Imaging in Glioblastoma Multiforme: Diagnosis, Treatment, and Follow-Up

Kimberley Mak, HMS III
Gillian Lieberman, MD

Harvard Medical School
Radiology Clerkship, BIDMC

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Overview of Management: Clinical and Radiologic Presentation

Patient 1

- 52 M presents with 2 month h/o bifrontal headaches worsened by cough or Valsava

- Head CT performed in ED
Patient 1: Mass on Head CT

- Large mass in R frontal lobe with extensive surrounding edema crossing corpus callosum* into contralateral frontal lobe

- 7.3 mm leftward midline shift and compression of R lateral and 3rd ventricles
Radiologic Presentation

Patient 1: Mass on Head CT

- Gamuts DDx for common low attenuation supratentorial lesions on CT:
  - Infarct
  - Edema (vasogenic vs. cytotoxic)
  - Astrocytoma (including GBM)
  - Metastasis
  - Hematoma (3-6 wk)
  - Cyst
  - Cystic neoplasm
  - Abscess
  - Granuloma
  - Multiple sclerosis (periventricular)

- Narrowed DDx for corpus callosum edema
  (Courtesy Dr. Lee)
  - GBM
  - Primary CNS lymphoma
  - Metastasis
  - Demyelination

- Hypodensity extending through cortex to surface of brain
- Corpus callosum edema

Highly suspicious for Glioblastoma multiforme
Glioblastoma Multiforme: *What’s in a name?*

- Harvey Cushing and Percival Bailey coined the term in 1926.
- Malignant cells thought to be derived from "Glioblasts", the most primitive precursors of glial cells:
  - Now thought to be misnomer: malignant cells arise from dedifferentiated mature cells.
- "Multiforme" as complex and highly variable morphology.
Glioblastoma Multiforme: *What’s in a name?*

- Classified as Grade IV astrocytoma by 1993 WHO criteria:

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>Name</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Circumscribed astrocytoma</td>
<td>Generally benign, well-circumscribed; most common example is juvenile pilocytic astrocytoma</td>
</tr>
<tr>
<td>II</td>
<td>Astrocytoma</td>
<td><strong>Diffusely infiltrating</strong>, well-differentiated; minimal pleomorphism or nuclear atypia; no vascular proliferation or necrosis</td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td><strong>Pleomorphism and nuclear atypia;</strong> increased cellularity and mitotic activity; no vascular proliferation or necrosis</td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma Multiforme</td>
<td><strong>Poorly-differentiated</strong>, increased cellularity; variable mitotic activity; <strong>prominent vascular proliferation or necrosis</strong></td>
</tr>
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- Regardless of initial grade at diagnosis, all diffuse astrocytomas tend to progress to GBM
Diagnosis: Examples of “Multiforme” Appearances of GBM on Head CT and MRI

- Multifocal
- ‘Cyst with a nodule’
- Large intra-axial hemorrhage

Peripheral location, resembling dural process

Posterior fossa

Leptomeningeal

All images from Rees et al.
Epidemiology

- MOST COMMON primary brain malignancy in adults
  - 20% of all primary brain tumors
  - 12-15% of all intracranial neoplasms
- Annual incidence 15,000-20,000
- Male:female = 1.6:1
- Caucasian > African, Asian, Latin American
- Most frequently in cerebral hemisphere at 45-70 yr
- Primary GBM if no evidence of precursor lesion, mean age 55 yr
- Secondary GBM if progression of existing astrocytoma, mean age 40 yr
- Rarely in cerebellum, spinal cord and children

- 2nd most common cause of death due to intracranial disease after stroke
- Very poor prognosis: despite surgical resection with adjuvant chemoradiation, **median survival 12-14 months**
  - 90% die within 18 months from diagnosis
  - 5-yr survival 3.3%
- Without therapy, survival is <6 months
- No substantial improvement in survival since 1970s
Symptoms

