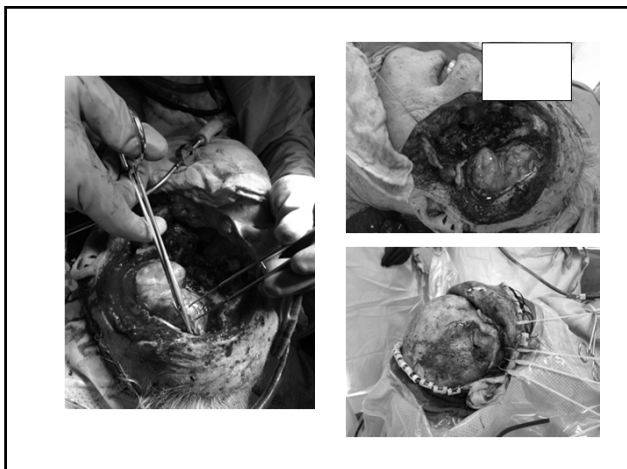
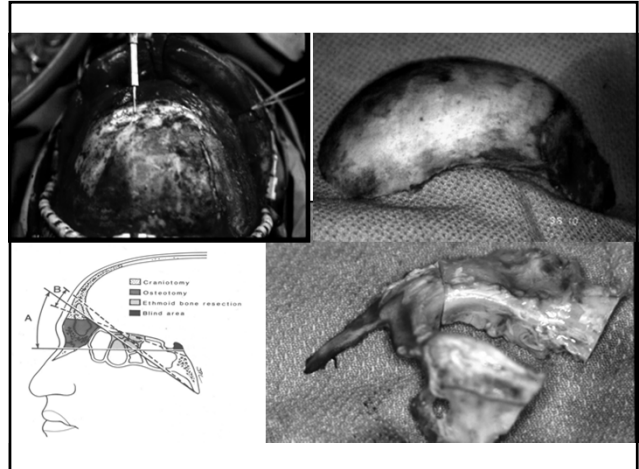


# New Treatment for Brain Tumors

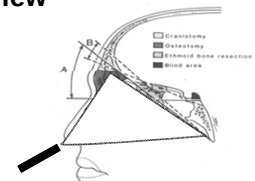
## Neurological Perspective – Part 1

**Daniel Prevedello, MD**  
 Associate Professor  
 Department of Neurological Surgery  
 The Ohio State University Wexner Medical Center



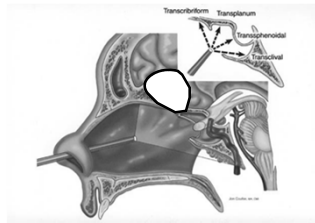
## Principles Endoscopic Endonasal

- › “Remove Bone and Mucosa - but leave the brain alone!”
- › Single cavity - Modular approaches
- › Bimanual Dissection - microsurgery
- › Team work - Dynamic view

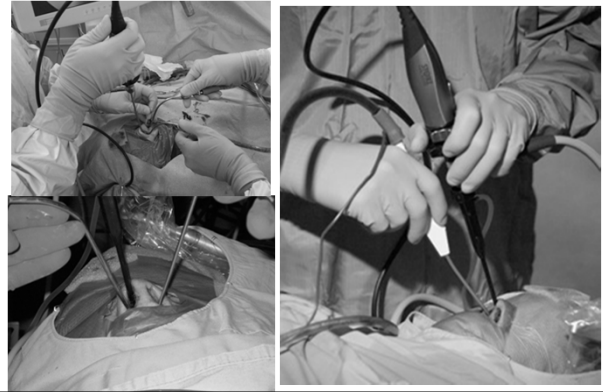


## Principles Endoscopic Endonasal

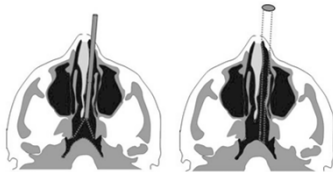
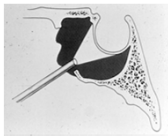
- Skull base tumor = Convexity tumor
- Earlier devascularization
- Simpson 1 (more often)
- Vascularized reconstruction



