



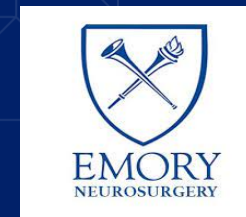
CONTROVERSIES AND THE EVOLVING MULTIDISCIPLINARY MANAGEMENT OF BRAIN METASTASES

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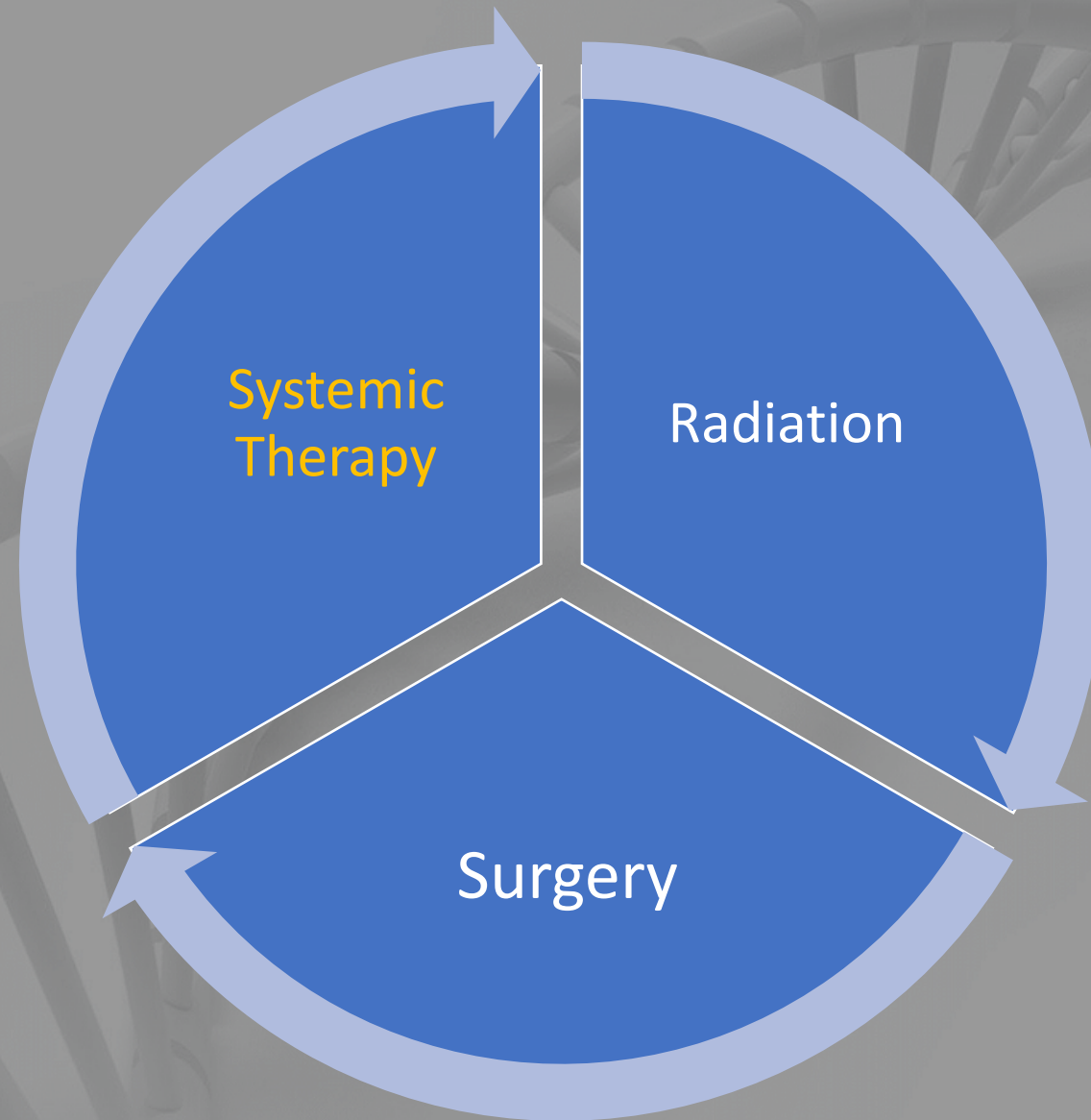
“It’s just a met.....”

What is the role of surgery in this disease and how is it evolving?



A few areas of debate....

Controversy 1: is the role and timing of surgery / radiation /systemic tx changing for newly diagnosed brain mets??



Shifting role of systemic therapy in brain mets

Melanoma
Avg tumor size approx 1.5cm (asymptomatic)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

Hussein A. Tawbi, M.D., Ph.D., Peter A. Forsyth, M.D., Alain Algazi, M.D., Omid Hamid, M.D., F. Stephen Hodi, M.D., Stergios J. Moschos, M.D., Nikhil I. Khushalani, M.D., Karl Lewis, M.D., Christopher D. Lao, M.D., M.P.H., Michael A. Postow, M.D., Michael B. Atkins, M.D., Marc S. Ernstoff, M.D., David A. Reardon, M.D., Igor Puzanov, M.D., Ragini R. Kudchadkar, M.D., Reena P. Thomas, M.D., Ph.D., Ahmad Tarhini, M.D., Ph.D., Anna C. Pavlick, D.O., Joel Jiang, Ph.D., Alexandre Avila, M.D., Ph.D., Sheena Demelo, M.D., and Kim Margolin, M.D.

Variable	Intracranial (N = 94)	Extracranial (N = 94)	Global (N = 94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53

NSCLC

EGFR +

- High rate of IC mets
- Osimertinib (TKI) with improved CNS penetration
- FLAURA study (NEJM, brain - JCO 2020)

ALK +

- Multiple agents with promising CNS penetration
 - Alectinib, lorlatinib, certinib
 - Active clinical trials
- Delay asymptomatic brain mets progression by 6-12 months in about 50% or patients across multiple studies

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC

Suresh S. Ramalingam, M.D., Johan Vansteenkiste, M.D., Ph.D., David Planchard, M.D., Ph.D., Byoung Chul Cho, M.D., Ph.D., Jhanelle E. Gray, M.D., Yuichiro Ohe, M.D., Ph.D., Caicun Zhou, M.D., Ph.D., Thanyanan Reungwetwattana, M.D., Ying Cheng, M.D., Busyamas Chewaskulyong, M.D., Riyaz Shah, M.D., Manuel Cobo, M.D., [et al.](#), for the FLAURA Investigators*

