City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Tumor Board: Management of Patients with Gliomas

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Radiation Oncology: Stephanie Yoon, MD

Medical Oncology: Jana Portnow, MD

Panel & Disclosures

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- *No relevant financial relationships*

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Co-Director, COH Brain Tumor Program
Vice-Chair, NCCN Guidelines Panel for CNS Tumors

- *Other Financial Relationship (DSMB Chair) with IN8bio*

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

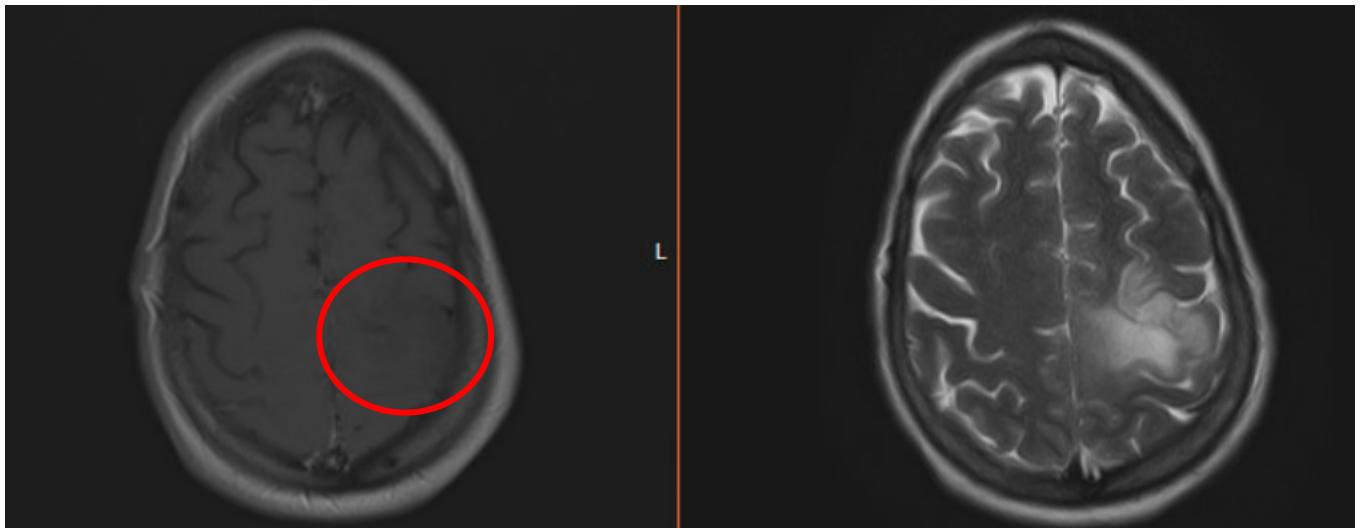
- *How age might determine the type and level of care in this patient population*
- *Respectfully demonstrate and effectively communicate care to patients with diverse values and behaviors that relate to social and cultural needs related to health.*
- *Recognize that potential cost, insurance, transportation, nutrition, access to resources to rehabilitation, and caregiver availability are all necessary yet sometimes difficult to ascertain as a part of a patient's care.*

Case 1

Management of Adult Low Grade Glioma

Case 1

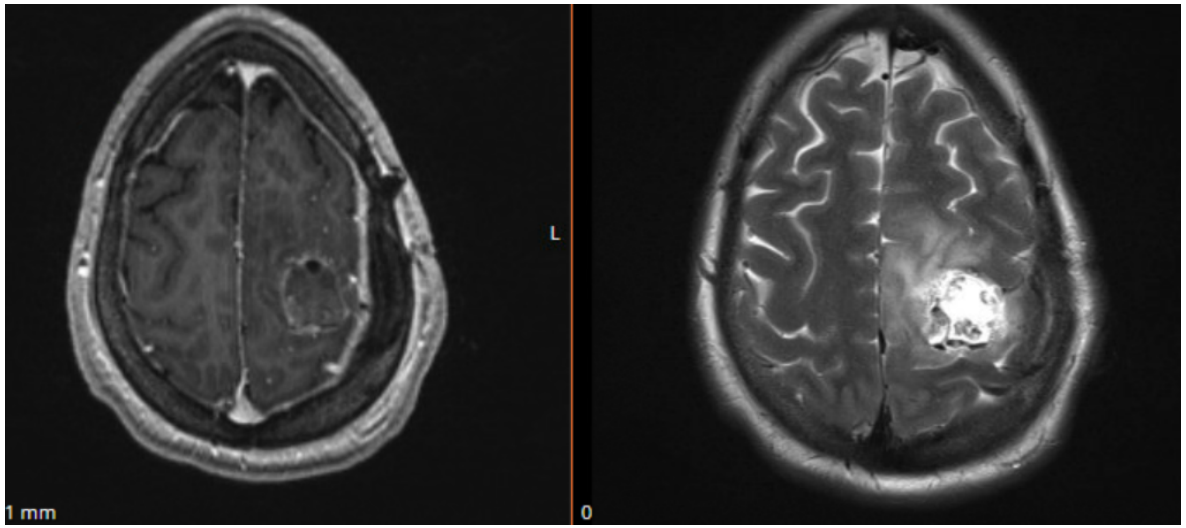
- 38-year-old, right-handed woman with no significant PMH began experiencing nocturnal seizures, which were witnessed by her parents. When she woke up, she would be disoriented for a little while. Her brother has a seizure disorder, and so she did not worry about her seizures and did not seek medical evaluation until she experienced a generalized seizure.