## Positioning of Instruments

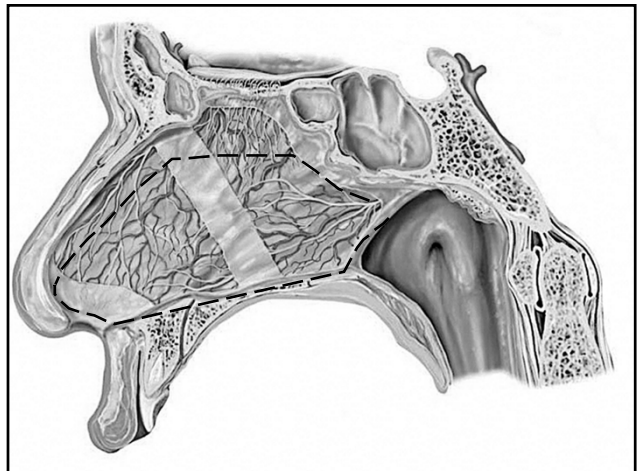


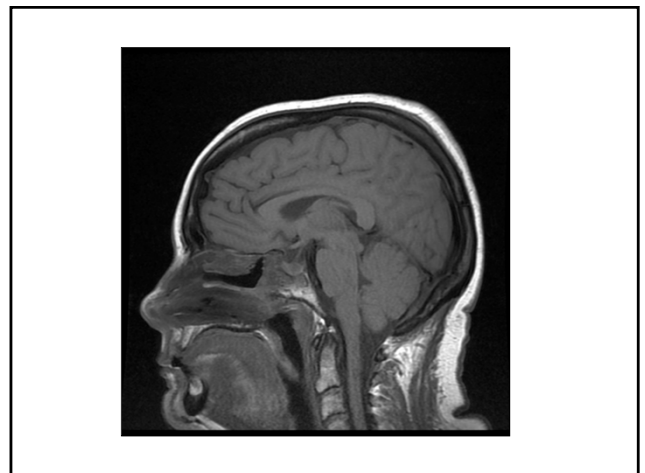
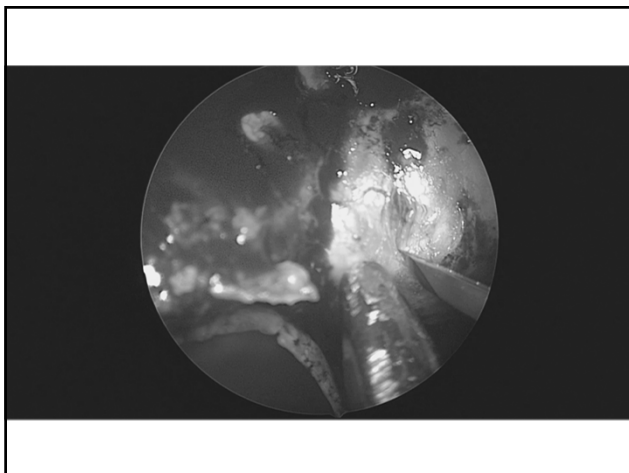
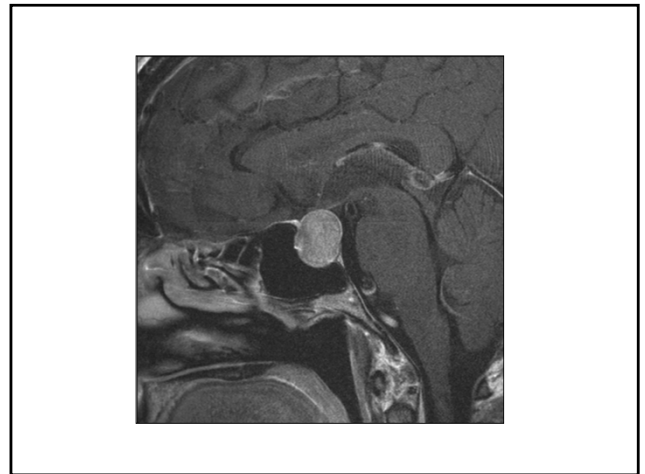
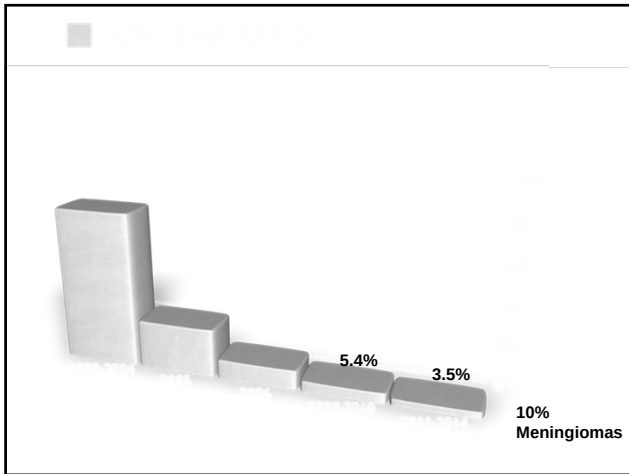
## Cone of light vs. Flash light

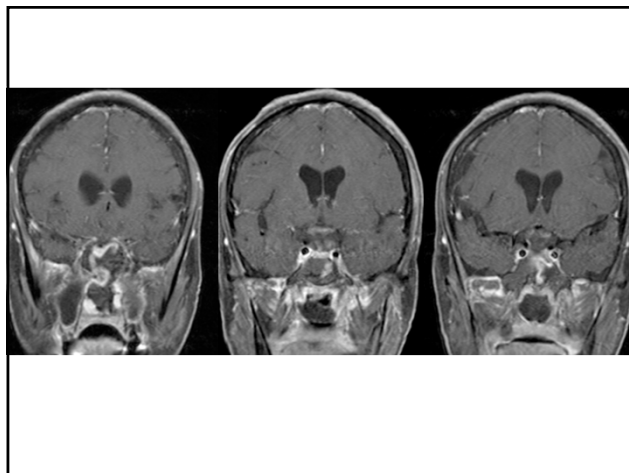
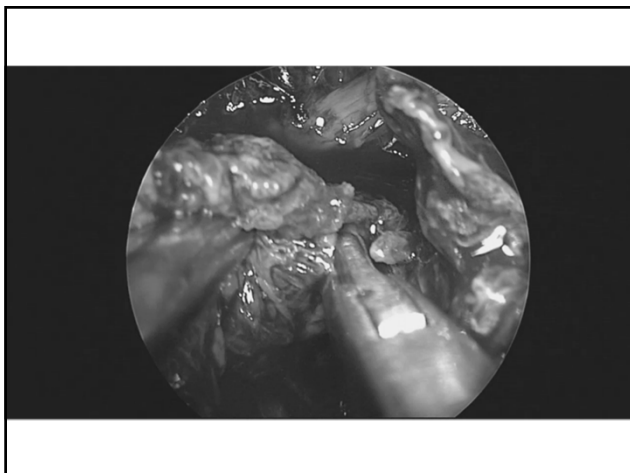
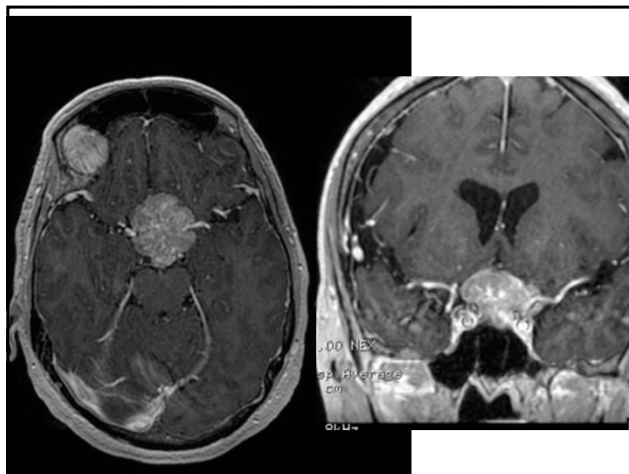
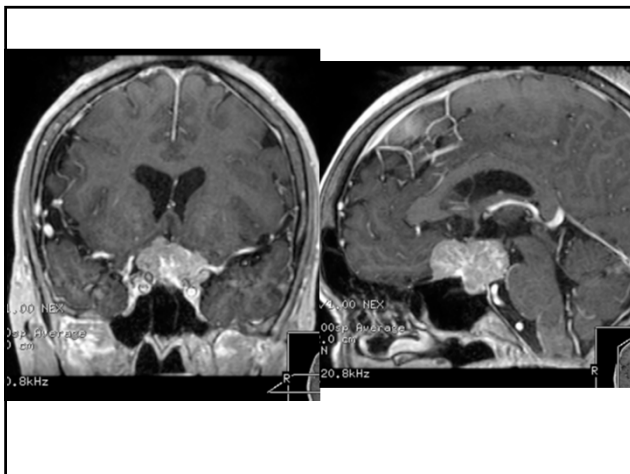


