Understanding and Treating Brain Tumors: An Overview

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Anatomy
Brain Function

- Left side of the brain controls the right side of the body
- Right side of the brain controls the left side of the body
Compilation of individual cerebral maps

Wilder Penfield, M.D.
Brain Mapping

• Awake mapping of the brain with electrical stimulation
• Motor/sensory
  • Activation
• Speech
  • De-activation (Speech arrest)
Brain Mapping

- Mapping with a grid can be accomplished in the operating room or later in the patient room
  - Need a second operation to remove grid and tumor
Functional MRI
"Whoa! That was a good one! Try it, Hobbs — just poke his brain right where my finger is."
Right Brain

Left Brain

- Controls language, dexterity of the right hand, the ability to classify, general routine behavior

Right Brain

- Involved with reacting to emergencies, organizing things spatially, recognizing faces, processing emotions, music
Everything is connected to everything else
Cerebral Ventricles
VENTRICLES OF THE BRAIN

LATERAL VIEW

CENTRAL CANAL OF SPINAL CORD

TOP VIEW

A.H. — ANTERIOR HORN OF LATERAL VENTRICLE
C. — CEREBELLUM
C.A. — CEREBRAL AQUEDUCT
F.L. — FORAMEN OF LUSCHKA
F.M. — FORAMEN OF MAGENDE
F.Mo. — FORAMEN OF MONRO
4.V. — FOURTH VENTRICLE

I.H. — INFERIOR HORN OF LATERAL VENTRICLE
L.V. — LATERAL VENTRICLE
P. — PONS
P.H. — POSTERIOR HORN OF LATERAL VENTRICLE
3.V. — THIRD VENTRICLE
Coverings of the Brain (Meninges)

1. dura
2. frontal lobe
3. middle meningeal artery
4. temporal lobe
The meninges are the membranes covering the brain and spinal cord.
Brain Cells
Neurons
Glia
Terminology

- Tumor designated by cell of origin and suffix “-oma”
  - “-oma” means “mass”
  - Glioma
    - Glial cell
      - Astrocytoma
        - Astrocyte
      - Oligodendroglioma
        - Oligodendrocyte
      - Ependymoma
        - Ependymal cell
  - Meningioma
    - Meningial cells (Dura)
Tumor cell Origins

Unclear which at which stage cell is responsible

Likely cell with stem cell properties
Blood-BRAIN Barrier

• Normal brain capillaries have tight junction resulting in “blood-brain barrier”
• Significant barrier to all large molecules including chemotherapy
Human Chromosomes
Fluorescence Detection of Chromosome Deletions (FISH)

- 1p deleted cell
- Normal cell
Radiology
(Neuro-imaging)
MRI and CT

- Both have the ability to “slice” up the brain
  - CT – X-rays
  - MRI – magnetic waves
- Both allow for 3-D reconstructions
CT of the Head

- Bone is white
- Brain is grey
- Water is black
- Fat is black
- Fresh blood clot is white
- Old blood clot is grey
- Left is on the right
- Right is on the left

Injected contrast (Iodine) is white
Blood on CT Scan

Chronic subdural hematoma  Intracerebral hemorrhage  Intraventricular hemorrhage
CT is also good for identifying calcium in a tumor and for following hydrocephalus.
MRI of the Head

• Bone is black
• Brain is grey
• Water is black (T1) or white (T2)
• Fat is white
• Fresh blood clot is black, grey or white
• Old blood clot is white
• Left is on the right
• Right is on the left
• Injected contrast (Gadolinium) is white
Injected Contrast

- CT – Iodine  MRI – Gadolinium
  - Both appear white
- Contrast will collect where ever there are “leaky” blood vessels (capillaries)
- Normal brain has blood vessels that do not leak (the blood-brain barrier)
- Tumors, infections, strokes, MS, damaged brain, etc. all have “leaky” blood vessels and will “enhance” with contrast.
Contrast Enhancement
MRI - FLAIR

T1 w/o contrast  T1 w/ contrast  FLAIR
Radiological Diagnosis

Abscess

Malignant Glioma

Also – Multiple sclerosis
Tumors

• Tumor is a Latin word for “mass”
  • “Mass lesion” is technically a tumor
  • “Neoplasm” is a type of mass lesion
  • For most purposes, tumor = neoplasm
Tumor types

