NEURO-ONCOLOGY

Brain Tumor Diagnosis and Management

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OBJECTIVES

1. Explain how brain tumor diagnosis has changed in recent years
2. Examine an advance in treating tumors based on the use of molecular testing through a case study
3. Understand how the severity of a brain tumor diagnosis is compounded by treatment

Disclosures: None

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Neuro-Oncology: what Is It?

The study, diagnosis, management, and treatment of neoplasms within the central and peripheral nervous system

Givens Brain Tumor Center

- Primary CNS neoplasms
- Tumors of the peripheral nerves
- CNS metastases
- Neurologic complications of cancer and it's treatments

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PRIMARY BRAIN TUMORS

- Tumors that start in the brain
- In most cases, they are cancer
- Arise from cells in the nervous system
- High-grade gliomas are the most common
- Glioblastomas have a nearly 100% recurrence rate
- Low-grade gliomas carry a much better prognosis but can be just as devastating
- Life changing diagnosis
- Cannot be cured

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PRESENTING SYMPTOMS

MRI is the primary diagnostic tool in Neuro-Oncology

- Headache
- Seizures
- Nausea
- Focal neurologic deficit
- Mental status changes
- Visual changes
- Incidental finding
- Duration of symptoms may be acute or chronic
- Monro-Kellie Doctrine

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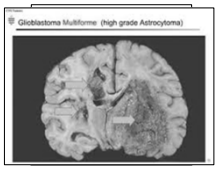
SURGERY