A. Endoscopic view

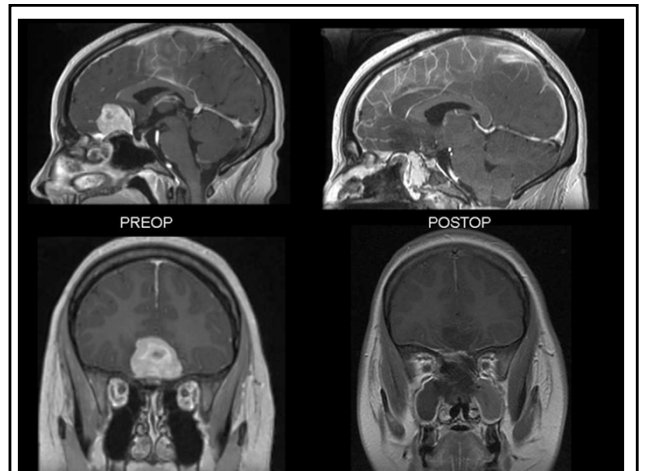
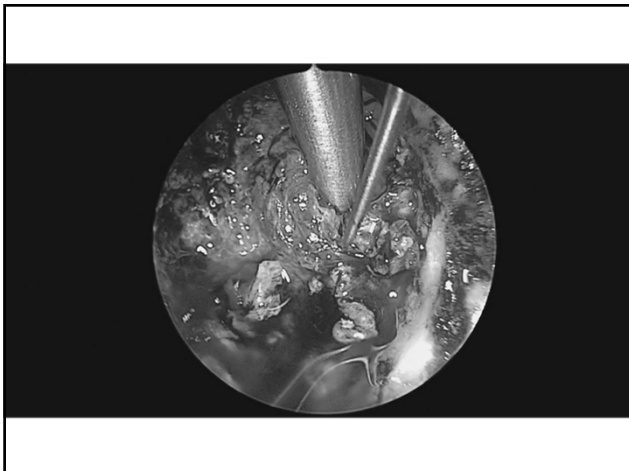
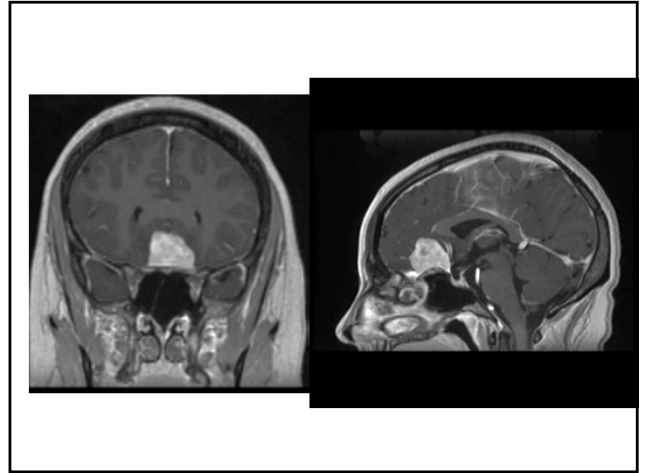
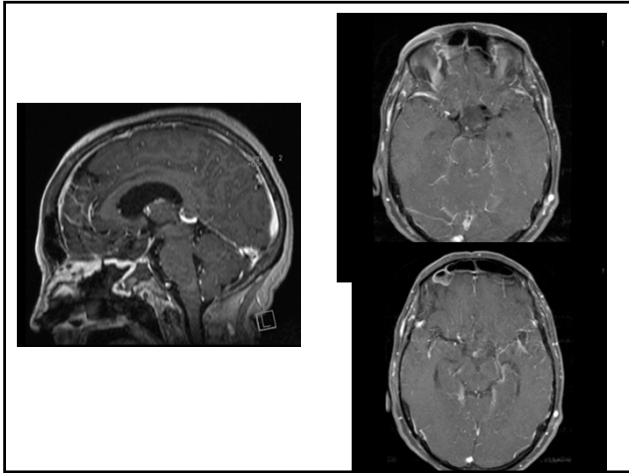
B. Microscopic view



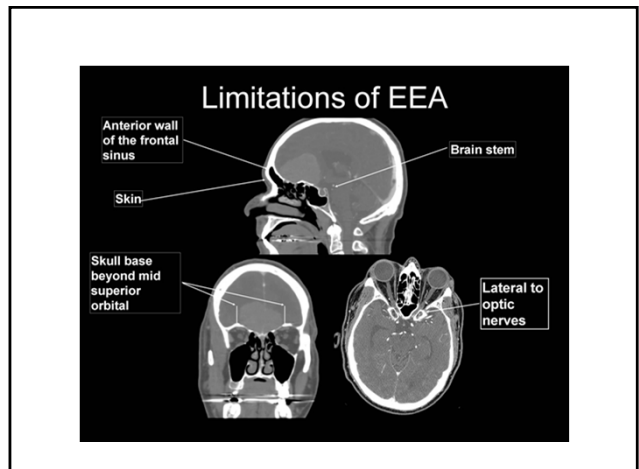
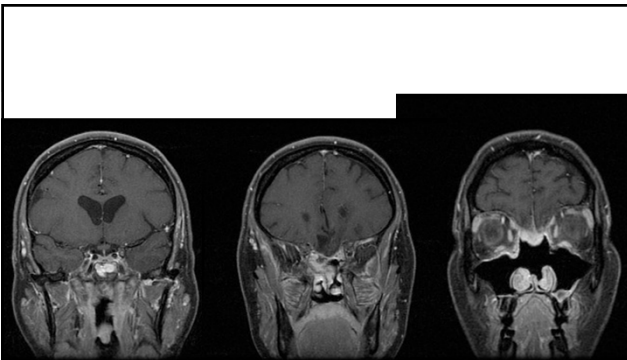
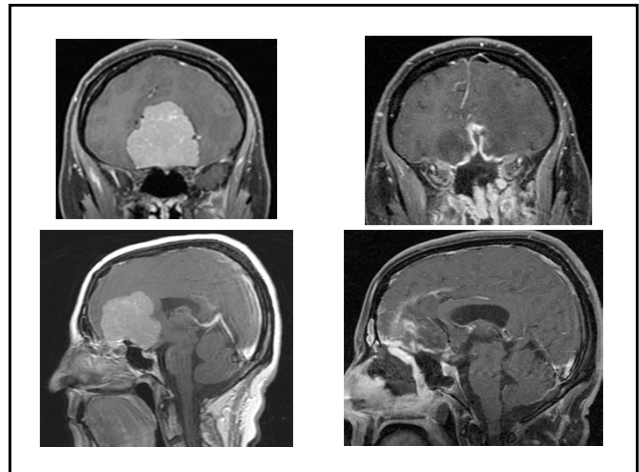
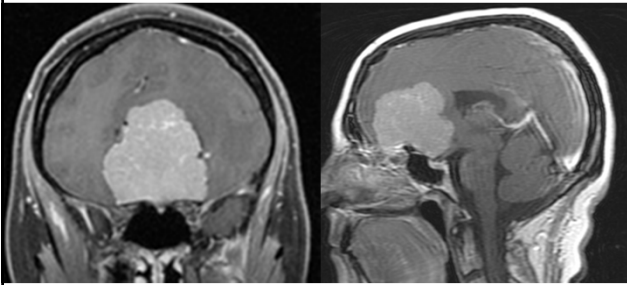


