

## MALIGNANT GLIOMAS: TREATMENT AND CHALLENGES

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## DISCLOSURE

- Speaker's Bureau – Novocure, Inc.

## THEN ONE DAY, EVERYTHING CHANGED

## OBJECTIVES

- Review epidemiology of brain tumors
- State goals of surgery
- Explain WHO classification of glioma pathology
- Compare treatment options in malignant gliomas
- Describe neurologic deficits associated with brain tumors
- Discuss patient care issues in this patient population

## EPIDEMIOLOGY

- There are more than 120 different types of brain tumors, both benign and malignant
- Brain tumors ARE cancer
- 2017—estimated 26,000 new primary glial tumors
  - 2.2% of all tumors diagnosed each year
  - 12,390 will be glioblastoma
- 17,000 deaths related to CNS tumors
  - 2.4% of all cancer deaths

## CNS TUMORS

- Infiltrating
- No known causes
- Often complicated by other co-morbidities
- Originate from a variety of cells within the nervous system
- High-grade gliomas are most common
  - ~65% of all brain tumors
  - Most aggressive-glioblastoma which has nearly a 100% recurrence rate
- Low-grade gliomas carry a much better prognosis
- Life changing diagnosis

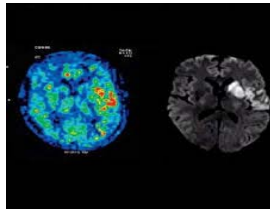
Cell of Origin	Tumor Type	Cell Function
<b>Astrocyte</b> —star shaped Most abundant cell in the brain	• Glioma (astrocytoma, anaplastic astrocytoma, glioblastoma)	• Involved in the physical structuring of the brain • Regulate transmission of electrical impulses within the brain
<b>Oligodendrocyte</b>	• Oligodendroglioma (anaplastic oligodendroglioma)	• Provide a supporting role for neurons • Form the electrical insulation around the axons of CNS nerve cells
<b>Ependymal</b>	• Ependymoma	• Lines ventricles, aids circulation of CSF, makes blood-brain barrier
<b>Meninges</b>	• Meningioma	• Covers/protects brain and spinal cord
<b>Lymphocyte</b>	• Lymphoma	• Immunomediation
<b>Neuron</b>	• Neuroma	• Cognitive function

## IMAGING STUDIES

- MRI is the primary diagnostic tool in Neuro-Oncology
  - CT is used when a patient cannot have an MRI due to metal in the body, defibrillators, non-MRI safe pacemakers, etc
- No ionizing radiation exposure with MRI
- Through the use of magnets and radiofrequency waves, an MRI triggers hydrogen atoms in the body to spin and realign. As the molecules are “excited” and energy is released, the signal is sent to a computer which processes the signals and generates it into an image

## PERFUSION MRI

- Imaging which is done to assist in better identifying changes seen on MRI
- Goal is to identify hyperperfusion vs hypoperfusion
  - Tumor vs Pseudo-progression/treatment effect



## SURGERY

- Types of surgery
  - Biopsy
  - Craniotomy
  - Laser Ablation
- Goal of Surgery
  - Establish definitive diagnosis
  - Removal of tumor
  - Prolong survival
  - Decrease intracranial pressure
  - Improve neurologic status
  - Facilitate other therapies

## PATHOLOGY

- Brain tumor pathology first described by Virchow in 1865 as low-grade and high-grade gliomas
- 1926—first modern classification of glioblastoma by Bailey and Cushing
- More precise definitions ongoing based on molecular testing

WHO Classification		Tumor Type
<b>WHO grade I</b>	• Cancer cannot be seen through the microscope • The cell growth looks like normal cells • Early stage of cancer, can be cured successfully by surgery	• Meningioma • Pilocytic astrocytoma
<b>WHO grade II</b>	• The damaged cells start growing at a significant rate • At this stage, the cancer can be treated and possibly cured • The possibility of re-occurrence of cancer, even after it has been treated, is very high	• Astrocytoma (mean age-34) • Oligodendroglioma (mean age-43)
<b>WHO grade III</b>	• At this stage, the cells grow at a very high rate.	• Anaplastic Astrocytoma (mean age-41) • Anaplastic Oligodendroglioma (mean age-49)
<b>WHO grade IV</b>	• Possibility of curing the cancer is very low • In systemic cancer, the cancer is spread to other parts of the body and this stage is called metastasis • In brain tumors, metastatic spread to other organs is very rare	• Glioblastoma (mean age-53) • Gliosarcoma

