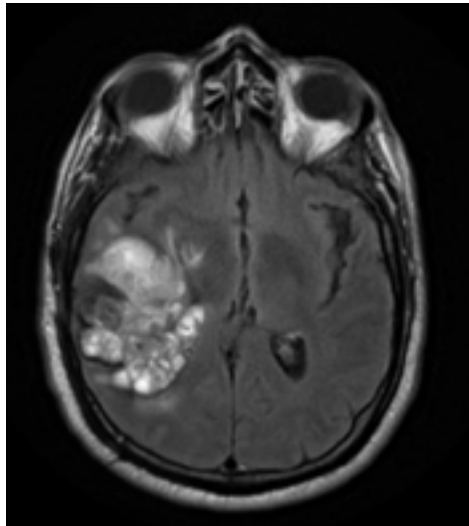
Jul 2015

Progression after surgery plus adjuvant SRS

T1 gado

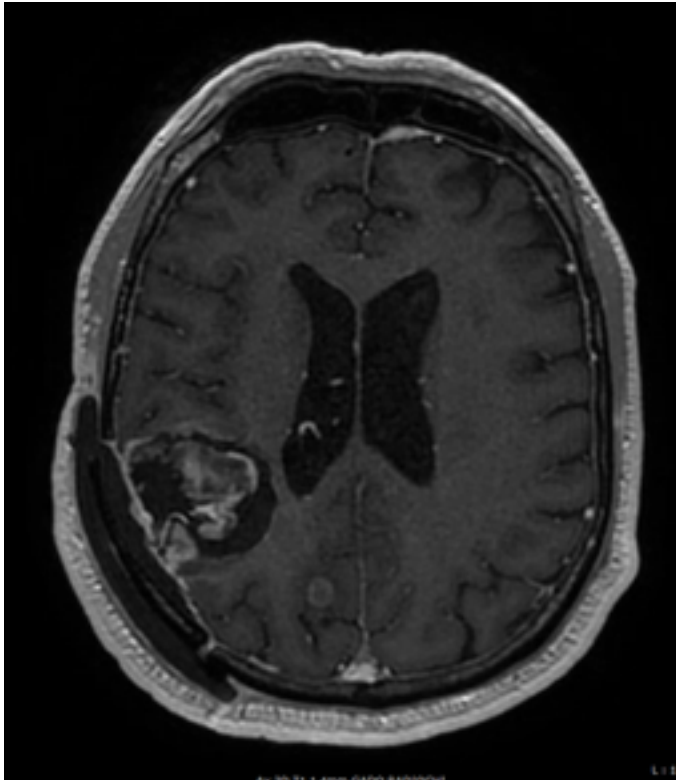


T2 FLAIR



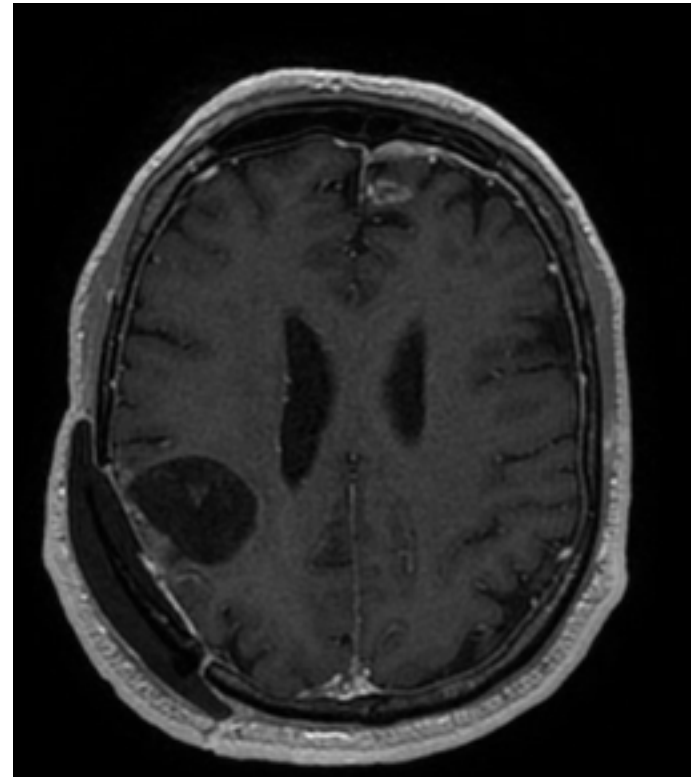
Fev 2018

Progression after surgery plus adjuvant SRS

