ARRO Case: Low Grade Glioma (LGG)

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Case

- **44F presents with new onset seizure**
  - First seizure of life 5 months prior to presentation. Ongoing seizures 1-2x/month since onset. No health insurance so did not immediately seek medical evaluation.
    - Seizures occur at night, generalized tonic-clonic with loss of bladder function and occasional tongue lacerations
  - History of chronic frontal headaches for years with no recent change in quality or severity
  - No other neurologic symptoms

Physical Examination

- Karnofsky Performance Status (KPS) 80, Eastern Cooperative Oncology Group (ECOG) 1

- Neurologic exam:
  - Alert and oriented to person, place, time
  - Speech fluent
  - CN II-XII intact bilaterally
  - Motor 5/5 all extremities
  - Sensation to light touch intact
  - No dysdiadochokinesia
  - Normal heel-to-shin and finger-to-nose test
  - Tandem, heel walk, toe walk, and normal gait
  - Negative Romberg

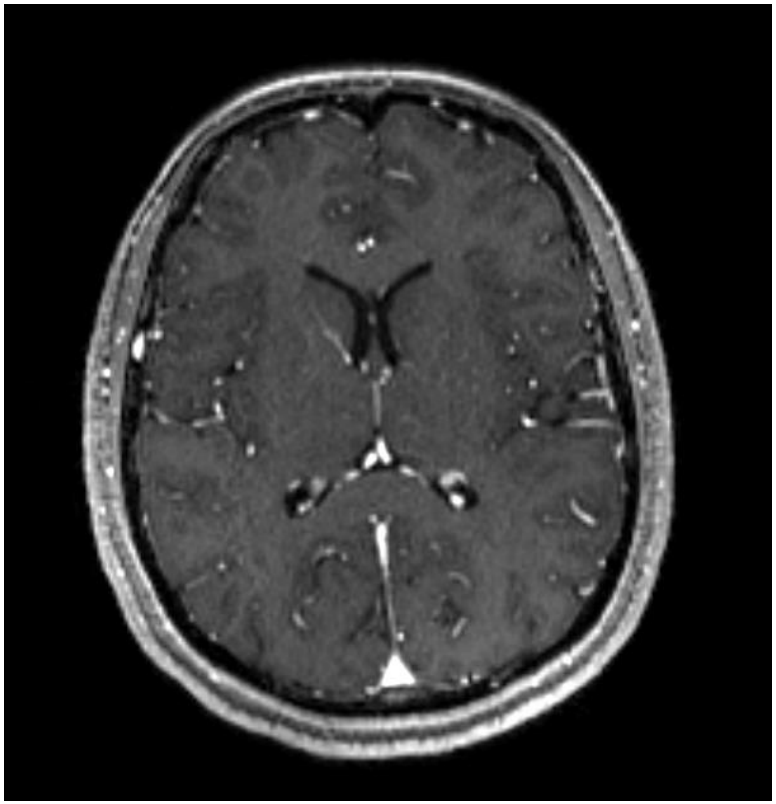
Workup

- Labs:
  - Hgb: 9.8
  - Hct: 30
  - WBC: 12.4
- EEG: normal
- Imaging
  - CT
    - LGG typically demonstrates ill-defined, diffuse, non-enhancing low-density region
    - Enhancement less common in LGG than high grade glioma (HGG) (21% vs. 57-96%)
    - Exception is pilocytic astrocytomas