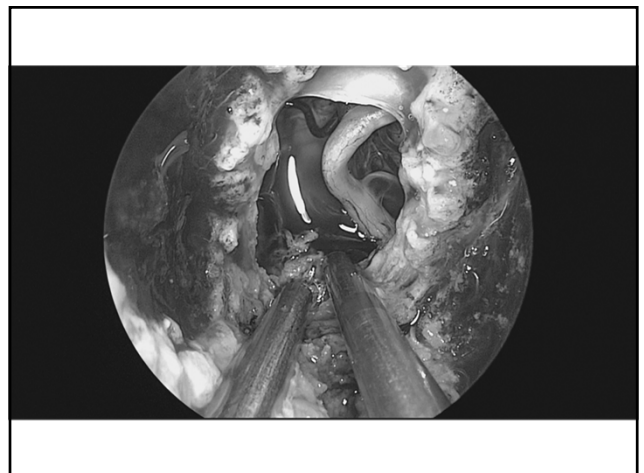
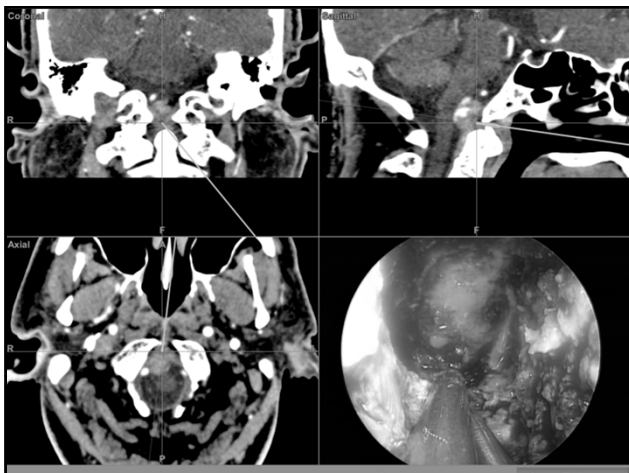
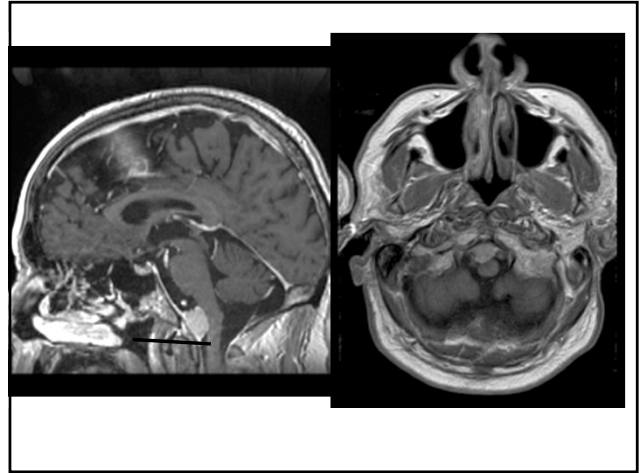
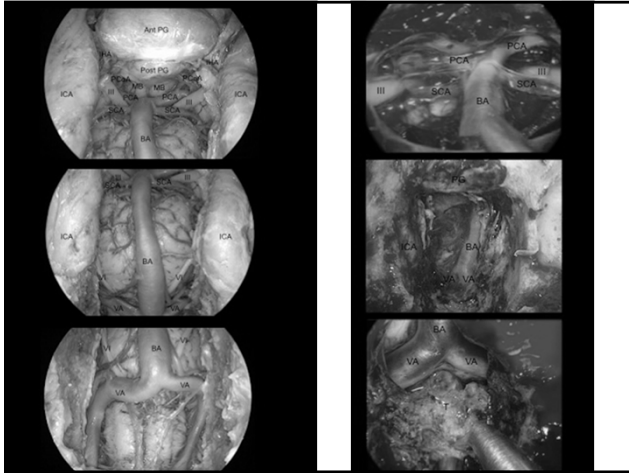


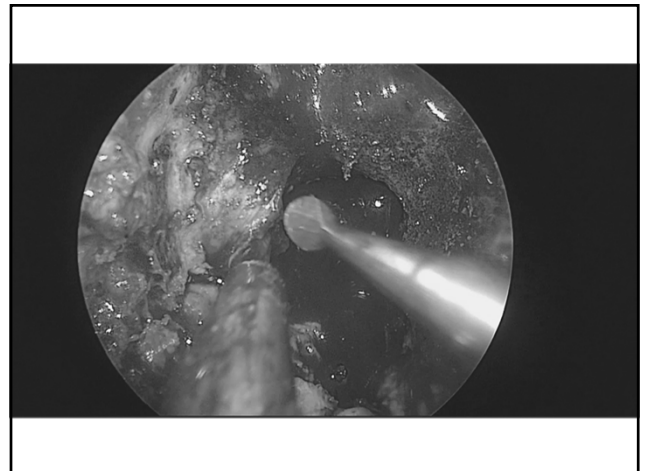
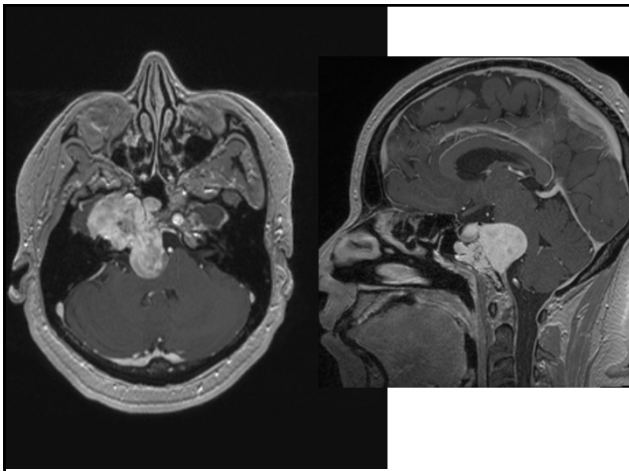
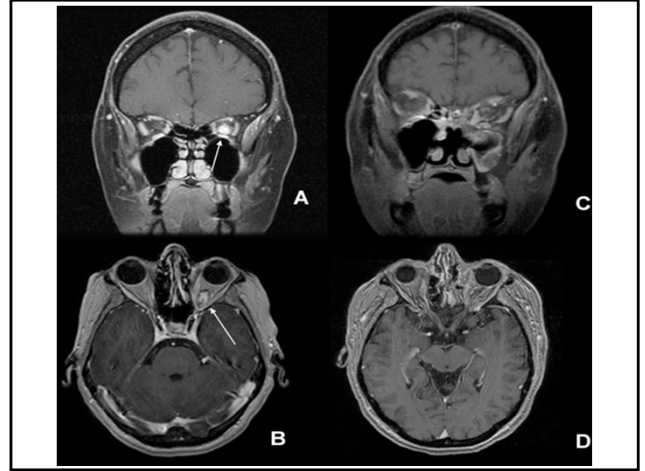
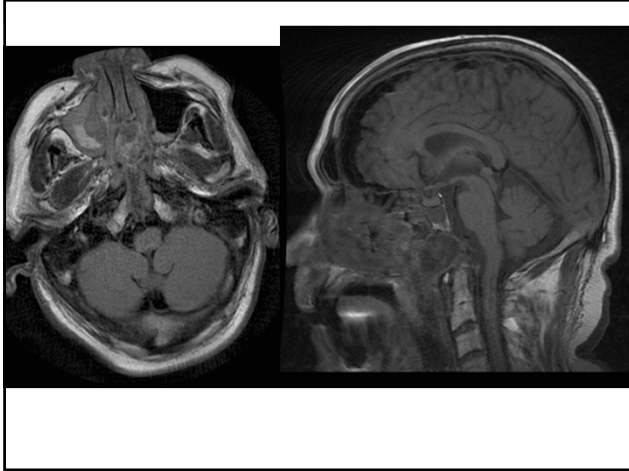