- **Localizing** signs such as focal neurologic deficits, seizures, behavioral changes, or strokelike symptoms
- **Non-localizing** symptoms such as severe headaches, tonic-clonic seizures, Jacksonian seizures
- Uncommonly **asymptomatic** and diagnosed as incidental finding for e.g. head trauma

- **Most common symptoms:**
  - Headache (30-50%)
  - Seizures (30-60%)
  - Focal neurologic deficits (40-60%)
Diagnosis of GBM

- Made by imaging prior to tissue diagnosis
- CT +/- contrast offers information on calcification (rare in GBM)
- MRI +/- contrast modality of choice
  - Improved capacity for tumor detection vs. CT because of superior soft-tissue resolution
  - High sensitivity with standard T1- and T2-weighted MRI
  - Typically see a large, heterogeneous mass in supratentorial white matter
    - Defining features: hemorrhage and necrosis
    - Surrounding “fingers of edema” (extensive)
    - Usually considerable mass effect
Patient 2: Mass on Head CT

- **64 M with left-sided weakness for 3 months, s/p 2 falls**

- **7x7x8 cm area of low attenuation consistent with vasogenic edema** in R frontal lobe surrounding large mass

- **Edema in corpus callosum**

- Significant **mass effect** with compression of R lateral and 3rd ventricles, subfalcial herniation and 2.5 cm L displacement of septum pellucidum

- **No calcifications**
Classic Buzzword Appearance: “Butterfly”

- Rim-enhancing mass crosses midline via the corpus callosum
- Ddx is *narrow*:
  - High grade astrocytoma (usually GBM)
  - Primary CNS lymphoma
  - Edema or infection unlikely to cross midline
- Most frequently in frontal lobes, but can be posterior

Coronal Head MRI (T1), Contrast +

Patient 1: T1-Weighted MRI

- **Area of low signal intensity** in R frontal lobe
- 4.7 X 3.6 x 4.2 cm **heterogeneously rim-enhancing, necrotic lesion**
**DDx Rim-enhancing lesion**

- M etastasis
- A bscess
- G lioma (GBM) or
  - 1° CNS lymphoma
- I nfarction
- C ontusion
- D emyelination
- R esolving hematoma

- Heterogeneous enhancement due to hemorrhage with blood products in various stages of liquidity or oxidation, necrosis, and edema
Patient 1: T2-Weighted MRI

- Heterogeneously enhancing lesion
- Extensive surrounding edema in vasogenic pattern
- Sulci effaced in brain surrounding lesion

Patient 1: MRI (FLAIR)

- “Fluid attenuated inversion recovery” sequence
- CSF suppressed while edema enhanced
Patient 1: MRI - Susceptibility Weighted Imaging (SWI)

- Exploits magnetic susceptibility differences of various tissues such as blood, Fe, calcification
- **Demonstrates hemorrhage and calcification**
- Levels of ferritin and transferrin receptors correlated with human grade in human gliomas

Axial Head MRI (SWI)

No evidence of hemorrhage
Perfusion MRI

- Relative tumor blood volume (rTBV): ratio of maximal tumor blood volume to region of interest in normal white matter.
  - *Increases with neoplasm grade*
  - *Exception: low-grade oligodendrogliomas (high rTBV)*

- Neoplasms have increased permeability parameters on imaging due to abnormal angiogenesis
Magnetic Resonance Spectroscopy (MRS)

- Analyzes chemical composition of a brain region to assist in differentiating tumor from other lesions.
- Helpful in determining extent of tumor within volume of T2 signal change (edema).

Diagnosis
Magnetic Resonance Spectroscopy (MRS)

**ELEVATED IN GBM:**

- **CHOLINE**: in all cell membranes, thus increased with cell membrane turnover
- **LACTATE**: product of anaerobic respiration, thus increased in necrotic tumors, infection or stroke
- **LIPID**: indicates necrosis, thus increased in high-grade neoplasms
- Elevated **Choline:Creatine** ratio >1 distinguishes tumor from abscess (Se 79%, Sp 77%; accuracy increased using additional MRS variables)
DECREASED IN GBM:

- **CREATINE**: marker of cellular bioenergetics, decreased to varying degrees in GBM.

