Introduction to ACRODeck

- The goal of ACRODeck is to introduce standard treatments of oncologic malignancies for early radiation oncology residents.

- Please note that there is often considerable variation in standard treatment recommendations.

- Moreover, the landscape of oncology is ever-changing; for practice changing landmark studies and feedback, please email: resident@acro.org.
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Clinical Presentation and Differential Diagnosis

- As with any CNS lesion, the location of the lesion will determine the clinical presentation
  - LGGs most commonly present with seizures
  - Other symptoms may include neurologic deficits, headaches, altered mental status, motor and sensory deficits, nausea and vomiting

- Differential Diagnosis:
  - Glioma
  - Ependymoma
  - Lymphoma
  - Brain metastasis
  - Intracranial abscess
  - Empyema
  - Multiple sclerosis

In contrast to higher grade tumors, LGGs are more prevalent in the younger adult population.
Initial Workup

- **H/P**
- **CBC and CMP**
- **MRI brain with and without contrast (obtain one within 24-48 hours of resection as well)**
  - Classic findings: T2 hyperintense; minimal contrast enhancement (apart from pilocytic astrocytomas)
- Consider steroids and anti-epileptics
- **Maximal safe resection**
  - Molecular testing includes IDH, 1p19q codeletion, BRAF

<table>
<thead>
<tr>
<th>MRI Sequence</th>
<th>Appearance</th>
<th>Visualization of...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Isointense/Hypointense</td>
<td>Anatomy</td>
</tr>
<tr>
<td>T1c</td>
<td>Minimal Contrast Enhancement</td>
<td>Pilocytic Astrocytomas</td>
</tr>
<tr>
<td>T2 / FLAIR</td>
<td>Hyperintense</td>
<td>Tumor</td>
</tr>
</tbody>
</table>

In contrast to higher grade tumors, most LGGs have minimal contrast enhancement.
Staging

- Primary CNS tumors are graded, not staged

<table>
<thead>
<tr>
<th>Tumor</th>
<th>WHO Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma (and others)</td>
<td>1</td>
</tr>
<tr>
<td>Diffuse low-grade glioma</td>
<td>2</td>
</tr>
<tr>
<td>Anaplastic glioma</td>
<td>3</td>
</tr>
<tr>
<td>Glioblastoma Multiforme</td>
<td>4</td>
</tr>
</tbody>
</table>

Most glial neoplasms in adults are WHO grade 4
Pathology

- Low grade gliomas are a heterogenous group of tumors
- They are broadly classified into:
  - WHO grade 1 (noninfiltrative tumors)
  - WHO grade 2 (infiltrative/diffuse tumors)

- Traditionally, histology and MEAN criteria were used to characterize these tumors
  - Mitotic index, endothelial proliferation, nuclear atypia, and necrosis

- Now, we are moving towards an era of incorporating molecular classification into WHO grading (see 2021 update)
  - Astrocytomas: 1p19q intact
  - Oligodendrogliomas: 1p19q co-deleted
Treatment Summary: Low Grade Gliomas

- **Surgery**
  - Maximal Safe Resection

- **Low Risk Patients**
  - Observation

- **High Risk Patients**
  - **Radiotherapy**
    - 45 – 54 Gy / 25 – 30 fx
  - **Chemotherapy**
    - Adjuvant PCV

**Histologies**

**Observation**

**ACRODeck: LGG**
Risk Stratification

**RTOG Risk Factors:** either one of these risk factors leads to a categorization of high risk
- Age greater than 40
- Subtotal resection

**EORTC (Pignatti Risk Factors):** need three of these risk factors for a categorization of high risk
- Age greater than 40
- Tumor that crosses midline
- Tumor size greater than 6 cm
- Astrocytoma histology
- Neurologic compromise prior to surgery

**Per NCCN, there are certain low risk histologies which can be observed** (even after an incomplete resection)
- Pilocytic Astrocytomas
- Pleomorphic Xanthoastrocytomas
- Subependymal Giant Cell Astrocytomas
- Gangliogliomas

NCCN utilizes the RTOG risk factors
Surgery

As with other gliomas, a maximal safe resection is indicated

- A gross total resection is prognostic for survival
- A simple biopsy has a high risk of underrating tumor grade, as gliomas tend to be quite heterogeneous

As these patients have a long natural history, doing no harm is of utmost importance!
Chemotherapy