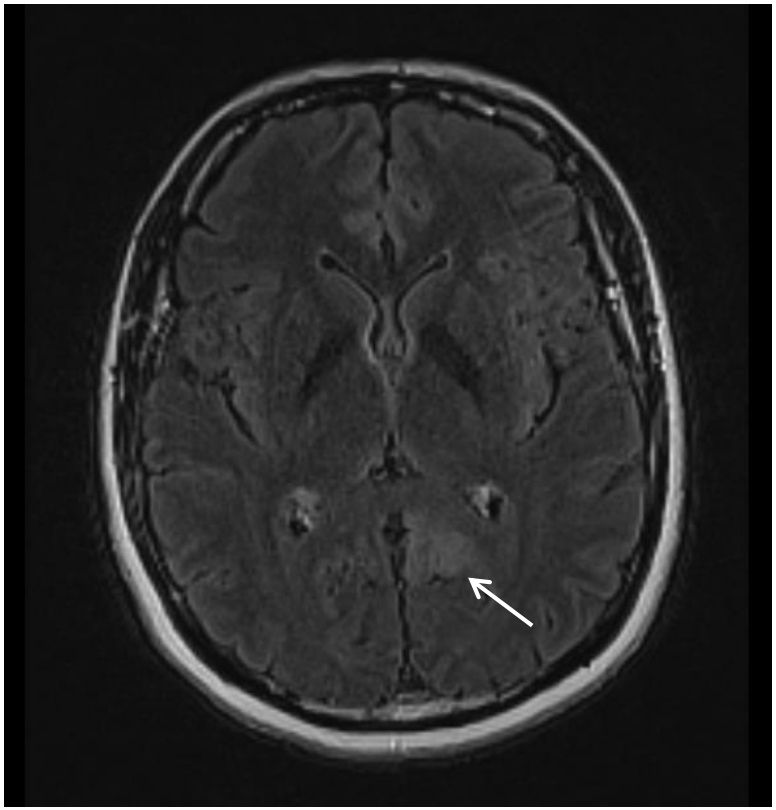
Imaging

- MRI is study of choice
  - T1 - Hypointense and non-enhancing
  - T2 - Hyperintense
  - Ill-defined tumor margins, best seen on T2-weighted MRI or FLAIR images
  - Calcification up to 20% of astrocytomas and up to 90% of oligodendrogliomas
  - Mass effect, rim enhancement or vasogenic edema uncommon

