Management of Low Grade Gliomas

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WHO Grading System (evolves)

Low-grade

- WHO Grade I i.e., Juvenile Pilocytic Astrocytoma

- WHO Grade II i.e., Diffuse Astrocytoma

High-grade

- WHO Grade III i.e., Anaplastic Astrocytoma
- WHO Grade IV i.e., Glioblastoma Multiforme

WHO Grading :

WHO grade I – low proliferative potential. Possible cure with surgery alone

WHO grade II – infiltrating, but low in mitotic activity. Can recur and progress to other grades

WHO grade III – Histologic evidence of malignancy (mitotic activity), infiltrative, anaplastic

WHO grade IV – mitotically active, necrosis, rapid pre and post-surgical progression

LOW GRADE GLIOMA

- A glioma is a primary brain tumor that originates from the supportive cells of the brain, called glial cells.
- Three types of glial cells are there, from which gliomas arise.
 - Astrocytes: Astrocytoma
 - Oligodendrocytes: Oligodendroglioma
 - Ependymal cells: Ependymoma

Introduction

- Slower growing than high grade counter parts
- 10-20% of all primary brain tumors
- Median survival between 4.7 to 9.8 years
- Goal Prolong OS while maintaining good quality of life.

Central Nervous System Glial Tumors (who glial tumor classification)

- Astrocytic tumors
- Diffusely infiltrating astrocytomas
- Diffuse astrocytoma
- Anaplastic astrocytoma
- Pleomorphic astrocytoma
- Glioblastoma
- Giant cell glioblastoma
- Gliosarcoma
- Pilocytic astrocytoma
- Pleomorphic xanthoastrocytoma

Ependymal tumors

- Ependymoma
- Anaplastic ependymoma
 - Myxopapillary ependymoma
 - Subependymoma
 - Choroid plexus tumors
- Neuroepithelial tumors of uncertain origin
- Astroblastoma
- Chordoid glioma of the third ventricle
- Gliomatosis cerebri

- Oligodendroglial tumors and mixed gliomas
- Oligodendroglioma
- Anaplastic oligodendroglioma
- Oligoastrocytoma
- Anaplastic oligoastrocytoma

Diffuse astrocytomas

- Most common LGG
- Peak ~ mid-30s
- Survival highly variable, average ~ 7 yrs
- Three types-gemistocytic, fibrillary, protoplasmic
- Typically, slow clinical/radiographic progression initially
 - Usually speeds & eventually progresses to ~ HGGs



Oligodendrogliomas

- Peak incidence in 4th to 5th decade
- Survival highly variable, but ~ 10 yrs
- Most common site is frontal lobe
- Typically, seizures & often calcifications
- Typically, better outcome than other LGGs
 - Especially with 1p/1q co-deletions
- Typically, more responsive to chemotherapy
 - Especially with 1p/1q co-deletions



Pilocytic astrocytomas

- Most common primary brain tumor in children, Typically, < 25 years
- In cerebellar hemispheres & around 3rd ventricle



- Cystic, well-demarcated, and contrastenhancing
- Substantially better outcome than other LGGs
- Can be cured by resection

Other subtypes

- Gangliogliomas
 - Typically, in temporal lobe
 - Typically, seizures
 - History and outcome similar to pilocytic astrocytomas
- Ependymomas
 - Typically, occur in young
 - Typically, around 4th ventricle
 - More variable outcome
 - impacted by age, extent of resection, histology
- Other rare LGGs
 - Pleomorphic xanthoastrocytomas
 - Subependymomas
 - Desmoplastic gangliogliomas

Treatment

Multidisciplinary Care Team

Definite Management

- Neurosurgeon
- Radiation Oncologist
- Medical Oncologist
- Pathologist
- Radiologist

Supportive Management

- Psychiatrists
- Genetic counselors
- Nutritionists
- Palliative & symptom care specialists
- Nurses
- Social workers

Tumor & Supportive Treatment

Goals:

- Prolong overall survival
- Prolong progression-free survival
- Promote quality of life (QOL)
 - Improve, maintain, slow the decline
- Promote neurologic function
 - Improve, maintain, slow the decline
- Minimize treatment-related effects
 - Prevent, minimize, delay the onset, improve

Tumor Treatment Options

• Maximal safe resection

Radiation

• Chemotherapy

Observation

The decision to Observe a patient with low-grade glioma has been justified in the literature for several reasons. These reasons include the relatively favorable natural history of the disease, the lack of proven benefit for invasive interventions such as surgical resection or radiation therapy, and the potential morbidities of treatment.