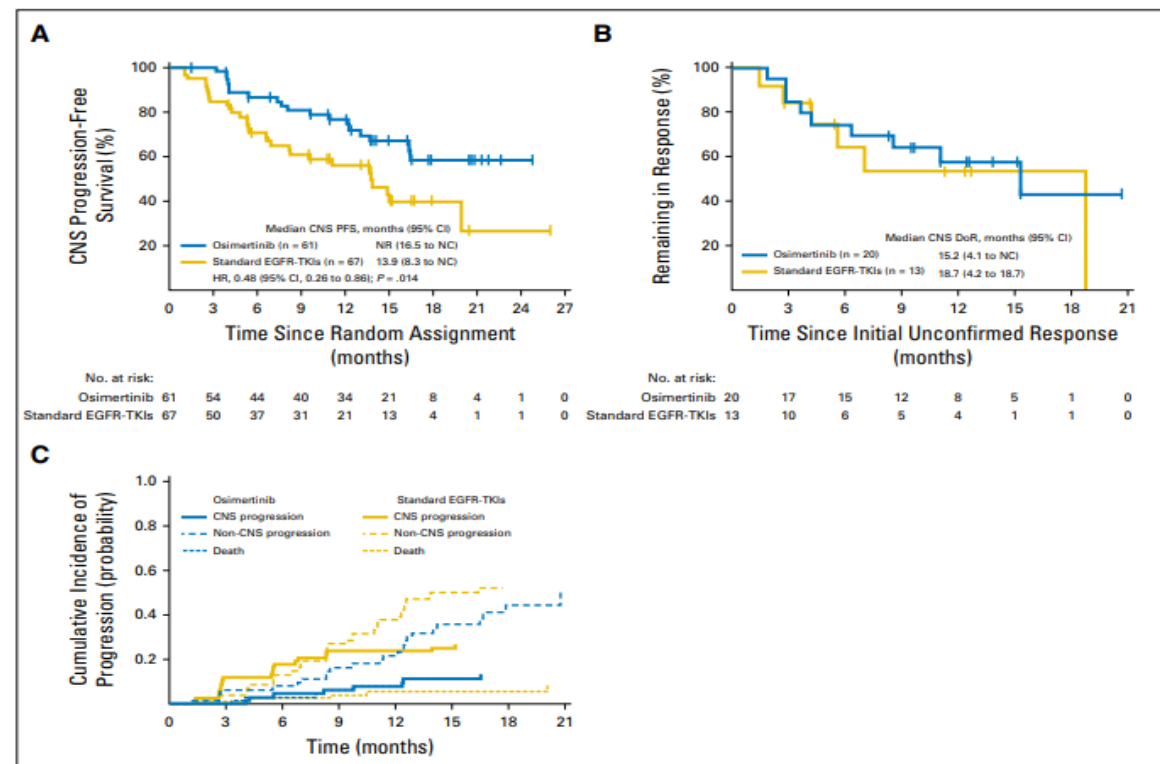
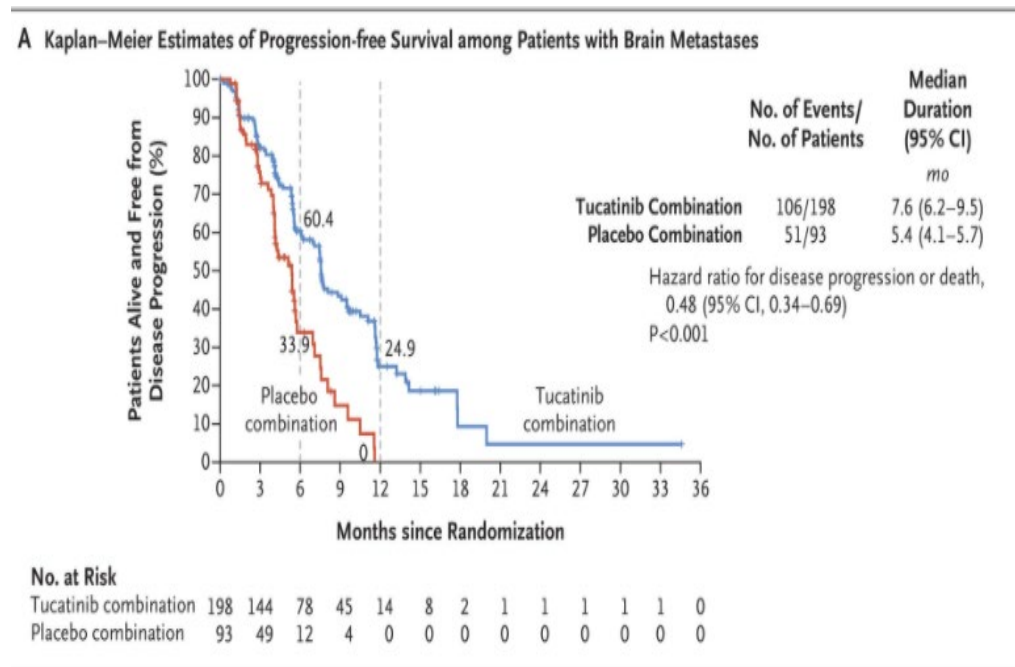


Fig 2. (A) CNS progression-free survival (PFS) in CNS full-analysis set (cFAS). (B) Duration of CNS response (DoR) in CNS evaluable-for-response set. (C) Cumulative incidence of CNS progression, taking into account competing risks of non-CNS progression and death resulting from any cause (cFAS). EGFR, epidermal growth factor receptor; HR, hazard ratio; NC, not calculable; TKI, tyrosine kinase inhibitor.

ORIGINAL ARTICLE

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

Rashmi K. Murthy, M.D., Sherene Loi, M.D., Alicia Okines, M.D., Elisavet Paplomata, M.D., Erika Hamilton, M.D., Sara A. Hurvitz, M.D., Nancy U. Lin, M.D., Virginia Borges, M.D., Vandana Abramson, M.D., Carey Anders, M.D., Philippe L. Bedard, M.D., Mafalda Oliveira, M.D., *et al.*



HER2+ Breast Ca

- HER2CLIMB: Increased OS and delay in brain mets progression in HER2 Breast CA patients
 - TKI-mAB-chemo combo
- All major brain mets subtypes: Not at a stage (yet) for neoadjuvant chemo prior to surgery
- Oncology adjusting post surgery/radiation algorithms and even pre-radiation in small mets in melanoma, lung (NCCN guidelines)

