Low Grade Glioma: Update in Treatment and Care

Nina A. Paleologos, MD
Division of Neuro-Oncology
Department of Neurological Sciences
Rush University Medical Center
Low Grade Glioma

- Overview
- Pathology
- Clinical characteristics
- Treatment
Low Grade Glioma: Grade I and II

• Grade II Astrocytoma: Most common type: Grade II.
• Grade II Oligodendroglioma: 8-20% of all primary CNS tumors.
• Grade II Mixed Oligoastrocytoma: with cells that look like both.

• Grade I: Pilocytic astrocytoma, pleomorphic xanthoastrocytoma (PXA), dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma: Most tend to be very slow growing.
Low Grade Glioma: Overview

• Arise from cells called glia, the supporting cells of the nervous system: astrocytes, oligodendrocytes primarily.
• Infiltrate/grow within the brain more slowly than higher grade gliomas.
• May evolve or transform into higher grades over time.
• Symptoms depend on location and size, but frequently patients may have few or mild symptoms. Seizures may occur but are usually controllable with medication.
Low Grade Glioma: Presentation

• Patients tend to be younger. Between 2\textsuperscript{nd} and 4\textsuperscript{th} decades of life
• Seizures are presenting symptom in 72- 89%
• Cognitive/mental status changes in 3-30%
• Signs of raised intracranial pressure, such as HA, nausea in 10-44%
• “Focal” symptoms, such as motor weakness, numbness, etc in 2-30%
• Many patients may have normal neurological examinations.
Low Grade Glioma: Diagnosis

- A thorough history and exam is important.
- MRI scan with and without contrast (gadolinium) is the best imaging test.
- Low grade gliomas do not tend to show leakage of gadolinium (enhancement) into the area of tumor, but some grade III tumors are also non-enhancing.
- High suspicion for a glioma may be deduced from the MRI scan. Cell type and grade must be determined by obtaining tissue.
- Tissue is obtained by either biopsy or resection of the tumor (most or partially).
Low Grade Glioma: MRI
Pathology: Grade is important
Oligodendroglioma

- Arises from oligodendrocytes
- 9.4% of all primary central nervous system tumors (8-25%)
- Median age of diagnosis – 41
- Males 75%
- 50% in frontal lobes
- 1p/19q deletions: predicts response to chemotherapy
- Many very indolent with long survival for many
Low grade Oligodendroglioma
Astrocytoma

• Fibrillary astrocytoma the most common type
• Most common LGG
• Not as responsive to chemotherapy on average than oligodendroglioma
• Most probably a bit more responsive to radiation therapy than chemotherapy
• Most common cell type for LGG located in the brainstem
Low grade Astrocytoma
Mixed Oligo-Astrocytoma

- Two main categories
  - Those with 1p and 19q deletions
    - Suggests oligodendrocyte lineage
    - Likely to behave like oligodendroglioma
  - Those with TP53 mutations
    - Suggests astrocyte lineage
    - Likely to behave like astrocytoma
Mixed Oligo-Astrocytoma

- Can have behavioral characteristics of both tumors
- Has the histologic characteristics of both tumors
- $1p/19q$ status helps
LGG: Molecular Markers

• Specific genetic markers helpful in dividing gliomas into subgroups with respect to prognosis and response to chemotherapy
• May help diagnostically
• **1p/19q Deletions**: 50-70% LG Oligodendroglial tumors
• Loss of 1p or both 1p/19q may predict chemosensitivity and predicts prolonged survival in LGO and LGOA
• There are patients that are deleted that do less well than most and there are some intact patients that do much better than most.
• **IDH 1 mutations**: 60-90% of LGG. Associated with improved survival.
• May help diagnostically differentiate: gliosis vs tumor or (in comb w BRAF) pilocytic tumors vs grade II astrocytoma
• We still do not know confidently if IDH 1 mutations should be used to direct treatment or, if so, how.
FISH: 1p and 19q deletions

1p deletion

19q deletion
LGG: Immunohistochemistry

- Ki-67 or MIB-1 Antibody: stain for proliferation related nuclear markers
- Provides prognostic information independent of grade and tumor location
- LG Astrocytomas: usually 1-2 %
- Some studies show that MIB-1/Ki-67 < or > 5% separates patients into low or high risk groups.
- Still some conflicting opinions on prognostic relevance of this in LGG.
- Still— if high would be concerning and perhaps question accuracy of the grade: Perhaps undergraded due to sampling.
LGG: Treatment

- Symptom Management
- Surgery
- Radiation Therapy
- Chemotherapy
- The Future
LGG: Symptom Management

- Seizures: Medications such as levetiracetam, lacosamide, topiramate, lamotrigine, and others such as phenytoin, carbamazepine, etc.
- Edema: Steroids, usually dexamethasone; however, long-term use has potential for side effects (skin changes, weight gain, muscle weakness, bone thinning, increased risk of infection, etc).
- Obstructive Hydrocephalus: may require surgery and perhaps placement of a “shunt” to bypass the blockage and lower the pressure.
LGG: Decision for Treatment