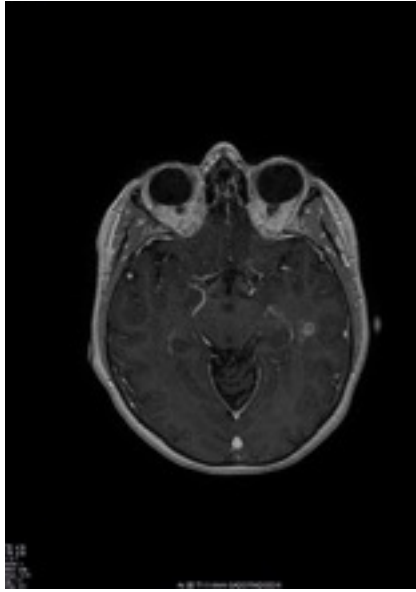


ADK BM

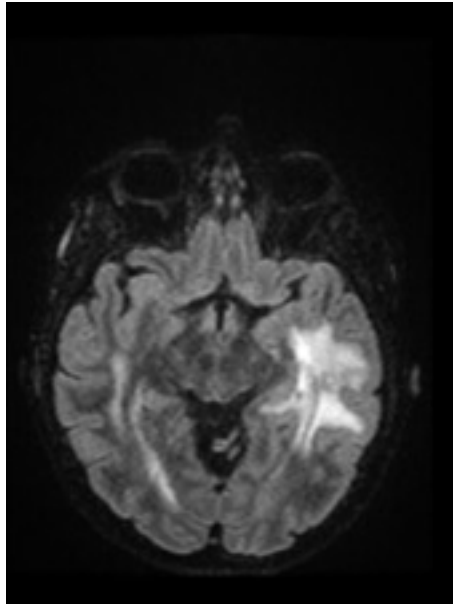
Mars 2018



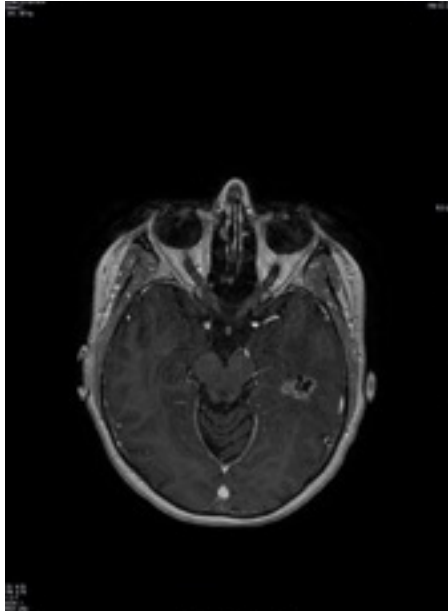
Progression after SRS alone



Nov 2016



Aug 2017

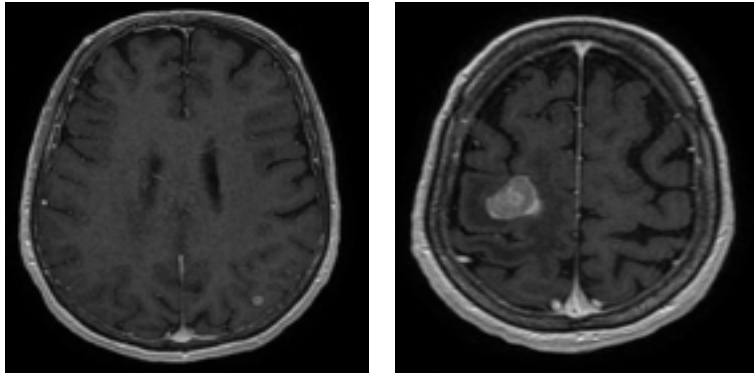
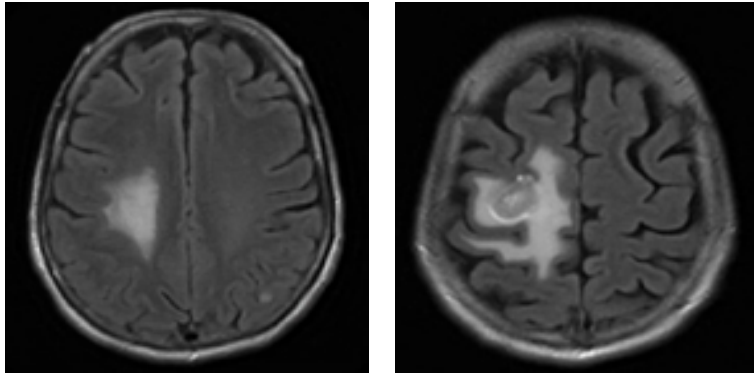