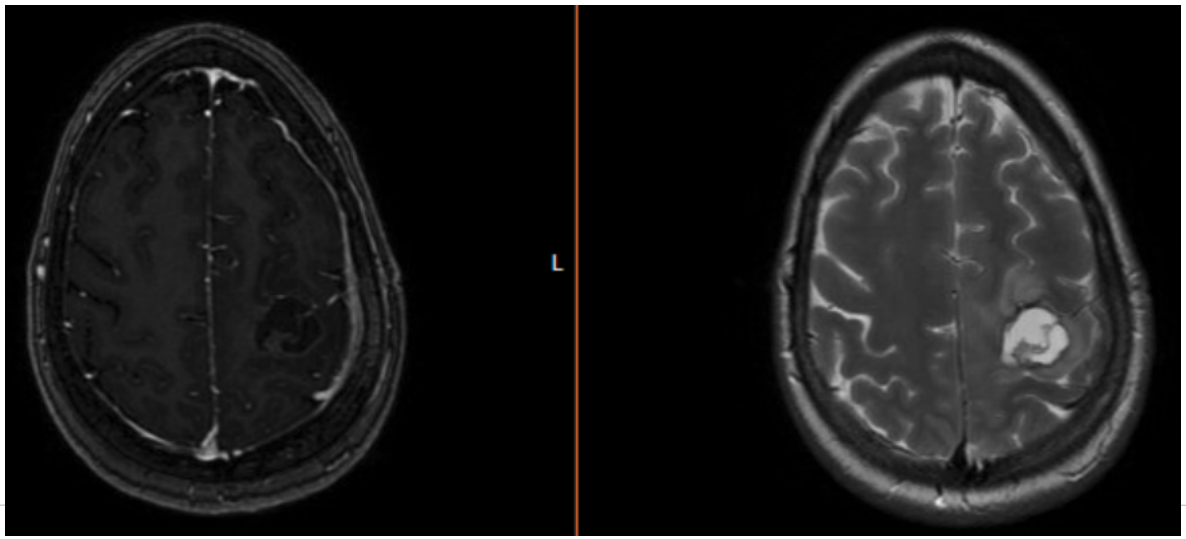
- A biopsy of the mass was performed at a local hospital and showed the presence of a grade 2 oligodendroglioma.

Transferred care to COH

Immediate post op



1 month post op



Surgical considerations

- Surgery in eloquent areas
  - Pre-operative functional MRI – diffuse tumor involved motor and subcortical motor areas
  - Intraoperative neuro-navigation and ultrasound
  - Surgery performed awake
    - Asleep for craniotomy and durotomy
  - Intraoperative SSEP monitoring with direct cortical stimulation for motor mapping
    - As tumor was debulked patient noted to have weakness in right hand which improved throughout operation; lateral edge of surgical cavity
    - Stimulation of motor and sensory tracts determined margins of safe resection

Low Grade Gliomas

RTOG 9802: Phase 3 study in newly diagnosed patients with low grade gliomas **(Buckner et al., New Eng J Med 2016)**

Randomized high risk patients (age ≥ 40 or had subtotal resection):

RT x 6 weeks — mOS: 7.8 years
Or (HR: 0.59; P=0.003)
RT + PCV* x 6 cycles — mOS: 13.3 years

*procarbazine/CCNU/vincristine

temozolomide?