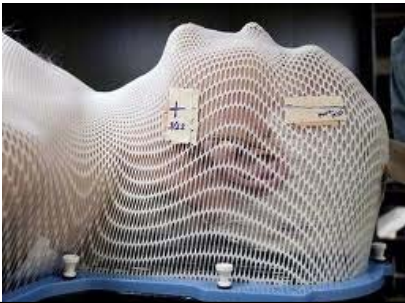
## MOLECULAR STUDIES

- MGMT Promoter Methylation Status
- IDH-1
- p53
- 1p/19q

## TREATMENT

- Gold Standard:
  - Radiation Therapy with concurrent chemotherapy
    - Substantially impacts survival
    - Treatment with 3d conformal radiation over 6-7 weeks
      - May be shorter duration with elderly
    - Standard total dose-5400-6000 cGy
    - Temozolomide —used as a radiosensitizer at 75mg/m<sup>2</sup> x 42 days
      - Starts on first day of radiation
      - Decision to use chemotherapy based on patient's age and functional status

## Radiation Treatment Mask



## ADJUVANT TREATMENT

- After completion of Radiation
  - New baseline MRI
  - Pseudo-progression
  - Repeat surgery
  - Temozolomide
  - Optune

## CHEMOTHERAPY

- Temozolomide—current drug of choice
- Low-grade gliomas—chemo alone is used as initial treatment, often without radiation
- Alternative dosing schedules
- Only a small portion of tumor cells are dividing at any given time impacts effectiveness
- Blood-brain barrier prevents drug from reaching the tumor
- Dose-limiting toxicity
- Metabolism
- Adherence to oral medications

## OPTUNE

- Treatment for glioblastoma—newly diagnosed and recurrent
- Low-intensity alternating electric fields called Tumor Treating Fields (TTFields)
  - Delivered by transducer arrays to the location of the tumor
- TTFields travel in waves to interfere with GBM cancer cell division
- Portable
- No systemic side-effects
- Scalp irritation

## RECURRENCE / PROGRESSION

- Radiation boost
- Re-challenge with temozolomide, depends on when recurrence or progression occurs, as well as other patient factors
- Intra-arterial chemotherapy
  - Carboplatin
  - Methotrexate
- Anti-angiogenesis inhibitor therapy
  - Bevacizumab
  - Humanized monoclonal antibody against VEGF
  - Inhibits the growth of new blood vessels

## CLINICAL TRIALS

- Right now there is, unfortunately, a paucity of clinical trials not only for newly diagnosed tumors but also for recurrent tumors
- Industry
- Investigator-initiated

## NEUROLOGIC DEFICITS

- Symptoms arise from both the disease and the treatments
  - Related to location of tumor
- Cognitive loss—common to all patients and may be very subtle or quite profound. Often progressive. Many patients are not able to return to their former occupations
- Personality changes
- Motor weakness
- Visual changes
- Speech-symptom which causes the most frustration

## PATIENT CARE ISSUES

- Cerebral edema
- Seizure—1/3 experience
- Thromboembolic events—2 to 6 fold increase
- Cognitive decline
- Depression
- Functional impairment
- Radiation side-effects—acute, subacute, and late
  - Fatigue
- Chemotherapeutic side-effects
  - Nausea
  - Constipation
  - Bone marrow suppression

## STEROIDS

- Dexamethasone-corticosteroid of choice
  - Long half-life
  - 4-5 times more potent than prednisone
- General side-effects
  - GI
  - Insomnia
  - Mood swings
  - Psychosis
  - Proximal myopathy
  - Immunosuppression

## When What We Are Doing Doesn't Work Anymore

- Quality of Life
- Decision to stop treatment
  - "curative" treatment becomes palliative
- Hospice
  - **NOT A DIRTY WORD**
- Peaceful process for most patients

## SUMMARY

- There are many types of brain tumors
- Low-grade tumors are often as injurious to the individual as high-grade tumors
- Recurrence highly probable for most patients
- Research and clinical trials are imperative to developing better treatments for brain tumors in the hope that someday long-term survival, if not cure, is the norm

- Care of this population requires collaboration with many other specialties due to the cognitive and functional deficits from the tumor, side-effects from the treatments, and the co-morbidities present not only at the time of diagnosis but those experienced as a sequelae of treatment

## TO CONTACT ME

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