



Universitätsklinikum
Hamburg-Eppendorf

Augmenting Surgical Control of Brain Metastases

Manfred Westphal

**Department of Neurological Surgery, University
Hospital Eppendorf, Hamburg, Germany**



Augmentation

**In this context augmentation means
additional measures taken during
surgery, not adjuvant treatments at any
time after surgery**



- **SURGICAL ISSUES**
- **Technique of Resection**
 - In toto Resection
 - Complete Resection
 - IGS, Fluorescence
 - Protection/Prevention of Seeding
- **Safety**
 - IOM
 - IOUS
 - Tractography, fMRI

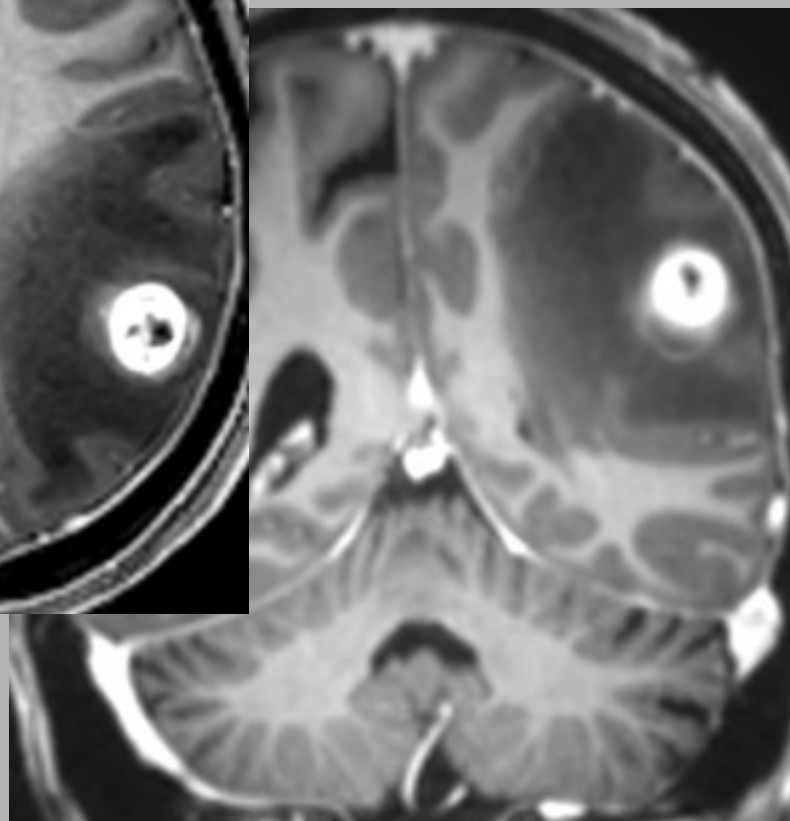
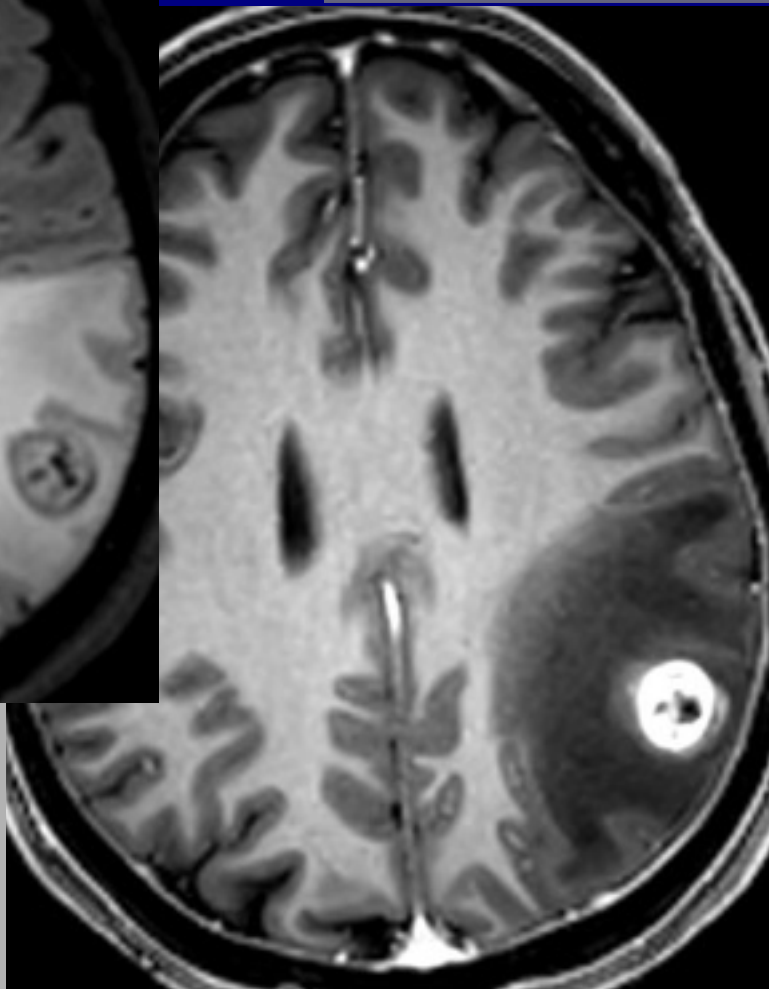
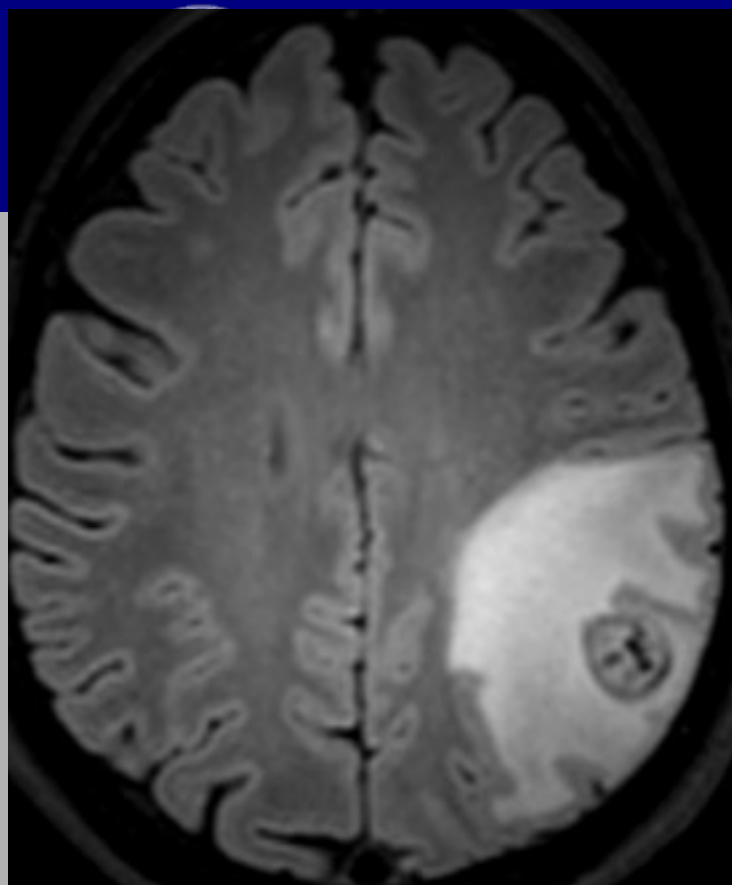


- **AUGMENTATION ISSUES**
- **Intracavitary Treatments**
 - Radiation
 - Chemotherapy
 - “Gene Therapy”



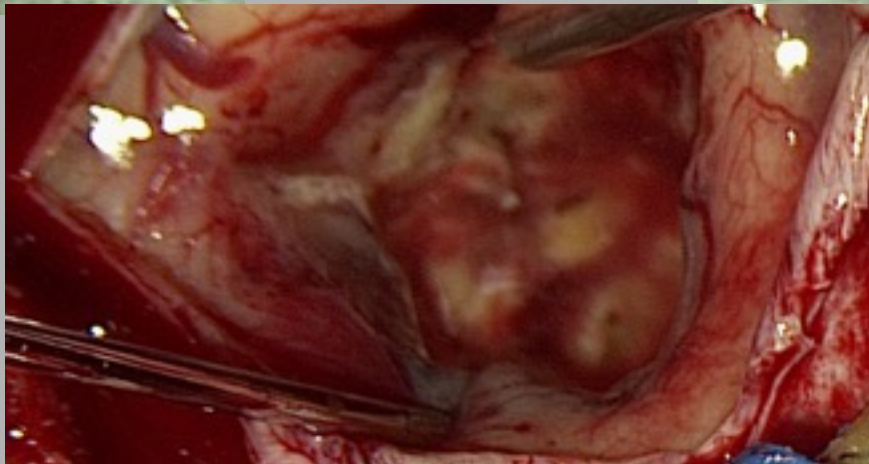
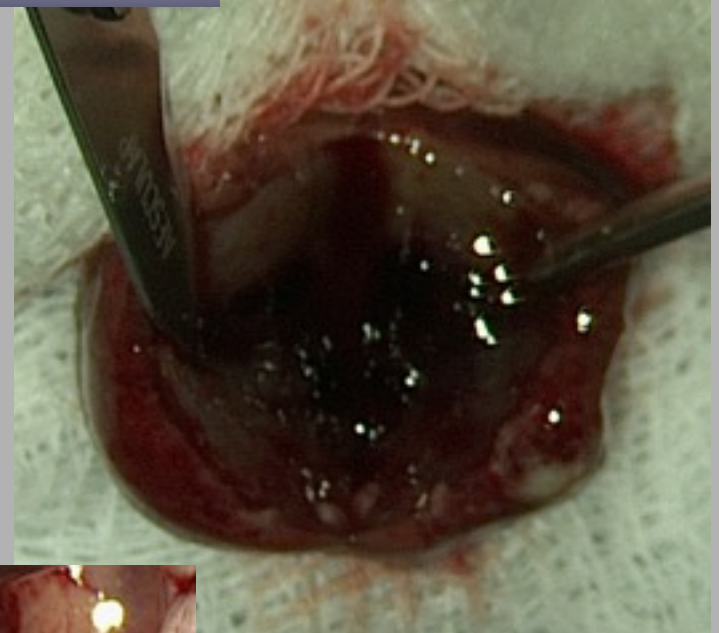
The Translational Gap in Modelling

• Resection

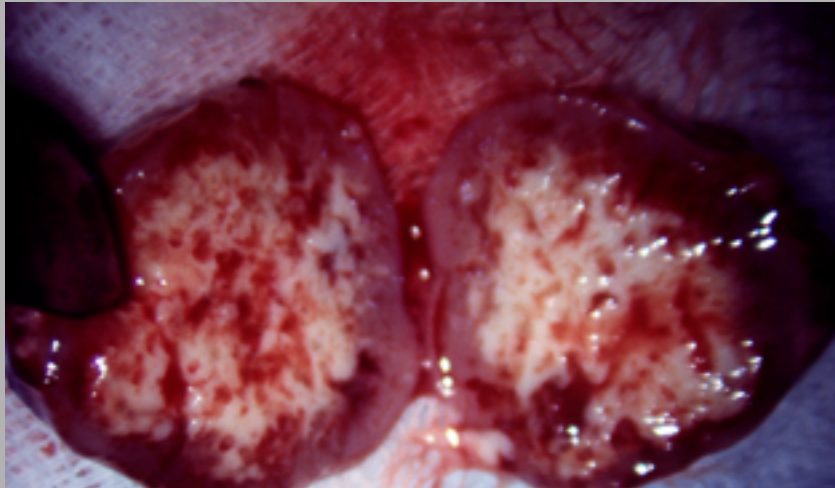
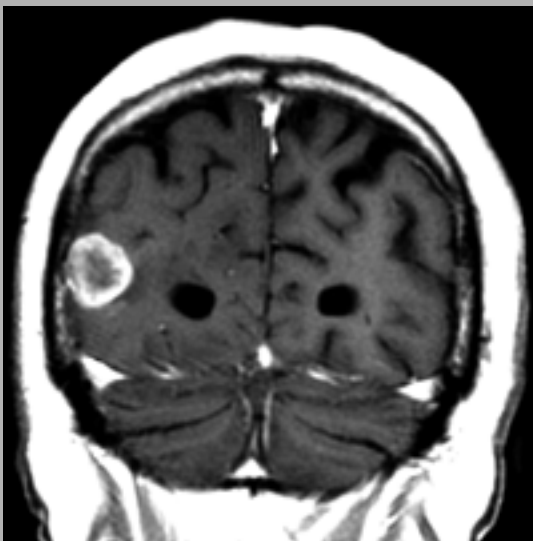
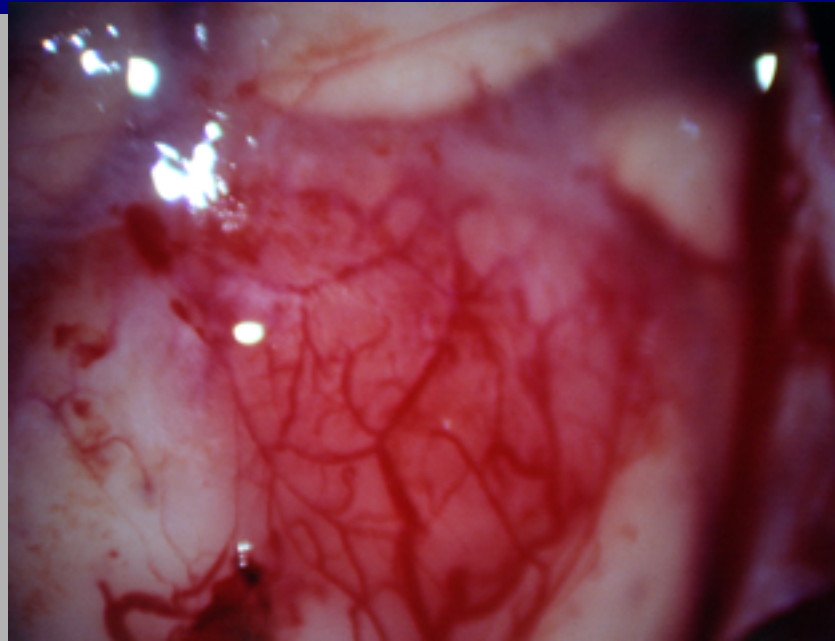
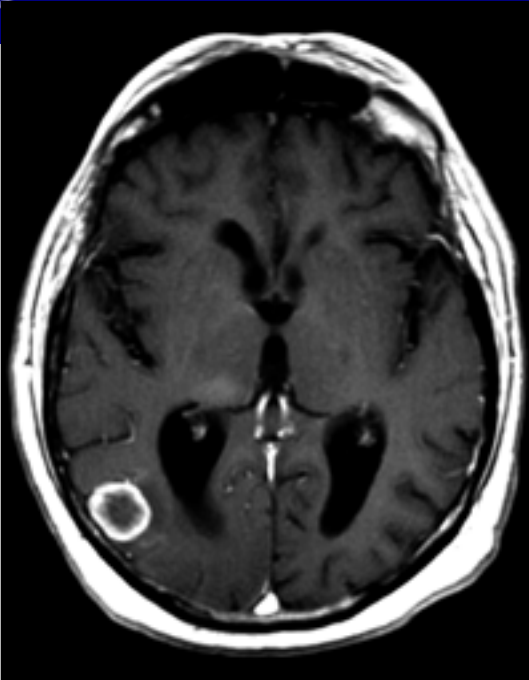