CODEL Trial (grade 2 and 3 oligos) **RT+PCV vs RT + temozolomide**

IDH Inhibitors

IDH inhibitors:

- ivosidenib: FDA approved for mut-IDH1 AML, cholangiocarcinoma
- enasidenib: FDA approved for mut-IDH2 AML
- vorasidenib: IDH1 & IDH2 inhibitor

- **First study to show safety and prolonged disease control of an IDH inhibitor (ivosidenib) in non-enhancing gliomas** **(Mellinghoff et al., J Clin Oncol 2020)**

	mPFS
35 pts with non-enhancing tumor	13.6 mo (95% CI, 9.2-33.2 mo)
31 pts with enhancing tumor	1.4 mo (95% CI, 1.0-1.9 mo)

- Peri-operative study of vorasidenib vs ivosidenib in patients with non-enhancing IDH1mut low grade gliomas **(Mellinghoff et al., Nat Med 2020)**

Both showed good brain penetration and consistent inhibition of IDH1mut (2-HG suppression)

Phase 3 Randomized, Double-Blind, Placebo Controlled Study of Vorasidenib in Low Grade Glioma Patients

INDIGO study design

Randomized 1:1 to vorasdenib 40 mg qd or placebo

Stratified by: 1p19q status (co-deleted or not)
Tumor size: > 2cm or smaller

Primary endpoint: mPFS

Other secondary objectives (*not reported yet*)

- Time to next cancer intervention
- Objective response
- Safety
- Tumor growth rate base on volume
- Health-related QoL
- Overall survival

INDIGO Study

Main Eligibility criteria

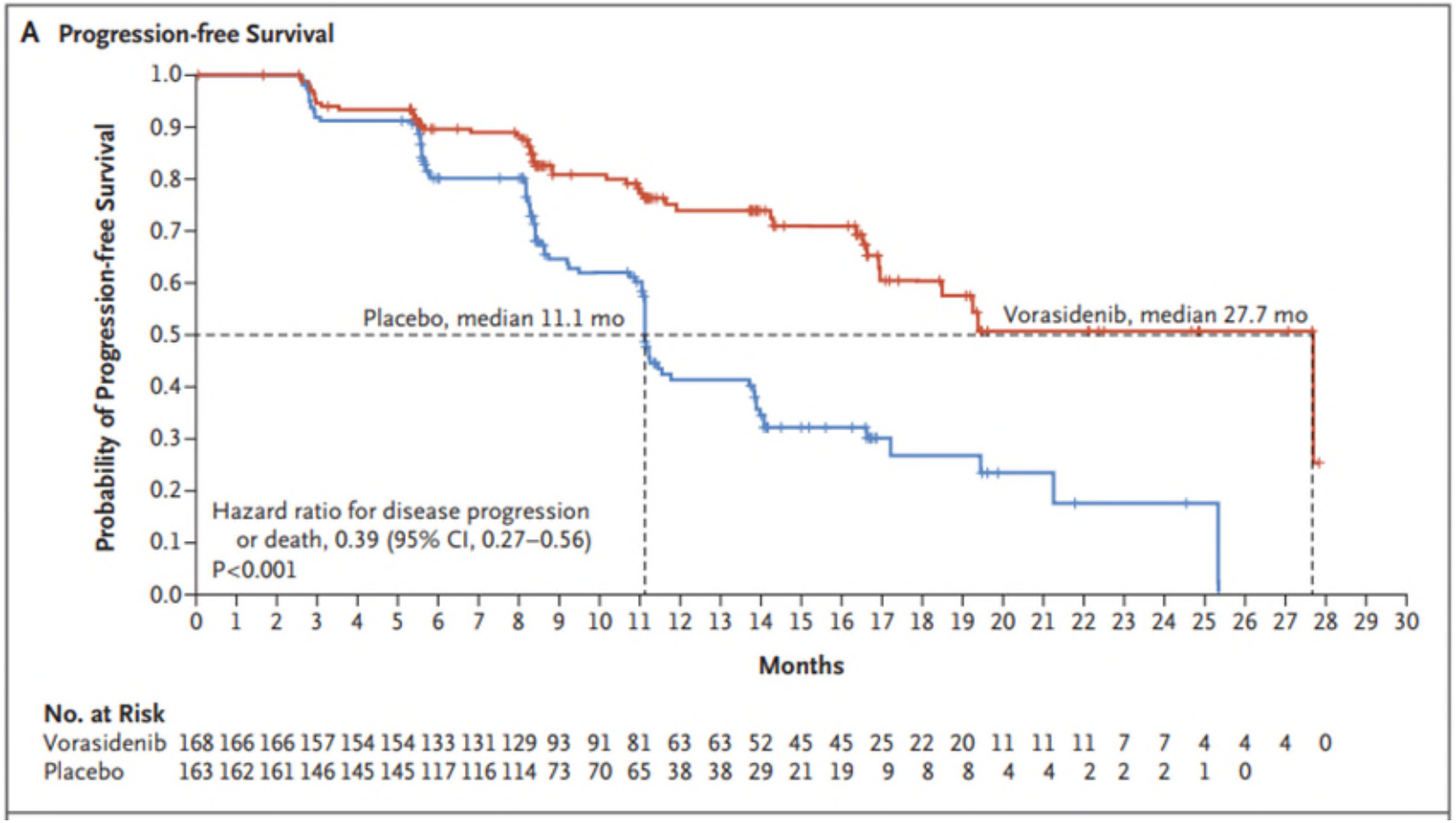
- Age 12 year or older
- Residual/recurrent grade 2 oligodendroglioma or astrocytoma
- IDH1 or IDH2 mutated
- KPS ≥ 80%
- At least 1 prior surgery (most recent one occurring between 1 and 5 yrs before randomization)
- No other anti-cancer therapy
- No glucocorticoids
- Measurable non-enhancing tumor
- QTc interval ≤ 450 msec