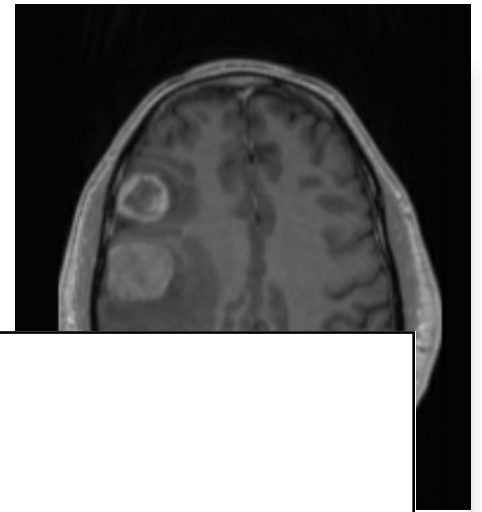
Table 2. Therapies for brain metastasis

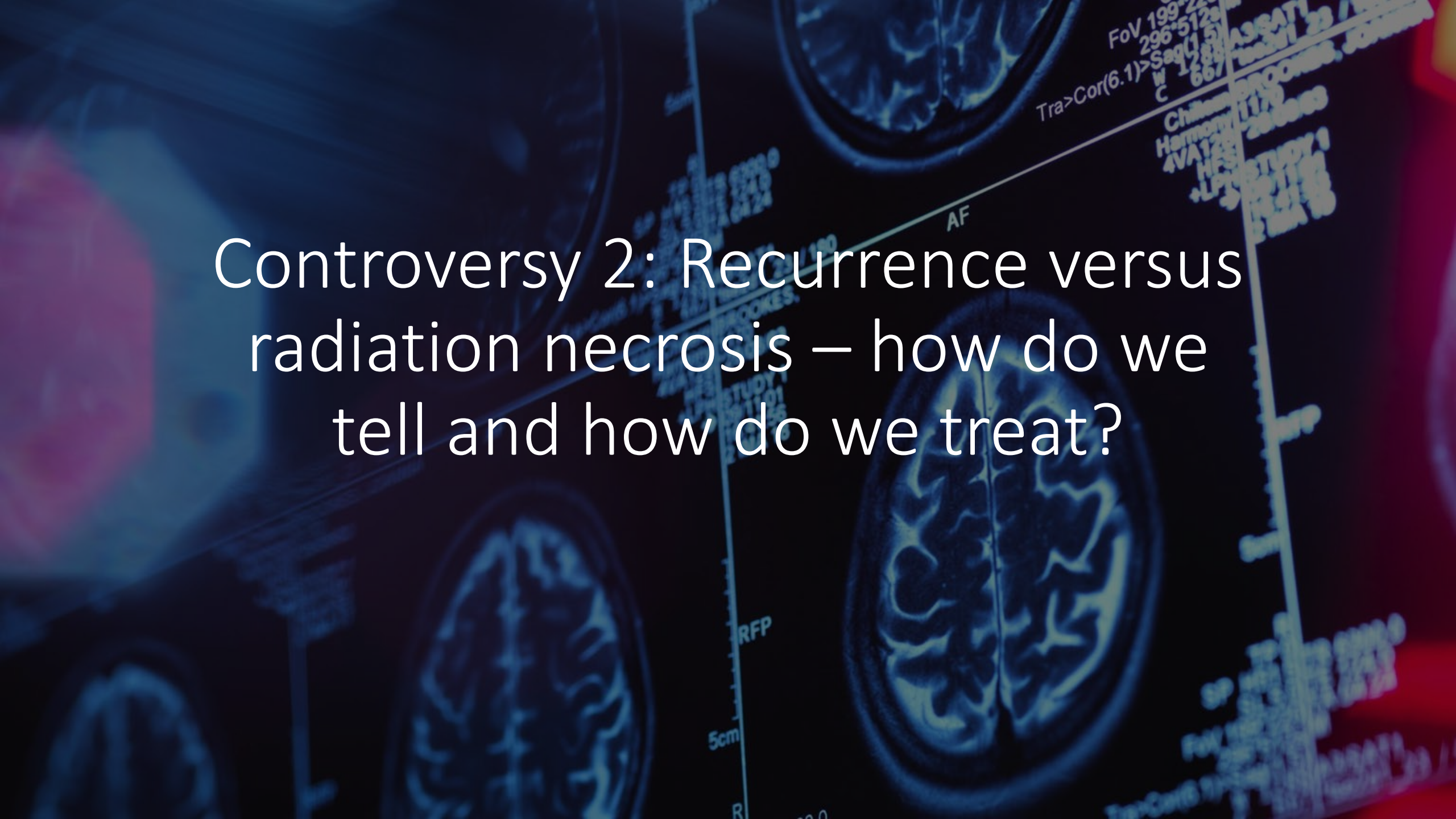
Cancer type	Drug/target	Clinical trial	Clinical trial outcome	P
Lung	Osimertinib (EGFR)	FLAURA	PFS = 18.9 months; HR 0.46; 95% CI, 0.37-0.57	9
Lung	Alectinib (ALK)	Global ALEX	CNS RR = 81%; response duration = 17.3 months	9
Lung	Ceritinib (ALK)	ASCEND-4	PFS = 10.7 months; HR = 0.70; 95% CI, 0.44-1.12	9
Lung	Lorlatinib (ALK)		IC-ORR = 40%-75%	9
Melanoma	Dabrafenib+trametinib (BRAF)	COMBI-MB	IC-ORR = 59%	9
Melanoma	Vemurafenib (BRAF)		IC-ORR = 15%; PFS 4.0 months; OS 9.6 months	9
Breast	Abemaciclib (CDK4/6)	NCT02308020	In progress	9
Breast	Pertuzumab +trastuzumab +docetaxel (HER2)	CLEOPATRA	OS = 34.4 months	9
Breast	Trastuzumab emtansine (HER2)	EMILIA	OS = 26.8 months	1
Breast	Tucatinib + capecitabine + trastuzumab (HER2)	HER2CLIMB	In progress	
Breast (TNBC)	Cisplatin ± veliparib	NCT02595905	In progress	
Breast	Etirinotecan pegol (NKTR-102)	NCT02915744	In progress	
Melanoma	Ipilimumab + nivolumab (CTLA-4+PD-1)	NCT02374242	Intracranial ORR = 46%	8
Lung, melanoma	Pembrolizumab (PD-1)	NCT02085070	Intracranial RR = 33% for NSCLC; intracranial RR = 22% for melanoma	8
NSCLC	Nivolumab ± Ipilimumab +radiation (PD-1, CTLA4)	NCT02696993	In progress	
Brain mets (any solid tumor)	Pembrolizumab (PD-1)	NCT02886585	In progress	

NOTE: Several clinical trials are underway to investigate disease-specific therapies for brain metastasis, as well as checkpoint blockade for brain metastasis. For all trials where data are available, outcomes are summarized.

Currently, surgical indications still include...

- > 2.5 – 3cm
- Neurologically symptomatic
- Solitary, dominant, or 2-3 dominant lesions
- Lots of mass effect
- Tissue diagnosis
- You have doubts radiation or systemic therapy will control quickly



The background of the slide features a collage of brain MRI scans. Several axial slices of a brain are visible, showing internal structures like the ventricles and gyri. Overlaid on these scans is various technical text in a light blue or white font. Some of the legible text includes 'FoV 199', '296', '512', 'Sag(1.5)', 'Tra>Cor(6.1)', 'W 128', 'C 66', 'AF', 'Chilom', 'Harmon', '4VA12', 'HFS', '+LP', 'STUDY 1', '1170', '200003', '5cm', and 'RFP'. The overall color scheme is dark with a blue tint, and the text is white for high contrast.

Controversy 2: Recurrence versus
radiation necrosis – how do we
tell and how do we treat?