MRI Images



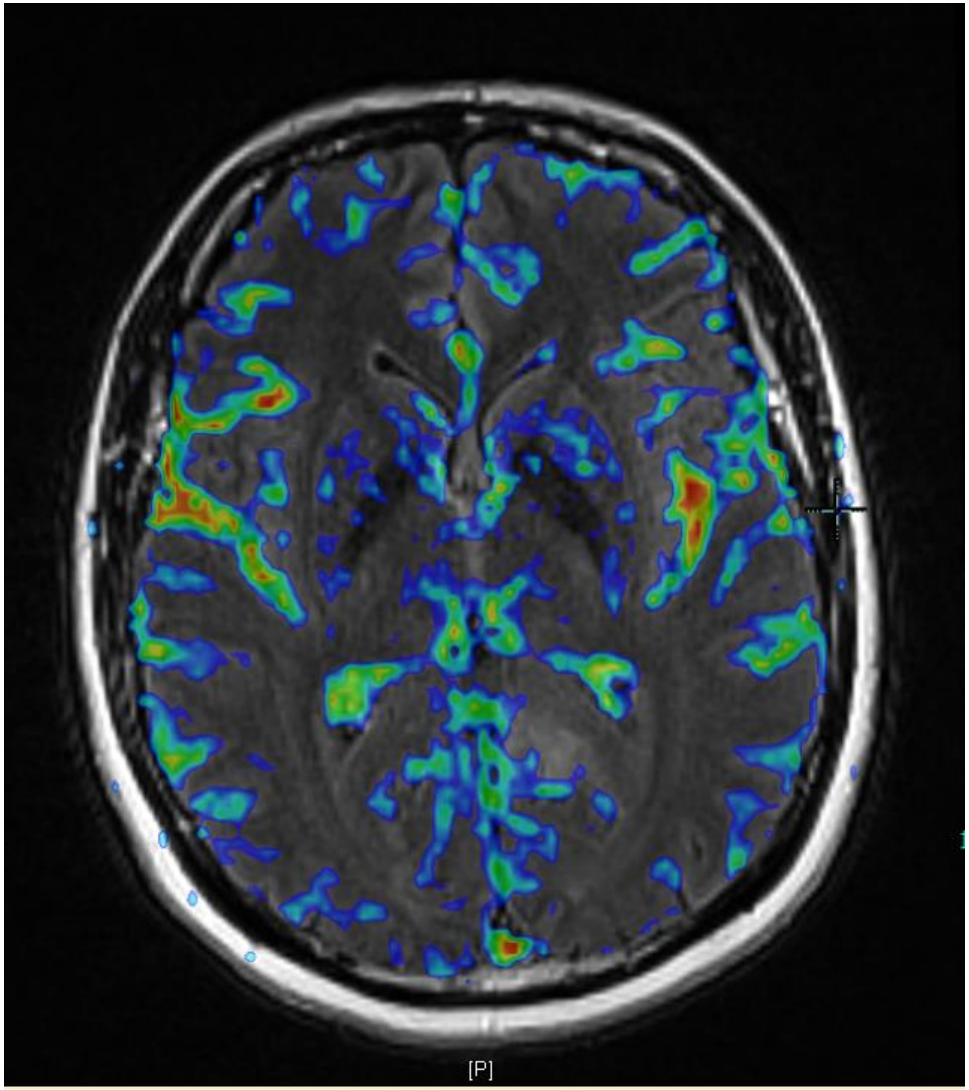
T1 post contrast imaging



T2 flair imaging

Findings: Left parietal lobe and left parieto-occipital region 2.3 x 2.0 x 1.8 cm mass with effacement of sulcus. No mass effect, midline shift or extra-axial collection.

MRI rCBV



Findings:

No associated elevated rCBV and overall unremarkable MR spectroscopy. Overall imaging findings favor a low-grade process, favor low-grade glioma.

Surgical Resection

- Left parietal craniotomy and inter-hemispheric microsurgical approach
- Stereotactic neuro-navigation was utilized for surgical resection due to proximity to corpus callosum
- Near total resection
- **Final Diagnosis:**
  - Infiltrating glioma, WHO grade II most consistent with **diffuse astrocytoma, IDH-mutant**

Low-Grade Glioma (LGG)

- 10-15% of primary intracranial tumors
- ~2000 LGG diagnosed in US per year
- Predominantly affect young adults
  - WHO grade II tumors present most commonly during fourth decade of life

LGG

- Gliomas represent a heterogeneous group of tumors with characteristics of neuroglial cells. Traditionally classified by The World Health Organization (WHO) into four grades based on histopathological features:
  - Atypia, Mitoses, Endothelial proliferation, Necrosis (MEAN)