Aug 2017



NECROSIS

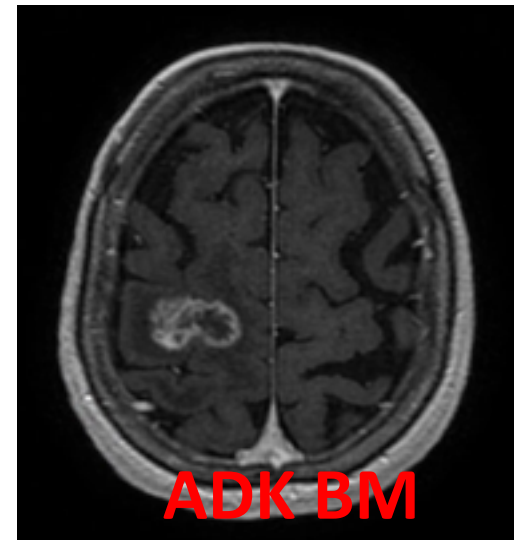
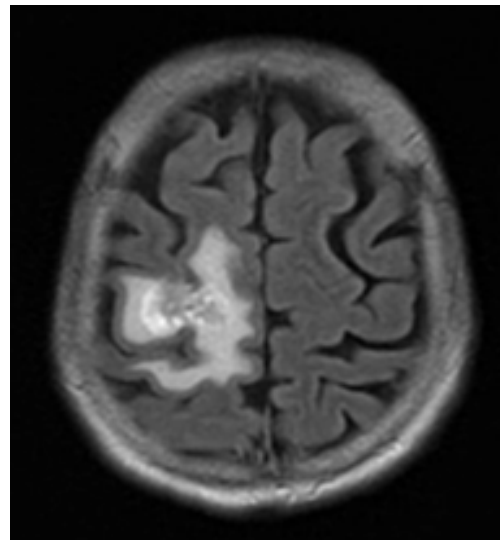
Progression after SRS alone



Oct 2016

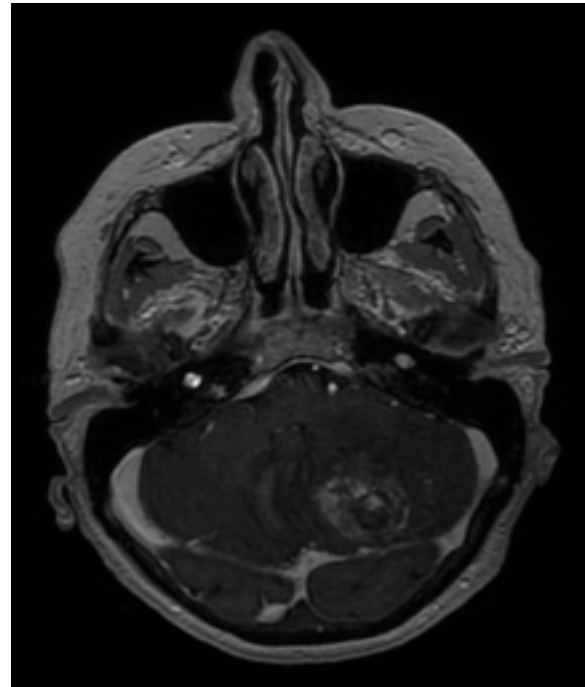
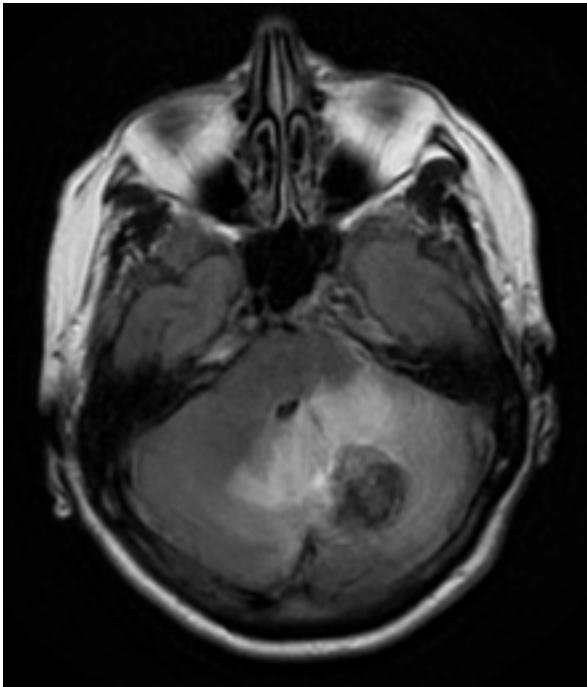
Nov 2017