- **N-ACETYLASPARTATE (NAA)**: byproduct of neurotransmitter glutamate, thus found in synaptic terminals of neurons and decreased in gliomas.
Overview of Management: Surgery and Pathology

Tissue Diagnosis

- Done at time of surgical resection

- In cases where lesion not amenable to resection (deeply situated, or diffuse and non-focal), or the patient’s clinical condition will not permit surgery, stereotactic biopsy is performed
Stereotactic Brain Biopsy

- CT or MRI performed with rigid frame including fiducial bars fixed to the skull to eliminate movement
- Or “frameless” stereotactic device with fiducial markers placed on scalp before imaging
- Coordinates created to pass needle within 1 mm accuracy to biopsy target, guided by known location of the fiducials relative to target
- Use of PET, perfusion imaging, or MRS may assist selection of biopsy site most likely to contain most aggressive portion of tumor
- U/S guidance also used

Patient 1: Surgical planning with Axial MRI (MP RAGE)

- High-resolution T1W sequence
- Used in pre-operative planning with 3D reconstruction
**Rationale: Gross Total Resection**

- Balancing maximal cytoreduction vs. preservation of neurologic function
- Because of diffuse tumor infiltration of grossly normal brain, “complete” resection” not realistic
- Retrospective studies indicate patients with gross total resections have longer median survival compared to those with subtotal resection
  - Due to therapeutic benefit vs. selection bias for those with less extensive tumors?
- Decreases mass effects (edema, hydrocephalus, impending herniation)

Linskey, [http://neurosurgery.uci.edu/articles/iomr.shtml](http://neurosurgery.uci.edu/articles/iomr.shtml)
Gross Total Resection: A Stereotactactic Approach

- Frameless, image-guided neuronavigation system displays location of surgical instruments and tumor superimposed on pre-operative MR or CT images
- Imaging updated intraoperatively using U/S, CT or MRI
Overview of Management: Adjuvant Chemoradiation Therapy (CRT)

Rationale for Adjuvant therapy

- High recurrence rate with gross total resection alone, due to infiltrative nature of tumor

- Adjuvant whole brain RT (WBRT) shown to improve survival in at least 3 randomized trials in 1970s
  - Representative trial from Brain Tumor Study Group: median survival increased from 14 to 36 weeks with addition of adjuvant WBRT to surgical resection

- Additional survival benefit when chemotherapy added to RT
  - Temozolomide (oral alkylating agent) is current standard agent for adjuvant chemotherapy in GBM
  - Phase III trial in which 573 patients with GBM randomized to involved-field RT (60 Gy in 30 fractions) versus the same RT plus concomitant then adjuvant temozolomide
  - Adjuvant temozolomide increased overall survival from 12.1 months to 14.6 months
  - Adjuvant temozolomide 2-year survival increased from 10% to 26%
Treatment: Adjuvant Chemoradiation Therapy (CRT)

Imaging in Radiotherapy (RT) Planning

- Improvements in imaging have translated into increased accuracy of radiotherapy
- Post-op Day 1 imaging obtained to assess for extent of resection and for RT planning
- Thin-slice (<3mm) CT +/- contrast for treatment planning
- Post-op MRI fused with this for definition of target volume
- T2 or FLAIR abnormality contoured as clinical target volume (CTV), with assumption that edematous region is at risk for microscopic tumor extension.
  - Compared with pre-op MRI to ensure post-op changes such as hemorrhage not confused with tumor
  - This volume targeted to 45-50 Gy.
- Post-contrast T1 images define gross tumor volume (GTV). If gross complete resection, then resection cavity is GTV.
  - Boost to GTV for total dose of 60 Gy.
  - Can also calculate CTV as GTV + 2 cm margin
Commonly used method of fractionated (conventional) RT, with total dose of 60 Gy administered in daily doses of 1.8-2 Gy doses
- Principle that small doses of radiation impart greatest damage to rapidly proliferating tumor cells, as normal cells can repair sublethal levels of DNA damage
- Use of cross-sectional images in 3 planes to create 3D-planning
- Radiation dose to tumor and normal tissue calculated in 3D, allowing design of treatment plans that limit dose to normal tissue e.g. brainstem
Treatment: Radiotherapy