- # Resection

**4 Weeks post-partum, one seizure
possibly angiofibroma ???**



- # Resection

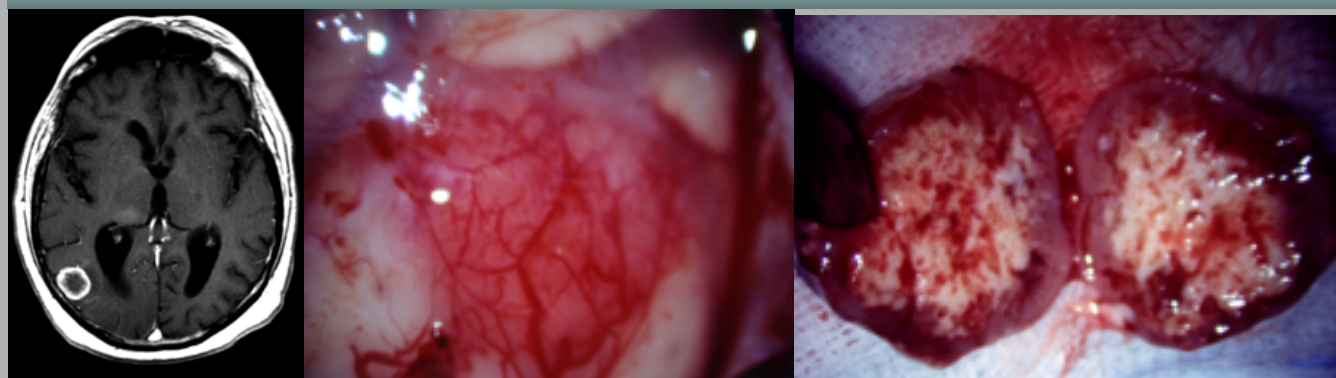


Solitary Metastasis of NSCLC



• Resection

In toto vs piecemeal : Complications



JNS

CLINICAL ARTICLE

J Neurosurg 122:1132-1143, 2015

Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis

*Akash J. Patel, MD,^{1,2} Dima Suki, PhD,¹ Mustafa Aziz Hatiboglu, MD,¹ Vikas Y. Rao, MD,² Benjamin D. Fox, MD,² and Raymond Sawaya, MD^{1,2}

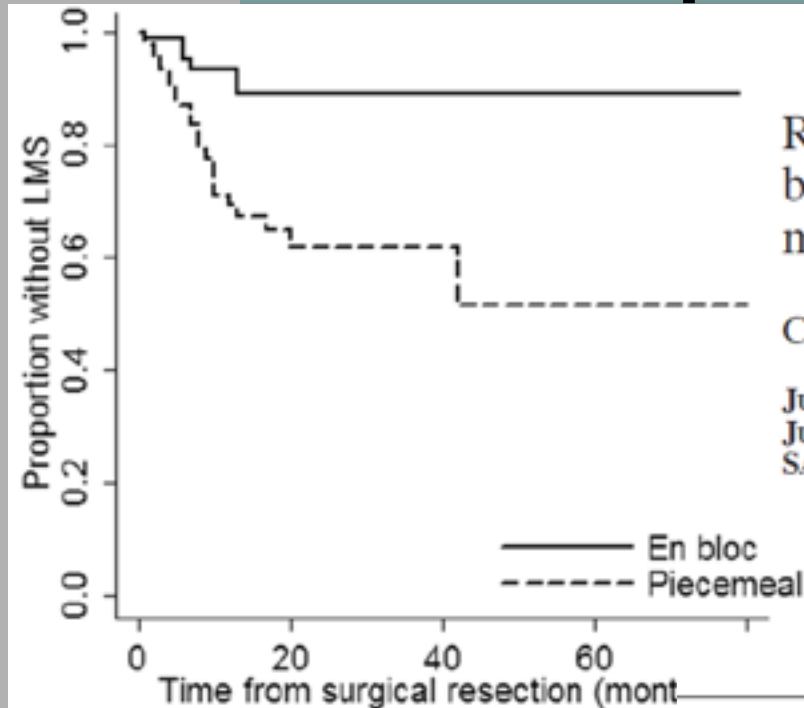
TABLE 4. Overall 30-day complications and complications according to surgical method in patients who underwent surgery for a single previously untreated brain metastasis*

Complication	All Patients (n = 1033)	Piecemeal Resection (n = 395)	En Bloc Resection (n = 638)	p Value
Overall complications	154 (15)	74 (19)	80 (13)	0.007
Major complications	84 (8)	41 (10)	43 (7)	0.04
All neurological complications	104 (10)	50 (13)	54 (8)	0.03



• Resection

In toto vs piecemeal : Seeding



Risk for leptomeningeal seeding after resection for brain metastases: implication of tumor location with mode of resection

Clinical article

JUN HYONG AHN, M.D.,¹ SANG HYUN LEE, M.D., PH.D.,² SOHEE KIM, M.S.,³
JUNGNAM JOO, PH.D.,³ HEON YOO, M.D., PH.D.,⁴ SEUNG HOON LEE, M.D., PH.D.,⁴
SANG HOON SHIN, M.D.,⁴ AND HO-SHIN GWAK, M.D., PH.D.⁴

Characteristics

Total (n = 242)

En Bloc (n = 87)

Piecemeal (n = 155)

sex

male

144 (60)

44 (51)

100 (65)

female

98 (40)

43 (49)

55 (35)

age

median

60.5

62

60

range

19–88

26–88

19–77

primary cancer

breast

25 (10)

13 (15)

12 (8)

lung

164 (68)

58 (67)

106 (68)

other

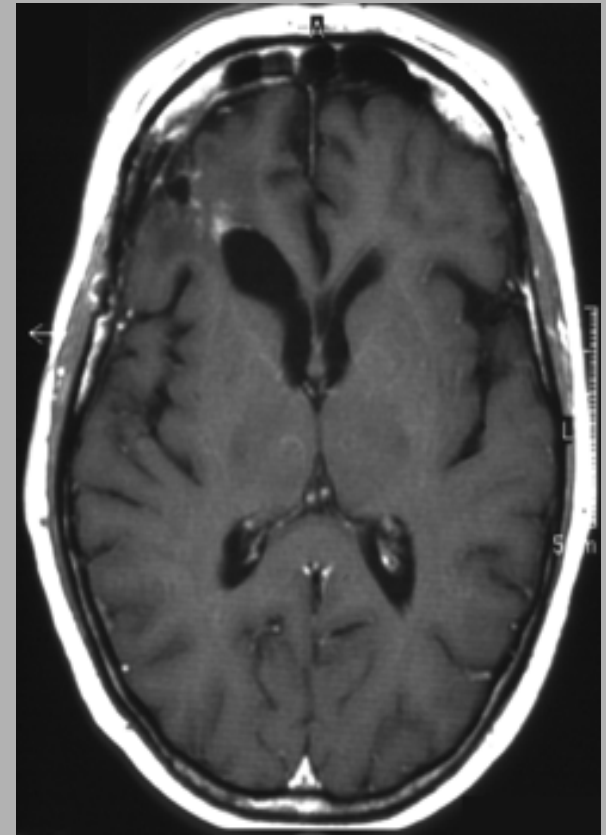
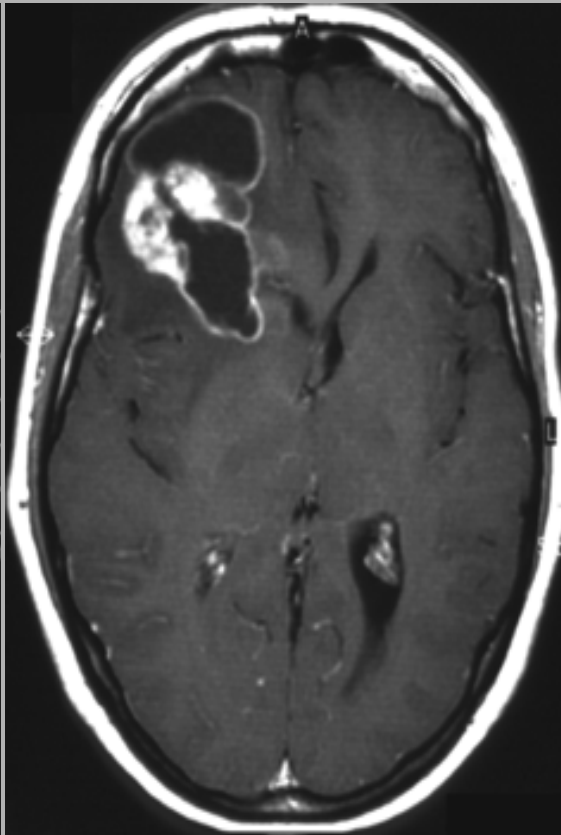
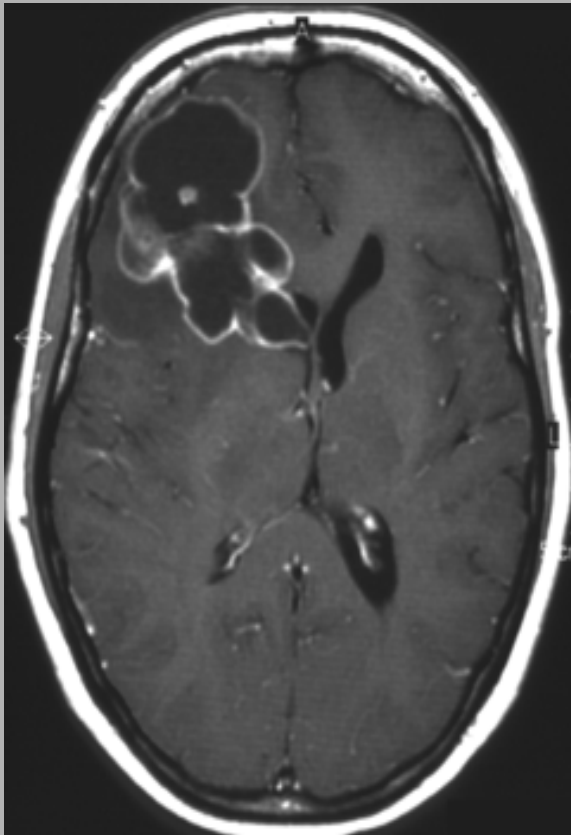
53 (22)

16 (18)

37 (24)