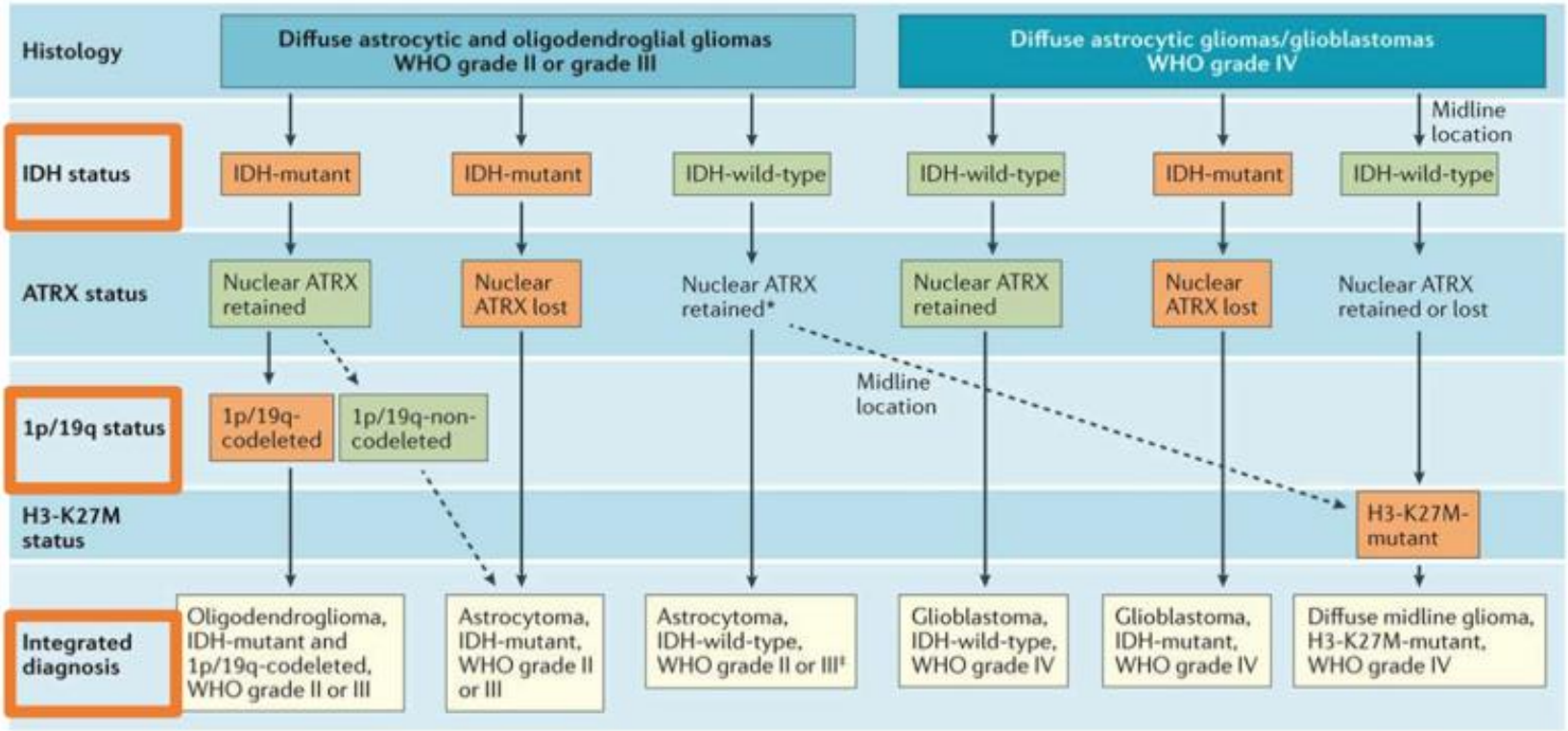
- LGG classically defined as WHO grade I (non-infiltrative) or WHO grade II (infiltrative/diffuse) tumors
  - Much of the evidence that supports current treatment paradigms is based upon this classification
  - Recently, a better understanding of molecular diagnostic markers is challenging our prior assumptions concerning definition of LGG

LGG Classification

- In 2016, WHO incorporated molecular parameters into classification of CNS tumor entities
  - Prognosis more closely associated with molecular diagnosis than with morphology, but grade remains prognostically important
- *Will focus mainly on diffuse WHO grade II gliomas here (both astrocytic and oligodendroglial histological types) in adults, as pediatric LGG exhibit different molecular alterations, clinical course, treatment*
- Diagnostic evaluation of LGG must now include a molecular assessment of isocitrate dehydrogenase (IDH) mutations and if needed, codeletion of chromosome arms 1p and 19q to be considered complete

WHO 2016 Classification

(LGG any grade II)



Nature Reviews | Clinical Oncology

*Note: cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO) was established to provide possible guidelines for practice between WHO updates and to facilitate future WHO classification updates

Louis, D.N., Perry, A., Reifenberger, G. et al. Acta Neuropathol (2016) 131: 803.

IDH1/IDH2 mutations

- Present in majority of WHO grade II gliomas, favorable prognosis with significantly longer OS compared to IDH-wildtype and predictive biomarker for chemotherapy benefit

- Likely one of the earlier genetic aberrations that occur during development of glioma

- Emerging evidence suggests patients with IDH-mutated grade II glioma are more likely to have seizures at presentation
  - IDH1 mutation causes increased production of D-2-hydroxyglutarate, an analogue of glutamate, an excitatory neurotransmitter
  - Treatment reduces tumor burden and can reduce frequency of seizures

1p19q Codeletion

- Defining feature of oligodendroglioma
- Prognostic biomarker associated with improved survival
- Predictive value for response to chemotherapy procarbazine/lomustine/vincristine (PCV)

ATRX mutation

- Characteristic of IDH-mutated astrocytomas and mutually exclusive from 1p19q codeletion
- Less favorable prognosis than 1p19q codeletion
- Associated with p53 mutation suggesting ATRX may drive lineage-specific formation of astrocytoma