Establish definitive diagnosis
Remove tumor
Prolong survival

GOAL



Biopsy
Partial resection
Gross total resection
Laser ablation

OPTIONS

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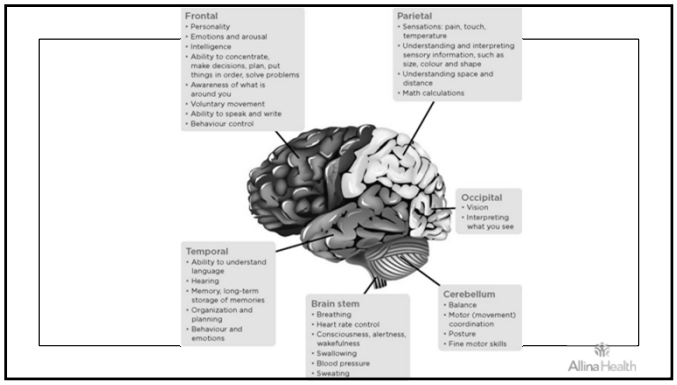
Frontal
• Personality
• Emotions and arousal
• Intelligence
• Ability to concentrate, make decisions, plan, put things in order, solve problems
• Awareness of what is around you
• Voluntary movement
• Ability to speak and write
• Behaviour control
Parietal
• Sensations: pain, touch, temperature
• Understanding and interpreting sensory information, such as size, colour and shape
• Understanding space and distance
• Math calculations
Occipital
• Vision
• Interpreting what you see
Temporal
• Ability to understand language
• Hearing
• Memory, long-term storage of memories
• Organization and planning
• Behaviour and emotions
Brain stem
• Breathing
• Heart rate control
• Consciousness, alertness, wakefulness
• Swallowing
• Blood pressure
• Sweating
Cerebellum
• Balance
• Motor (movement) coordination
• Posture
• Fine motor skills
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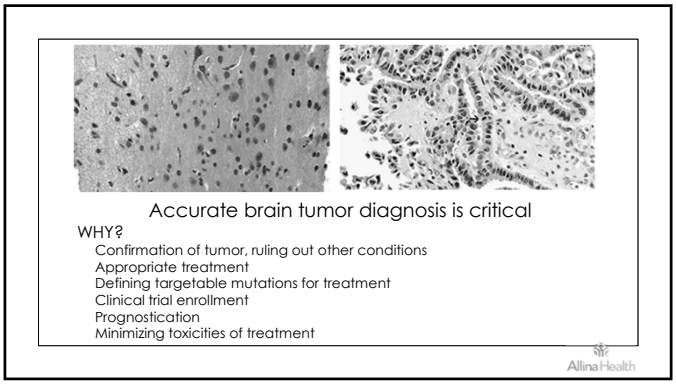
Accurate brain tumor diagnosis is critical
WHY?
Confirmation of tumor, ruling out other conditions
Appropriate treatment
Defining targetable mutations for treatment
Clinical trial enrollment
Prognostication
Minimizing toxicities of treatment
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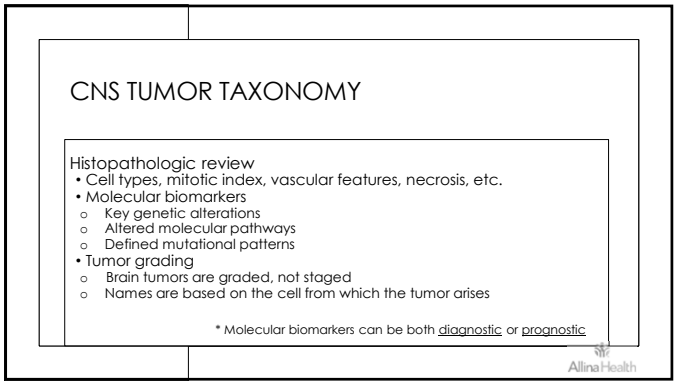
CNS TUMOR TAXONOMY
Histopathologic review
• Cell types, mitotic index, vascular features, necrosis, etc.
• Molecular biomarkers
o Key genetic alterations
o Altered molecular pathways
o Defined mutational patterns
• Tumor grading
o Brain tumors are graded, not staged
o Names are based on the cell from which the tumor arises
* Molecular biomarkers can be both diagnostic or prognostic
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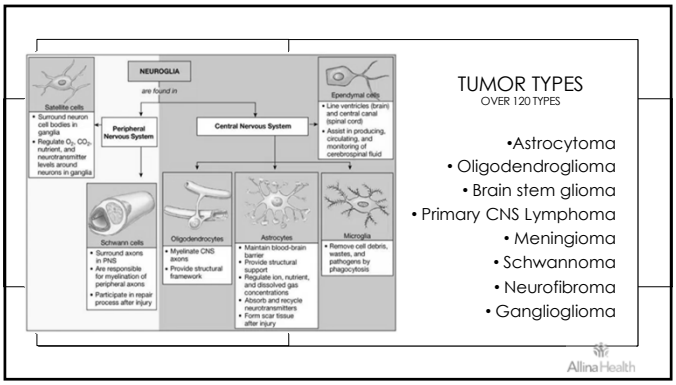
NEUROGLIA
are found in
Peripheral Nervous System
Central Nervous System
Satellite cells
• Surround neuron cell bodies in ganglia
• Regulate O_2, CO_2, nutrient, and neurotransmitter levels around neurons in ganglia
Ependymal cells
• Line ventricles (brain) and central canal (spinal cord)
• Assist in producing, circulating, and monitoring of cerebrospinal fluid
Schwann cells
• Surround axons in PNS
• Are responsible for myelination of peripheral axons
• Participate in repair process after injury
Oligodendrocytes
• Myelinate CNS axons
• Provide structural framework
Astrocytes
• Maintain blood-brain barrier
• Provide structural support
• Regulate ion, nutrient, and dissolved gas concentrations
• Absorb and recycle neurotransmitters
• Form scar tissue after injury
Microglia
• Remove cell debris, wastes, and pathogens by phagocytosis
TUMOR TYPES
OVER 120 TYPES
•Astrocytoma
• Oligodendroglioma
• Brain stem glioma
• Primary CNS Lymphoma
• Meningioma
• Schwannoma
• Neurofibroma
• Ganglioglioma
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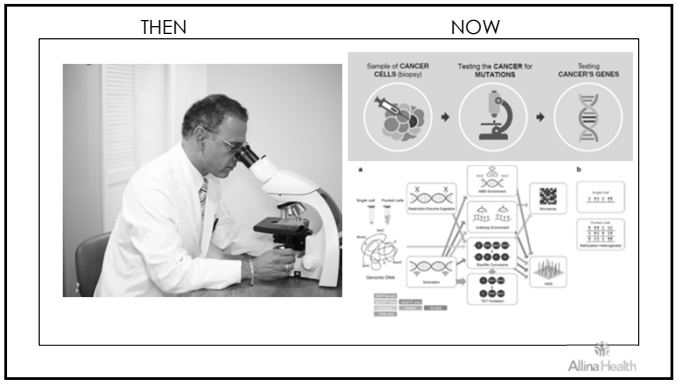
THEN
NOW
Sample of CANCER CELLS (biopsy)
Testing the CANCER for MUTATIONS
Testing CANCER'S GENES
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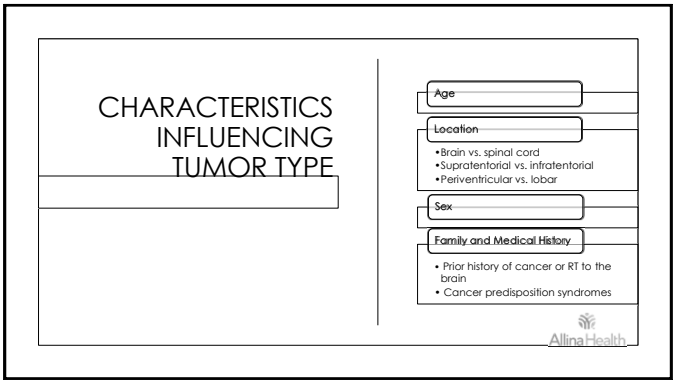
CHARACTERISTICS INFLUENCING TUMOR TYPE
Age
Location
•Brain vs. spinal cord
•Supratentorial vs. infratentorial
•Periventricular vs. lobar
Sex
Family and Medical History
• Prior history of cancer or RT to the brain
• Cancer predisposition syndromes
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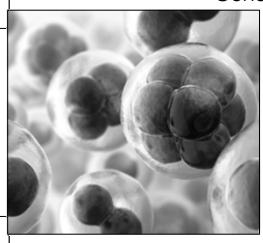
Genetic Tumor Predisposition Syndromes