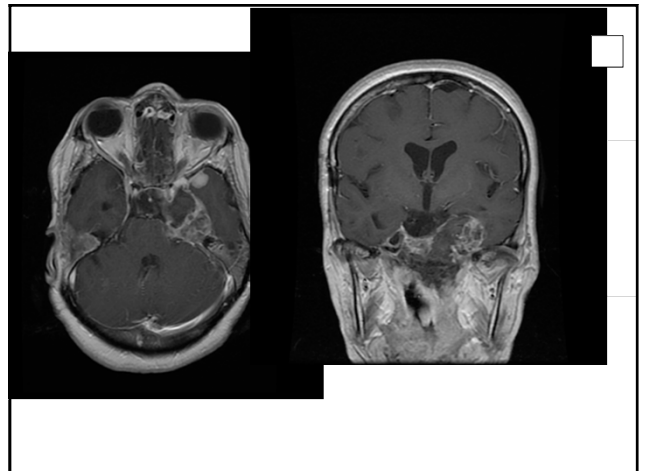
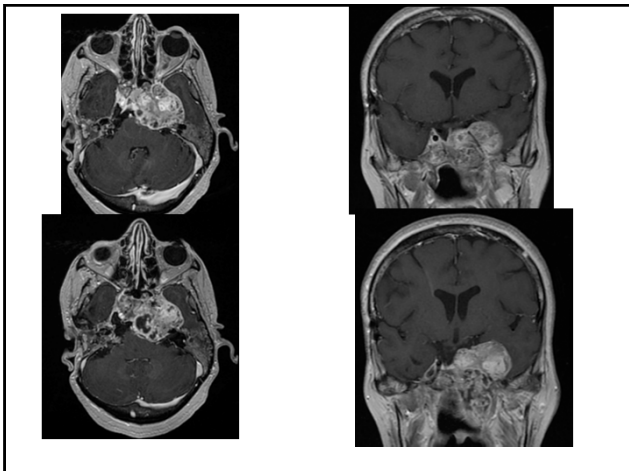
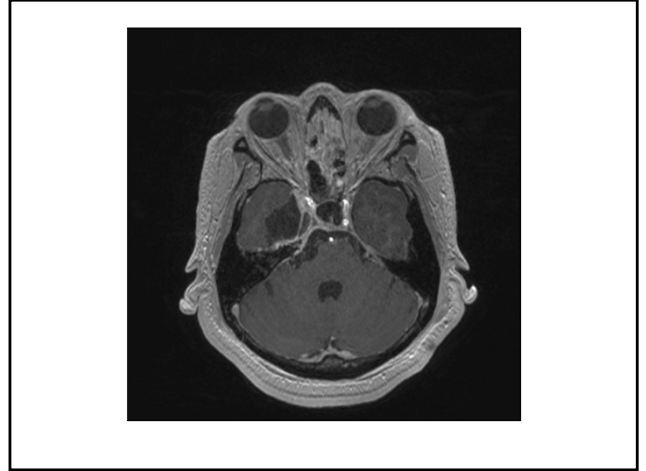
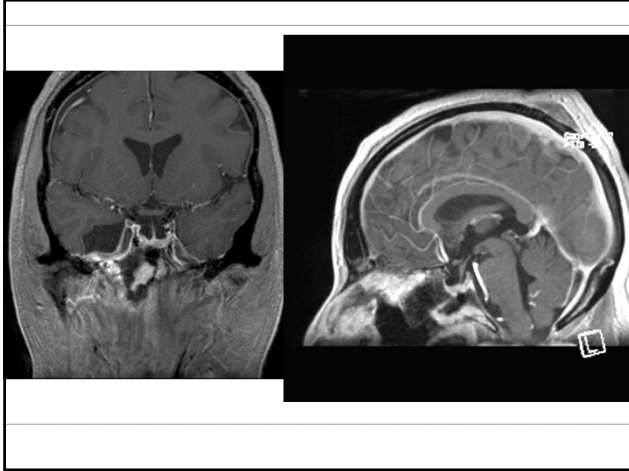


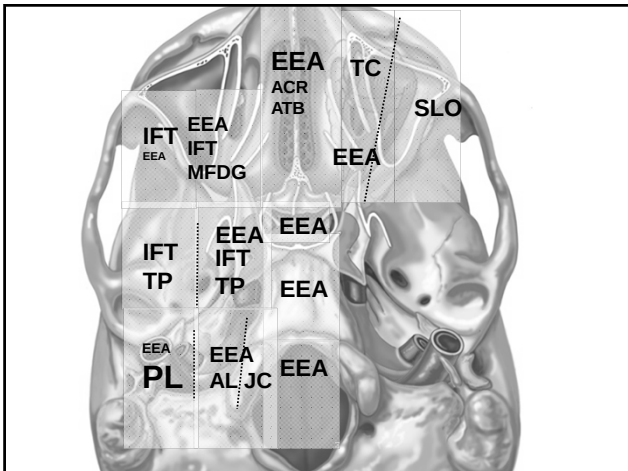
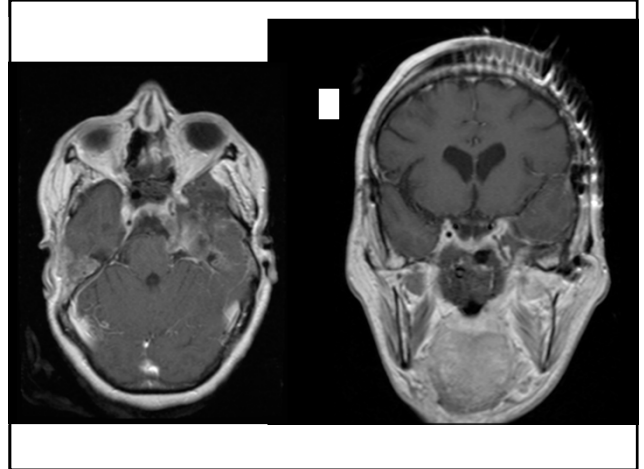
## Olfactory Groove Meningioma





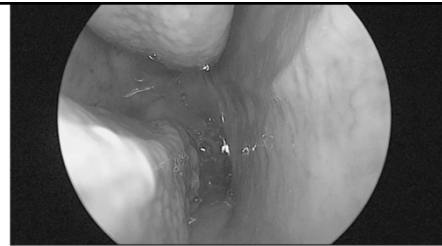
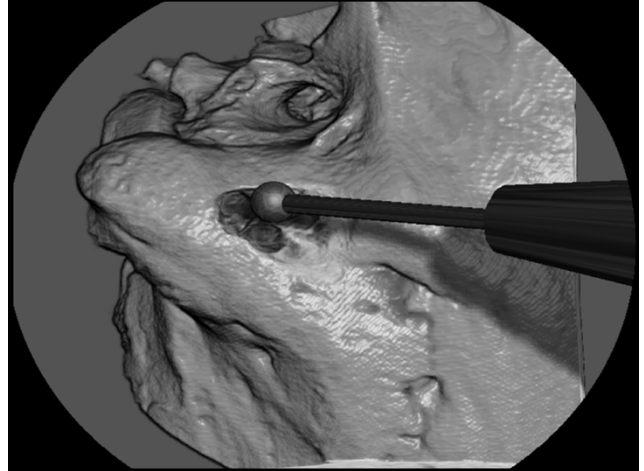