- # Resection

**How about cystic
metastases**





Available online at www.sciencedirect.com

ScienceDirect

Surgical Neurology 72 (2009) 703–706

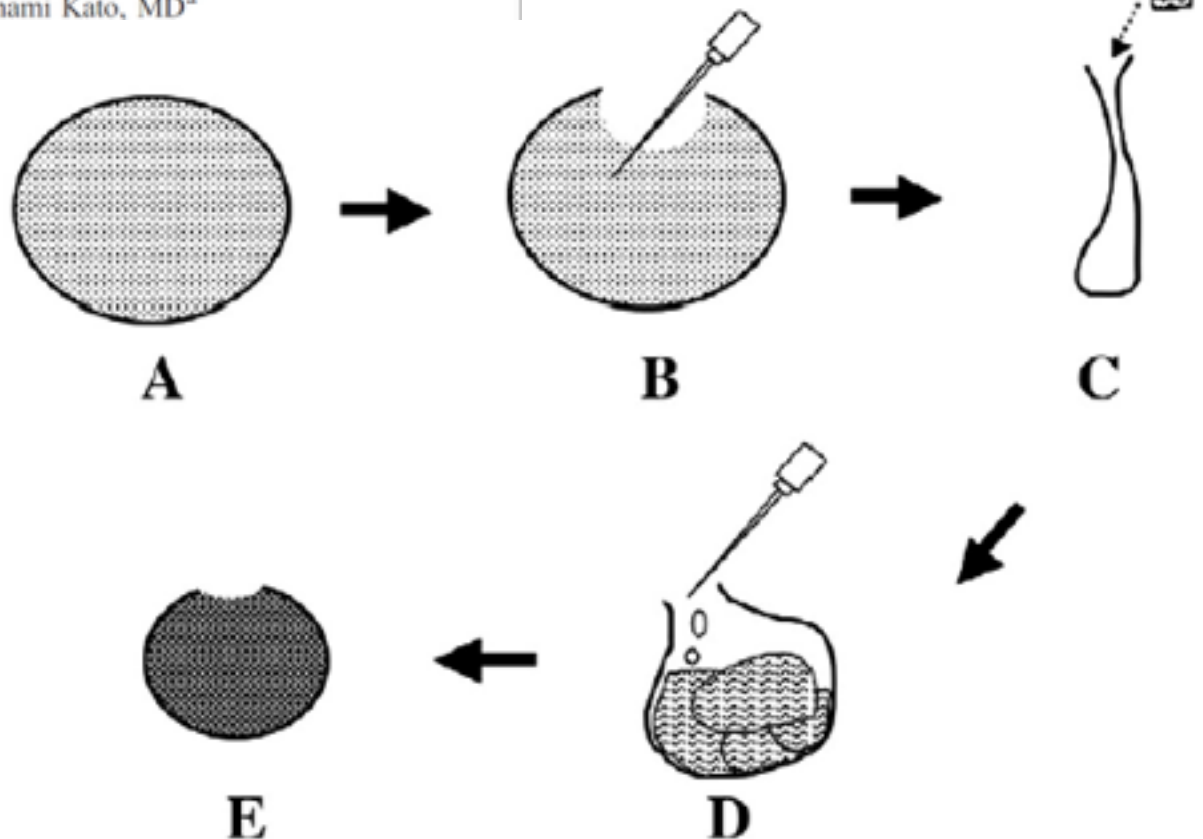
Technique

SURGICAL
NEUROLOGY

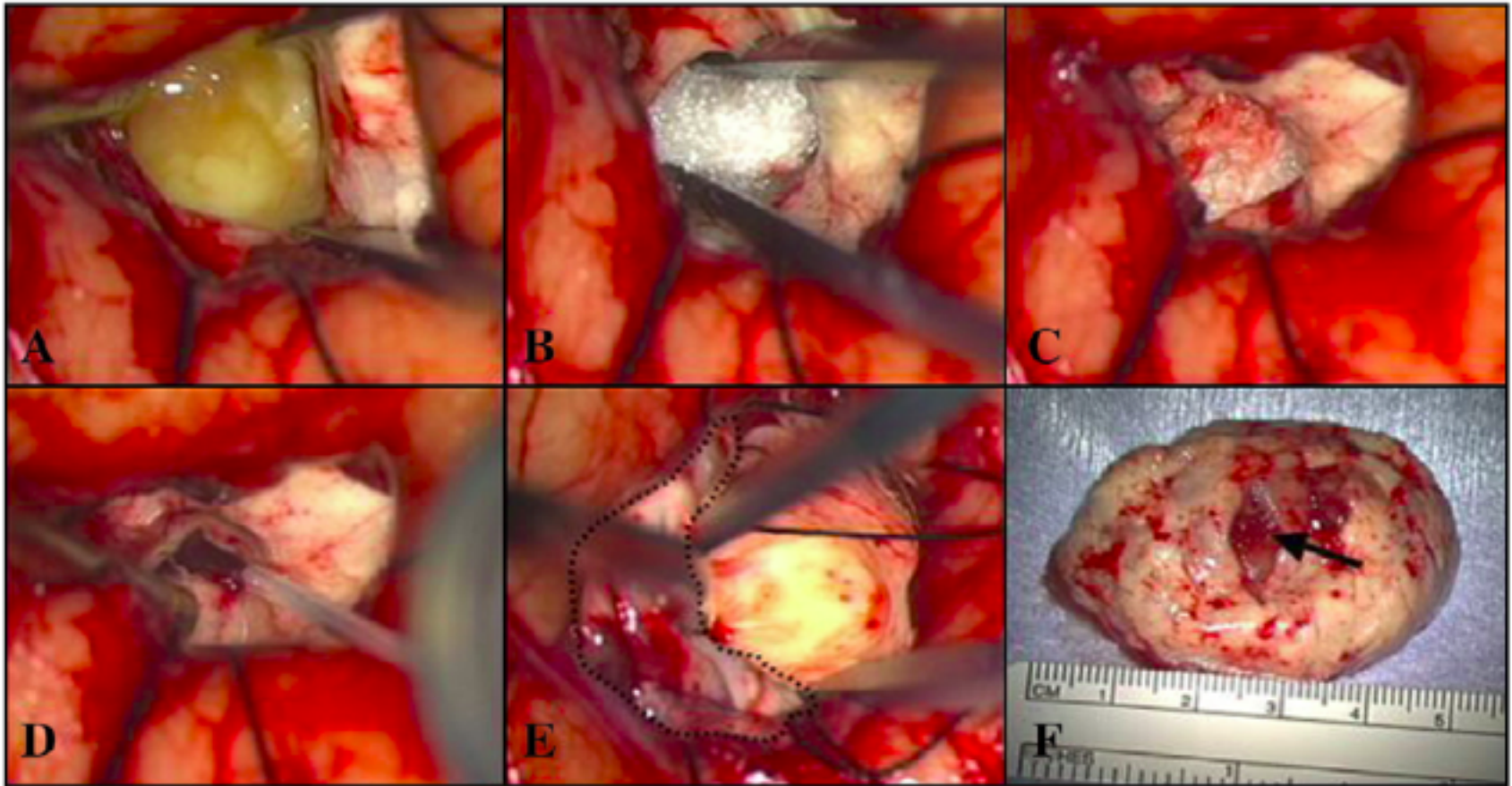
www.surgicalneurology-online.com

Surgical technique for a cystic-type metastatic brain tumor: transformation to a solid-type tumor using hydrofiber dressing

Takeshi Okuda, MD^{a,*}, Yoshifumi Teramoto, MD^a, Haruki Yugami, MD^a,
Kazuo Kataoka, MD^b, Amami Kato, MD^a



- # Resection



• Resection

Surgical Neurology International

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For entire Editorial Board visit:
<http://www.surgicalneurologyint.com>

Editor:
James I. Ausman
University of California,
Los Angeles, CA, USA

Technical Note

Novel surgical technique to solidify cyst-type metastatic brain tumors using autologous fibrin glue for complete resection

Takeshi Okuda, Mitsugu Fujita¹, Hiromasa Yoshioka, Takayuki Tasaki, Amami Kato

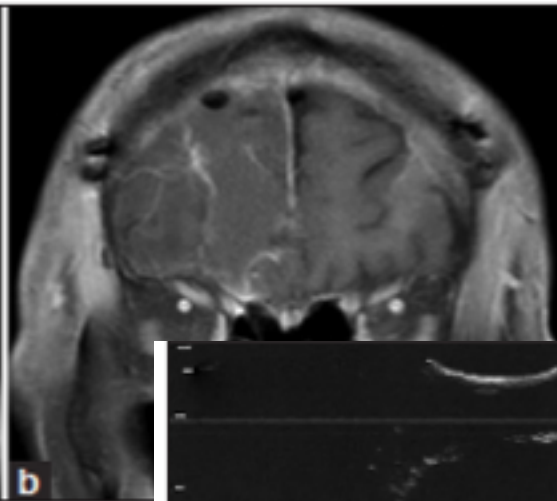


Figure 3: Intraoperative ultrasound photographs. (a) Before drainage



No Shinkei Geka, 45(1) : 29 - 32, 2017

テクニカル・ノート ◆ Technical Note

術中綿片洗浄細胞診（コットンダム細胞診） —転移性脳腫瘍摘出術における髄膜播種の評価と予防のために—*

三矢 幸一¹⁾, 中洲 庸子¹⁾, 大野 幸代²⁾, 林 央周¹⁾, 渡邊 麗子²⁾, 伊藤 以知郎²⁾

Cotton-Dam Wash Cytology : A Technique for Diagnosis and Prevention of Dissemination during Resection of Metastatic Brain Tumors

Koichi MITSUYA¹⁾, Yoko NAKASU¹⁾, Sachiyo ONO²⁾, Nakamasa HAYASHI¹⁾, Reiko WATANABE²⁾, and Ichiro ITO²⁾

Key words :

cytology,
dissemination,
metastatic brain tumor,
resection

The management of brain metastases has been important in neurosurgical oncology. Resection of a brain metastasis carries an increased risk of leptomeningeal dissemination than other treatment modalities such as irradiation or pharmacotherapy. We have utilized intraoperative wash cytology of cotton patties covering the brain surface. The cytology information contributes to making a decision of postoperative whole brain radiation. We named the method as "cotton dam", that serves as a check and catch of neoplastic cells on the brain surface during resection surgery.

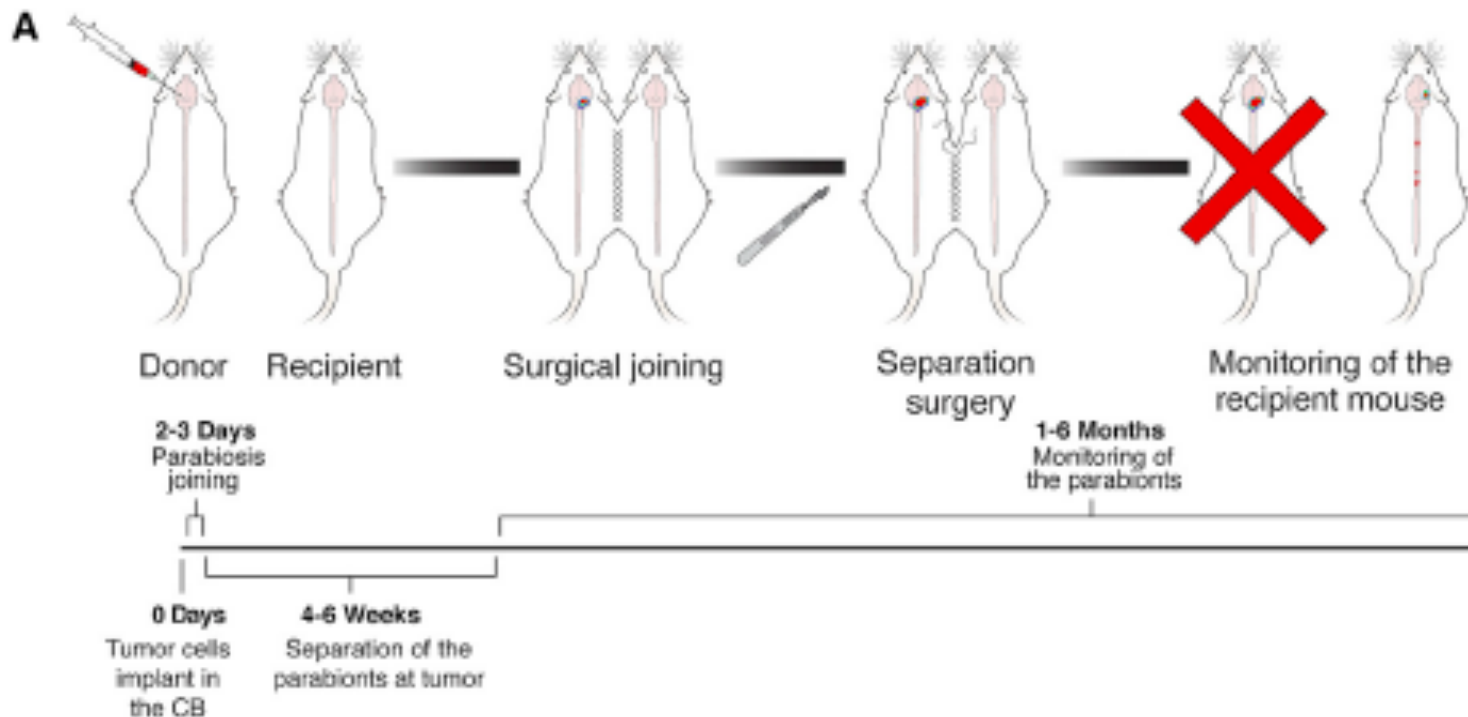
(Received : June 23, 2016, Accepted : September 28, 2016)

Issue : Dissemination

Article

A Hematogenous Route for Medulloblastoma Leptomeningeal Metastases

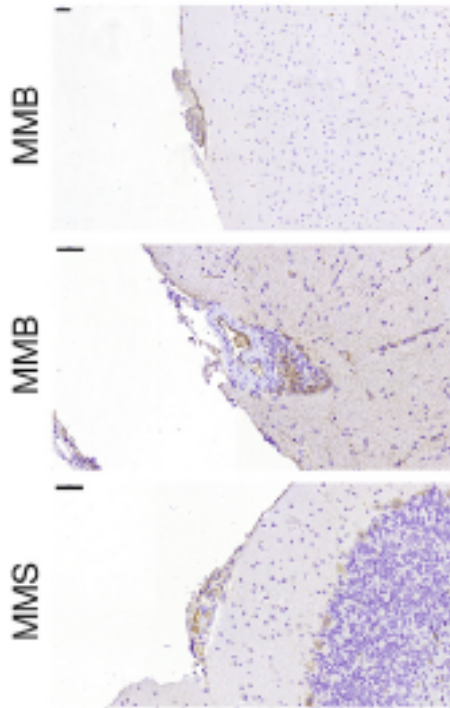
Livia Garzia,^{1,2,24} Noriyuki Kijima,^{1,2,24} A. Sorana Morrissy,^{1,2,24} Pasqualino De Antonellis,^{1,2} Ana Guerreiro-Stucklin,^{1,2} Borja L. Holgado,^{1,2} Xiaochong Wu,^{1,2} Xin Wang,^{1,2,3} Michael Parsons,⁴ Kory Zayne,^{1,2} Alex Manno,^{1,2} Claudia Kuzan-Fischer,^{1,2} Carolina Nor,^{1,2} Laura K. Donovan,^{1,2} Jessica Liu,^{1,2} Lei Qin,^{1,2} Alexandra Garancher,⁵ Kun-Wei Liu,⁵ Sheila Mansouri,⁶ Betty Luu,^{1,2} Yuan Yao Thompson,^{1,2,3} Vijay Ramaswamy,^{2,7} John Peacock,^{1,2} Hamza Farooq,^{1,2,3} Patryk Skowron,^{1,2,3} David J.H. Shih,^{1,2,3} Angela Li,⁸ Sherine Ensan,⁸ Clinton S. Robbins,^{8,9} Myron Cybulsky,^{3,10} Siddhartha Mitra,¹¹ Yussanne Ma,¹² Richard Moore,¹² Andy Mungall,¹² Yoon-Jae Cho,¹³ William A. Weiss,¹⁴ Jennifer A. Chan,¹⁵ Cynthia E. Hawkins,^{2,15} Maura Massimino,¹⁶ Nadia Jabado,¹⁷ Michal Zapotocky,^{7,18} David Sumerauer,¹⁸ Eric Bouffet,^{2,7} Peter Dirks,^{2,23} Uri Tabori,² Poul H.B. Sorensen,¹⁹





Issue : Dissemination

Leptomeningeal Mets



Cell line	Meningeal metastasis
MMB	2 of 4 (50%)
MMS	1 of 4 (25%)
Med-411FH	3 of 6 (50%)