Von Hippel Lindau Disease

Neurofibromatosis Type 1

NF2-Related Schwannomatosis

Li-Fraumeni Syndrome

Meningiomatosis

Lynch Syndrome

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MOLECULAR BIOMARKERS

ATRX - plays a key role in gene expression regulation

BRAF V600E – rarely found in high-grade gliomas. Common in pediatric population

TERT – telomerase reverse transcriptase; When mutated, allows for unlimited proliferative activation; Poor prognosis/survival noted

EGFR – epidermal growth factor receptor; Found in many cancers
High EGFR expression associated with a poor prognosis

KI-67 – a protein in cells which increases when a cell is preparing to divide
May be predictive of poor prognosis when it is overexpressed

1p / 19q – codeletion is seen in Oligodendrogliomas;
Consistent with better response to chemotherapy and improved survival

IDH – Isocitrate dehydrogenase – positivity consistent with a lower-grade tumor; Associated with a more favorable prognosis

TP53 - plays a role in apoptosis and suppresses the cell cycle
Involved in triggering the development and spread of glioblastoma

MGMT - O6-methylguanine methyltransferase - involved in repairing DNA damage in cancer cells

Tumor Mutational Burden TMB – refers to the total amount of cancer tissue in the body found in <3% of glioblastoma patients

Microsatellite Instability – MSI - caused by defects in the MMR system responsible for the correction of mismatches that occur during DNA replication.