## The Future

- Real-time imaging
- Ergonomic design of instruments
- New biomaterials for reconstruction
- Micromanipulators/ Robotics
- Surgical simulators





**Thank you**



**Current use of  
endoscopic and  
minimally invasive  
techniques in brain  
tumor surgery**

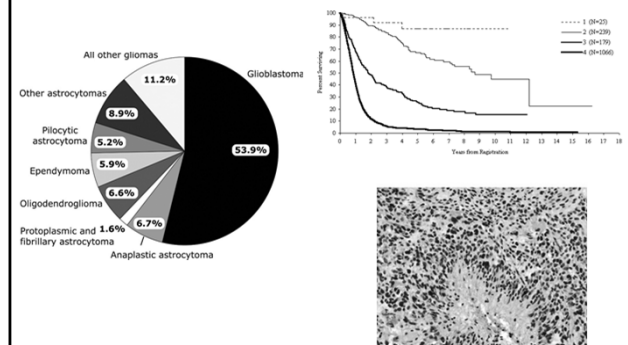
**Current use of  
robotics in brain  
tumor surgery**



## 'Personalized Medicine' for Brain Tumors

**J. Bradley Elder, MD**  
 Associate Professor  
 Director – Neurosurgical Oncology  
 Department of Neurological Surgery  
 The Ohio State University Wexner Medical Center

## Glioma subtypes



Smith JS and Jenkins RB. Genetic alterations in adult diffuse glioma: occurrence, significance and prognostic implications. *Frontiers in Bioscience* 5, d213-231 January 1, 2000

## Glioma – Personalized Care

- **Standard of Care**
  - Initial presentation
    - Surgery
    - Radiation
    - Chemotherapy
  - Recurrence
    - ??
- **Personalized Care**
  - Interpretation of molecular/genetic information
  - Optimize extent of resection
  - Local therapy
  - Clinical trials

## Glioblastoma pathogenesis

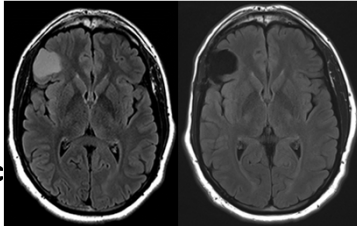
- **Accumulation of genetic alterations leads to glioblastoma phenotype**
  - Must translate into targeted therapy to improve outcomes



Smith JS and Jenkins RB. Genetic alterations in adult diffuse glioma: occurrence, significance and prognostic implications. *Frontiers in Bioscience* 5, d213-231 January 1, 2000

## Glioma – Standard Care

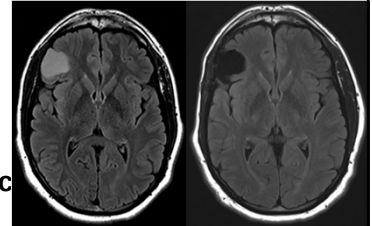
- Surgery
  - Extent of Resection
- +/- ChemoRT
- Recurrence?
- Molecular/genetic abnormalities?



## Glioma

- Surgery
  - Extent of Resection
- +/- ChemoRT
- Recurrence?
- Molecular/genetic abnormalities?

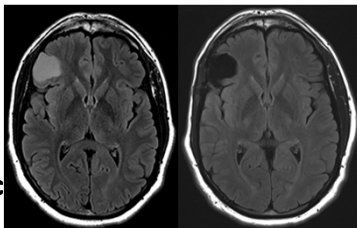
IDH1 mutation



## Glioma

- Surgery
  - Extent of Resection
- +/- ChemoRT
- Recurrence?
- Molecular/genetic abnormalities?

IDH1 mutation

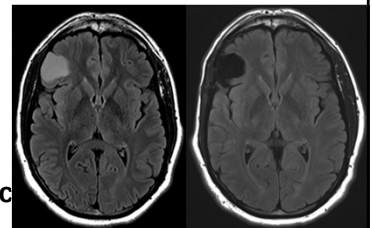


1p/19q co-deletion

## Glioma

- Surgery
  - Extent of Resection
- +/- ChemoRT
- Recurrence?
- Molecular/genetic abnormalities?

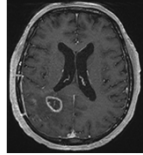
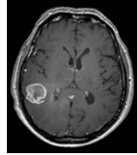
IDH1 mutation



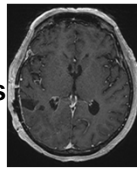
Prognostic value 1p/19q co-deletion

### Glioblastoma surgery – grade IV

- Surgery
  - Extent of Resection
- +/- ChemoRT
- Recurrence?
- Molecular/genetic abnormalities?



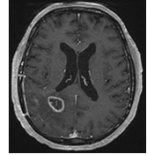
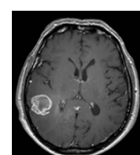
14 months postop



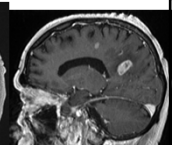
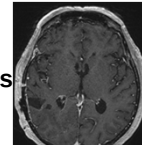
4 months postop

### Glioblastoma surgery – grade IV

- Surgery
  - Extent of Resection
- +/- ChemoRT
- Recurrence?
- Molecular/genetic abnormalities?



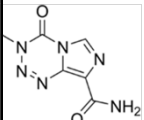
14 months postop



MGMT promoter methylation  
4 months postop

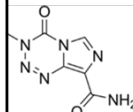
### Glioblastoma - Temodar

- Temozolomide (temodar): DNA alkylating agent
- Phase III clinical trial, 2005: 573 patients
  - Randomized to radiation (60 Gy total, 30 fractions) alone or radiation + temozolomide
  - Rad + Tem: median survival 14.6 months, 26% 2-year survival
  - Rad alone: 12.1 months, 10.4% 2-year survival



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- MGMT promoter methylation – improved response

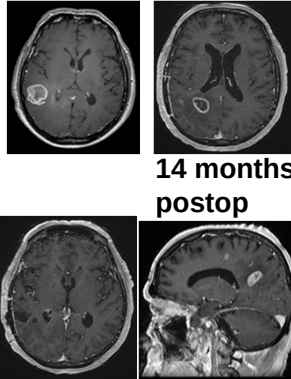


## Glioblastoma surgery – grade IV

- Surgery
  - Extent of Resection
- +/- ChemoRT
- Recurrence?
- Molecular/genetic abnormalities?