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Issue : Dissemination

Published OnlineFirst March 10, 2014; DOI: 10.1158/0008-5472.CAN-13-2660

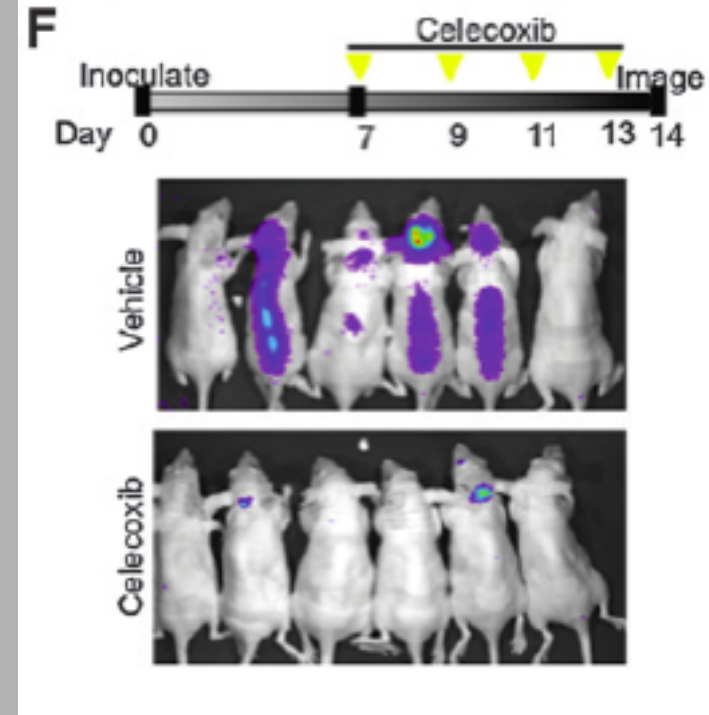
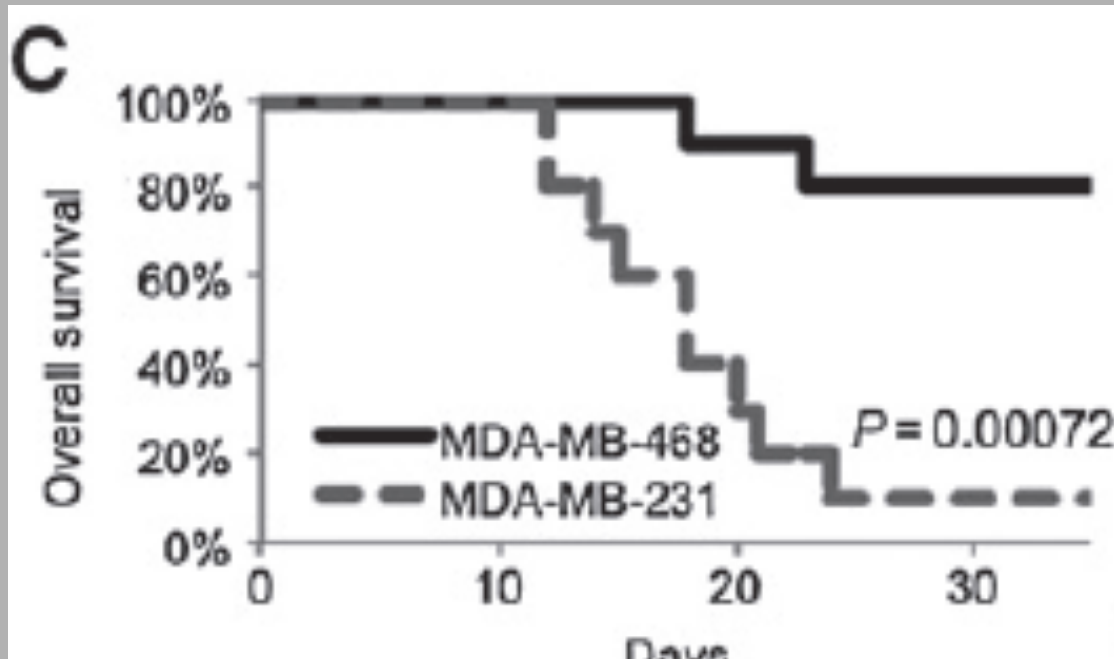
Priority Report

Cancer
Research

COX-2 Drives Metastatic Breast Cells from Brain Lesions into the Cerebrospinal Fluid and Systemic Circulation

Joshua E. Allen¹, Akshal S. Patel^{1,2}, Varun V. Prabhu¹, David T. Dicker¹, Jonas M. Sheehan², Michael J. Glantz², and Wafik S. El-Deiry^{1,3}

Issue : Dissemination





**Cochrane
Library**

Cochrane Database of Systematic Reviews

Image guided surgery for the resection of brain tumours (Review)

Barone DG, Lawrie TA, Hart MG

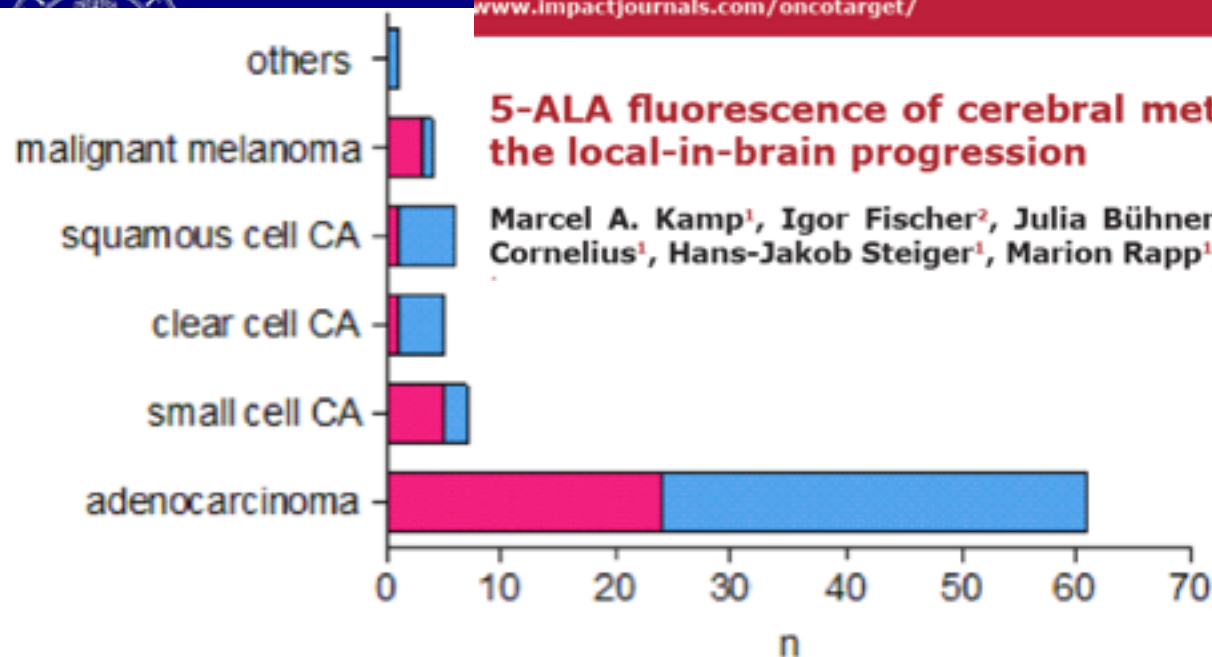
The majority of the trials only enrolled participants with probable HGG. A single trial also included LGG (Wu 2007). There were no identified trials for any of the other pre-specified tumour subgroups we sought to include (specifically pituitary tumours and skull base tumours). The benefit of intra-operative imaging in these groups therefore remains undefined and our results cannot be generalised to these other tumour groups.

5-ALA fluorescence of cerebral metastases and its impact for the local-in-brain progression

Marcel A. Kamp¹, Igor Fischer², Julia Bühner¹, Bernd Turowski³, Jan Frederick Cornelius¹, Hans-Jakob Steiger¹, Marion Rapp¹, Philipp J. Slotty¹, Michael Sabel¹