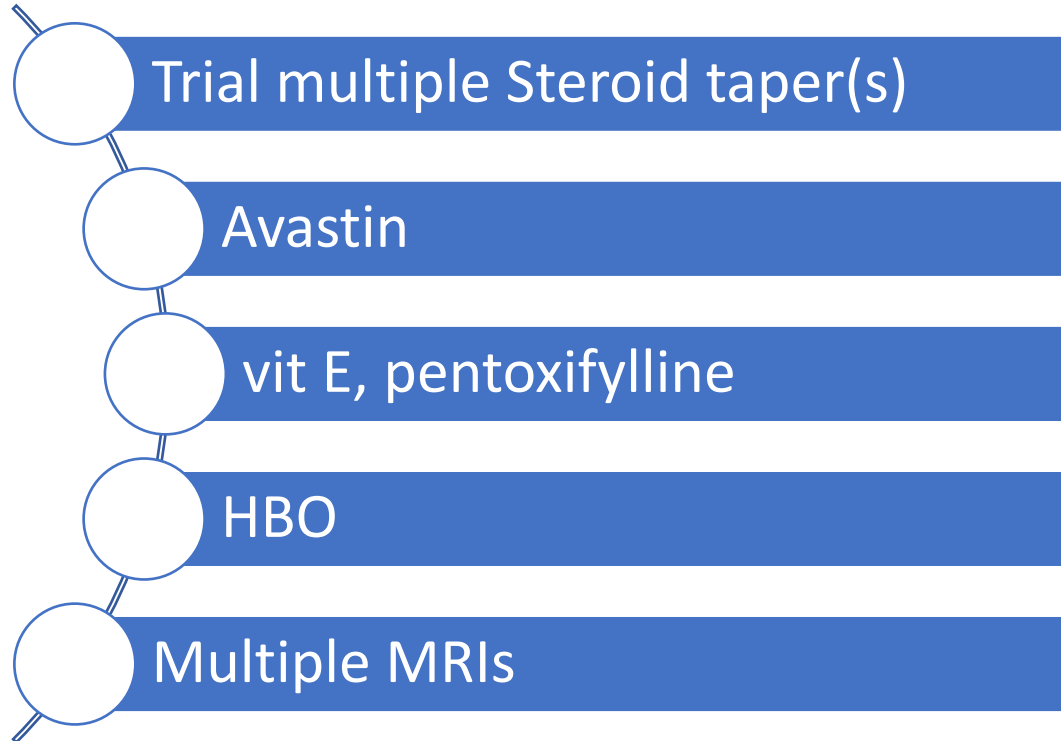
Salvage therapy: Rapidly growing population



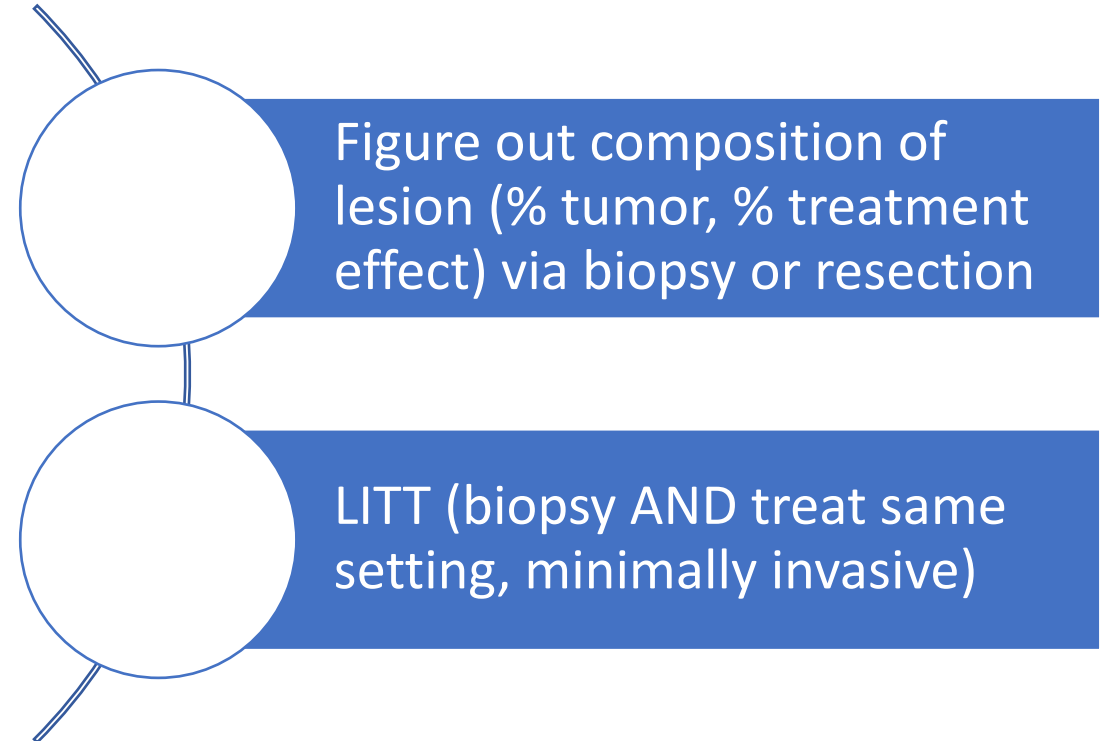
It is exceedingly challenging to distinguish recurrent tumor versus treatment effect

Salvage therapy

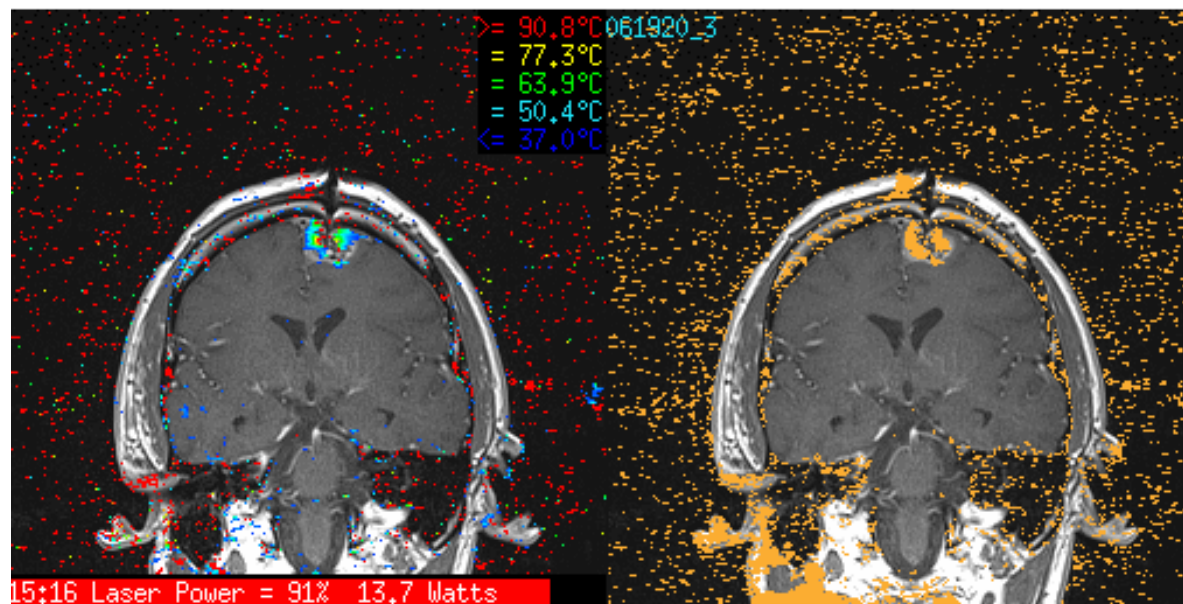
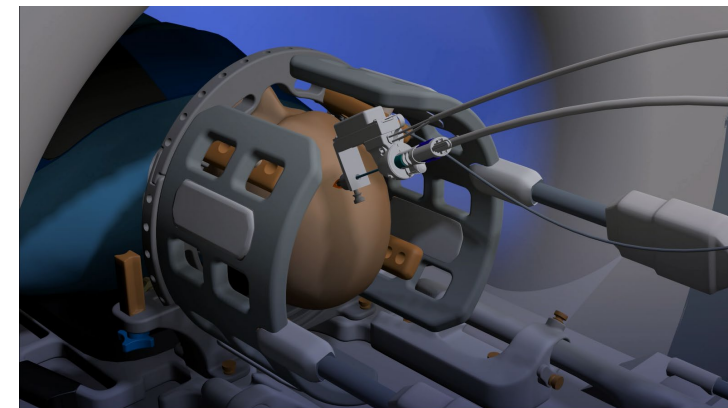
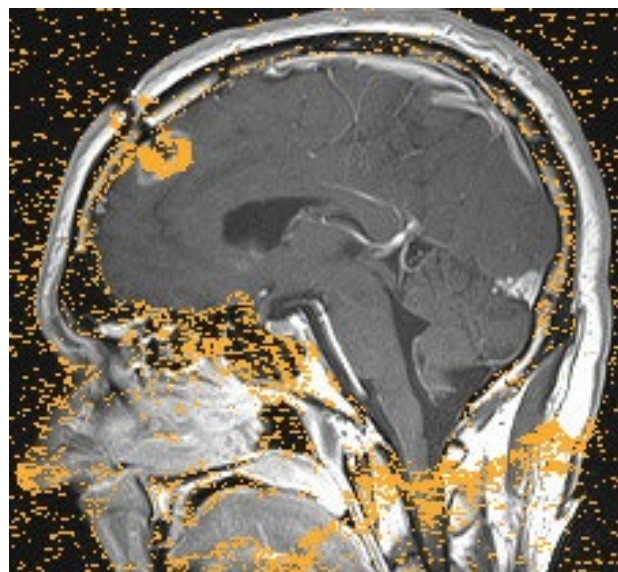
Medical treatment and surveillance