- **Procarbazine, Lomustine (CCNU), and Vincristine (PCV): NCCN Category 1**
  - **Schedule:**
    - PCV is given as adjuvant treatment alone

<table>
<thead>
<tr>
<th>Chemotherapeutic Agent</th>
<th>Route of Administration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procarbazine</td>
<td>Oral</td>
<td>Nausea and Skin Reactions</td>
</tr>
<tr>
<td>Lomustine</td>
<td>Oral</td>
<td>Marrow Suppression</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Intravenous</td>
<td>Neurotoxicity</td>
</tr>
</tbody>
</table>

- **Temozolomide (TMZ):**
  - **Schedules:**
    - TMZ can be given as adjuvant treatment alone
    - It can also be given concurrently with radiation and adjuvantly
  - **It is administered orally**
  - **Side Effects:**
    - Thrombocytopenia, development of a rash, diarrhea/constipation, nausea, mouth sores, edema, and hair thinning
Radiation

Simulation
- CT head non-contrast
- Brain MRI with and without contrast
- Face mask

Volumes
- **GTV** = surgical bed + any T2 abnormality (include enhancement on the T1c MRI)
- **CTV** = standard expansion is 1 – 2 cm, cropped from natural barriers
- **PTV** = 3 – 5 mm

Doses
- There are a variety of dosing schedules based on EORTC and RTOG trials
  - 45 Gy / 25 fx
  - 50.4 Gy / 28 fx
  - 54 Gy / 30 fx

Most centers utilize a single volume; some prefer an SIB
# Selected CNS Dose Constraints

<table>
<thead>
<tr>
<th>Organ at Risk (OAR)</th>
<th>Dose Constraint (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic Nerves and Chiasm</td>
<td>Max &lt; 54 – 60</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Max &lt; 54 - 60</td>
</tr>
<tr>
<td>Cochlea</td>
<td>Mean &lt; 45</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Mean &lt; 45</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Max &lt; 16, $D_{100%}$ &lt; 9</td>
</tr>
</tbody>
</table>

PMID: 25701297
Modern radiation techniques (i.e., IMRT, VMAT, and protons) are often utilized to minimize toxicities.

Radiation Toxicities

- Acute:
  - Fatigue
  - Alopecia
  - Nausea
  - Skin erythema

- Chronic:
  - Swelling
  - Radionecrosis
  - Location-Dependent: for example, if tumor is near the cochlea, radiation can possibly lead to sensorineural hearing loss (see dose constraints on previous slide)
Prognosis

- Most LGGs have a prolonged natural history
  - However, some can progress and malignantly transform
  - The rate of malignant transformation is unaffected by receipt of radiation

- Per historical data, the median overall survival range is 10 - 15 years
  - Given that these studies did not incorporate modern molecular classifications, the median survival of patients with LGGs (particularly those with 1p/19q-codeleted tumors) may be around 20 years
Review
Review #1: The Correct MRI

What of the following MRI sequences allows for the best visualization of most low-grade gliomas?

(A) T1
(B) T1 + Contrast
(C) T2
Review #2: Risk Stratification

Which patient with a WHO grade 2 astrocytoma would radiation followed by adjuvant chemotherapy most strongly be recommended?

(A) 50-year-old with subtotal resection
(B) 4-year-old with subtotal resection
(C) 23-year-old with gross total resection
(D) 37-year-old with gross total resection
Review #3: Systemic Therapy

Which chemotherapy regimen is an NCCN Category 1 recommendation for patients with low-grade gliomas?

(A) Procarbazine, Irinotecan, and Carboplatin
(B) Procarbazine, Lomustine, and Vincristine
(C) Concurrent Temozolomide
(D) Concurrent and Adjuvant Temozolomide
Review #4: Radiation Dosing

Which of the following doses is appropriate for adjuvant treatment following a subtotal resection of a WHO grade 2 oligodendroglioma?

(A) 30.6 Gy
(B) 50.4 Gy
(C) 59.4 Gy
(D) 64.8 Gy
Review #5: Dose Constraints

Which of the following is a reasonable dose constraint to the highlighted structure (red star)?

(A) Mean < 45 Gy  
(B) Max < 54 Gy  
(C) V_{20} < 37%  
(D) Max < 70 Gy
Answer Key

1. C
2. A
3. B
4. B
5. B