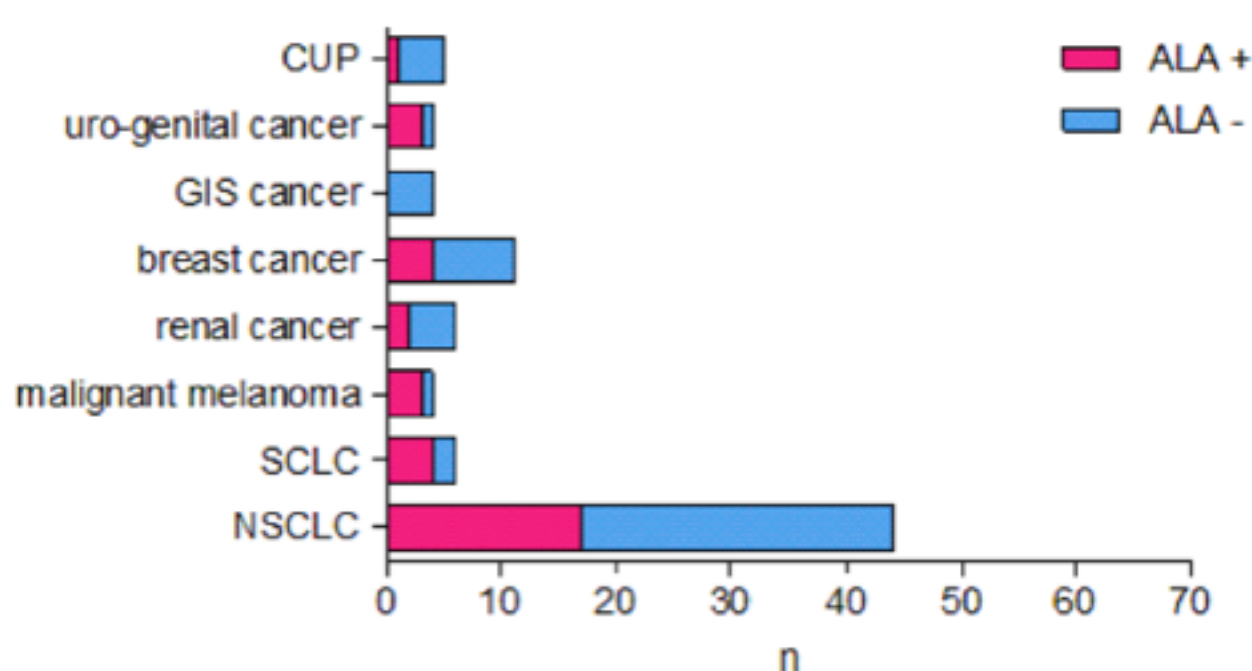
A

Histological subtype



B

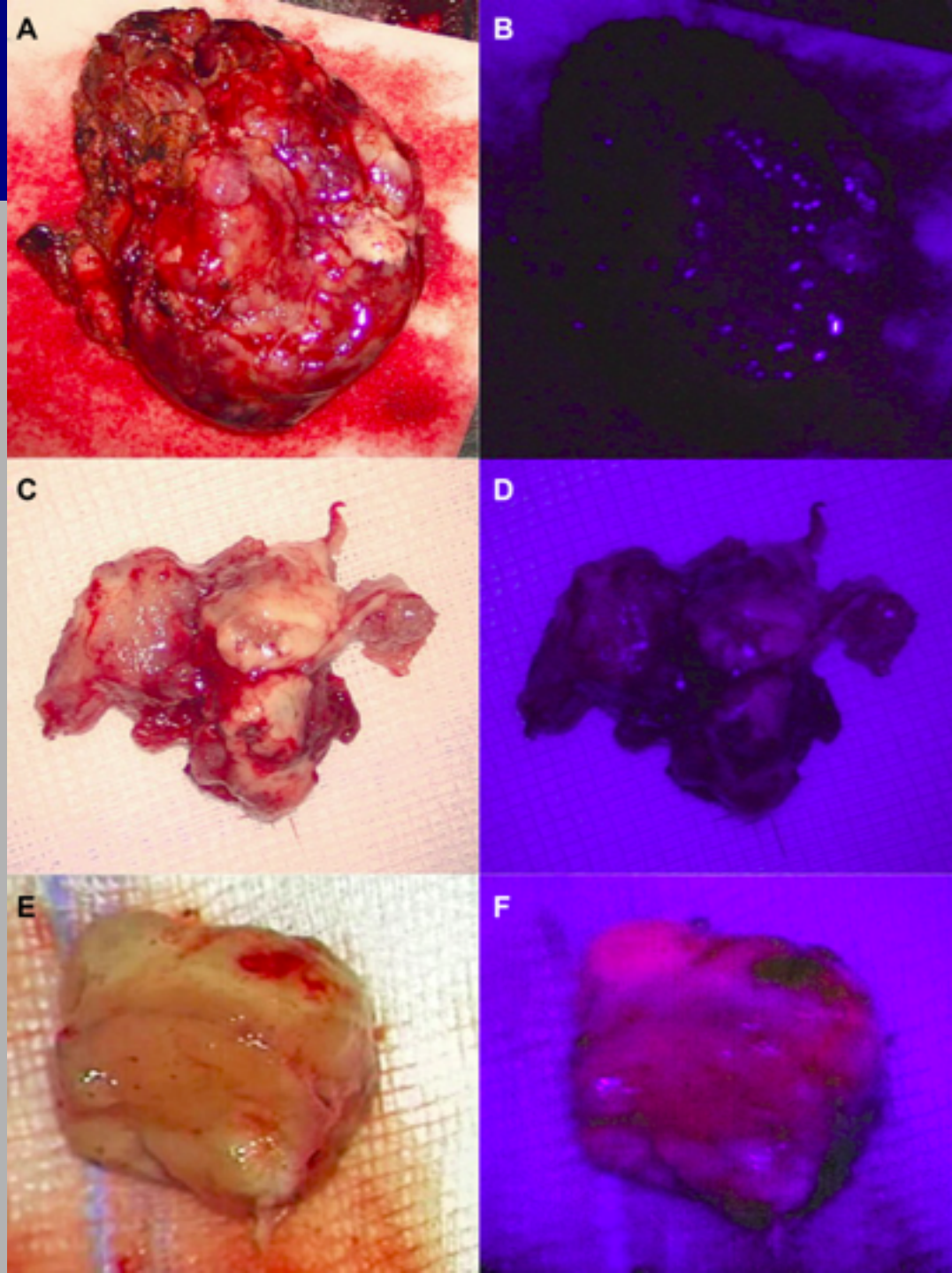
Primary site

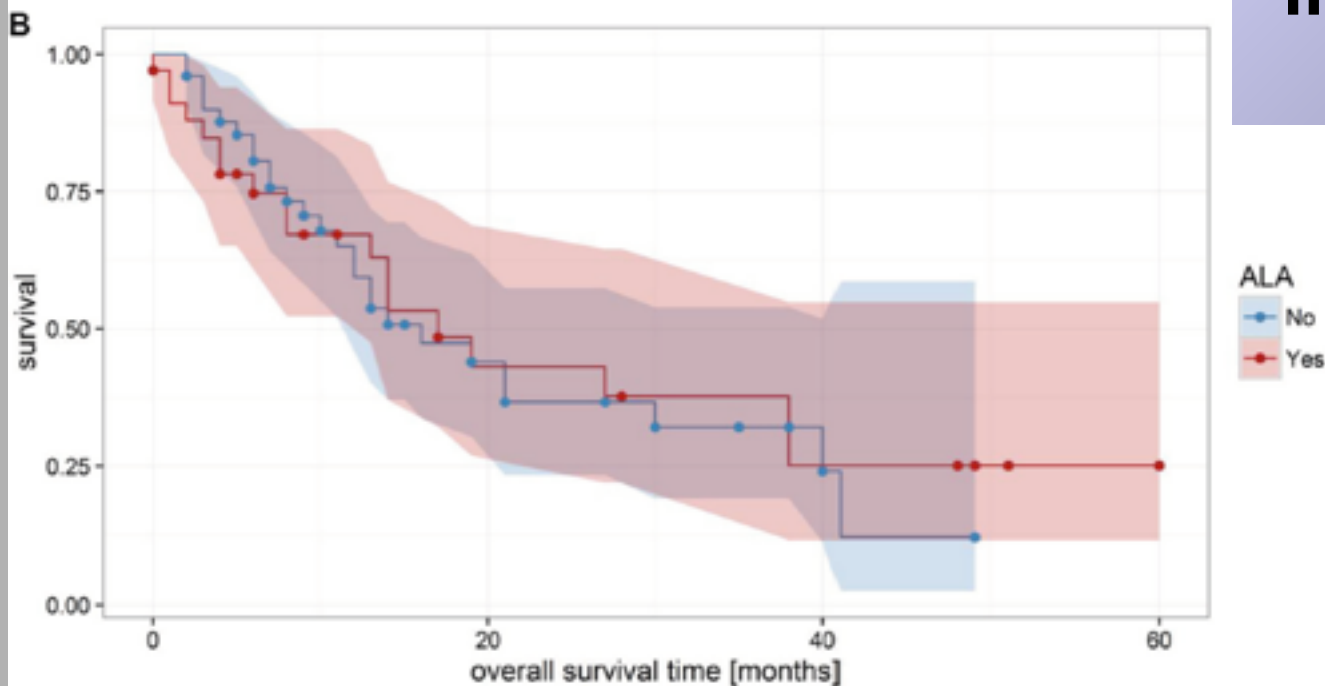
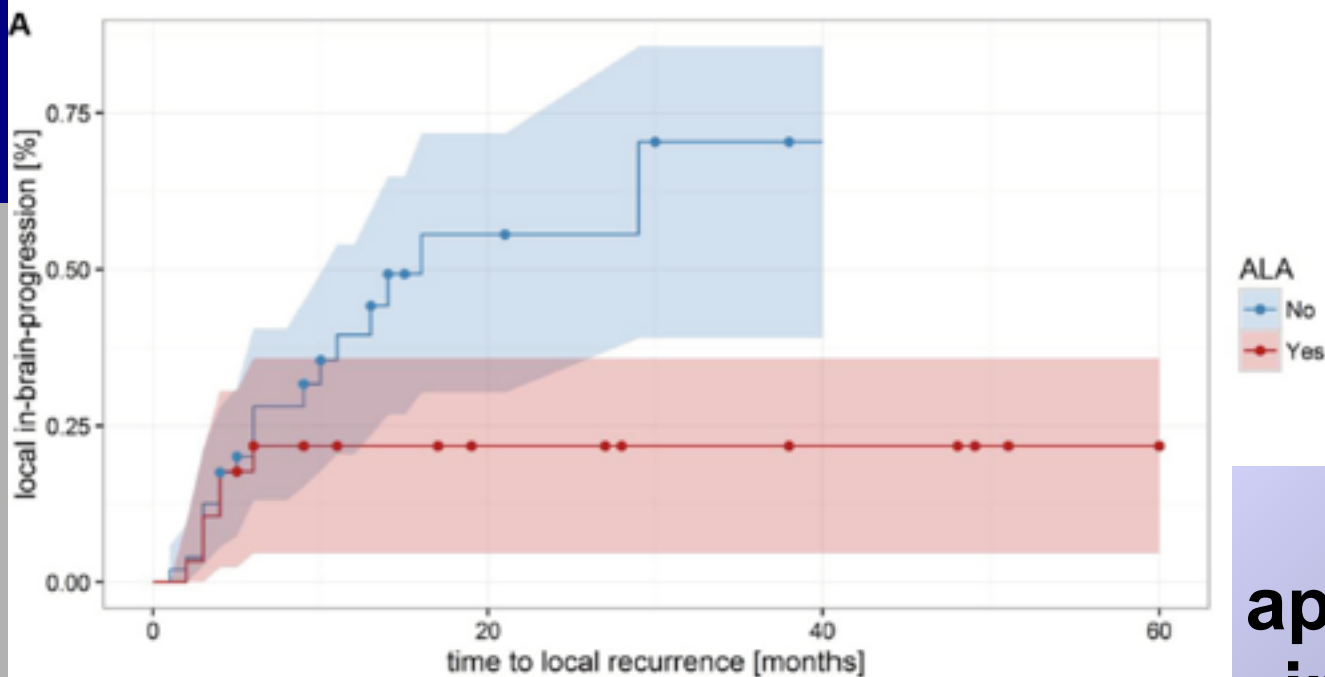


Resection

Fluorescence guidance

- 5-ALA
- Fluoresceine

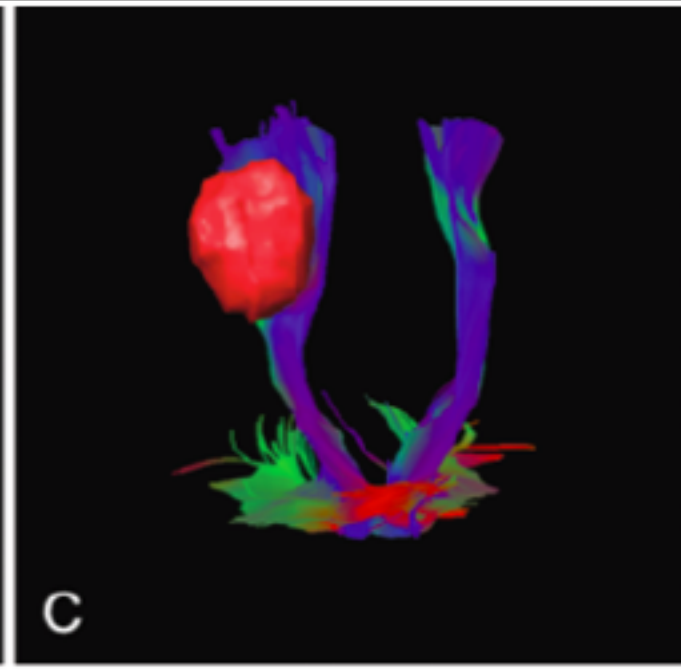
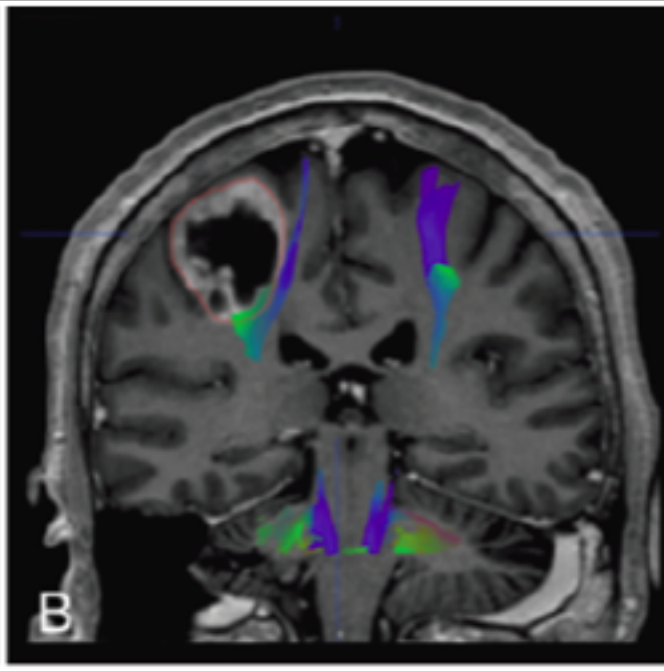
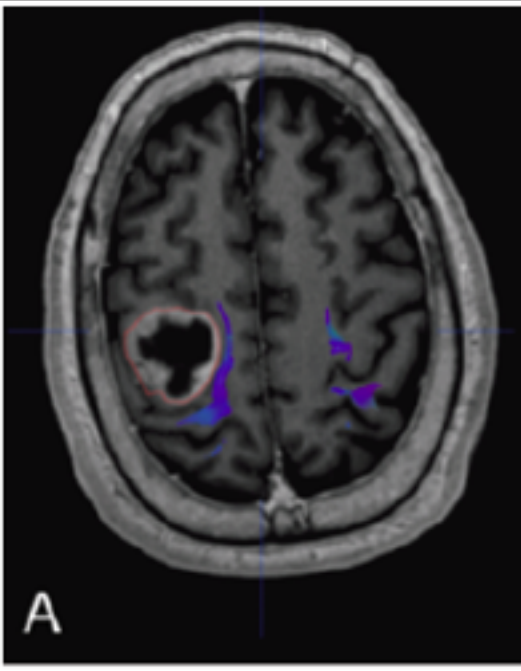


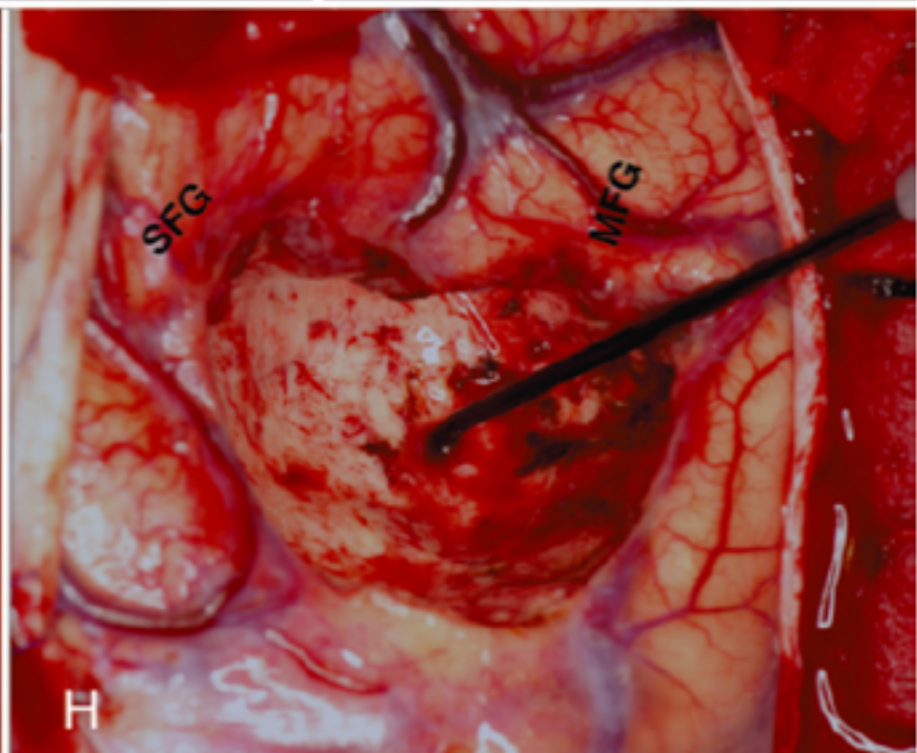
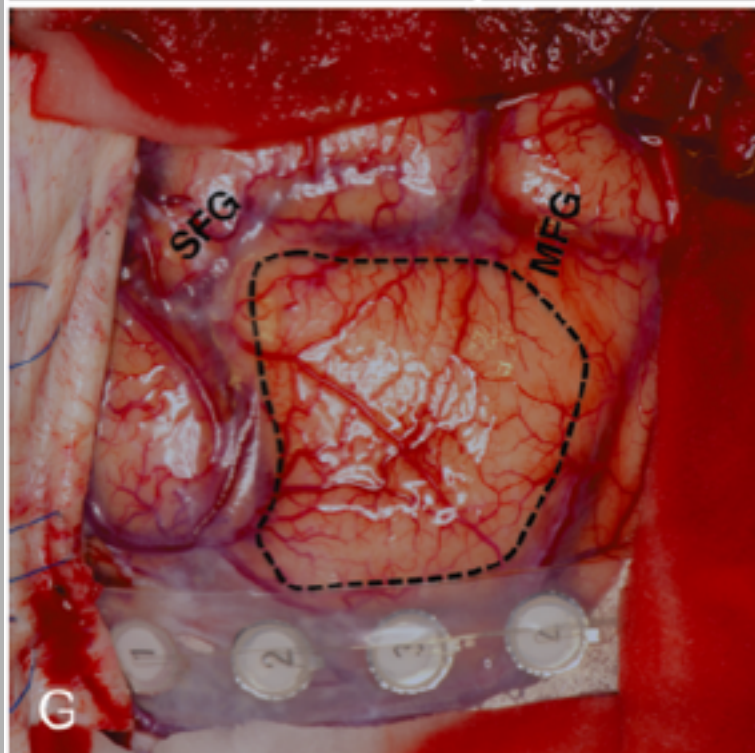
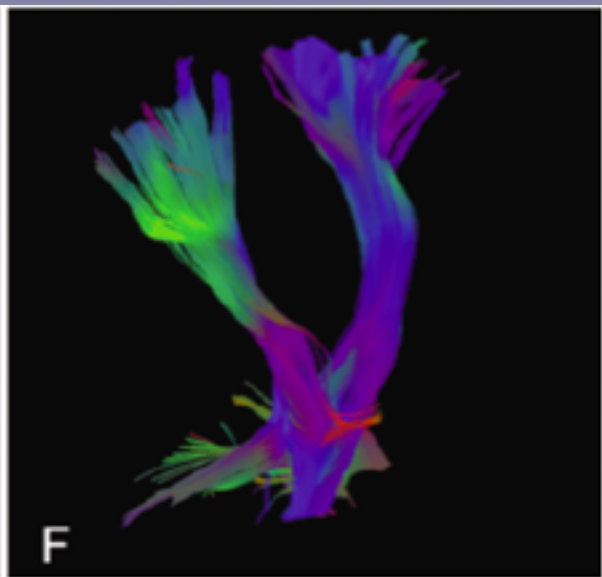
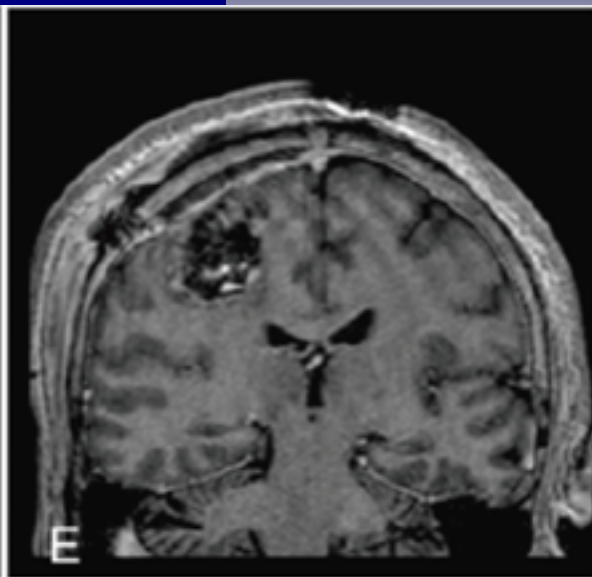
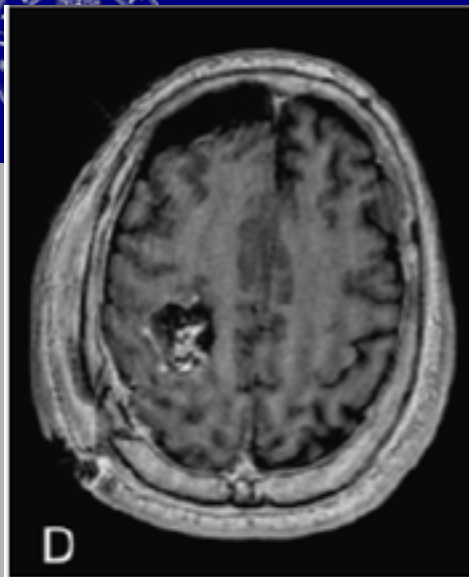