3D-CRT Planning Continued:
3D-Reconstruction of Patient

GTV
Brainstem
CTV


Linear Accelerator (LINAC) used to deliver RT
3DRT Planning Continued:
3D Reconstruction of Patient

- Critical structures such as eyes, optic nerve, optic chiasm, and brain stem demonstrated
Intensity-Modulated RT (IMRT)

- Specialized 3D-CRT technique whereby radiation intensity is varied across each treatment field to maximize radiation dose to tumor and minimize dose to normal tissue
  - Thus ideal for tumors that abut uninvolved radiation-sensitive structures (e.g. eyes, optic nerves, optic chiasm, brainstem)

- Complexity of RT planning requires adaptation of the hardware of linear accelerators, skilled physicist support, and increased planning/delivery time
Stereotactic Radiosurgery (SRS)

- Role not established in GBM

- Single large dose of radiation to small, precisely-defined target
  - Invasive stereotactic head frame placed followed by CT or MRI to plan treatment relative to landmarks

- Achieved by multiple non-parallel beams converging on target
Stereotactic Radiosurgery (SRS): Continued

- Photon-based radiation (Linac, Gamma Knife, Cyberknife®) or proton-based
  - N.B. Cyberknife® uses mobile linear accelerator that adjusts to patient position based on real-time x-ray cameras
  - Thus no head frame required

*N.B.* uses mobile linear accelerator that adjusts to patient position based on real-time x-ray cameras

Thus no head frame required
Brachytherapy

- Role not established in GBM
- \textit{Brachy} = ‘near’ in Greek; refers to placement of radiation source within body
  - Permits delivery of large RT dose to tumor with rapid fall-off in surrounding tissues
- Radioisotope seeds include $^{125}\text{I}$ or $^{192}\text{Ir}$
- Sources loaded into stereotactically placed catheters, or intraoperatively after resection
- GliaSite RT system: intracavitary device implanted after resection of tumor: solution of $^{125}\text{I}$ injected into closed catheter balloon, which inflates to fill resection cavity to deliver in doses of 40-60 Gy 5-10 mm from the balloon surface.

Overview of Management: Follow-Up

**Follow-Up**

Patient 2: s/p Resection and Adjuvant CRT

- Post-treatment follow-up by MRI and history/physical exam
- **Normal post-resection changes** at 10 and 12 months with Case 2
- Limitations with conventional contrast-enhanced MRI or CT
  - Combinations of abnormal enhancement patterns (e.g. multiple lesions, corpus collosum involvement) help distinguish necrosis from tumor progression
  - Use of MRS, perfusion MRI, and PET* developing
**A Note on PET**

- $^{18}$F-FDG-PET not commonly used in primary evaluation of GBM
  - High grade gliomas have similar uptake to normal grey matter, thus obscured
  - Arguably may be used to distinguish tumor recurrence from benign enhancing scar tissue or radiation necrosis

- Under development: radiotracers correlating with cell proliferation
  - Thus low background in normal brain
  - Thymidine analog, 3’deoxy-3’-[$^{18}$F]Fluorothymidine (FLT): uptake correlates to Ki-67 index

Follow-Up

GBM recurrence detected by FDG-PET

Schmitter, [http://gamma.wustl.edu/pt043te113.html](http://gamma.wustl.edu/pt043te113.html)
Overview of Management: Recurrence