Progressive hemiparesis



ADK BM

Differential diagnosis



Cavernoma

Prognostic issues

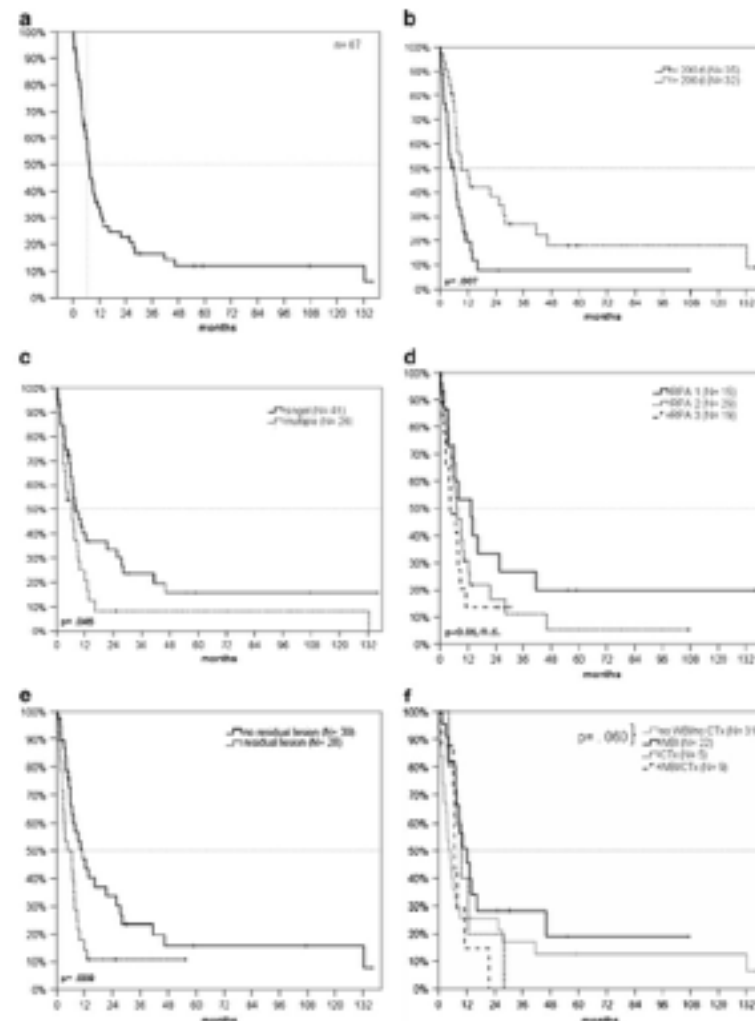
- Overall survival
- Local control
- Functional control
- *Systemic disease control*

Surgery of recurrent brain metastases: retrospective analysis of 67 patients

Gabriele Schackert • Konrad Schmiedel •
Claudia Lindner • Mario Leimert • Matthias Kirsch

Table 6 Multivariate analysis of prognostic factors for overall survival

Factor	Hazard ratio	95 % CI	<i>p</i> value	<i>p</i> -value
RPA I	5.2	1.3–21.0	.02	
Time to Recurrence >200 d	4.9	1.3–18.7	.02	





Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases

Marcel A. Kamp¹ · Igor Fischer² · Maxine Dibué-Adjei¹ · Christopher Munoz-Bendix¹ · Jan-Frederick Cornelius¹ · Hans-Jakob Steiger¹ · Philipp J. Slotty¹ · Bernd Turowski³ · Marion Rapp¹ · Michael Sabel¹