Local control apparently fails to increase overall survival

Functional approach using intraoperative brain mapping and neurophysiological monitoring for the surgical treatment of brain metastases in the central region

Jose L. Sanmillan, MD,¹ Alejandro Fernández-Coello, MD,¹ Isabel Fernández-Conejero, MD,² Gerard Plans, MD,¹ and Andreu Gabarrós, MD, PhD¹





- **AUGMENTATION ISSUES**
- **Intracavitary Treatments**
 - Radiation
 - Chemotherapy
 - “Gene Therapy“



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Resection : Augmentation

 **frontiers**
in Oncology

ORIGINAL RESEARCH
published: 26 March 2018
doi: 10.3389/fonc.2018.00074



Intraoperative Radiotherapy With INTRABEAM: Technical and Dosimetric Considerations

Anil Sethi, Bahman Emami, William Small Jr. and Tarita O. Thomas*

Resection : Segmentation



Intrabeam Floor Stand

Resection : Augmentation

Spherical Applicator

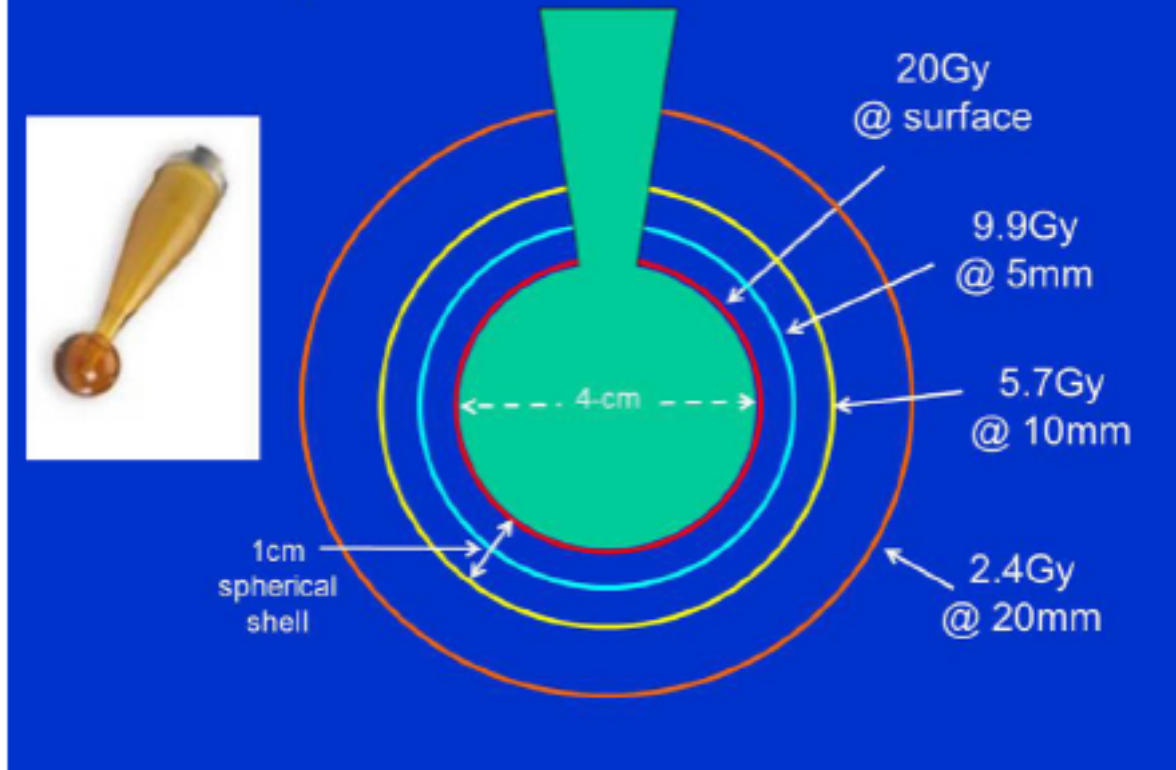

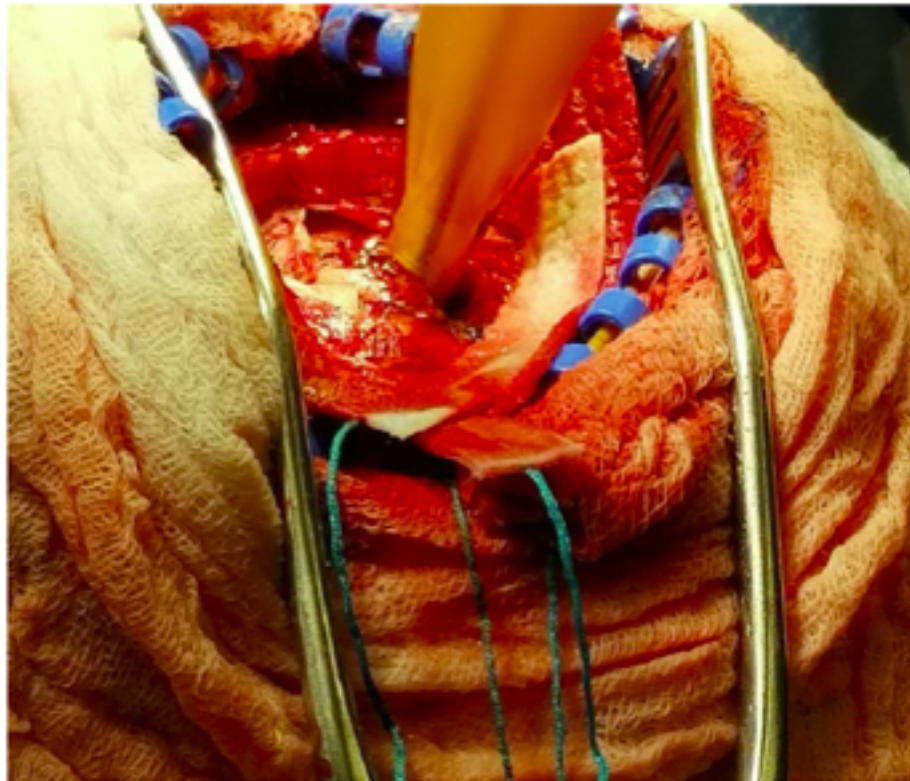


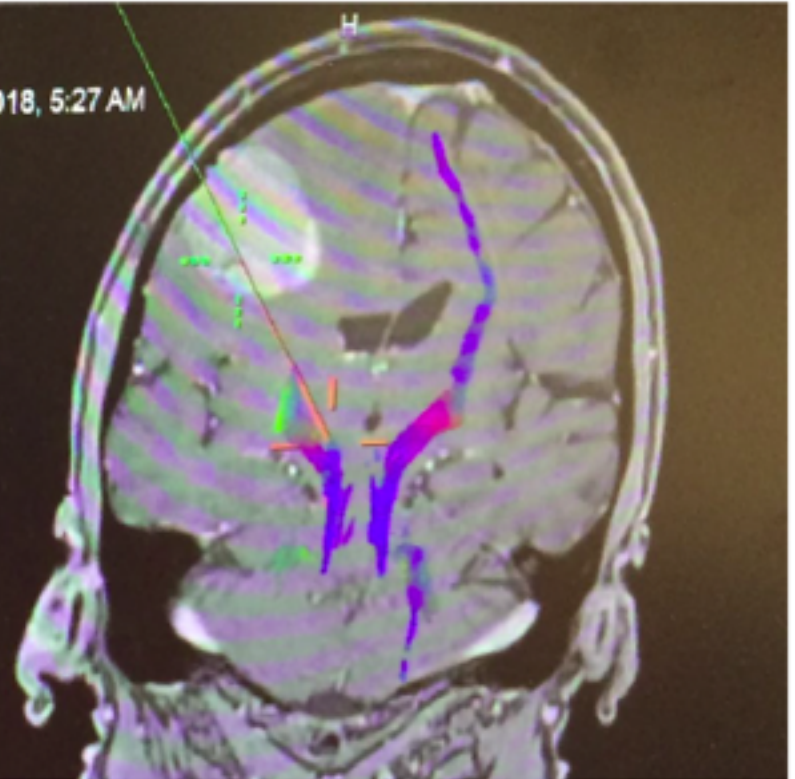
FIGURE 4 | Dose distribution produced by a 4 cm diameter spherical applicator. Doses are shown at the applicator surface and at 5, 10, and 20 mm distance from it. Dose homogeneity was evaluated in a 1 cm thick spherical shell surrounding the applicator. Applicator shown in inset.

Feasibility of dose escalation using intraoperative radiotherapy following resection of large brain metastases compared to post-operative stereotactic radiosurgery

John A. Vargo¹  · Kristie M. Sparks¹ · Rahul Singh² · Geraldine M. Jacobson¹ · Joshua D. Hack¹ · Christopher P. Cifarelli²

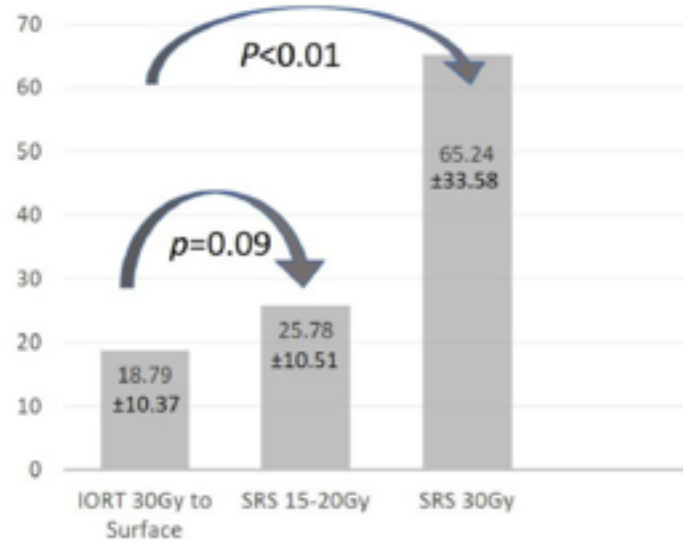


Coronal
#5 (MR)
06-Apr-2018, 5:27 AM

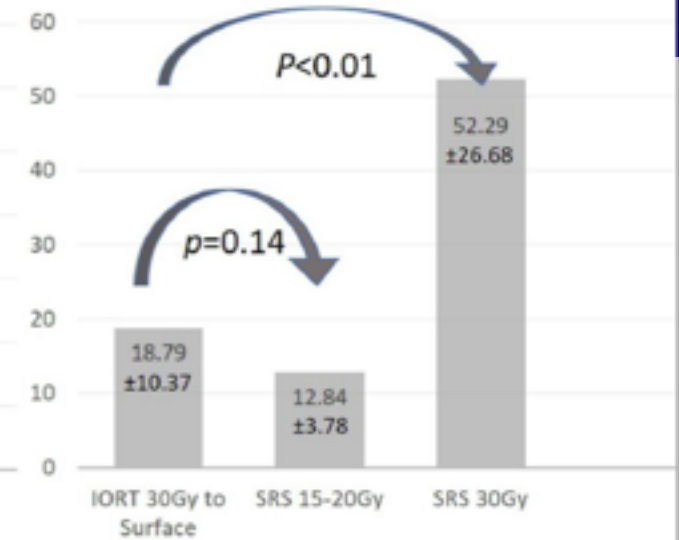




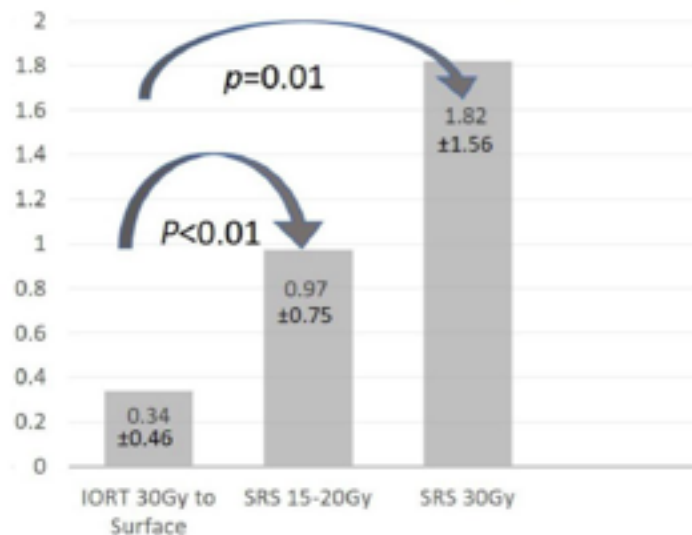
A Comparison of Brain V12 with SRS Total V12 (cc)



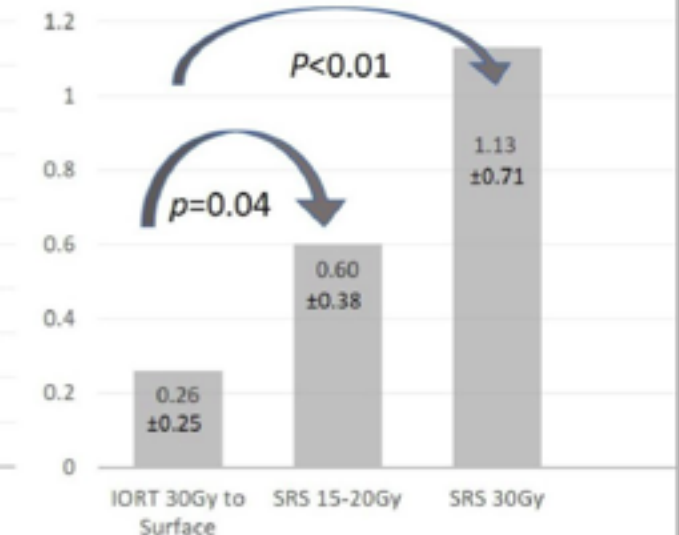
B Comparison of Brain V12 with SRS V12Gy sub GTV (cc)



C Comparison of Maximal Dose to Brainstem (Gy)



D Comparison of Maximal Dose to Optic Apparatus (Gy)





Intraoperative radiotherapy to treat newly diagnosed solitary brain metastasis: initial experience and long-term outcomes