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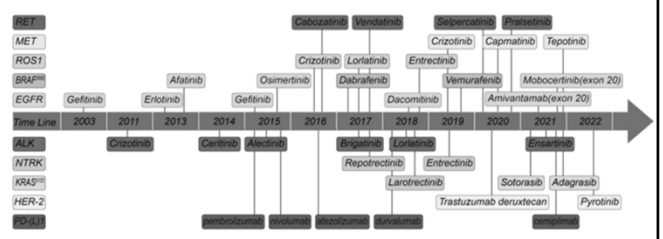

Timeline of targeted drugs which FDA approved for oncogene-driven NSCLC.

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Evolution of FDA-approved GBM treatment approaches.

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Brain Protection

Meninges – covers and protects the brain itself

CSF – filters blood and waste in the CNS

Blood-brain barrier – prevents most blood-borne toxins from entering the brain

- Estimated that 98% of FDA approved drugs do not cross the BBB

Therefore, when there is a tumor in the brain, it is difficult to get agents such as chemotherapy into the brain to treat the cancer

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BRAIN TUMOR TREATMENT

Radiation Therapy

- Conventional 6-week course
- Hypo-fractionated 3-week Course
- Concurrent chemotherapy
- Stereotactic Radiosurgery
- Proton Beam
- GammaTile
- FSRT
- Gamma Knife

Chemotherapy

Cytotoxic agents
- Interfere with cell division, damage DNA
- Do not discriminate between normal and cancer cells

Names
- Temozolomide
- Carboplatin
- Gleostine
- Methotrexate

- Side effects include cytopenias, nausea/vomiting, constipation, fatigue
- Adherence to oral medications

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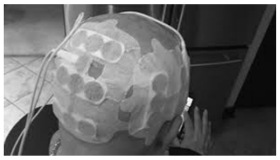
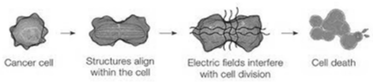


TUMOR TREATING FIELDS

/nv#unks`fd#dkdbsqhb`k#hl otkrdr# cdkhudqdc#hm#`ksdqm`shmf#ehdkcr#sn# hmsdqqtos#bdkk#chuhrhnm~#qdrtkshmf#hm# bdkk#cd`sg#

Skin Care

- Change arrays every 1-3 days
- Clean scalp with each change
- Use topical agents for red or open areas



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CLINICAL TRIALS

Immunotherapy
- Vaccines - such as the polio vaccine
  - Autologous – derived from one's own tumor cells
  - Allogeneic – developed in a lab from someone else's tumor

Agents used in other tumor types

Surgical interventions

Radiation interventions

Basket trials
- target a specific gene alteration or molecular signature rather than a specific tumor type

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IMMUNOTHERAPY

A type of cancer treatment

Uses substances made by the body or in a lab to boost the immune system and help the body find and destroy cancer cells

Can be used alone or in combination with chemotherapy or other cancer treatments

Many different types
- monoclonal antibodies
- immune checkpoint inhibitors
- non-specific immunotherapies
- oncolytic virus therapy
- T-cell therapy
- cancer vaccines

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DIFFERENT TYPES OF IMMUNOTHERAPY

1. Bevacizumab – EGFR receptor
2. Ibrutinib – Primary CNS Lymphoma
3. Ivosidenib – IDH1 inhibitor
4. Vorsidenib – IDH1 inhibitor
5. Selumetinib – Neurofibromatosis
   - Plexiform Neurofibroma
6. Belzutifan – Von Hippel Lindau
   - hemangioblastoma
7. Dabrafenib and Trametinib
   - targeted therapy
8. Pembrolizumab – immune checkpoint inhibitor

+ many others

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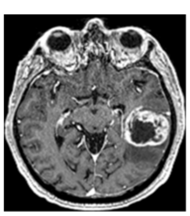
CASE #1: 73 YO M WITH HEMIPARESIS



Biomarker Findings

Microsatellite status - MS-Stable

Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

BRAF V600E

MTAP loss

PIK3R1 L573P

CDKN2A/B CDKN2A loss, CDKN2B loss

CDKN2C loss

TERT promoter -146C>T

A-B) BRAIN, LEFT TEMPORAL TUMOR, BIOPSY:
1. Glioblastoma (CNS WHO grade 4); see comment
2. IDH1 R132H immunostain negative
3. MGMT promoter methylation INDETERMINATE, see