• Benefits of treatment should outweigh the risks of treatment.
• Risks of not treating also needs to be considered
• Optimal treatment of LGG and particularly the timing of treatment is controversial to some degree and is made on a case to case basis taking multiple factors into account
• Treatment decisions must balance the benefits of therapy against the potential for treatment related complications
LGG: Imaging Issues

- Slow growth over time is hard to see from scan to scan: you have to go back and review older scans.
- Slow response to chemotherapy is sometimes hard to see from scan to scan: you have to go back and review older scans.
- Delayed radiation change near or at the edge of the tumor may be difficult to differentiate from growth of tumor.
- A lack of increased perfusion or blood volume on perfusion imaging or a lack of “classic” spectra on MR Spectroscopy imaging does not rule out a LGG.
LGG: Treatment Options

• “Watchful waiting” with serial MRI
  – Deferring treatment until progression
  – Appropriate for some low grade tumors
  – Appropriate for some who have had large or “gross total” resection
• Surgery
  – If technically feasible with goal of preservation of neurologic function
• Radiation Therapy
• Chemotherapy
LGG: Why treat?

- Progressively infiltrate brain causing increasing neurologic disability
- Symptoms: seizures, cognitive, focal
- Ultimately progress in size and transform in grade to more anaplastic forms
LGG: Surgery/Resection

- LGG grow into normal brain often with no distinct boundary between the tumor and normal tissue.
- Inevitably some normal brain cells are removed and even in “Gross Total Resection” some tumor cells remain.
- The remaining tumor cells continue to grow, eventually causing additional damage and symptoms.
- Therefore surgery rarely results in a cure.
- However, especially with “gross total resection” or close to it: long term control/survival may be accomplished.
LGG: Risks of Resection

• Standard risks
  – Infection, bleeding, anesthesia complications, medical complications
• Stroke/Neurological deficit
  – Solid vs. diffuse tumors
  – Proximity to eloquent areas
  – Tumor surrounding important blood vessels
• Seizures
• Spinal fluid leakage
LGG: Why Surgery?

- Verification of diagnosis
- Relief of signs/symptoms/mass effect
- Cytoreduction to improve outcome
- Allows lower steroid dose
- Reduces sampling errors encountered with biopsy alone
- If technically feasible with a goal of preservation of neurologic function
- Extent of resection is an independent variable associated with survival
- Some patients benefit from reoperation at time of tumor recurrence
LGG Surgery/Resection: Timing

• Early surgery at time of diagnosis: This recommendation based on studies suggesting that patients undergoing early surgery survive longer, possibly because the tumor is less likely to change into a more aggressive form—there are fewer cells available for that and fewer cells to divide.

• Delayed surgery with observation until tumor grows or symptoms worsen: This recommendation is based on slow growth, possibility that surgery may cause more symptoms than the tumor itself (at least at that time), and with careful frequent observation, delayed surgery in some cases may be just as beneficial.

• No resection: Biopsy only in cases where resection would be too risky—tumor in critical/eloquent brain.
Surgery: Technical advances

- Increased ability to resect tumor from eloquent brain with reduced morbidity
- fMRI to identify eloquent cortical areas
- DTI to identify white matter pathways
- Awake craniotomy with cortical mapping and stimulation
- May facilitate more complete and safer resection in pts with tumors in or near eloquent areas of brain
Surgery

DTI and Functional MRI (Language)
Surgery
Functional Mapping and Cortical Stimulation
LGG: Post op: When Should We Treat?
Timing controversial in pts with low grade tumors

• **Defer Treatment**
  - After large or GTR
  - Minimal disease
  - No enhancement
  - Sz controlled
  - Few or no Sx
  - Younger age

• **Treat**
  - Suspicion: ? Higher grade
  - Progressing LG
  - Enhancement
  - Mass effect
  - Symptomatic
  - > age 40
  - Surgery not indicated or significant residual and Rx necessary
LGG: Radiation Therapy

• Became a cornerstone of therapy many yrs ago
• Oligodendrogliomas, Astroctomas, Mixed OA all respond
• Proton beam thought to decrease risk to normal brain however efficacy has not been compared to standard external beam with margins. Risk is under treating the margins
• Stereotactic: Not usually indicated. Focused to small area, but these tumors are infiltrative and “spread out”
• RT may not always be best initial choice: Chemotherapy may be the 1st choice for some pts, particularly with Oligodendroglionioma or Mixed OA whose tumors show 1p/19q deletions— deferring treatment with RT
LGG: Why Radiation?

- Improves time to tumor progression
- Several studies show improved survival in patients with progressing or aggressive tumors
- No systemic side effects
- Defined treatment time
LGG: Why not radiation therapy?

