New Treatment for Brain Tumors
Neurological Perspective – Part 1

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‣ “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. Microscope view
Olfactory Groove Meningioma
The Future

- Real-time imaging
- Ergonomic design of instruments
- New biomaterials for reconstruction
- Micromanipulators/ Robotics
- Surgical simulators
Current use of endoscopic and minimally invasive techniques in brain tumor surgery

Current use of robotics in brain tumor surgery

Thank you
‘Personalized Medicine’ for Brain Tumors

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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

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Glioma – Standard Care

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

Glioma

• Surgery
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Glioma

• Surgery
  ▪ Extent of Resection
• +/- ChemoRT
• Recurrence?
• Molecular/genetic abnormalities?
  ▪ Prognostic value

Glioma

• Surgery
  ▪ Extent of Resection
• +/- ChemoRT
• Recurrence?
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IDH1 mutation

1p/19q co-deletion
Glioblastoma surgery – grade IV

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

  [Images of brain scans labeled 4 months postop and 14 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

[Molecular structure of Temozolomide]

MGMT promoter methylation – improved response
### Glioblastoma surgery – grade IV

<table>
<thead>
<tr>
<th>Surgery</th>
<th><img src="image1.png" alt="Image" /></th>
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<tbody>
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**EGFR vili mutation**

| 4 months postop | ![Image](image2.png) |

### Glioblastoma – vaccine

- Mutated EGFRvili 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 EGFRvili
  - Phase III trial (NCT01480479) ongoing

### Targeted therapy - vaccine

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

| 20 months post surgery | ![Image](image3.png) |

### Targeted therapy - vaccine

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

| 20 months post surgery | ![Image](image4.png) |
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

- 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

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


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 Carbolplatin

- 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

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<th>Post-op</th>
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Conclusions

- Personalized care for Glioblastoma
  - Targeted therapy
  - Surgical techniques

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


Targeted therapy for brain tumours


Direct delivery of medication into a brain tumor through multiple chronically implanted catheters. Sonmez G, Fein RC, Klein JS, Redel JG, Russell MJ.