Summary Glioma Molecular Classification

- Oligodendroglioma
  - IDH mutated
  - 1p19q codeleted
- Astrocytoma
  - IDH mutated
  - 1p19q intact
- LGG with IDH wildtype
  - Subset are molecular GBM (EGFR amp, +7/-10, TERT)

Key Trials

- NCCTG/RTOG/ECOG
- EORTC 22844 “Believers Trial”
- EORTC 22845 “Non-Believers Trial”
- RTOG 9802
- EORTC 22033-26033
- RTOG 0424

NCCTG/RTOG/ECOG

- Randomized LGG patients (95% grade 2) after surgery to 50.4 Gy in 28 fx vs. 64.8 Gy in 36 fx
  - **No difference in 5-yr OS with higher rate of radiation necrosis in high dose arm (5% vs. 2%)**

EORTC 22844 "Believers Trial"

- Randomized LGG patients after surgery to 45 Gy in 25 fx vs. 59.4 Gy in 33 fx
  - **No difference in 5-yr OS or PFS with dose escalation**

Shaw et al. JCO 2002
Karim et al. Int J Radiat Oncol Biol Phys 1996

EORTC 22845 "Non-Believers Trial"

- Randomized patients with LGG after surgery to early RT vs observation with RT at progression
  - **Early (vs delayed) RT improved PFS and decreased seizure rate (25% vs. 41% at 1 year), but did not improve OS**
    - 65% patients in *observed* arm eventually received RT
    - Malignant transformation equal between arms 70%
    - QOL not studied (?relationship between time to progression and neurocognitive deterioration)

- Lack of OS benefit used by some to justify deferring RT until progression
  - Can be considered for patients with highly favorable prognostic features, minimal known disease, careful continued observation
  - RTOG 9802 included observation cohort of low-risk LGG s/p resection

van den Bent al. Lancet 2005

RTOG 9802

- Created risk groups for adult patients with supratentorial WHO grade II astrocytoma, oligodendroglioma, mixed oligoastrocytoma:
  - Low-risk: age < 40 and GTR
  - High-risk: age ≥ 40 and/or status post STR/biopsy
- Phase II component observed low-risk patients post surgery
  - **Significant correlation between amount of residual tumor on imaging and recurrence**
- Phase III component randomized high-risk pts to RT alone vs. RT followed by 6 cycles PCV
  - **Addition of PCV to RT almost doubles OS in high-risk patients**
    - Greatest effect size in oligodendroglioma patients (no 1p19q data)
    - Patients with IDH1 mutation significantly higher OS

Buckner J et al. NEJM 2016

EORTC 22033-26033

- Patients with ≥ 1 high risk feature randomized to RT alone vs. dose-dense TMZ alone
  - **No significant difference in PFS for LGG treated with RT alone vs. TMZ alone**
  - **HR QOL and global cognitive function did not differ in LGG pts treated with RT alone vs. TMZ alone**
  - **Median PFS 39 mos (TMZ alone) and 46 mos (RT alone) far less than median PFS of 10.4 years (RT + PCV) in RTOG 9802**

Baumert et al. Lancet Oncol 2016

RTOG 0424

- Single arm phase II high-risk LGG (at least 3 high-risk features) treated with RT with concurrent daily TMZ followed by 12 cycles of monthly TMZ
  - **3-yr OS 73.1% compares favorably to historical rate of 54%**
  - Later analysis of MGMT data (Bell et al) : MGMT promoter methylation independent prognostic biomarker of high-risk, low-grade glioma treated with TMZ and RT

Bell EH et al. JAMA Oncology 2018.
Fisher BJ et al. IJROBP 2015.