Patients who are observed should be monitored at regular intervals (e.g., every 6 months) to detect radiologic progression before new signs and symptoms occur. ✤ Despite the favorable survival rates observed in certain subsets of patients with low-grade gliomas, the natural history of all pathologic types of supratentorial low-grade gliomas, including the pilocytic astrocytomas (WHO I), diffuse astrocytomas, oligoastrocytomas, and oligodendrogliomas (WHO II), is significantly worse than that of an age- and sex matched control population, for which the expected survival rate is greater than 95%.

Sased on this observation, some have argued that all such patients should undergo Maximal Safe Surgical Resection followed by postoperative radiation therapy.



Surgery vs. Observation

Pros:

i)If symptoms are uncontrolled medically, then benefits of surgery on seizures / raised ICT are fairly dramatic
ii)Imaging can be misleading in upto 40% cases
iii)Early Surgery delays reappearance of symptoms and tumor growth
iv)Survival advantage to gross resection in retrospective literature

***** Cons:

i)Possibility of complications in a minimally symptomatic person

Maximal Safe Resection

Surgery is the mainstay of treatment:

Goals of surgery :

- Establish a tissue diagnosis.
- Removal of as much tumor as possible without increasing the neurologic deficit.
- Removal of an epileptogenic focus if present.

Surgery Cont'd

• Timing

- Immediately, if a large mass or extensive symptoms
- Delayed, if small mass or minimal symptoms
- Subsequent resection, if concern for progressive mass or symptoms
- Extent of resection
 - Maximal safe resection when feasible, especially if symptomatic or presumed diagnosis is unclear
 - Biopsy when resection not feasible, if minimal symptoms, if presumed to be LGG
- No prospective randomized trials

Complete resection is achieved in approximately 80% of cerebral, cerebellar, and spinal-cord tumors and 40% of diencephalic tumors.

In case of **smaller tumors** & **non eloquent part** of brain, usually tumors are completely resectable.

Resectability

- In fact, resectability is a complex concept that is a frequent subject of disagreement between surgeons
- Factors influencing rates of resection include pt-related (age, KPS, marital status); tumorrelated (size, location, fuzziness of borders) and provider-related (specialist status, volume of practice, training and experience, economic and professional incentives)
- Resectable and nonresectable tumors may well have different molecular pathology

Resectability

- Eloquent / noneloquent
 - Eloquent areas: sensorimotor, visual, language cortices, internal capsule, basal ganglia

Grade I: Noneloquent Brain	Grade II: Near- eloquent Brain ^a	Grade III: Eloquent Brain
Frontal or temporal polar lesion	Near motor or sensory cortex	Motor/sensory cortex
	Near calcarine fissure	Visual center
Right parieto- occipital lesions	Near speech center	Speech center
	Corpus callosum	Internal capsule
Cerebellar	Near dentate nucleus	Basal ganglia
hemisphere lesions	Near brain stem	Hypothalamus/ thalamus
		Brain stem
		Dentate nucleus

imaging scans, includes tumors in the supplementary motor area.

Radiation (RT)

Role of radiotherapy as adjuvant

therapy

• Patient selection for and the timing and dose of postoperative irradiation are controversial issues.

• Major concerns are:

□<u>No improvement of overall survival</u>

Though progressive disease free survival is appreciated

□Incidence is high among Young age population

Ineurocognitive decline , dementia , behavioural changes, vasculopathy, development of 2nd malignancy are very high in postRT young patient as RT causes disruption of myelination and cortical atrophy.

Gradual decline of IQ over time.

Radiation (RT), Cont'd

- Timing
 - Immediate, if significant mass or symptoms
 - especially if only biopsy or presence of <u>"high-risk"</u> <u>features</u>
 - Delayed, if minimal mass or symptoms
 - including after resection
 - Subsequent RT, rarely performed
 - i.e., unless recurrence/progression is in new location
- Extent
 - Typically conforming to within 1-2.5 cm of abnormality
 - Typically ~54 Gy, external beam, fractionated, in six weeks

EORTC 22845

✤311 patients (WHO 1-2, 51% astro., 14% oligo., 13%mixed oligo-astro)

✤ Treated with surgery (42% GTR, 19% STR,

35% biopsy)

Randomized to observation vs. post-op RT to 54 Gy.

RT improved median **PFS** (5.3 year vs. 3.4 year), 5-year **PFS** (55 vs. 35 %), but not **OS** (68 vs. 66%).

- No difference in rate of malignant transformation (66– 72%).
- No survival benefit, but RT delays time to relapse by ~2 years

EORTC 22844

✤343 patients (WHO 1-2, astro., oligo. and mixed) treated with surgery (25% GTR, 30% STR, 40% biopsy)

✤Randomized to post-op RT 45 Gy vs. 59.4 Gy radiation therapy using multiple localized treatment fields.