CLINICAL ARTICLE

J Neurosurg 122:825–832, 2015

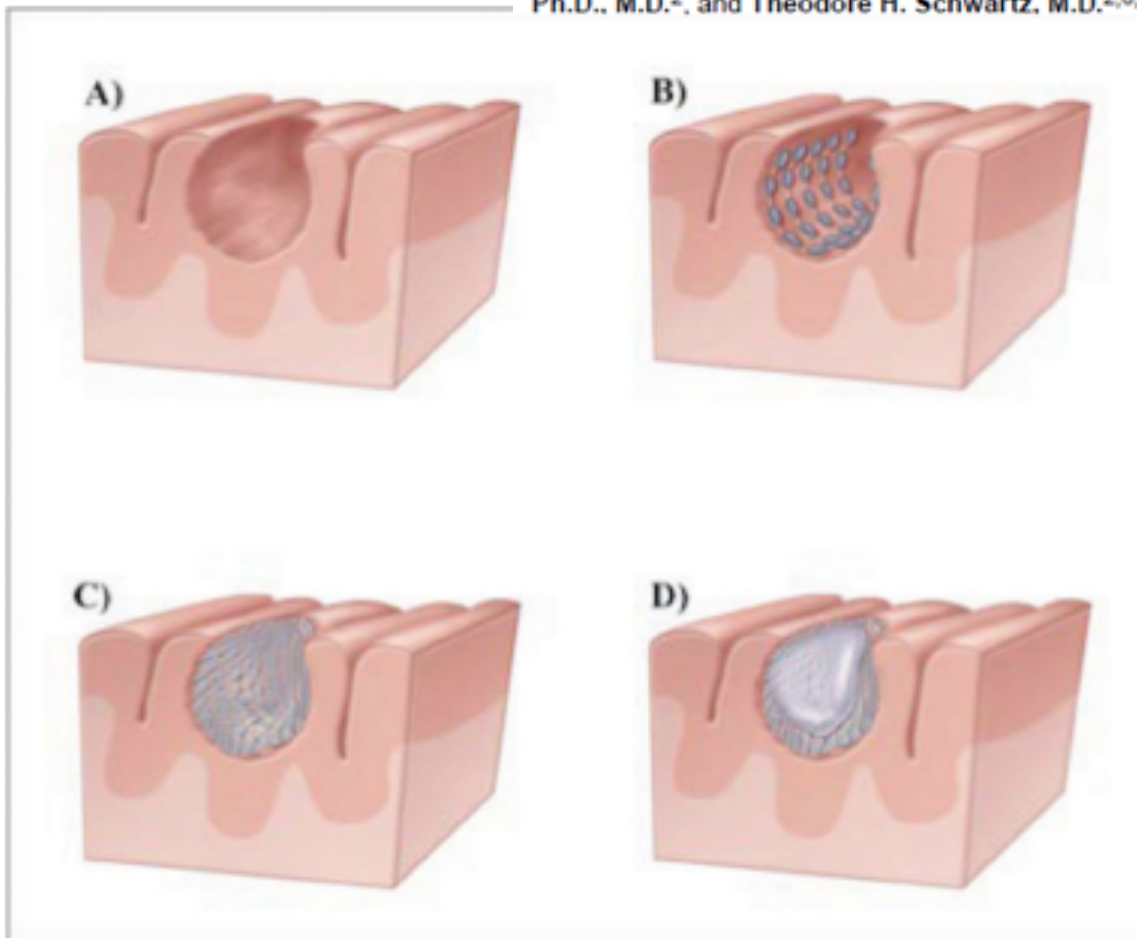
Robert J. Weil, MD,^{1,2,4} Gaurav G. Mavinkurve, MD,² Samuel L. ...
Michael A. Vogelbaum, MD, PhD,^{1,2,4} John H. Suh, MD,^{1,3,4} Matthew Kolar, MS,³
and Steven A. Toms, MD, MPH⁵

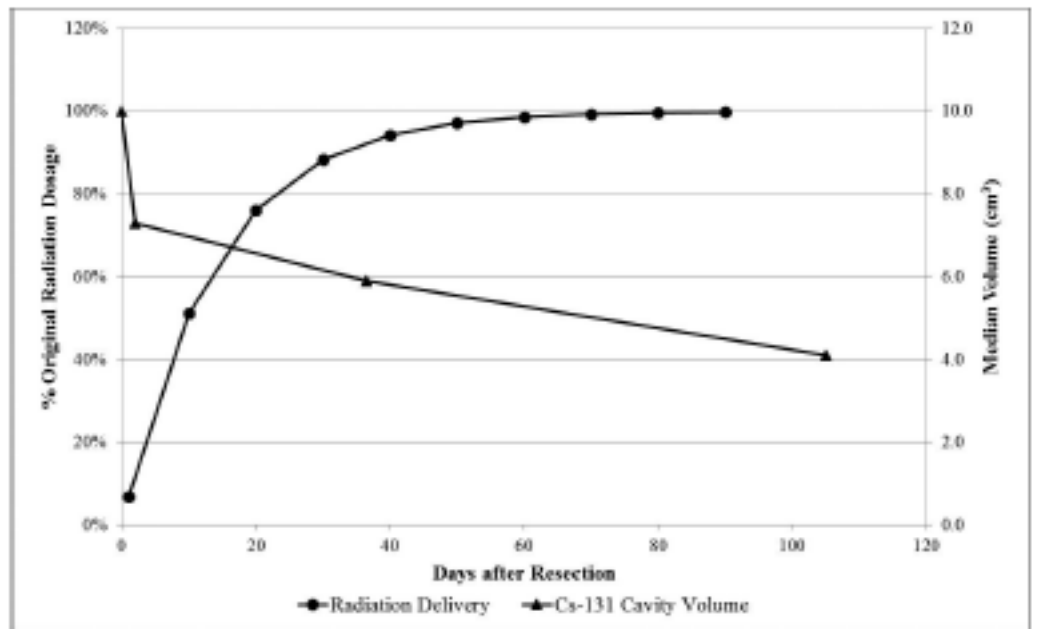
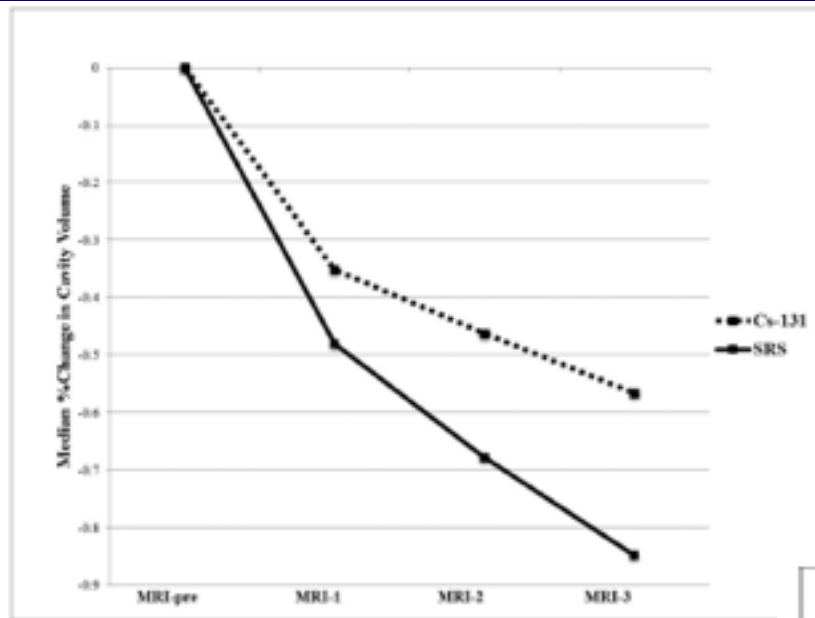
TABLE 2. Patient characteristics and outcomes* (*continued*)

Patient No.	KPS Score			PFS (mos)	OS (mos)	CNS Survival (mos)‡
	Preop	1 Mo*	3 Mos†			
23	70	70	90	5	13	5
Mean	NA	NA	NA	21.9	71.1	29.6
SD	NA	NA	NA	32.8	63.5	31.5
Median	80	90	90	9	36	18
Mode	80	90	90		35	10

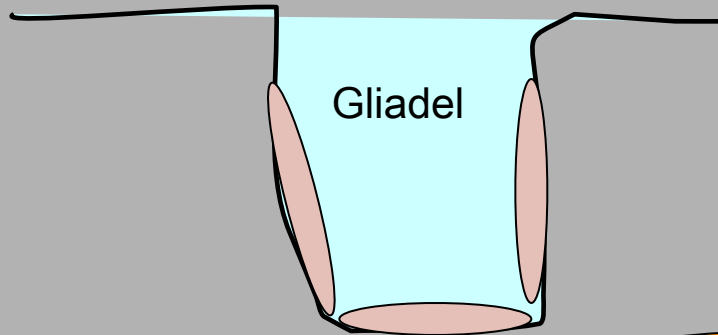
Surgical Technique and Clinically Relevant Resection Cavity Dynamics Following Implantation of Cesium-131 (Cs-131) Brachytherapy in Patients With Brain Metastases

A. Gabriella Wernicke, M.D., M.Sc.^{1,2}, Stefanie P. Lazow, B.A.³, Shoshana Taube, B.A.¹, Menachem Z. Yondorf, B.A.¹, Ilhami Kovanlikaya, M.D.⁴, Dattatreyudu Nori, M.D.¹, Paul Christos, Dr.P.H., M.S.⁵, John A. Boockvar, M.D.², Susan Pannullo, M.D.², Philip E. Stieg, Ph.D., M.D.², and Theodore H. Schwartz, M.D.^{2,6,7}

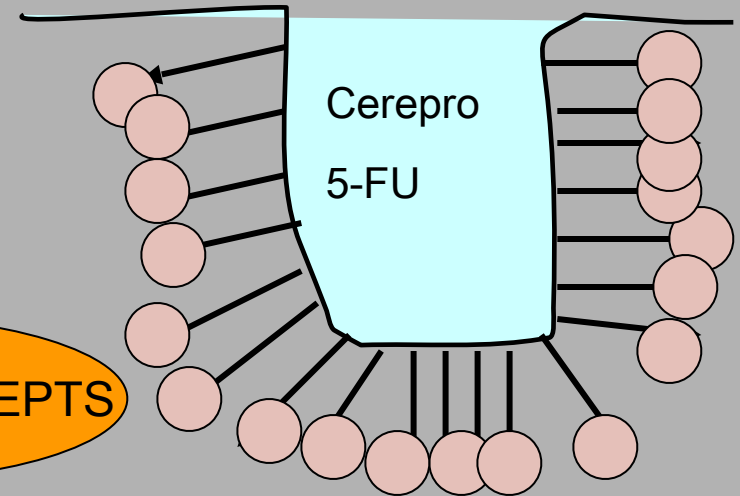




Intracavitary Polymer Placement

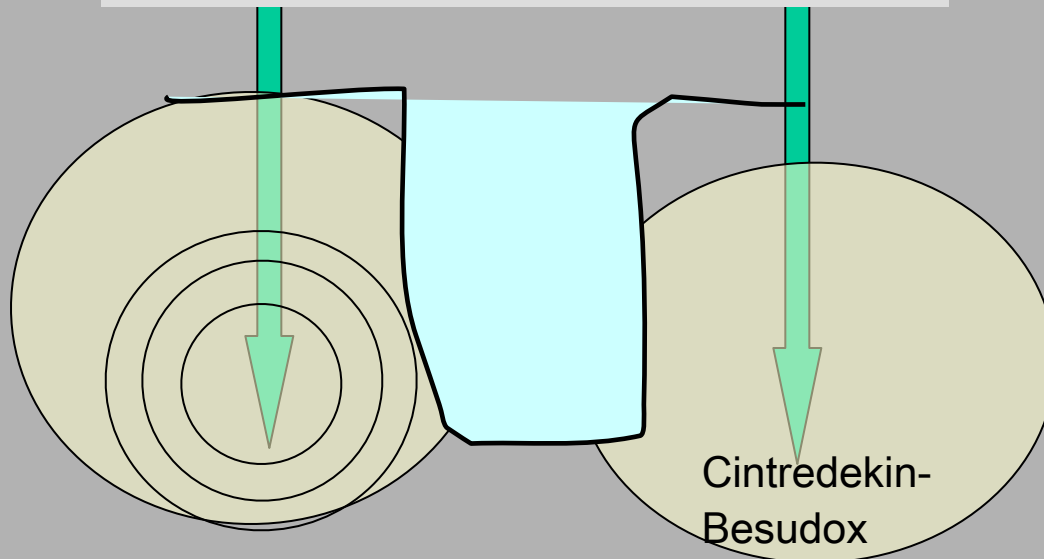


Pericavitary Reagent Injections

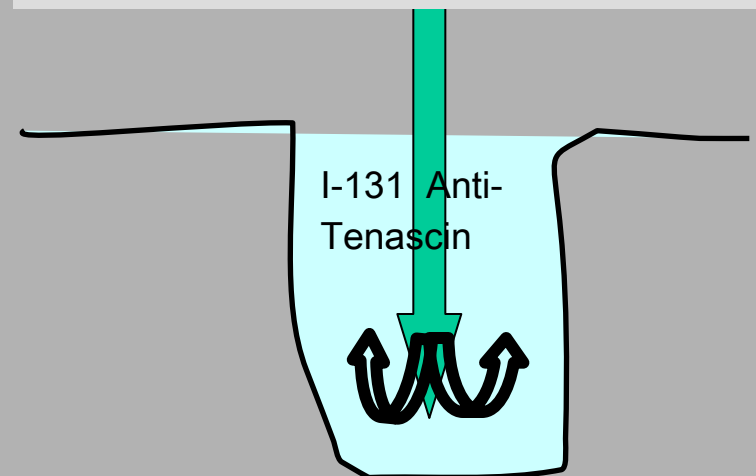


DELIVERY CONCEPTS

Perilesional Interstitial Infusion (CED)



Intracavitary Reagent Instillation



Safety and efficacy of carmustine (BCNU) wafers for metastatic brain tumors

Chibawaye I. Ene, John D. Nerva, Ryan P. Morton, Ariana S. Barklev, Jason K. Barber, Andrew L. Ko, Daniel L. Silbergeld