Randomized Trial Summary

Trial	Treatment Arms	Median PFS	Median OS
NCCTG/RTOG/ECOG	50.4 Gy in 30 fx 64.8 Gy in 36 fx	NA (5yr PFS 55%) NA (5yr PFS 52%)	NA (5yr OS 72%) NA (5yr OS 64%)
EORTC 22844	45 Gy in 25 fx 59.4 Gy in 33 fx	NA (5yr PFS 47%) NA (5yr PFS 50%)	NA (5yr OS 58%) NA (5yr OS 59%)
EORTC 22845	Observation 54 Gy in 30 fx	3.4 years 5.3 years (p<0.001)	7.2 years 7.4 years
RTOG 9802	54 Gy in 30 fx alone 54 Gy in 30 fx → PCV x 6	4 years 10.4 years (p<0.001)	7.8 years 13.3 years (p=0.003)
EORTC 22033-26033	12 cycles TMZ 50.4 Gy in 28 fx	39 mos 46 mos	NR NR

Comment on High vs. Low Risk

- Various cooperative groups have defined risk factors differently

- RTOG 9802 stratified patients based on age and resection status

- Pignatti combined EORTC trials and established five poor prognostic factors: ≥ 3 variables is high risk; low risk up to 2
  - Age ≥ 40
  - Astrocytoma histology
  - Tumors ≥ 6 cm
  - Tumor crossing midline
  - Preoperative neurologic deficits (not seizure)

Pignatti F et al. Prognostic factors for survival in adult patients with cerebral low grade glioma. J Clin Oncol (2002).

Treatment Paradigm

- In general, most patients recommended maximal safe resection followed by postoperative MRI within 72 hrs of surgery to evaluate extent of resection
  - Select low-risk patients may be observed whereas high-risk patients typically recommended adjuvant chemoRT. Patients with high-risk low-grade gliomas should be considered for early adjuvant RT.
    - RT alone = chemo alone. RT and chemo is better than RT alone
    - PCV vs. TMZ question still controversial
    - Incorporation of molecular data
    - Multidisciplinary review and care important

Maximal safe resection	GTR	Low risk	Observation, CHT, chemoRT
		High risk	ChemoRT
	STR or biopsy		ChemoRT

- Given longer survival outcomes compared to HGG, treatment decisions regarding observation vs. aggressive intervention must take into account potential acute and long-term side-effects and QOL

Tom, MC and Murphy, ES. Essentials of Clinical Radiation Oncology: Low Grade Glioma (2017) 16.

Radiation Planning

Dose

- 5040 to 5400 cGy (to balance efficacy and toxicity)

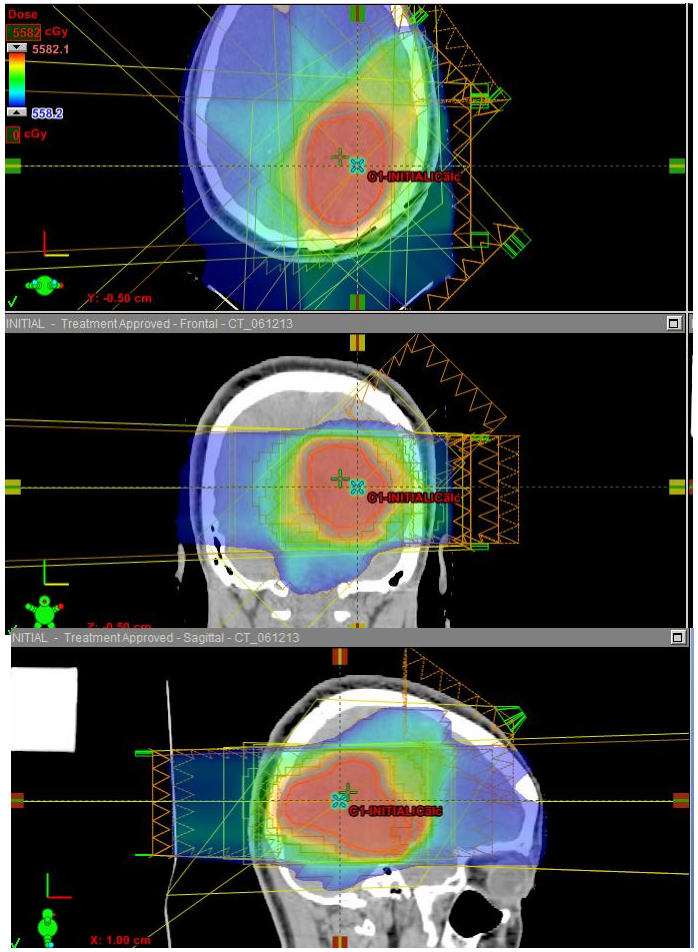
Volumes

- GTV = surgical cavity + T2/FLAIR +T1gad
- CTV = GTV + 1-1.5 cm margin
- PTV = CTV + 0.3-0.5 cm