Tissue sampling up front



LITT (Laser Interstitial Thermal Therapy)



The background features a collage of brain MRI slices. Overlaid on these are various technical labels and text. In the top right, there is a block of text including 'FoV 199', '296', '512', 'Sag(1.5)', 'Tra>Cor(6.1)', 'W 128', 'C 66', 'ASSET1', '23 / 180', 'Chilom', 'Harmony', '4VA12', 'HFS', '+LP', 'STUDY1', '1170', '200803', '1170', '1170', '1170', '1170', '1170'. In the center, the letters 'AF' are visible. Below that, 'RFP' is written. At the bottom left, '5cm' is indicated. The overall color scheme is a mix of blue and red gradients.

Controversy 3: Preoperative SRS

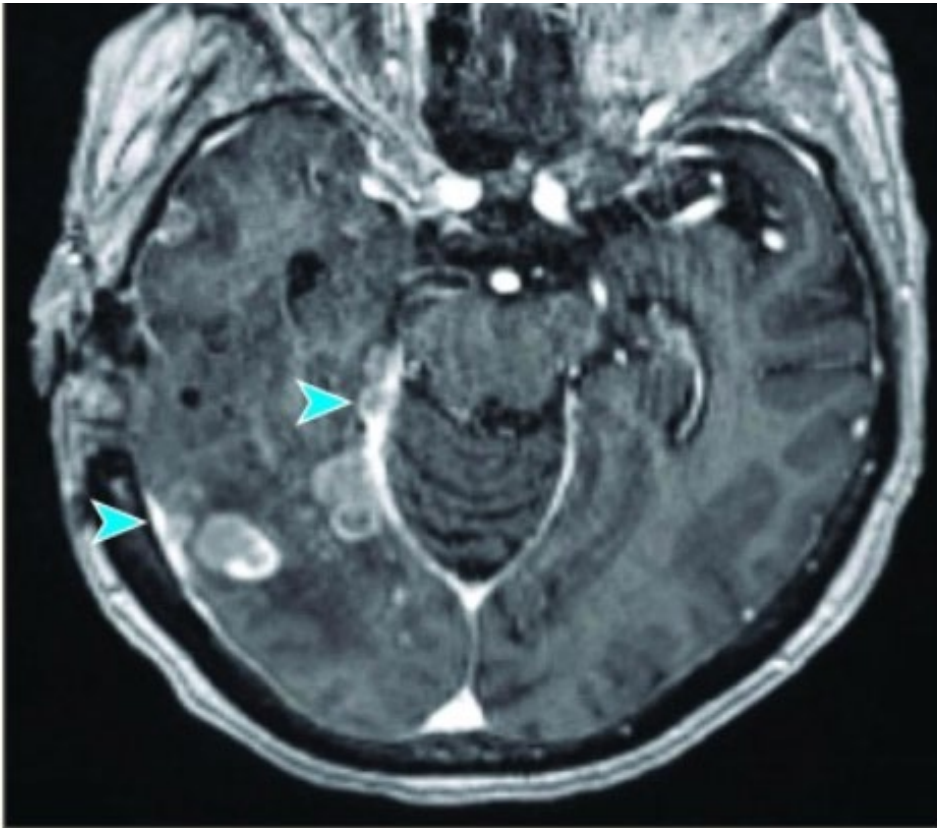
> JAMA Oncol. 2019 May 1;5(5):703-709. doi: 10.1001/jamaoncol.2018.7204.

Association of Neurosurgical Resection With Development of Pachymeningeal Seeding in Patients With Brain Metastases

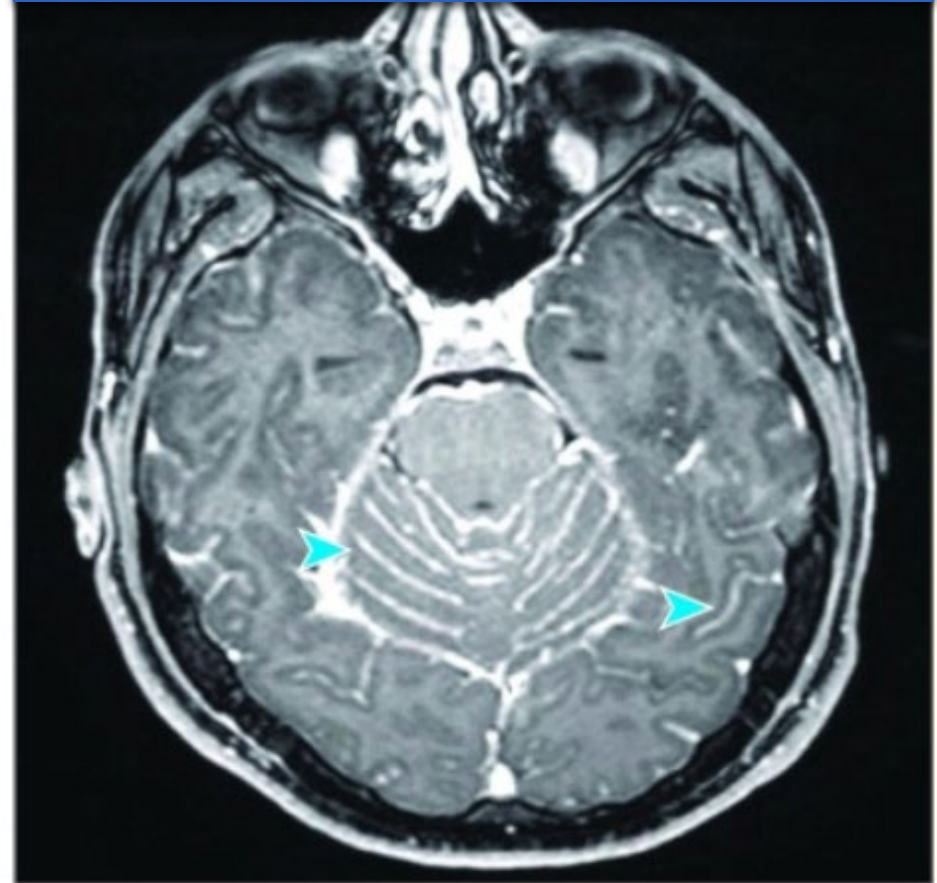
Daniel N Cagney¹, Nayan Lamba^{1 2}, Sumi Sinha³, Paul J Catalano^{4 5}, Wenya Linda Bi⁶, Brian M Alexander¹, Ayal A Aizer¹

Affiliations + expand

PMID: 30844036 PMCID: PMC6512273 DOI: 10.1001/jamaoncol.2018.7204



Resection associated with increased risk of pachymeningeal seeding ($p < 0.001$) but not LMD. Rate of 8.6%.