INDIGO Study

331 participants enrolled from 77 centers in 10 countries.

	Vorasidenib	Placebo
Median age (years)	41	39
Oligodendroglioma	88 (52%)	84 (52 %)
Astrocytoma	80 (48%)	79 (48%)
mutIDH1	97%	93%
mutIDH2	3%	7%
Tumor size ≥ 2 cm	83%	84%

INDIGO Study Results



Mellinghoff et al., N Engl J Med 2023

IDH Inhibitors for Gliomas: Future Directions

- This patient population was in the earliest clinical phase of tumorigenesis:
  - No prior cancer treatment except for surgery
  - No measurable enhancement on MRI

Future directions:

Assess vorasidenib

in combination with chemotherapy, immunotherapy

in patients treated with radiation and chemotherapy

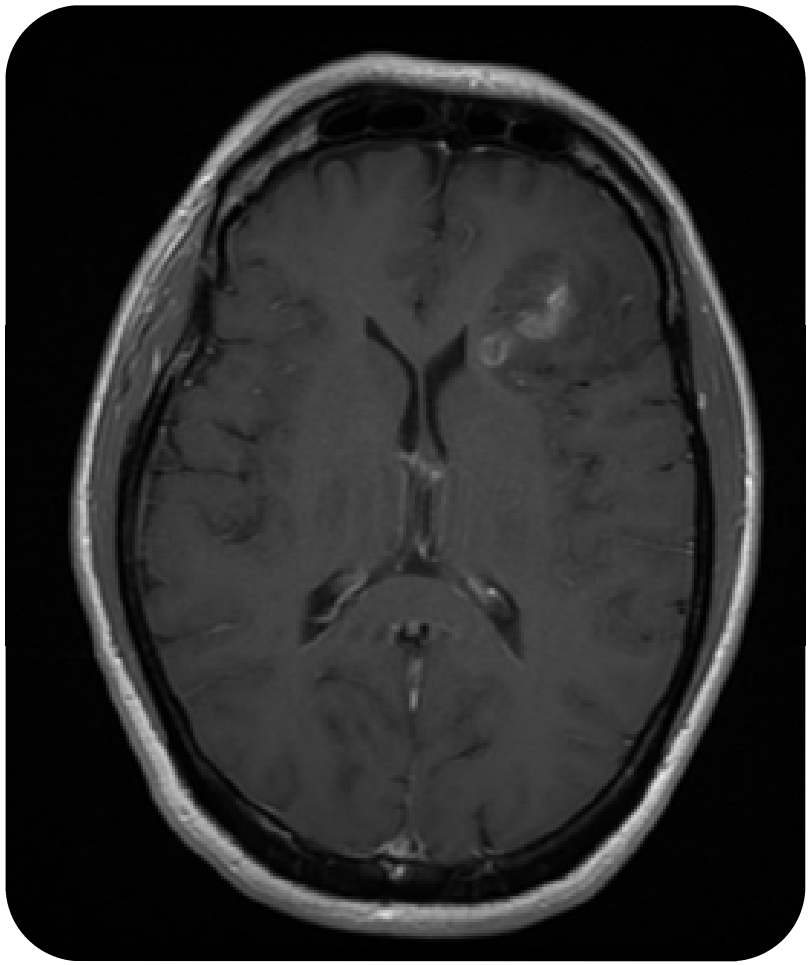
in grade 3 and 4 astrocytoma patients

Case 2

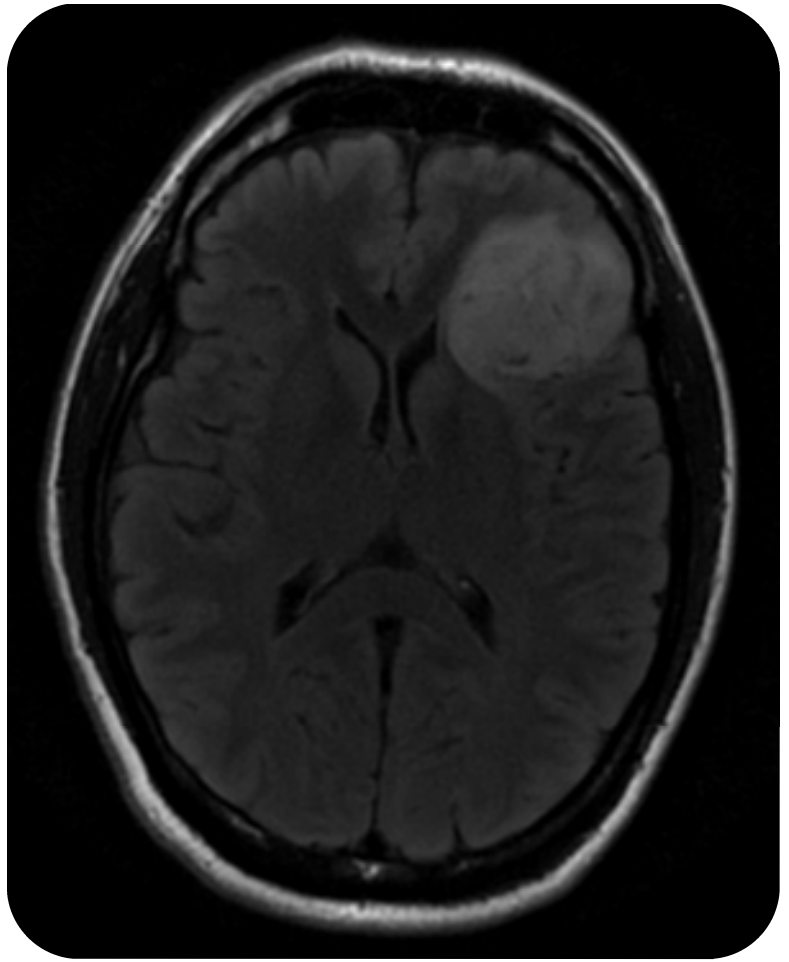
Diagnosis and Management of Radiation Necrosis

Presented with Expressive Aphasia

- 38 year-old male with PMHx of hypertension presents with sudden-onset word-finding difficulties.
- MRI of Brain with and without contrast
    - Large left frontal lobe lesion with enhancing and non-enhancing areas