EGFR vIII  
mutation

4 months  
postop

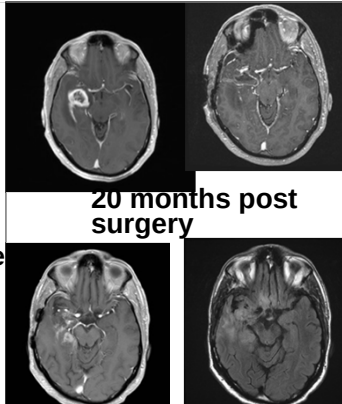


## Glioblastoma – vaccine

- Mutated EGFRvIII found in ~30% of GBM, but not in normal brain tissue
  - Constitutively activated
  - Enhanced migration and resistance to radiation and chemotherapy
- Intradermal vaccine with peptide containing an *EGFRvIII*-specific epitope
  - Improved PFS and OS in phase I and phase II trials
  - Histology - recurrent tumors showed no EGFRvIII
  - Phase III trial (NCT01480479) ongoing

## Targeted therapy - vaccine

- Vaccine – clinical trials ongoing
  - EGFR vIII
  - Heat shock protein
  - Whole cell lysate



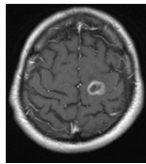
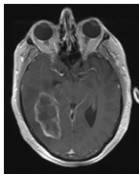
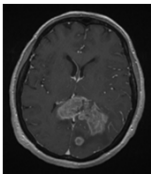
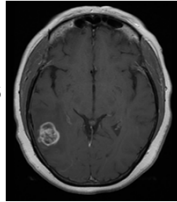
## Targeted therapy - vaccine

- Vaccine – clinical trials ongoing
  - EGFR vIII
  - Heat shock protein
    - HSPPC-96 phase II trial
  - Whole cell lysate



## Glioblastoma

- Targeted treatment
- Tailored surgical approaches
- Local Therapy

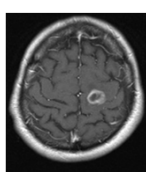
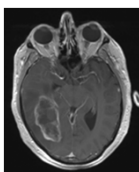
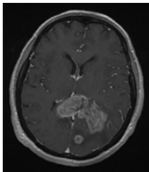
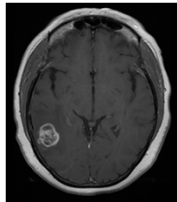


## Glioblastoma surgery – how can we 'personalize'?

- Imaging adjuncts – increase EOR, decrease neurologic morbidity
  - DTI
  - fMRI
  - Intraoperative MRI
- Surgical techniques
  - Intraoperative or pre-operative mapping
  - Awake craniotomy
  - 5-ALA
  - Minimally invasive surgery

## Glioblastoma

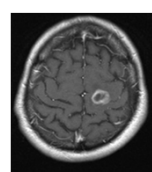
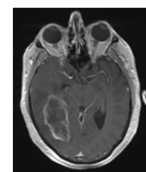
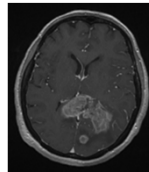
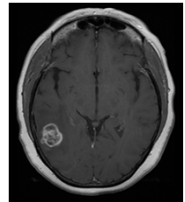
- Targeted treatment
- Tailored surgical approaches
- Local Therapy



## Glioblastoma

- Targeted treatment
- Tailored surgical approaches
- Local Therapy

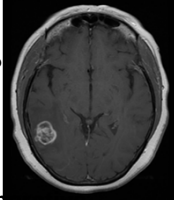
fMRI?



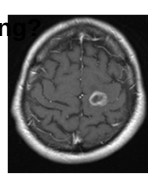
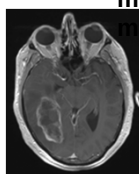
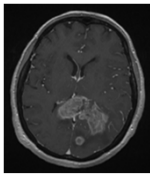
## Glioblastoma

- Targeted treatment
- Tailored surgical approaches
- Local Therapy

fMRI?



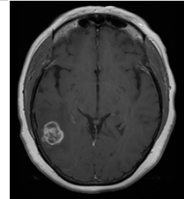
Intraoperative  
motor  
mapping?



## Glioblastoma

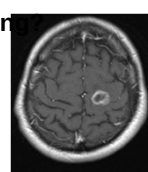
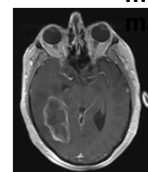
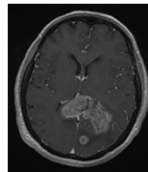
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5-ALA?

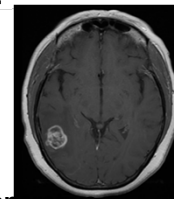
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## Glioblastoma

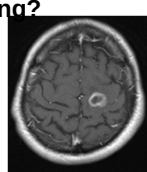
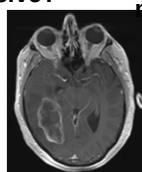
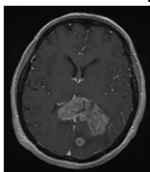
- Targeted treatment
- Tailored surgical approaches
- Local Therapy

fMRI?



5-ALA?  
Minimally  
invasive?

Intraoperative  
motor  
mapping?



## Glioblastoma surgery – how can we 'personalize'?

- Imaging adjuncts – increase EOR, decrease neurologic morbidity
  - DTI
  - fMRI
  - Intraoperative MRI
- Surgical techniques
  - Intraoperative or pre-operative functional mapping
  - Awake craniotomy
  - 5-ALA
  - Minimally invasive surgery

## Glioblastoma- 5-ALA

- 5-ALA: 5-aminolevulinic acid
  - Prodrug – leads to intracellular accumulation of fluorescent porphyrins in glioma cells
  - Phase III trial
    - 322 patients with new malignant glioma randomized to receive 5-ALA or nothing with surgery
    - 5-ALA: 65% GTR; 41% 6-month PFS
    - Control: 36% GTR; 21% 6-month PFS



Valle RD, Solis ST, Gastereana MAI, et al. Surgery guided by 5-aminolevulinic fluorescence in glioblastoma: volumetric analysis of extent of resection in a single center experience. J Neurooncol (2011) 102:105-113.

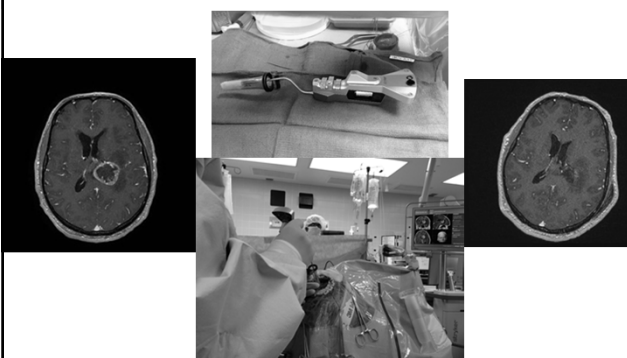
## Glioblastoma- 5-ALA

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  - Patient selection

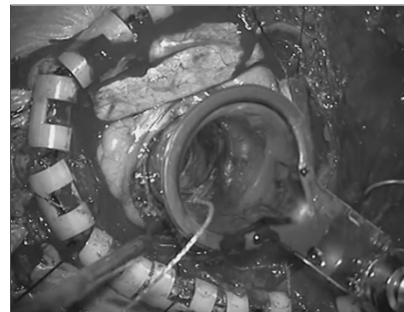


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## Glioblastoma – minimally invasive surgery