Advantages

Increased local control via target delineation

Less LMD

Less Rad Nec (less normal brain radiated and radiated tissue is resected)

Improved time to systemic therapy

Disadvantages

Lack of pathological confirmation

Impaired wound healing

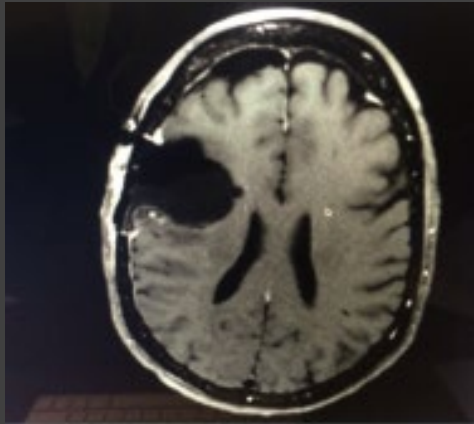
Increased time with neurologic deficit, need agile radiation dept

Multiple ongoing national and institutional trials to evaluate

WINSHIP TRIAL - RAD5234-21: *Preoperative radiosurgery for brain metastases planned for surgical resection: a two arm pilot study* (PI: Zach Buchwald, MD)

NRG trial soon to open

Hypofractionation



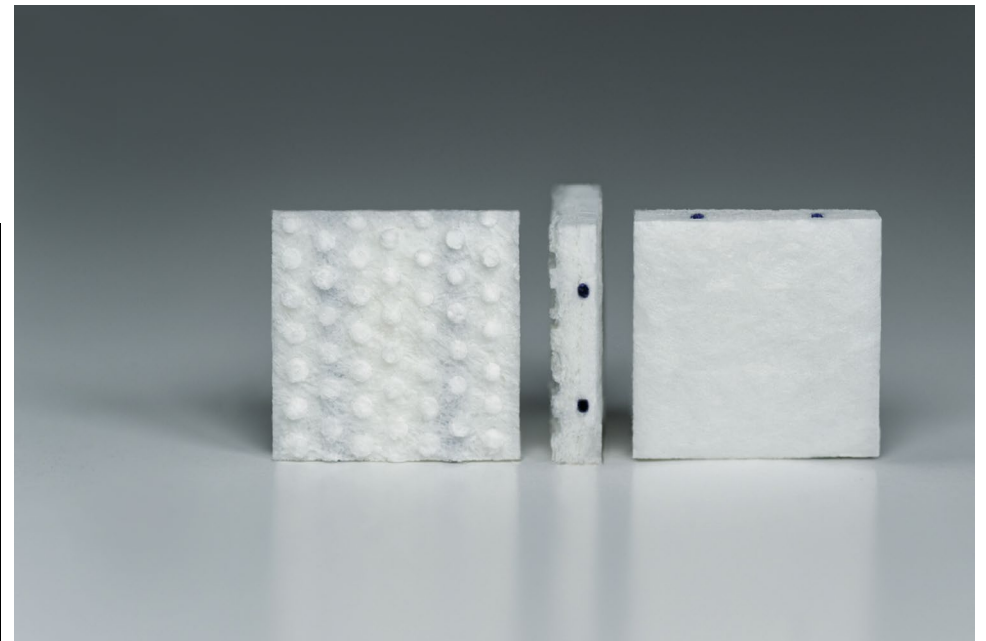
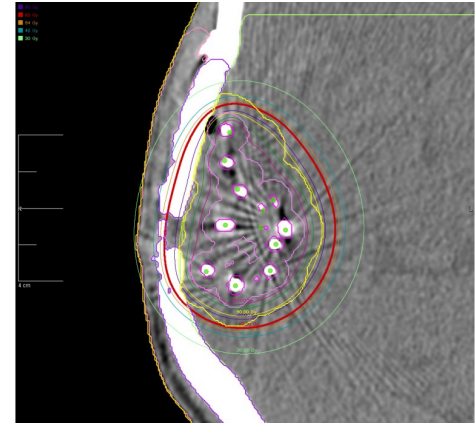
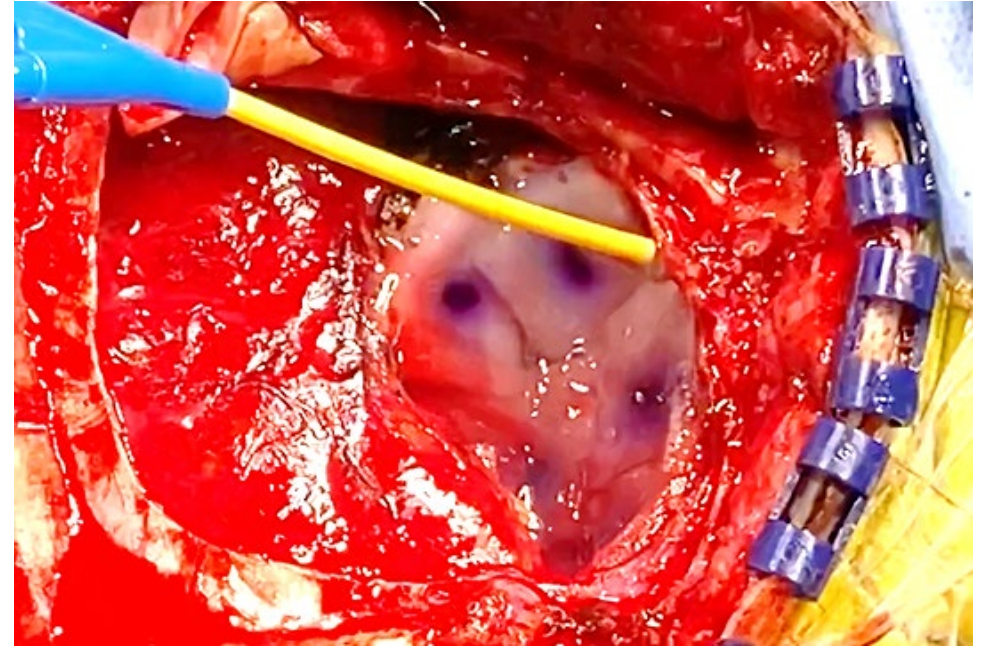
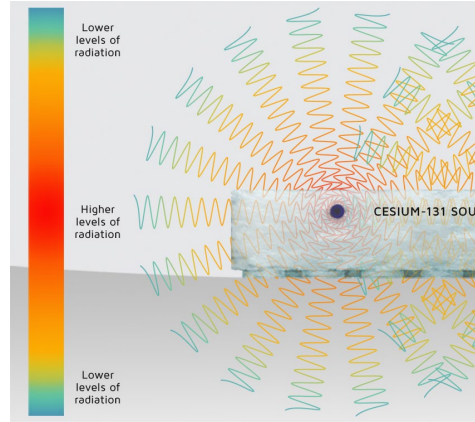
TRIAL @ WINSHIP