✤Initial analysis failed to demonstrate a difference in survival rates between the two doses. The 5-year OS was 58% with 45 Gy and 59% with 59.4 Gy.

✤Five-year OS oligo vs. astro = 75 vs. 55%,

<40 year vs. >40 year = 80 vs. 60%.

Age <40 year, oligo histology, low T-stage, GTR, and good neurologic status are important prognostic factors

INT/NCCTG

✤203 patients (WHO 1-2, astro, oligo, mixed) treated with surgery (14% GTR, 35% STR, 51% Bx) randomized to post-op RT 50.4 Gy vs. 64.8 Gy

Initial analysis also failed to demonstrate a difference in survival rates between the two doses. The 5-year OS was 73% with 50.4 Gy and 68% with 64.8 Gy.

◆Best survival in patients <40 year, tumor <5 cm, oligo histology and GTR.

✤Pattern of failure: 92% in field, 3% within 2 cm of RT field.

INDICATION OF ADJUVANT RT

- **1.Tumor progression**
- **2.**Compromise neurologic function
- 3.Unresectable (NOT SUITABLE FOR 2ND LOOK SURGERY)

Dose of ADJ. RT:

 Consequently, low-dose radiotherapy, 50.4 Gy-54 Gy in 1.8 Gy-2Gy per fractions, has become an accepted practice for patients with low-grade gliomas.

Radiotherapy planning

- **Midcerebral tumors** crossing the midline are treated with parallel-opposed bilateral portals,
- Posterior parietal or occipital lesions can be treated with posterior and lateral beams (may be wedged for dose homogenization)
- Brainstem lesions are adequately treated with parallel-opposed lateral portals which may be combined with a posterior midline portal that does not irradiate the eyes.
- Unilateral cerebellar lesions can be covered by appropriately wedged posterior and lateral portals.

Role of IMRT

<u>Advantages</u>

- In complex tumor structure
- > In odd location like temporal region
- ➤ to increase conformality
- ➤ to better spare the normal tissue

Disadvantages

- ✓ Low grade glioma admixed with normal tissue, it results in dose heterogeneity.
- \checkmark There will be heterogeneity of 10% or more in the target.
- This increased heterogeneity results in an increased daily dose per fraction and an increased biologically equivalent dose approaching towards high-dose which increases the risk of radiation necrosis.

Cranio-spinal RT



• To cover the clinical target volume for craniospinal irradiation, lateral opposed fields are used to treat the brain and a direct posterior field is used to cover the spinal axis.

Cranio Spinal Irradiation

- Currently only CSF seeding proven by MRI or CSF study is candidate for CSI.
- Coverage of entire target volume that includes the meninges overlying the brain and spine including the extensions along the nerve roots is critical

Treatment dose:

- Improved tumor control is seen with dose of >45 to 50 GY upto 54 GY.
- patients with neuraxis spread shold receive CSI (40 to 45 GY) with boost to the areas of gross disease and to the primary tumor site upto 54 GY.
- Current standard of treatment in children > 18 months / supra-infratentorial tumors Dose is upto 54 GY.

Chemotherapy

- Most of the data extrapolated from the treatment of high grade gliomas
- Chemotherapy increases PFS, but not OS
- Controversy regarding
 - Ideal chemotherapy agent
 - Ideal time of administration
 - Optimal duration of chemotherapy treatment

- Ideal chemotherapy agent
 - PCV vs TMZ
 - PCV- intravenous, hematopoietic toxicity
 - TMZ-better tolerated, easy to administer
- Ideal time of administration
 - During RT, adjuvant to RT, or at progression
- Optimal duration of chemotherapy treatment
 - 6-12 cycles

Supportive Management

- Anti convulsants(may be given prophylactically)
- Steroid (dexamethasone) to decrease the vasogenic oedema
- CSF diversion procedure- VP shunt
- Mangement of side effects- myelo-suppression, infection, fatigue, neuro-cognitive
 Extraordinarily Important!

Prognostic factors

EORTC trials 22844 & 22845

- High risk factors
 - Age >40
 - Astrocytoma histology
 - Presence of neurological deficits before surgery
 - Tumor diameter 6 cm or greater
 - Tumor crossing midline
- Favorable prognostic score- 2 or less
 - Median survival 7 years
- High risk- 3 or more factors
 - Median survival 3.2 years

EORTC/RTOG and NCCTG

- Worse baseline neurological status
- Shorter time since first symptoms (<30 weeks)
- Astrocytic histology
- Tumor size > 5cm in diameter

Age did not show prognostic importance

Chang et al

- Tumor size > 4 cm
- Eloquent tumor location
- Age > 50
- KPS below 80

Total score was inversely proportional to predicted survival

Hartmann et al

- 1p/19q chromosomal codeletion
- Isocitrate dehydrogenase 1 (IDH 1)

Presence was associated with prolonged PFS and OS

•Most of the low grade gliomas present with seizure

• Seizures are associated with a better survival

Recurrence

Treatment at Recurrence/Progression

- Controversy over true tumor progression vs. pseudoprogression (aka: treatment effect, radiation-necrosis)
- Single or multimodality combinations of re-resection, radiation, and chemotherapy are all used
- Highly individualized
 - Goals & preferences, age, overall health, etc.!