T1 + contrast

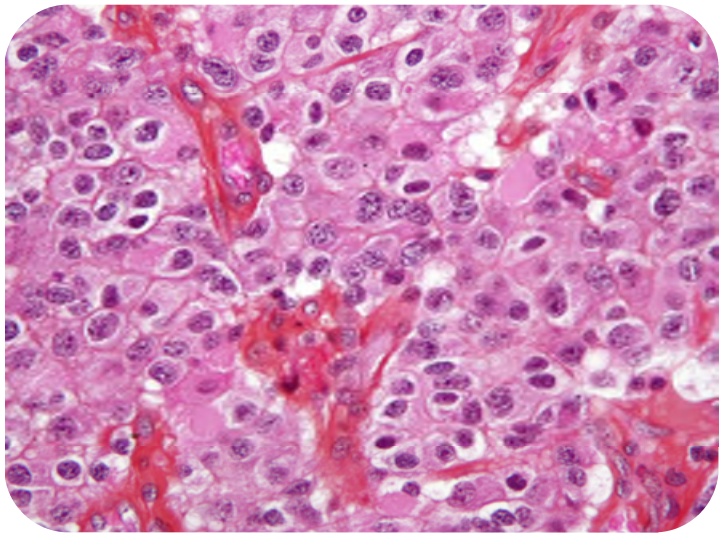


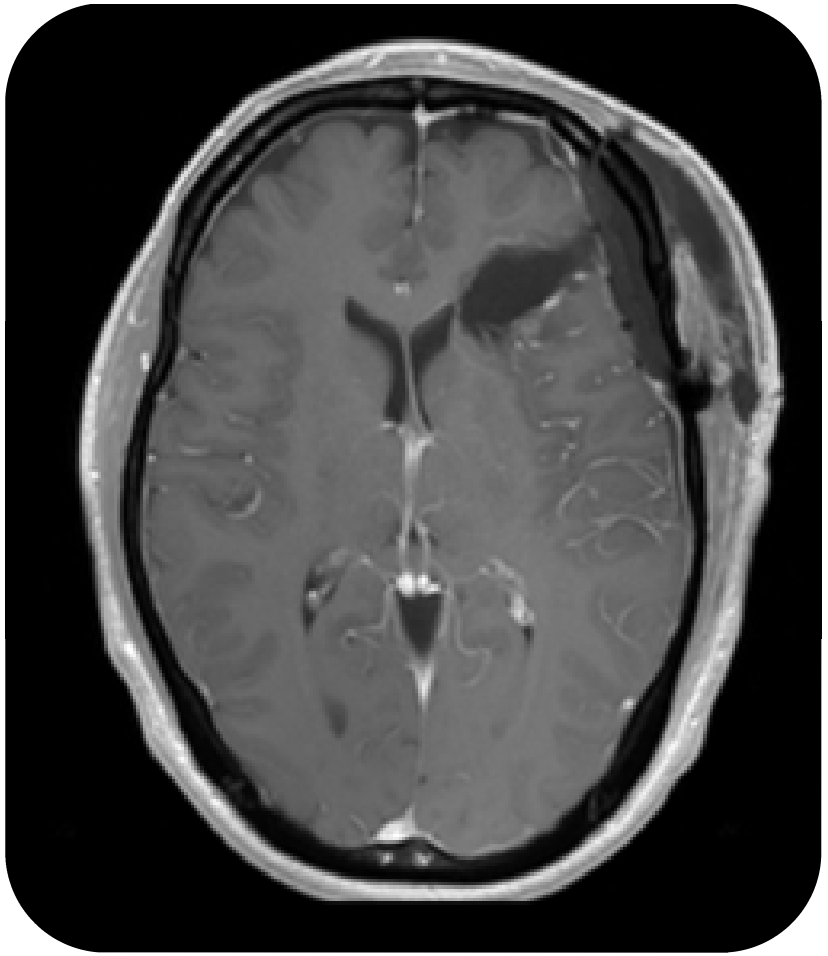
T2/FLAIR