- Benign tumors
  - Not really considered to be a cancer
  - Usually slow growing
  - Self contained
  - Do not spread (metastasize)
  - Can sometimes grow in very inconvenient places and therefore cause major problems
  - Often do not respond to radiation or chemotherapy
Tumor types

• Malignant tumors
  • Are “cancers”
  • Usually fast growing
  • Often spreads through tissues
  • Often spreads to other parts of the body (metastasize)
    • Primary brain tumors (tumors arising in the brain) very rarely metastasize
    • Brain is often the place where malignant tumors from other parts of the body go

Usually respond to radiation and chemotherapy
WHO Grading

- World Health Organization
- Grades 1-4
  - Grade 1 – most benign
  - Grade 4 – most malignant
  - Grade 2 and 3 - intermediate
Benign Brain Tumors

• Extra-axial (inside the skull but outside the brain)
  • Can push normal brain aside
  • Rarely invade normal brain
Meningiomas

- Arise from the meninges (coverings of the brain)
- Usually slow growing
- Usually do not invade brain
- Common in older women
Meningiomas

• Surgical treatment is usually required
  • Open surgery
  • Stereotactic Radiosurgery
• Often can be “cured”
Meningiomas

- Can sometimes grow in difficult and inconvenient places (skull base)
Other Benign Extra-axial Tumors

- Pituitary Tumors
- Craniopharyngiomas
- Dermoid cysts
- Pineal cystomas
- Nasal / ethmoid tumors
- Chordomas
- Acoustic schwannomas
Metastatic Tumors

- Malignant tumors
- Arise from a tumor that has started outside the brain
- Lung, Melanoma, Breast, Kidney, Liver,
- Treated with surgery (radiosurgery) and radiation

Sometimes occur after successful chemotherapy
Primary Brain Tumors

- Gliomas
  - Pilocytic Astrocytoma (Grade 1)
  - Astrocytoma (Grade 2)
  - Anaplastic Astrocytoma (Grade 3)
  - Glioblastoma multiforme (Grade 4)
  - Oligodendroglioma (Grade 2)
  - Anaplastic Oligodendroglioma (Grade 3)
  - Oligo-astrocytomas
  - Pleomorphic Xanthroastrocytoma
  - Ependymomas
Primary Brain Tumors

- Medulloblastoma
- Primitive neuroectodermal tumor
- Choroid Plexus Papilloma
- Neurocytoma
- Ganglioglioma
- Germinoma
- Hemangioblastoma
- Subependymoma
- Primary CNS Lymphoma
Oligodendroglioma

T1 w/o contrast  T1 w/ contrast  FLAIR
Oligodendroglioma

- Slower growing
- Can be Grade 2 or Grade 3
- Often respond well to chemotherapy
- Chromosome deletions
  - 1P
  - 19q
Anaplastic Astrocytoma
Glioblastoma
Glioblastoma
After Surgery
Goals of Brain Tumor Surgery

To achieve a diagnosis

To eliminate as many tumor cells as possible without injuring normal cells
Surgery

• **Fundamental Questions:**
  - Do the benefits of surgery outweigh the risks of surgery?
  - Do the risks of not doing surgery outweigh the risks of surgery?
  - Do not do surgery just to make the x-ray picture look better
Risks of Surgery

• General
  • Infection, Hemorrhage (bleeding), Anesthesia Complications, Medical Complications

• Specific
  • Stroke (temporary or permanent)
  • Seizures
  • Spinal fluid leakage

No benefit without risk
Stereotactic Biopsy

- To achieve a diagnosis
- Framed and frameless

Advantages
- Small incision
- Home the next day

Disadvantages
- Tumor is still there
- Small risk of hemorrhage/stroke
- Risk of missing worst part of the tumor
Figure 2. The diagram represents an intraventricular glioblastoma in a 48-year-old man. The shaded regions are tumor and the geographic symbols represent neoplastic cells. (a) A biopsy needle is sampling both the tumor and the hypodense rim that corresponded to a contrast-enhancing ring. (b) The diagnosis of glioblastoma is readily made given the tumor and neoplastic composed of small anaplastic cells (small oval circles).