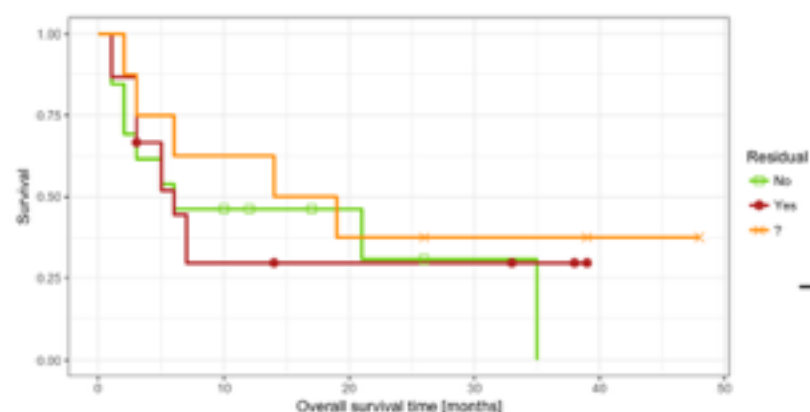
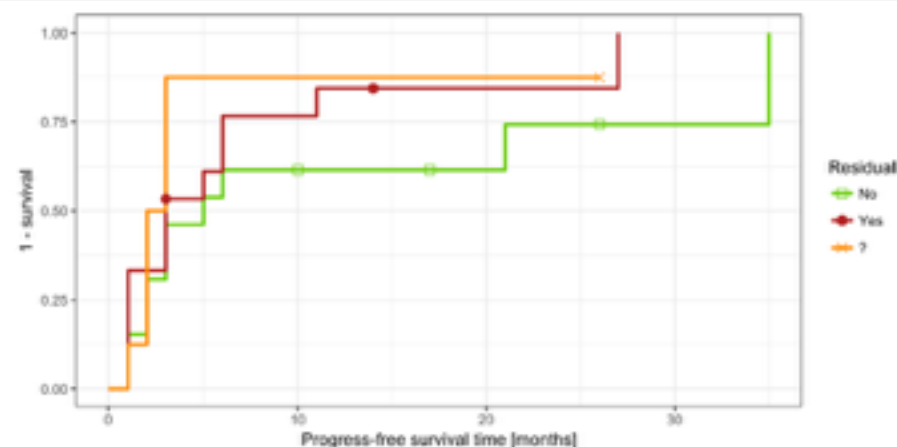


Fig. 3 Overall survival after surgery of a locally recurrent cerebral metastasis



Strategic issues

- When diagnosis of progression is clear
- When pattern of progression favored a non-invasive SRS management
- When recurrent BM patient is asymptomatic
- Is there still a place for surgery?

Strategic issues

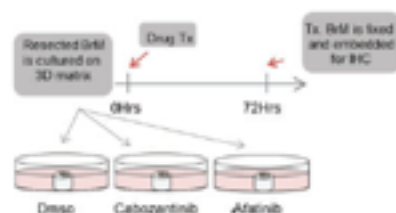