Systemic Treatment Options:
1) Chemotherapy: temozolomide, lomustine
2) VEGF inhibitor: bevacizumab
3) BRAF & MEK inhibitors

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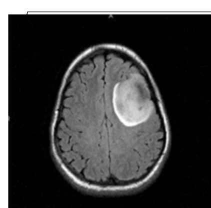
Final Diagnosis

A,B) BRAIN, RIGHT FRONTAL MASS, EXCISION:
1. Oligodendroglioma, IDH-mutant and 1p/19q-codeleted (CNS WHO grade 2)
2. Ancillary testing
   a. IDH1 R132H immunostain positive
   b. ATRX immunostain with preserved immunoreactivity
   c. p53 immunostain with variable pale (usually wildtype) immunoreactivity
   d. BRAF V600E negative
   e. Fluorescence in situ hybridization of 1p/19q confirms codeletion



Systemic Treatment Options:
1) Chemotherapy:
   - temozolomide
   - procarbazine, lomustine + vincristine
2) IDH-inhibitor

Case #2: 28 yo F with seizures

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Steroids use

Seizures

–IDConfusionH1

Cerebral edema

Anxiety

Sleep disturbance

Steroid psychoses

Hypertension

Hypercoaguable

Pancytopenia – neutropenia and thrombocytopenia use

Common Issues in the Inpatient Setting

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CEREBRAL EDEMA

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AVASTIN --- AKA BEVACIZUMAB, MVASI, ZIRABEV

Blocks a protein called vascular endothelial growth factor, or VEGF. Normal cells make VEGF, but some cancer cells make too much. Blocking VEGF may prevent the growth of new blood vessels, inhibiting growth of the tumor

Bevacizumab works by reducing vascular permeability and alleviating blood-brain barrier damage and brain edema through its binding to VEGF

Radiation Necrosis causes tissues to have elevated levels of VEGF which leads to increased vascular permeability, damage to the blood-brain barrier, and subsequent brain edema

CAN CAUSE HYPERTENSION, STROKE, WOUND HEALING ISSUES, PRES

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COST OF A GLIOBLASTOMA

Has the highest per-patient initial cost of care for any cancer group, with an annualized cost over $150,000

Has the highest cost for the last-year-of-life care relative to other cancers at $135,000 - $210,000 per-patient

These costs do not take into account the personal cost due to cognitive and functional disabilities, socioeconomic ramifications, or the out-of-pocket dollars not covered by insurance

Newer drugs have an even steeper price

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SUMMARY

Brain tumors carry dismal statistics with regard to survival and cost

Over the past 20 years, we have seen relatively small gains in survival (glioblastoma: 44w to 65w) and treatment options compared to other tumor types

Survival is NOT enough!

Research and clinical trials, especially in the area of immunotherapy, are absolutely necessary to further impact survival with molecular testing being at the forefront

We need to identify how to protect the brain from the long-term effects of treatment which often results in significant cognitive impairment and decreased quality of life

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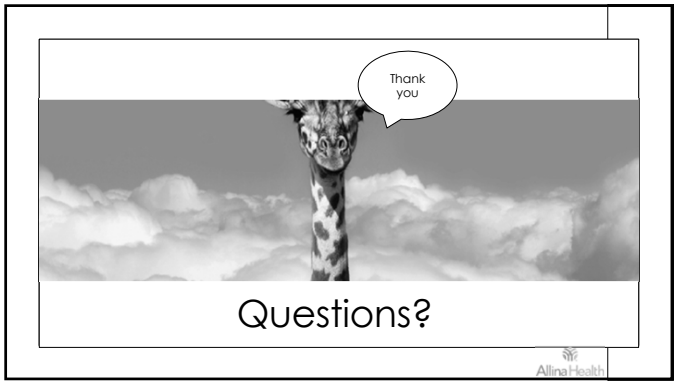

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