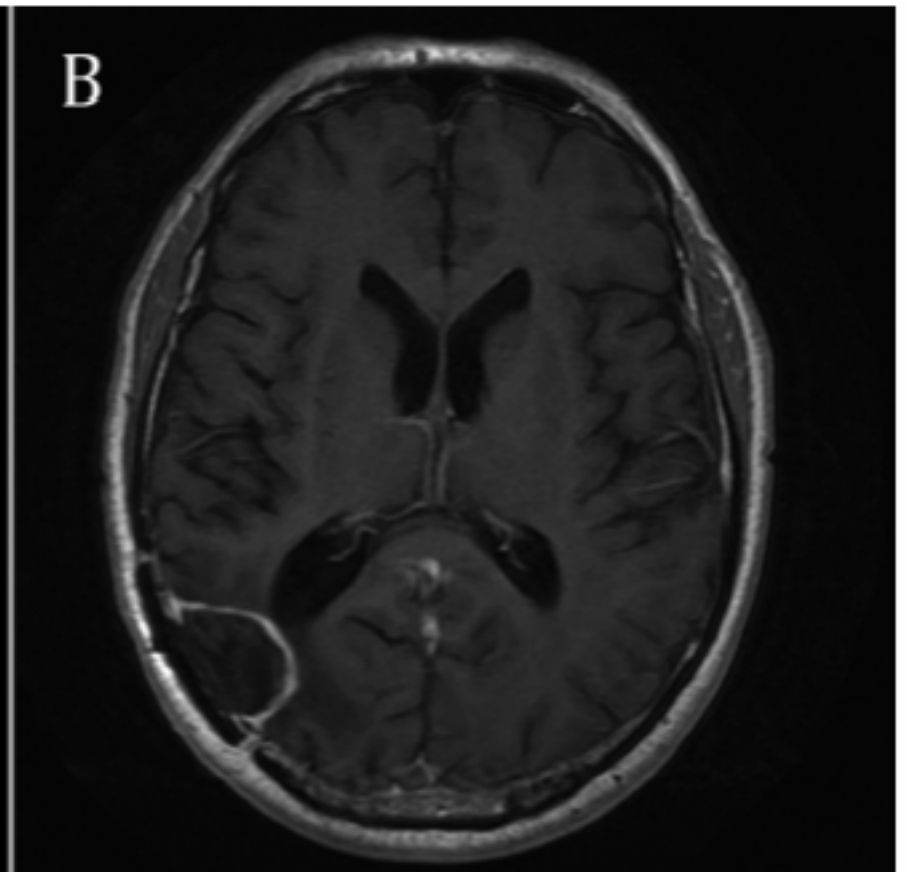
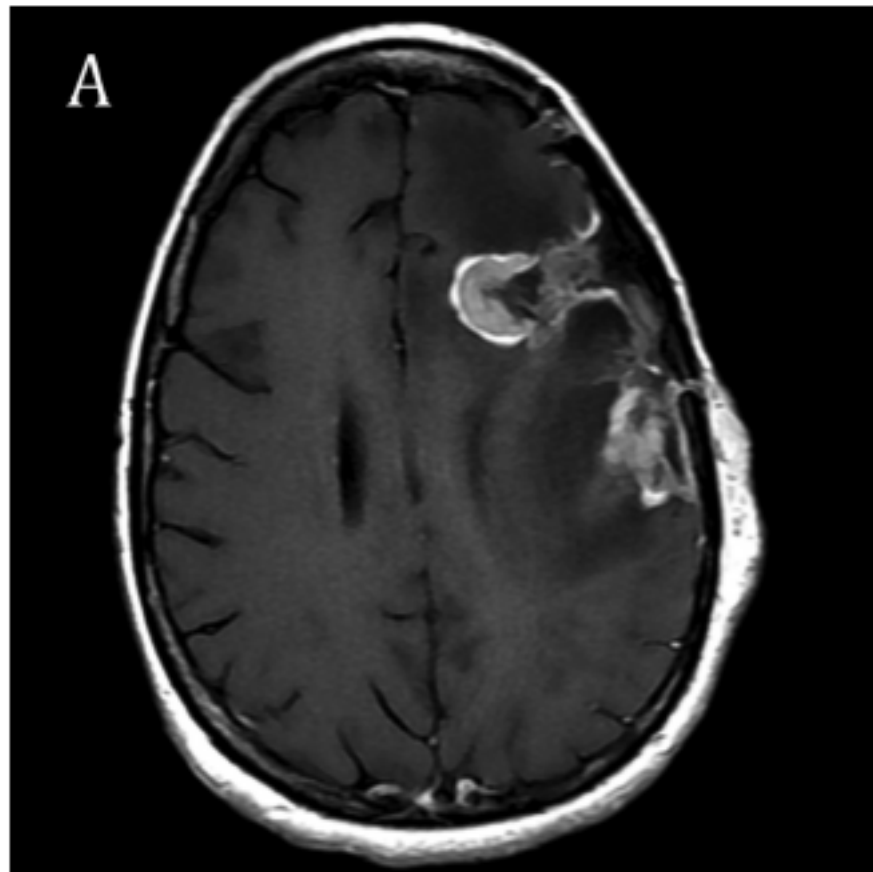
Table 3: Survival data

	<i>n</i> (%)	Mean time to progression (years)	<i>P</i>	Mean time to death (years)	<i>P</i>
Age					
Mean \pm SD	51.7 \pm 12.6				
<53	7 (50)	0.52	0.02	1.8	0.062
53+	7 (50)	4.29		3.79	
Sex					
Male	6 (43)	2.48	0.579	2.92	0.46
Female	8 (57)	1		3.15	
Presenting KPS					
Mean \pm SD	77.1 \pm 18.2				
<90	7 (50)	3.81	0.259	3.59	0.67
90+	7 (50)	0.76		2.51	
Brain mets					
Mean \pm SD	1.4 \pm 0.6				
1	10 (71)	0.86	0.816	1.17	0.357
2+	4 (28)	2.69		4.71	
Tumor volume					
Mean \pm SD	185 \pm 170				
<100	6 (43)	0.76	0.537	2.35	0.664
100+	8 (57)	3.58		4.05	

Clinical Study

Tumor resection with carmustine wafer placement as salvage therapy after local failure of radiosurgery for brain metastasis

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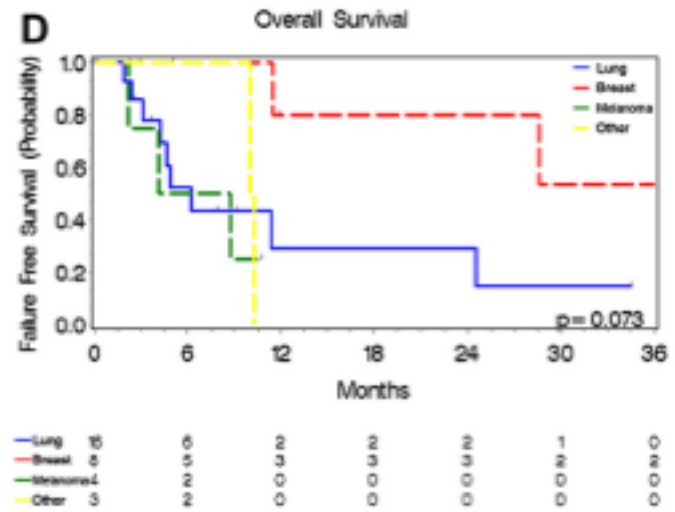
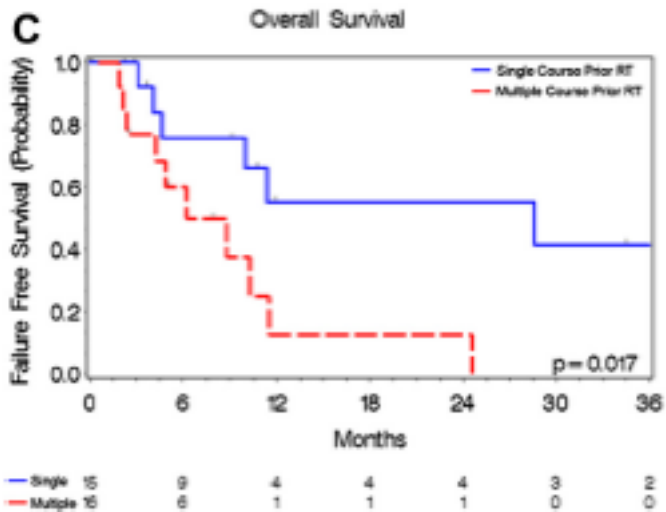
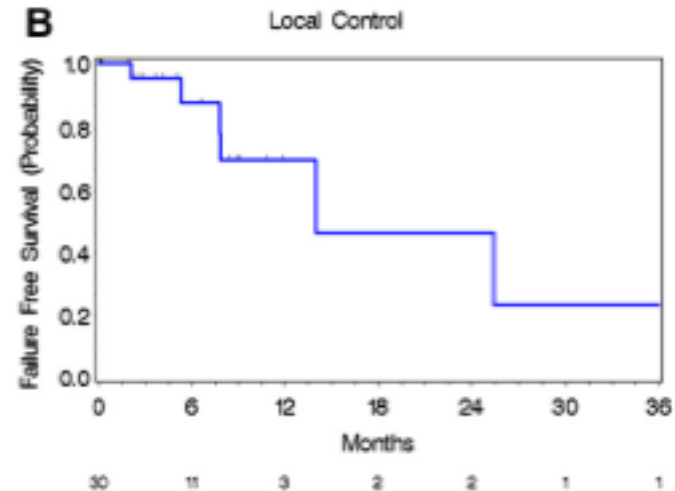
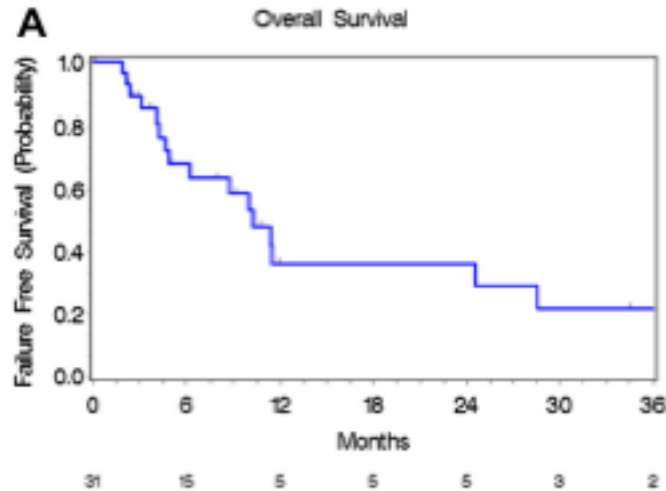


Clinical Study

Tumor resection with carmustine wafer placement as salvage therapy after local failure of radiosurgery for brain metastasis

Frank
Adria

and ^a,





- ❖ **This could mean that one needs total resection**
- ❖ **That post RS there could also be local radiation necrosis**
- ❖ **That within the complex heterogeneous group of metastases there is limited activity of BCNU**



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Gliadel® Wafer Use in Patients With Metastatic Brain Cancer



AUTHOR/ YEAR	N	TYPE OF METASTASIS	ENDPOINT	RESULT	COMMENT
Ewend 2001	25	Lung, melanoma, renal cell, breast, other	Toxicity Tumor recurrence Survival	Median survival 434 days; No local recurrence; Seven treatment-related adverse events	Phase I-II in initial surgery
Brem 2003	29	Lung, melanoma, breast, colon	Toxicity Tumor recurrence Survival	No local recurrence; Mean survival 18.2 months	Consecutive patient series; 23 initial and 6 recurrent surgery
PROLONG 2003 (interim report)	10	Lung, breast, esophageal, T- cell lymphoma, unknown	Toxicity Tumor recurrence	No local recurrence in initial and recurrent surgery patients; No adverse events reported	PROLONG: observational patient registry; 9 initial and 1 recurrent surgery



AUTHOR/ YEAR	N	TYPE OF METASTASIS	ENDPOINT	RESULT	COMMENT
Hobbs, Ewend 2004	6	NSCLC, melanoma	Tumor recurrence	No local recurrence in 4/6 patients	Retrospective chart review in recurrent surgery
Brem 2004	42	NSCLC, melanoma, renal, breast, sarcoma, colon, ovarian	Survival Tumor recurrence Hospitalization	Mean survival 16.8 months; No local recurrence	Prospective controlled trial; 34 initial and 8 recurrent surgery
PROLONG 2004	36	Lung, breast, other, unknown	Toxicity Tumor recurrence	No local recurrence in initial surgery patients; 55% survival and progression-free survival at 48 weeks	PROLONG: observational patient registry; 31 initial and 5 recurrent surgery



- Multi-centered, phase I-II trial
- Surgery + GLIADEL[®] Wafer + WBRT (44Gy)
- Patients assessed for
 - Neurotoxicity
 - CNS recurrence
 - Survival



- N=25
- Initial surgery for CNS metastasis
- ECOG status 0 and 1 (2 if potentially reversible following surgery)
- Malignancy type
 - 13 – lung
 - 3 – renal cell
 - 4 – melanoma
 - 2 – breast
 - 3 – other



- Median survival in 16 patients was 14.2 months
- No local recurrence
 - 4/25 (16%) distant recurrence
- Adverse events
 - No infection related to resection or implantation noted
 - Seven were possible or probably related to treatment
 - Seizures (2), nausea/vomiting (2), fever (1), constipation (2), alopecia (2), respiratory distress (1), eye pain (1)
 - One re-operation was needed for brain edema and mental status decline



- Surgery + GLIADEL[®] Wafer +/- WBRT (44Gy)*
- Patients assessed for
 - Neurotoxicity
 - CNS recurrence
 - Survival

*WBRT (3000-3400 Gy administered to newly diagnosed patients only)



- 29 consecutive patients enrolled (9 from multicenter trial)*
 - Single brain metastasis
 - Stable systemic disease and life expectancy of ≥ 12 months
 - 23 initial and 6 recurrent surgery for CNS metastasis
- Malignancy type
 - 18 – lung
 - 8 – melanoma
 - 2 – breast
 - 1 – colon



- No local recurrences in newly diagnosed patients
- Early deaths (< 3 mo) generally due to systemic (non-neurological) medical illness
- Mean survival 18.2 mo for 21 patients with f/u > 12 mo



- Prospective clinical trial
- 42 initial and recurrent surgery patients with brain metastases
 - 34 were initial surgery and 8 were recurrent surgery patients
- Treatment
 - Surgical resection
 - Gliadel Wafer
 - WBRT 30–44 Gy for newly diagnosed patients
- Follow-up visits every 2–3 months
 - MRI



- **Survival**
 - Median survival was 16.8 months (n=41)
 - 56% (23/41) patients died due to systemic disease
 - 9 patients were still alive with no evidence of recurrent CNS disease
- **Recurrence**
 - No local recurrence in any initial surgery patient (0/34)
 - Distant recurrence occurred in 3 patients
- **Hospitalization**
 - Median length of stay after surgery was 1 day



Augmentation

- ❖ **We see a constantly evolving field of surgical augmentation as for safety and efficacy.**
- ❖ **There is slow adaptation of local radiotherapy and local chemotherapy but with no background of standardized clinical trials**



The Translational Gap in Modelling new therapeutic concepts such as oncolytic virus or local immunotherapy

- **Prevention of meningeal disease ?? The last mechanistic study is from 2014**
- **Many studies to improve local control in mouse models in a broad spectrum of histologies but NO translation and no unifying theme**
 - **if there is one**



The neurosurgeon has many opportunities to augment local control but that is not biology driven

Augmentation of resection will only set the stage for better adjuvant entity targeted approaches getting at residual disease, - with BBB completely left out of this discussion



Oncologist

Dermatology
Melanoma

Ob/Gyn
Breast Cancer
Ovarian Cancer

Gastroenterology
Colon Cancer

Urology
Pulmonology
others

Guidance by **Entity** and molecular defined trials

Brain Metastasis Neurosurgery

Brain Metastasis Radiation Oncologist

Neuro - Oncologist