Sites of Recurrence

- GBM spreads most commonly by:
  - 1) Direct local extension, along white matter tracts
  - 2) CSF pathways in <2%
  - 3) Subependymal spread even more uncommon, correlates with poor prognosis
  - 4) Hematogenous spread most rare, causing dense osteoblastic bone lesions

- Wide margin of resection not often possible due to proximity to eloquent brain, but even when possible, failure occurs most commonly at resection margin
  - Recall diffuse infiltrative nature of tumor
Patient 2: Recurrence at 14 months

- 2 new lesions suspicious for GBM recurrence on conventional MRI:
  - 1) 4 cm lesion in R frontal lobe abutting central sulcus
  - 2) New 1.6x2.0 cm lesion in L parietal lobe tracking back through white matter
Patient 2: Diffusion Tensor MRI (DTI)

- Extent of directionality of water diffusion can be expressed as a fractional anisotropy (FA) value
  - Water flows along axons in white matter
- Lesion 2 in L parietal lobe causes disruption of white matter tract
  - Disruption of white matter tract potential early sign of recurrence
- Lesion 1 visible
Arterial Spin Labelling (ASL)

“Endogenous contrast agent”:
- $\text{H}_2\text{O}$ protons in arterial blood labeled by perturbing their magnetization with RF pulses
- Thus non-invasive

- Higher blood flow and blood volume in \textbf{R frontal} and \textbf{L parietal} recurrences
**Recurrence**

**Treatment of Recurrence**

- Surgical resection if possible, or biopsy of suspicious lesion

**Residual tumor <4-6 cm**
- SRS (<4 cm)
- Brachytherapy (<6 cm)
- Retreatment with RT (3DCRT, IMRT)
- Wafer chemotherapy

**Residual tumor >4-6 cm**
- 2nd line chemotherapy (PCV, BCNU, CPT-11)
- Retreatment with RT (IMRT)

**Necrosis from “treatment effect”**
- Further resection
- Steroids

*Fiveash et al.*
Example: Treatment of Multifocal Recurrence with SRS
Overview of Management: Salvage and Prognosis

Prognosis in GBM: A Role for Imaging?

- Clinical indicators of poor prognosis:
  - Extent of necrosis
  - Younger age
  - Karnofsky Performance Status <80
  - Presence of tumor cysts

- 2005 study by Pope et al. in AJNR: Findings on conventional MRI correlate with survival in GBM
  - Edema, multifocality, and satellite lesions associated with shortened survival
  - Presence of non-contrast-enhancing tumor (likely regions of lower grade tumor without necrosis) associated with increased survival

- Studies with Perfusion MRI:
  - Contrast transfer coefficient ($K_{\text{trans}}$, a reflection of blood flow and endothelial permeability) predicts length of survival in high-grade gliomas
Patient Outcomes

■ Patient 1:
  ■ Doing well s/p gross resection
  ■ Will commence adjuvant chemoradiation (3D-CRT and temozolomide)

■ Patient 2:
  ■ Recurrent lesion in R frontal lobe to be resected, followed by SRS to resection bed
  ■ Second recurrent lesion in L parietal lobe will be treated by SRS
GBM is the most common primary brain malignancy of adults

**Diagnosis** is by CT and MRI (other imaging techniques developing)
- Defining features of rim-enhancement, necrosis, and hemorrhage
- Also extensive edema and mass effect
- Classic “butterfly” appearance, but can be “multiforme”

**Tissue diagnosis** at surgical resection or by stereotactic biopsy
- Stereotactic guidance for both procedures relies on CT or MRI
- Perfusion MRI, MRS, PET developing for

**Standard treatment** is gross resection if possible, followed by adjuvant chemoradiation therapy

Close **follow-up** by MRI (other imaging techniques developing)

Treatment for **recurrence** varies

Very poor prognosis, which may be predicted by imaging
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