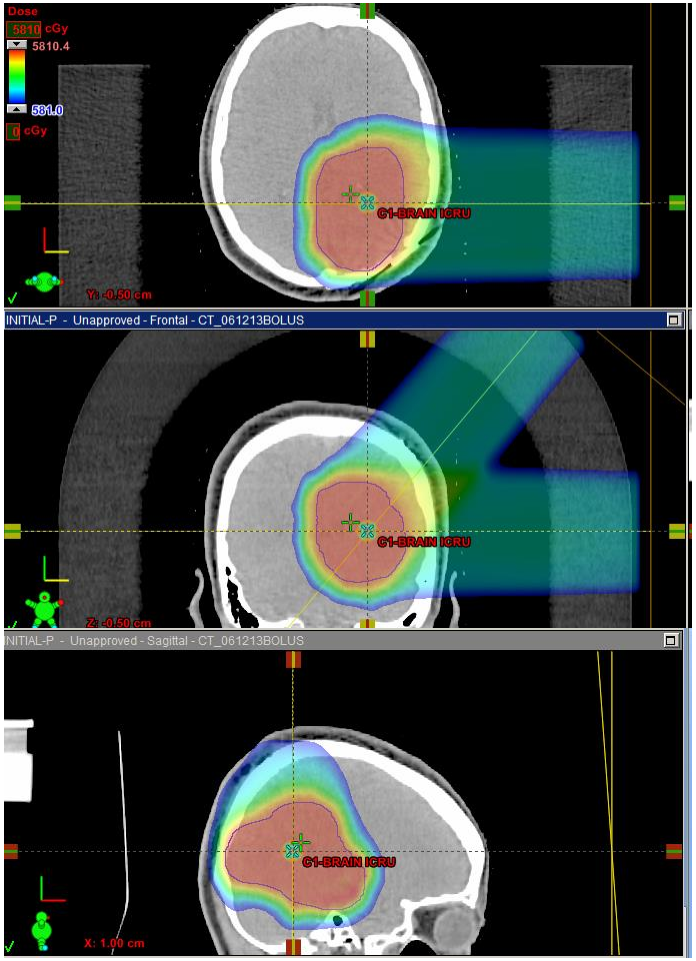
Dose Constraints

- Brainstem: max 5500 cGy
- Optic Chiasm/Nerves PRV: max 5400-5500 cGy
- Spinal cord: max 4500 cGy
- Eye/Retina: max 4000-4500 cGy
- Lacrimal Gland: max 4000 cGy
- Lens: max 500-700 cGy
- Cochlea: mean 4500 cGy