Figure 3. (a) In the same neoplasm shown in Figure 2, the ventricle is displaced somewhat inferiorly, anterior from the area of necrosis. (b) In this latter region, the neoplasm is composed largely of well-differentiated tubular astrocytes (closed triangles), granular astrocytes (open triangles), and a few small undifferentiated cells (small closed circles). The diagnosis of malignant astrocytoma would be appropriate for this region.
Resective Brain tumor Surgery

• To achieve goal must balance:
  • Safety
  • Extent of resection
Surgical Technique

Safety vs. Extent of resection

• Intra-operative guidance
• Macrosurgical technique
• Microsurgical technique
Craniotomy

- Can achieve both goals of surgery
- Increased risk but also increased benefit
- Allows greater control of bleeding, tumor removal, etc.
Gross Total Resection (GTR)
New Strategies for Glioma Resection

- Navigation
  - Frame-based stereotactic guidance
  - Frameless stereotactic guidance
- Intra-operative imaging
  - Ultrasound
  - MRI
- Direct tumor visualization
  - Fluorescence
Tumor Fluorescence
Other Therapies

• Many brain tumors cannot be cured in the operating room no matter how much tumor has been removed

• In those cases we depend on other (“adjuvant”) therapies
  • Radiation
    • Standard
    • Stereotactic Radiosurgery
  • Chemotherapy
  • Targeted therapies
Fig. 23.1 Multimodality therapy of malignant gliomas. Combined use of various therapeutic methods, including reoperation, attempts reduction of tumor cell number.
Radiation and Chemotherapy

- Targets rapidly dividing cells (fast growing tumors)
- Disrupts DNA so that the cell cannot complete cell division
- Only those cells that are in the process of dividing (mitosis) are vulnerable
Standard Radiation

• Relies on the differential sensitivity of tumor cells vs normal cells
• In the brain, very few normal cells are undergoing cell division
Stereotactic Radiosurgery

- "Gamma Knife"
- Actually kills the cells – doesn't just disrupt the DNA
- Relies upon the focus of the radiation
- No part of the brain gets very much radiation except for the area of radiation focus which gets a tremendous amount of radiation – resulting in immediate cell death
- Requires precise targeting
- Size limits
- Not for every tumor
A cell toxin is fused to a delivery molecule which delivers the toxin only to the tumor cell and not to normal cells. Sometimes requires novel techniques for drug delivery to bypass BBB.
Brain Swelling

- Reaction of brain to a “foreign” object
- Treated with dexamethasone (Decadron)
Seizures

• Abnormal activity of neurons
• Usually from irritation from tumor or surgery
Treatment of Seizures

Usually medical treatment is best
- Dilantin
- Keppra

Occasionally surgical option needed
- Resect area where seizures arise
Genetics and Outcomes

New Sub-classifications of Glioblastoma using Integrated Genomic Analysis
Glioblastoma Sub-types

Sources:
- Phillips et al.:
  - Pro-neural: Olig2/DLL3/SOX2
  - Proliferative: MBP/MAL
  - Mesenchymal: YKL40/CD44
- Verhaak et al.:
  - Pro-neural: TP53 mutations, PI3K, PDGFRA
  - Neural: chrom7 gain, chrom10 loss
  - Classical: PDGFRA
  - Mesenchymal: NFkB, NF1

Clinical features:
- Pro-neural: Non-responder to chemotherapy
- Neural: Clinical outcome improved with temozolomide/radiation
- Classical: Clinical outcome improved with temozolomide/radiation
- Mesenchymal: Clinical outcome improved with temozolomide/radiation

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Genetics and Treatment

Hot off the Press!!

Drugs can be targeted to tumor cells with specific gene defects

Some Brain Tumors Are Linked to a Gene Defect

BY RON WINSLOW

A genetic mutation appears to be behind some cases of a common and aggressive brain cancer, researchers at Columbia University said, and targeting the abnormality with a drug prolonged the lives of mice with the condition.

The findings, published online Thursday by the journal Science, are the latest in a string of discoveries that illustrate the potential of genomic research to lead to new approaches to attacking cancer. Still, the researchers cautioned that only a fraction of the type of brain tumor studied,