## Glioblastoma – Minimally Invasive Port

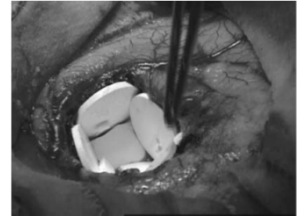


## Local therapy

- Average GBM contains  $10^{11}$  cells and surgery reduces this to  $10^9$  cells (99% reduction)
- Local therapy
  - maximize local effect and minimize systemic toxicity
  - Overcome BBB
    - Drug eluting implants
    - Local injection/infusion of anti-tumor agent
    - Gene therapy

## Gliadel – BCNU wafers

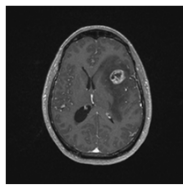
- 1996: FDA approved Gliadel for treatment of recurrent GBM
  - First FDA approved treatment for GBM since 1973
  - FDA approved for use at initial resection in 2003
- Current concerns
  - Relative efficacy
  - Higher adverse events in recurrent tumors



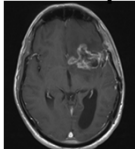
Lesniak MS and Brem H. Targeted therapy for brain tumors. Nature Reviews Drug Discovery 3, 499-508 (June 2004).

## Gliadel

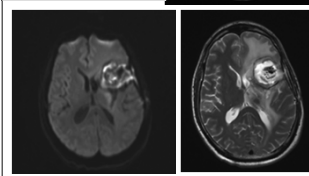
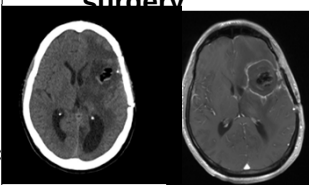
Presentation



6 months postop



1 month after 2<sup>nd</sup> surgery



## CED: Convection-enhanced delivery

- Under normal physiological conditions, interstitial fluids move through the brain by both convection and diffusion
  - Factors that influence diffusion
    - molecular weight – higher MW = slower diffusion
    - ionic charge – positive = slower
    - concentration gradient
  - Convection or “bulk” flow:
    - pressure gradient
    - independent of the molecular weight



## CED

### • Bolus injection versus CED

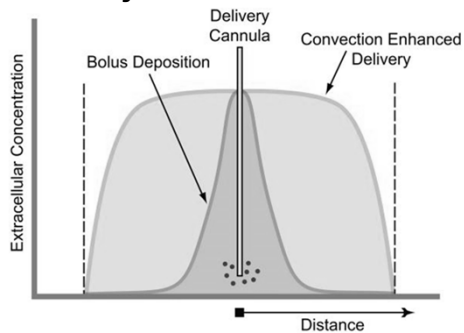


Image provided Courtesy of Rolf Barth, MD

## CED carboplatin - rodent

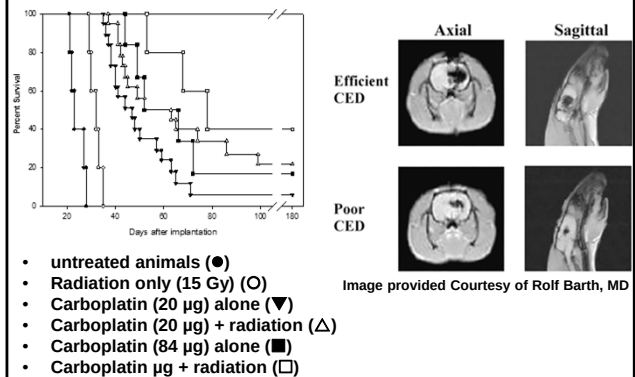
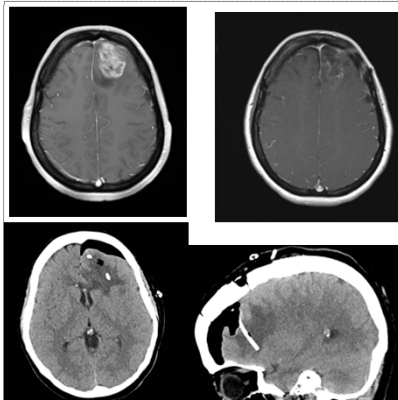


Image provided Courtesy of Rolf Barth, MD

## CED Carboplatin

- Phase I clinical trial – dose escalation
- Recurrent GBM
- 54 ml over 72 hrs
- 2-4 catheters
- MTD not yet reached



## CED: Targeted therapy

- CED targets in clinical trials:
  - IL-13
  - EGFR
  - IL-4
  - TGF-beta2
- Cintredekin-besudotox (CB)
  - Recombinant protein consisting of IL-13 and a truncated form of Pseudomonas exotoxin (PE38QQR)
  - Progressed through to phase III trials

## CED: PRECISE study

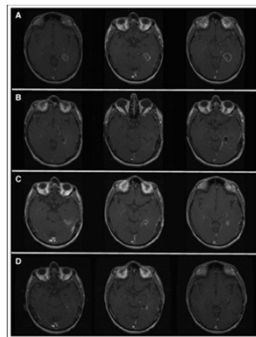
- IL13-PE38QQR
  - cintredekin-besudotox (CB)
  - IL-13 + pseudomonas exotoxin A
- Phase III trial comparing CED of CB to Gliadel wafer
  - First randomized phase III involving CED for recurrent GBM
  - Nearly 300 patients at 52 centers
  - Median overall survival: 36.4 weeks (9.1 months) for CB and 35.3 weeks (8.8 months) for GW (P = .476)
    - Efficacy evaluable population: 11.3 months for CB and 10 months for GW (p = 0.31)
  - Pulmonary embolism was higher in the CB arm (8% vs 1%, P = .014)

## Glioblastoma

- Gene therapy
  - Direct injection of viral vector into brain is most common technique
    - Virus vectors – transfer genes with toxicity-inducing intracellular effects
    - Oncolytic virus – lytic life cycle selectively destroys tumor cells

## Glioblastoma – direct injection

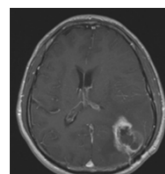
- Suicide gene HSV-tk common in GBM trials
  - Phase III trial (2000): 248 patients
  - Retrovirus with HSV-tk injected into walls of resection cavity
  - Only dividing cells incorporate gene
  - Ganciclovir (prodrug) given IV -> toxic metabolites
  - Activation of immune response to HSV-tk and tumor antigen release after apoptosis
  - No efficacy



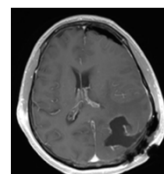
## Glioblastoma – Toca 511

- Direct injection of replication competent retrovirus
  - Cytosine deaminase converts 5-FC to 5-FU
  - Treat with ER 5-FC after surgery

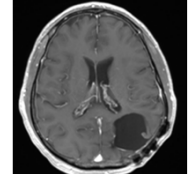
Recurrence



Post-op



20 months



## **Conclusions**

- Personalized care for Glioblastoma

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  - Surgical techniques

## **Conclusions**

- Personalized care for Glioblastoma
  - Targeted therapy
  - Surgical techniques
  - Local therapy

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