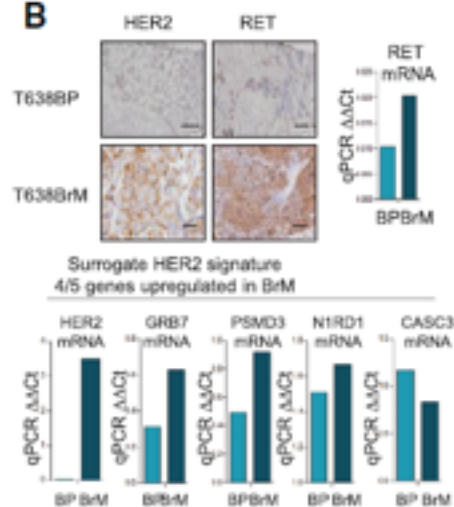
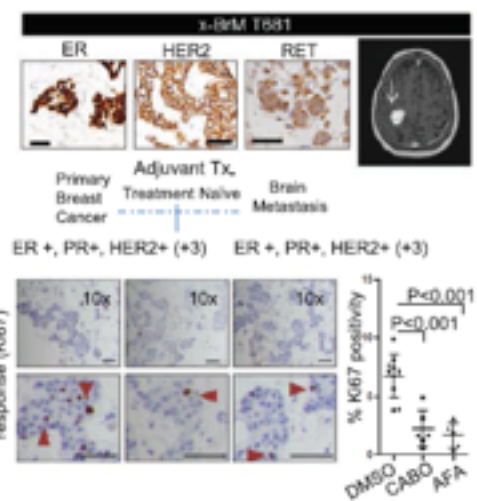
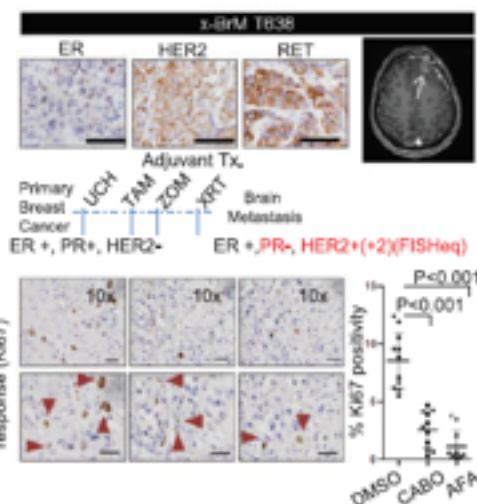
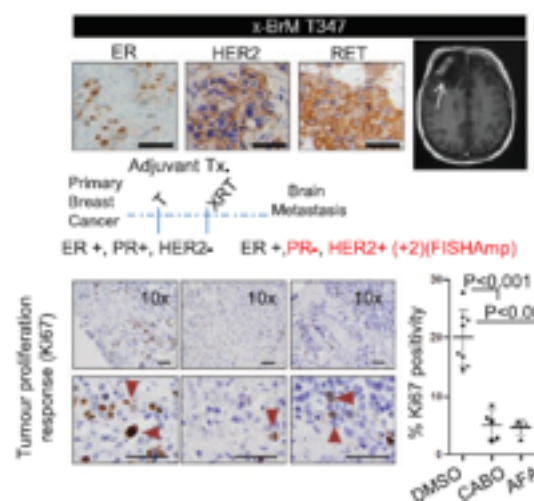
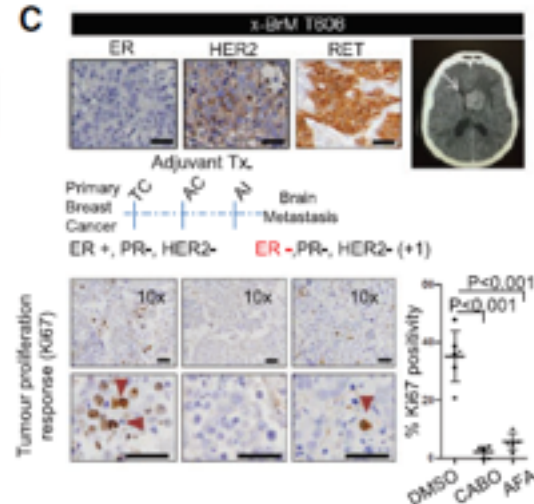
- When diagnosis of progression is clear
- When pattern of progression favored a non-invasive SRS management
- When recurrent BM patient is asymptomatic
- Is there still a place for surgery?