5-Field IMRT Plan

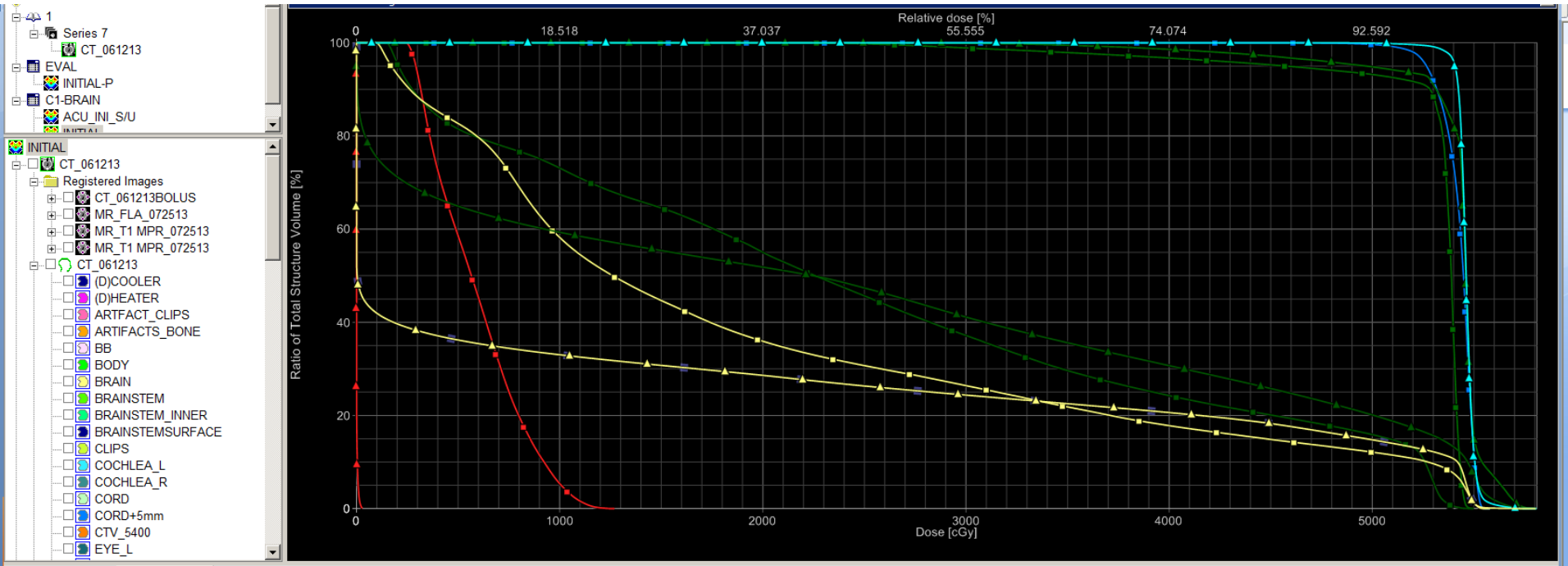


2-Field Proton Plan



DVH Comparison of Proton and IMRT

Initial-P=Proton



Dose Prescription | Dose Statistics

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		TEMPORAL LOBE_L	Approved	INITIAL	C1-BRAIN	41.4	100.0	100.0	142.7	5500.3	2490.3
☑		TEMPORAL LOBE_L	Approved	INITIAL-P	EVAL	42.1	100.0	100.0	0.0	5775.8	2389.0
☑		PTV_IMRT_5400	Approved	INITIAL	C1-BRAIN	114.8	100.0	100.0	4461.2	5582.1	5426.2
☑		PTV_5400	Approved	INITIAL-P	EVAL	115.4	100.0	100.0	4686.8	5810.4	5461.8
☑		PITUITARY	Approved	INITIAL	C1-BRAIN	0.9	100.0	100.0	243.2	1272.0	590.0
☑		PITUITARY	Approved	INITIAL-P	EVAL	1.0	100.0	100.6	0.0	33.2	1.4
☑		HIPPOCAMPUS_L	Approved	INITIAL	C1-BRAIN	2.5	100.0	100.0	2210.4	5500.8	5283.9
☑		HIPPOCAMPUS_L	Approved	INITIAL-P	EVAL	2.8	100.0	100.2	2656.1	5810.4	5402.4
☑		BRAIN	Approved	INITIAL	C1-BRAIN	1127.9	100.0	100.0	91.5	5582.1	1992.5
☑		BRAIN	Approved	INITIAL-P	EVAL	1130.1	100.0	100.0	0.0	5810.4	1407.4

Ongoing Phase III Trials

- Long-term results and additional studies needed to address role of adjuvant TMZ combined with RT and benefits of advanced RT technologies

- NRG-BN005 (Identifier: NCT03180502)
  - 54 Gy (photons) with adjuvant TMZ vs. 54 Gy (protons) with adjuvant TMZ
- Adjuvant TMZ for Low Grade Glioma (Identifier: NCT01649830)
  - 54 Gy vs 54 Gy with adjuvant TMZ
- ECOG-E3F05 (Identifier: NCT00978458)
  - 50.4 Gy vs 50.4 Gy with adjuvant TMZ

Follow Up

- MRI q3-6 mo for 5 years then at least every 6-12 mo or as clinically indicated thereafter

- Anaplastic transformation from LGG to HGG
  - Slow growth until they undergo malignant transformation

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