- No clear evidence of improved survival with immediate post op RT vs delayed RT
- Delayed radiation induced neurotoxicity
- RT vs no RT
  - Perform worse on cognitive tests
  - Have lower Karnofsky score
  - Not accounted for by histology, location, extent of removal, progression

Surm-aho et al, 2001
Delayed Radiation Encephalopathy
LGG: Radiation Therapy

• Standard approach
  – Administered 5d/wk over 5 -6 wks
  – Ports encompasses T2-weighted/FLAIR abnormality with 1-3 cm margin
  – Dose for low grade tumors: ~5400 cGy
  – Dosing calculated to maximize killing tumor cells and to minimize damage to normal brain cells
LGG: Early Radiation Therapy

- RT of benefit
  - Gannett et al, 1994
  - Wallner et al, 1988
  - Mork et al, 1985

- RT of no benefit
  - Shaw et al, 1992
  - Bullard et al, 1997
  - Nijjar et al, 1993

- RT of benefit in some, but not all
  - Mork et al, 1985: not in pts with GTR
  - Celli et al, 1994: not in pts with indolent tumors; seizures only, nl neuro status
LGG: Radiation Therapy

- Low grade glioma: EORTC 22845 (2005)
  - Early RT (after diagnosis/surgery) vs RT at progression
  - Modest improvement in TTP
  - No effect on survival
  - Trial not specific to cell type
- Effective but has delayed consequences: primarily risk of cognitive decline unrelated to tumor
- Subsets for whom it is prudent to defer
- Almost all patients will ultimately receive RT at some point.
LGG: Why Chemotherapy?

- Spares the normal tissue of the brain the delayed effect of RT
- Some low grade gliomas are quite large → meaning larger radiation ports resulting in larger areas of normal brain exposed to RT
- Some low grade gliomas; particularly ones with 1p/19q deletions are particularly sensitive
LGG: Why not Chemotherapy?

- Responses disappointing in some low grade gliomas; particularly those without 1p or 1p/19q deletions
- Prolonged treatment
- Systemic (body) toxicity
- Quality of life over time
LGG: Chemotherapy

• Many/most low grade Oligodendrogliomas respond to chemotherapy; sometimes dramatically and for prolonged periods
• Clinical improvement, decreased sz even in patients without obvious improvement on MRI
• PCV (procarbazine, CCNU, vincristine)
• Temozolomide
• Length of treatment? Clearer with PCV than TMZ but PCV more toxic
• 1p/19q loss predicts response- in almost all pts
• Pts with 1p/19q intact LGO, LGOA, LGA less likely to respond to chemotherapy; may be better served by RT if/when they need treatment
LGG Oligodendroglioma 1p/19q deleted
6 cycles of Temozolomide
LGG: Chemotherapy Risks/Toxicity

- Myelosuppression: acute, chronic, delayed
- Other organ toxicities
- Quality of life
- Toxicity of PCV significant and dose limiting
- Temozolomide significantly less toxic
  - Length of treatment & response rate need to be defined
LGG: Chemotherapy: 1p/19q deleted

• Reasonable to recommend protracted treatment
  – Responses are slow over multiple cycles. May not be seen from scan to scan
  – Tolerability of TMZ is excellent
  – Long term or delayed toxicity? So far not significant.
  – PCV benefit/risk ratio being re examined
• Frequent and careful monitoring with serial neuroimaging required
• Some patients respond clinically (decreased sz, improved cognition, language, etc) even without significant change in the MRI
• Reasonable treatment option allowing deferral of RT
LGG: RT vs Chemotherapy

• Both are reasonable options
• There are no completed controlled trials comparing these two treatment modalities
• Histopathology matters
• Molecular analysis may help to decide which might be best
• EORTC 22033-26033 Trial: RT vs Temozolomide. Completed accrual in 2010. Results pending. 1p status used as stratification factor.
• ECOG E3F05 Trial: RT vs RT + daily TMZ followed by 12 cycle of std TMZ. Opened 2009. 1p/19q deletions used as stratification factor.
LGG: New Therapies

• Most clinical trials are in high grade astrocytomas
• Many therapies may be useful in low grade gliomas as well
• Targeted therapies
• Angiogenesis inhibitors may not be as helpful in low grade tumors as in high grade tumors
Targeted Therapy

- Glioma cells express receptors for several different growth factors
- PDGF, VEGF, EGF
- Targeted therapies aim to inhibit these growth factor receptors and their tyrosine kinase based intracellular signaling pathways
- Agents bind to cell surface receptors and either compete w/ or block the normal substrates from binding or bind directly to the growth factor
- In tumors dependent on such pathways for growth, the use of these agents can potentially result in tumor cell death
LGG: Genetics—Where Do We Go?

• What are the specific tumor suppressor genes located on 1p and 19q?
• What do they code for?
• Is 1p/19q an epiphenomenon?
• IDH1 mutation: we need to know more
• What are the other factors?
• Stratification needed in all studies
  – When and how should 1p/19q be used to determine treatment?
  – IDH1, others?
• 1p/19q testing in tumors with oligodendroglial elements has become standard
• IDH 1 mutation testing not yet standard everywhere
Thank you

• To the ABTA
  – for all the good work they do
• To my patients and their families
  – They are the bravest people I know
• To everyone here today for their time and attention
THANK YOU
Any Questions?

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