Toward an integrated molecular biology strategy

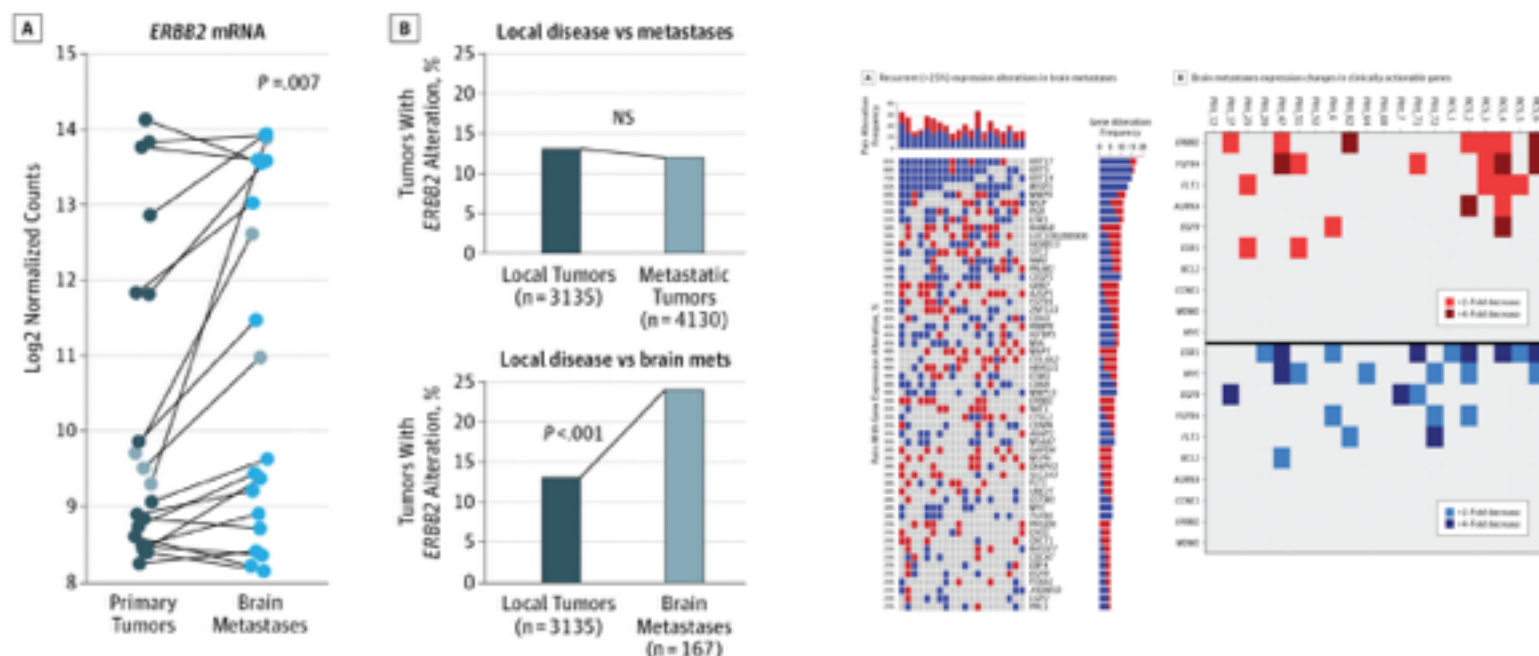
ARTICLE

Transcriptome Characterization of Matched Primary Breast and Brain Metastatic Tumors to Detect Novel Actionable Targets

Damir Varešlija*, Nolan Friedigkeit*, Ailís Fagan, Siobhan Purcell, Nicola Cosgrove, Philip J. O'Halloran, Elspeth Ward, Sinéad Cocchiglia, Ryan Hartmaier, Carlos A. Castro, Li Zhu, George C. Tseng, Peter C. Lucas, Shannon L. Puhalla, Adam M. Brufsky, Ronald L. Hamilton, Aju Mathew, Jose P. Leone, Ahmed Basudan, Lance Hudson, Róisín Dwyer, Sudipto Das, Darran P. O'Connor, Patrick G. Buckley, Michael Farrell, Arnold D. K. Hill, Steffi Oesterreich, Adrian V. Lee*, Leonie S. Young*

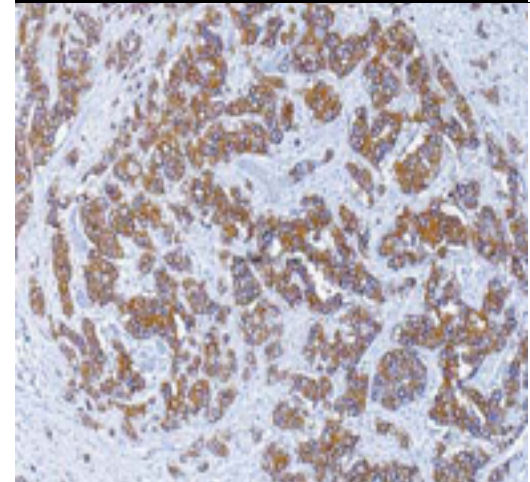
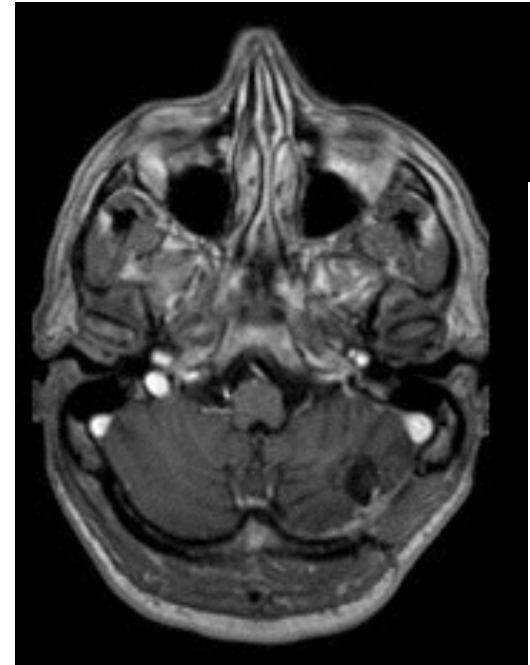
A**B****C**

Nolan Friedigkeit, BS¹, Ryan J. Hartmaier, PhD², Yijing Chen, BS¹, Damir Vareslija, PhD³, Ahmed Basudan, BS¹, Rebecca J. Watters, PhD¹, Roby Thomas, MD¹, Jose P. Leone, MD⁴, Peter C. Lucas, MD, PhD¹, Rohit Bhargava, MD¹, Ronald L. Hamilton, MD¹, Juliann Chmielecki, PhD², Shannon L. Puhalla, MD¹, Nancy E. Davidson, MD¹, Steffi Oesterreich, PhD¹, Adam M. Brufsky, MD, PhD¹, Leonie Young, PhD³, and Adrian V. Lee, PhD¹