*Alliance 071801: Phase III Trial of Post-Surgical
Single Fraction SRS compared with fractioned SRS
for resected met brain disease (PI: Eaton MD,
Hoang MD)*

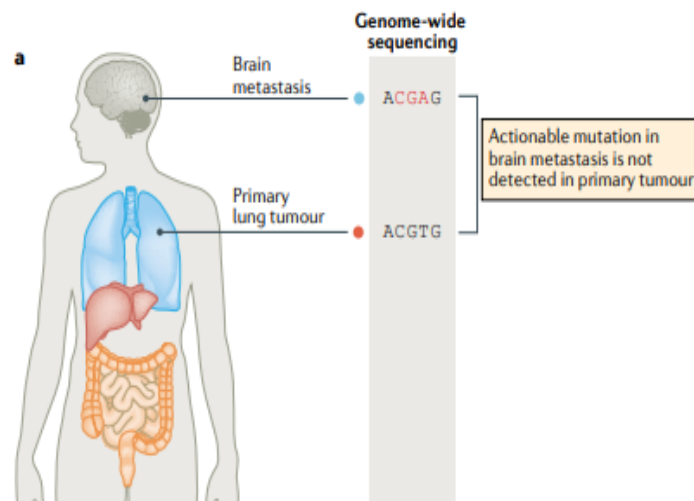
- Better LC with RTOG recommended dose of 24 Gy
- For large lesions (>2cm) or large cavities, however, single dose 24 Gy associated with higher acute and late CNS toxicity, primarily rad nec
- Hypofractionation (3-5 fx) for larger lesions / cavities
 - 3x9Gy versus, 5x6Gy
- Multiple retrospective studies, now onto **national** and institutional prospective trials

Brachytherapy

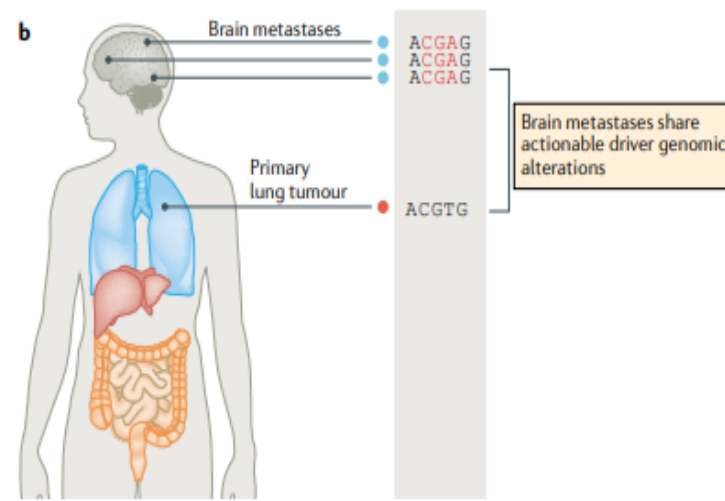
- Cesium brachytherapy
 - Recurrent or newly diagnosed mets
 - Patients who are noncompliant
 - WINSHIP TRIAL: GTM-102 A
Phase 3 Randomized Controlled Trial of Post-Surgical Stereotactic Radiotherapy (SRT) versus Surgically Targeted Radiation Therapy (STaRT) with Gamma Tile for Treatment of Newly Diagnosed Metastatic Brain Tumors (PI: Hoang)
- IORT



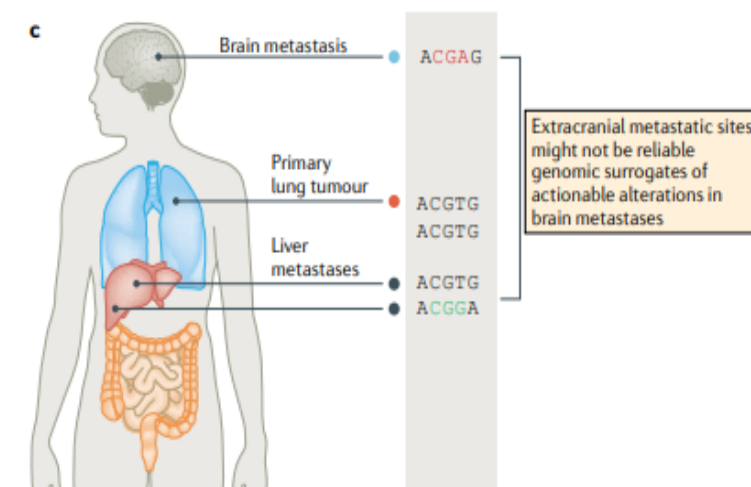
Controversy 4: Tissue sampling of brain mets to identify actionable mutations



Brain met different than primary



All the brain mets the same



Secondary visceral diff than primary diff than brain met

Genomic profiling – actionable mutations (53%)

Published in final edited form as:
Cancer Discov. 2015 November ; 5(11): 1164–1177. doi:10.1158/2159-8290.CD-15-0369.

Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets

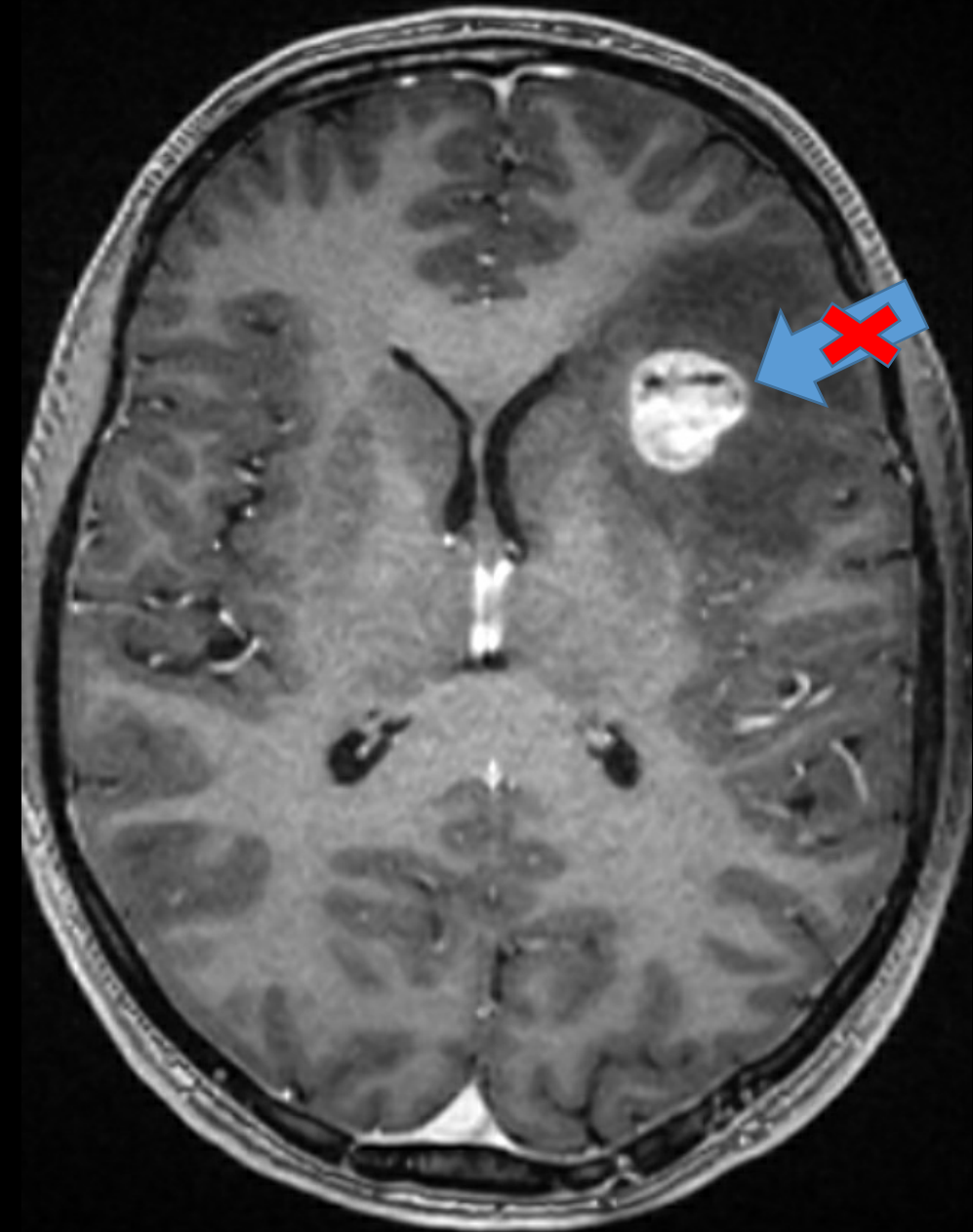
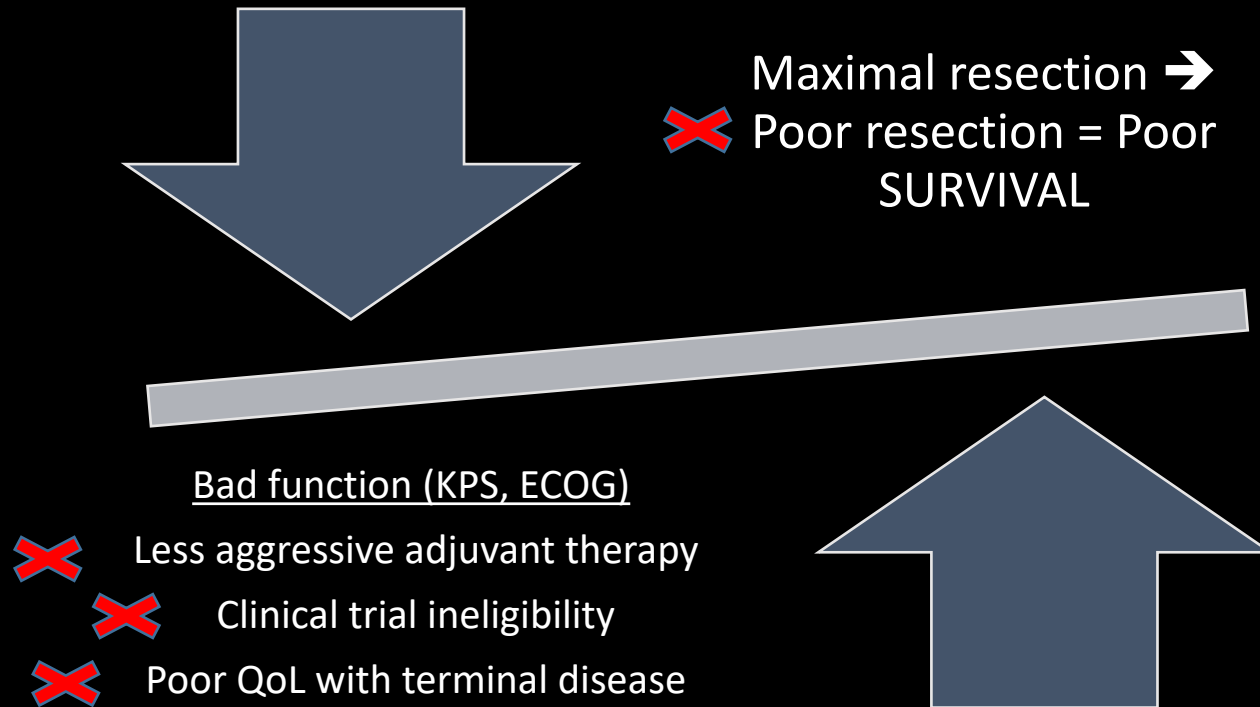
Priscilla K. Brastianos^{#1,3,5,6,10}, Scott L. Carter^{#8,10}, Sandro Santagata^{7,11}, Daniel P. Cahill², Amaro Taylor-Weiner¹⁰, Robert T. Jones^{6,9}, Eliezer M. Van Allen^{6,10}, Michael S. Lawrence¹⁰, Peleg M. Horowitz¹², Kristian Cibulskis¹⁰, Keith L. Ligon^{6,11}, Josep Tabernero¹⁴, Joan Seoane¹⁴, Elena Martinez-Saez¹⁵, William T. Curry², Ian F. Dunn¹², Sun Ha Paek¹⁶, Sung-Hye Park¹⁶, Aaron McKenna¹⁰, Aaron Chevalier¹⁰, Mara Rosenberg¹⁰, Frederick G. Barker II², Corey M. Gill⁵, Paul Van Hummelen^{6,9}, Aaron R. Thorner^{6,9}, Bruce E. Johnson⁶, Mai P. Hoang⁴, Toni K. Choueiri⁶, Sabina Signoretti¹¹, Carrie Sougnez¹⁰, Michael S. Rabin⁶, Nancy U. Lin⁶, Eric P. Winer⁶, Anat Stemmer-Rachamimov⁴, Matthew Meyerson^{6,9,10,11}, Levi Garraway^{6,8,10}, Stacey Gabriel¹⁰, Eric S. Lander¹⁰, Rameen Beroukhi^{5,7,10}, Tracy T. Batchelor³, Jose Baselga¹³, David N. Louis⁴, Gad Getz^{14,5,10}, and William C. Hahn^{6,9,10}

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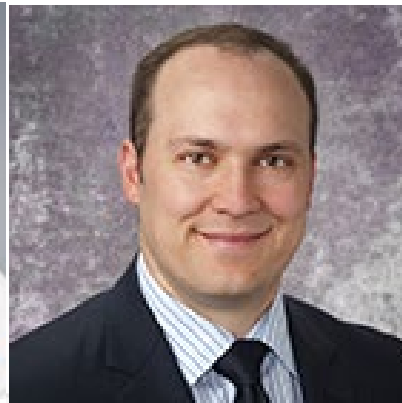
³Department of Neurology, Massachusetts General Hospital, Harvard Medical School, all in Boston

Consider tissue sampling?

- Is brain disease quite different from systemic disease control
- “Onco - functional balance”



THANK YOU TO OUR TEAM + QUESTIONS?



Neurosurgery

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Christopher Diebert, MD

Gustavo Pradilla, MD

Dan Refai, MD

Medical / Neuro-Oncology

Shawn Kothari MD

Madison Shoaf MD

Will Read MD

And all of you!!

WINship Brain Tumor Registry (WINBTR)

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