Role of SRS in recurrent/unresectable tumors

SRS is usually used

- in boosting after RT for residual tumor in early post-operative period
- salvage treatment at the time of recurrence.
- SRS following pathological diagnosis for tumors located in eloquent areas & unresectable tumors.(but dose reduction is necessary to avoid increased normal tissue dose and thus compromising tumor control.)

Our Future

Future Improvements Needed!

- Areas of remaining controversy include:
- Extent of resection
- Timing of RT +/- chemo
 - Upfront or at recurrence/progression
 - Immediate surgical intervention versus a delayed intervention in patients with limited disease and symptoms
- Role of chemotherapy
 - Are newer chemos really safer and more effective?
- Importance of treating different LGG subtypes differently
 - Molecular/genetic profile, etc.
- QOL, neurological performance status

To revise

Recommended Treatment

 Juvenile Pilocytic Astrocytoma, Subependymal Giant Cell Astrocytoma, Pleomorphic Xanthoastrocytoma,
 Dysembryoblastic Neuroepithelial tumor :

i) Gross Total Resection \rightarrow Observation

ii) Sub Total Resection → consider Observation
 vs. Re-resection
 vs. Radiotherapy
 vs. Stereotactic Radiosurgery,
 depending on the location of tumor, symptoms, age of patient

Oligodendroglioma, Oligoastrocytoma, Astrocytoma (adults) :

 Maximal safe resection (GTR or STR) →
 Observation if - age <40 years, oligodendroglioma, GTR, good function
 Serial MRIs - if progresses → Radiotherapy 50-54 Gy (standard dose for low-grade gliomas is 54 Gy)

Or,

 ii) Immediate Post-operative Radiothrapy to 54 Gy. No survival benefit, but RT delays time to relapse by ~2 years (EORTC study)
 Quality of life gained by delaying recurrence must be weighted against QOL lost due to late toxicities of RT Oligodendroglioma, Oligoastrocytoma, Astrocytoma (children) :

- Maximal safe resection (GTR or STR) →
 Observation and serial MRIs.
 Adjuvant Radiotherapy may improve DFS, but not recommended for children <3 years.
- ii) Consider Second Surgery for operable progression, and Radiotherapy for inoperable progression (doses 45-54 Gy)

***** Dose : EBRT: 1.8 Gy/fx to 50.4–54 Gy.

Volume of Treatment :

Pilocytic Astrocytomas

GTV: contrast-enhancing lesion and any associated cyst

PTV: GTV plus 1-1.5 cm

Infiltrating Low-Grade Gliomas

GTV: (FLAIR)/T2 abnormality and any contrast enhancement PTV: GTV plus 1–1.5 cm

✤ Follow Up :

MRI 2–6 weeks after Radiotherapy, then every 6 month for 5 years, then annually.

 ✓ Surgery is the mainstay of treatment.
 ✓ Complete resection is achieved in approximately 80% of cerebral, cerebellar, and spinal-cord tumors and 40% of diencephalic tumors

 ✓ Residual tumor of 1 cm or more according to MR imaging is found to be predictive of a poorer PFS

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 ✓ Complete resection is achieved in approximately 80% of cerebral, cerebellar, and spinal-cord tumors and 40% of diencephalic tumors

 ✓ Residual tumor of 1 cm or more according to MR imaging is found to be predictive of a poorer PFS

- ✓ Indications of RT :1.Tumor progression ,2.Compromise neurologic function
 3.Unresectable (NOT SUITABLE FOR 2ND LOOK SURGERY
- ✓ low-dose radiotherapy, 50.4 Gy-54 Gy in 1.8 Gy-2Gy per fractions, has become an accepted practice for patients with low-grade gliomas

✓ Chemotherapy has no proven benefits.

- CSI has a doubtful role in routine prescription.
 Definite indication is csf seeding proven by imaging or CSF study
- Current standard of treatment in children > 18 months / supra-infratentorial tumors Dose is upto 54 GY.

Lets shift our focus.....

The PERSON with cancer Versus The person with CANCER

A small difference with BIG EFFECT....