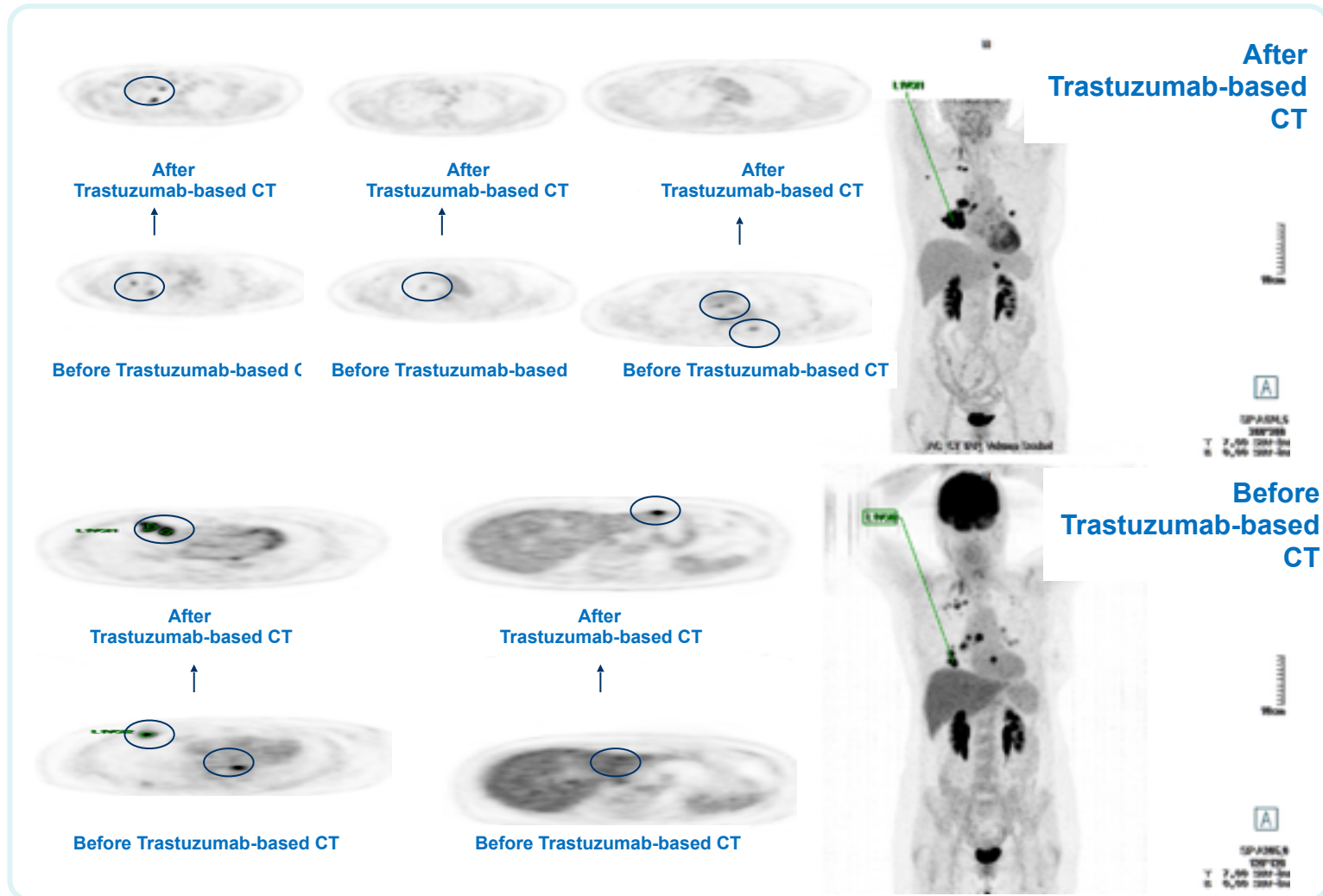


Her2 differential expression in primary tumor and breast cancer BM

- Woman 49 year-old
- Diagnosis of BC Her2- in 2008
- Trt: 3 FEC 100-Docetaxel
- 2010 lymph node relapse
- Trt Paclitaxel - Bevacizumab
- 2011 cerebral progression
 - **Surgery + SRS**
 - Introduction of Trastuzumab
 - 2012 good local control but ...



Dissociated systemic response to Trastuzumab : Phenotypical heterogeneity of metastatic disease



Concluding remarks

- Surgery at recurrence is important for the actual diagnosis of progression
- Surgery probably impact positively prognosis in these patients
- Place of surgery is also strategic in the management of these patients