Underwent gross total resection of tumor

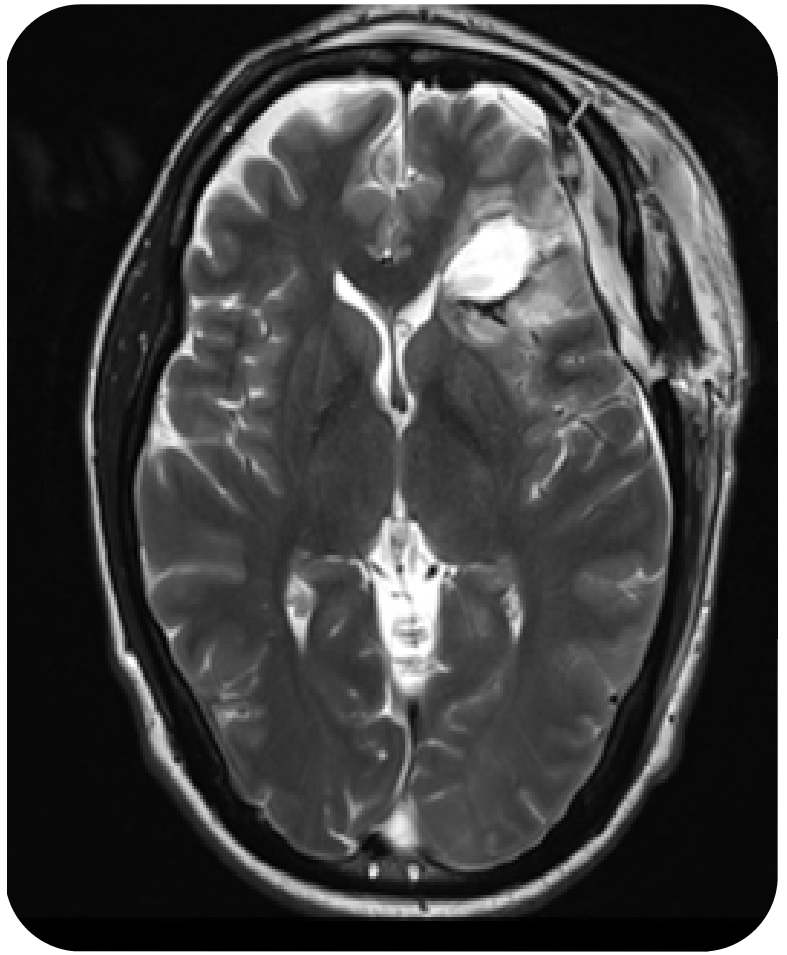
Surgical pathology:

- Oligodendroglioma grade 3
- IDH1-mutant (R132H)
- 1p/19q co-deleted
- ATRX expression retained





T1 + contrast

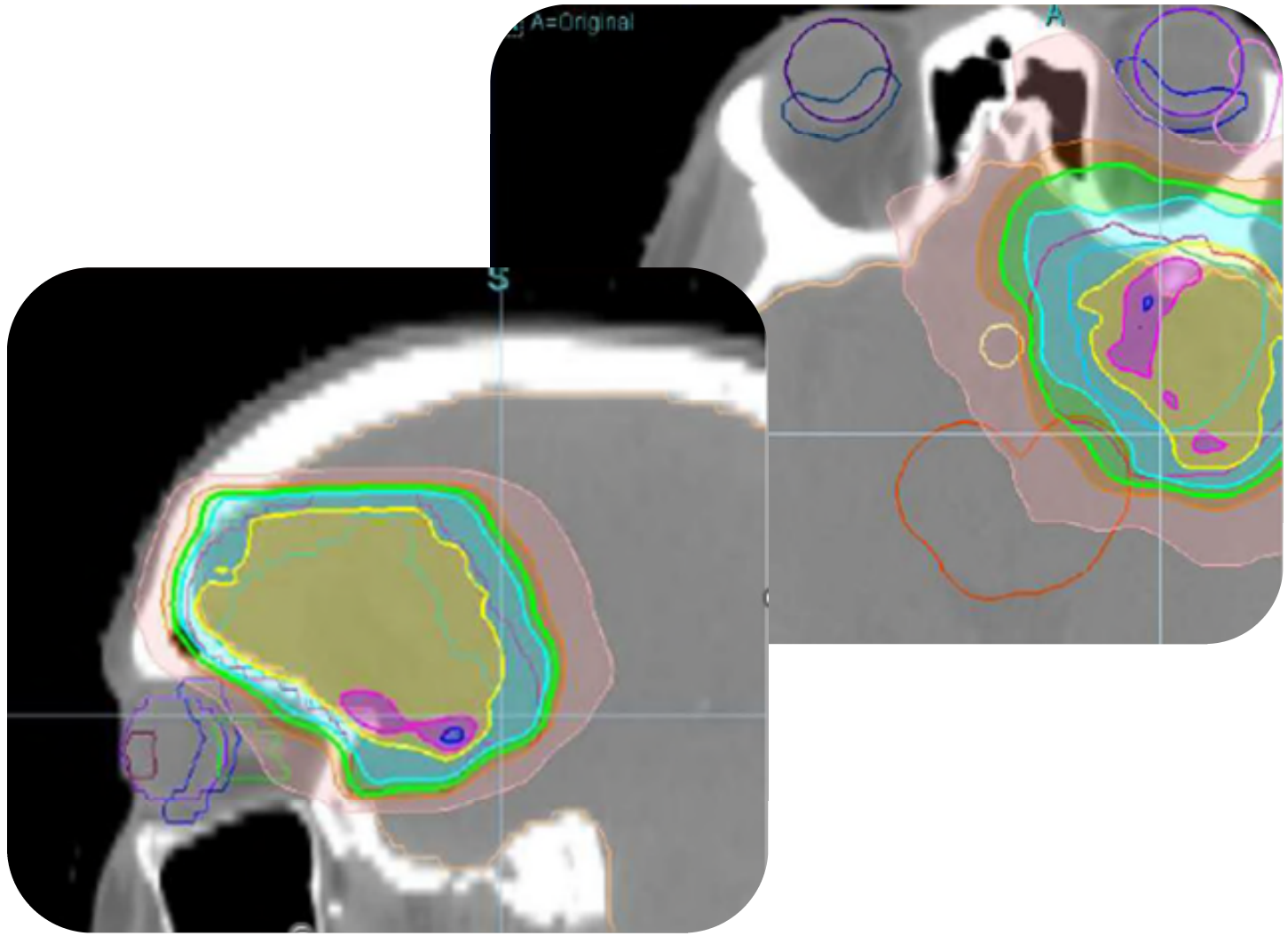


T2

Completed standard-of-care adjuvant treatments

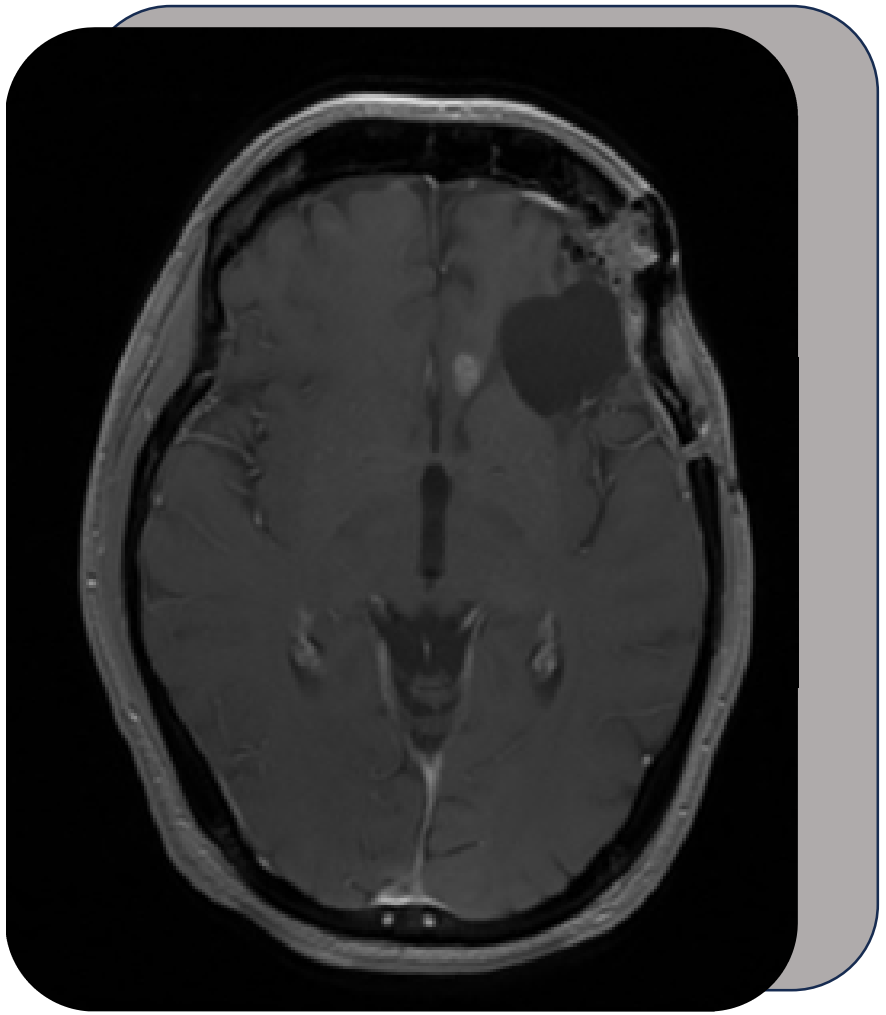
- Focal radiation to 59.4Gy in 33 fractions
- Followed by PCV for 5 cycles (patient declined 6th cycle)

***RTOG 9402**:* *RT vs RT + PCV*
mOS *7.3 vs 14.7 years*



New radiographic findings

- MRI Brain ~2 years after completing radiation
    - New enhancing nodule medially adjacent to anterior horn of left lateral ventricle.
- Repeat MRI Brain ~2-3 months later:
    - Enhancing nodule in left corpus callosum increased in size concerning for radiation necrosis vs tumor progression



T1 + contrast

Diagnosing radiation necrosis non-invasively

MR Spectroscopy

- Lactate peak
- Choline / Cr ratio > 1
- Choline / NAA > 1.8

18F-PET/CT

- RN appears hypometabolic
- No consensus on optimal radiotracer (MET, FLT, FET)

Quantitative

- Exploratory
- Relative cerebral blood volume (rCBV), DWI / ADC

Diagnosing radiation necrosis non-invasively

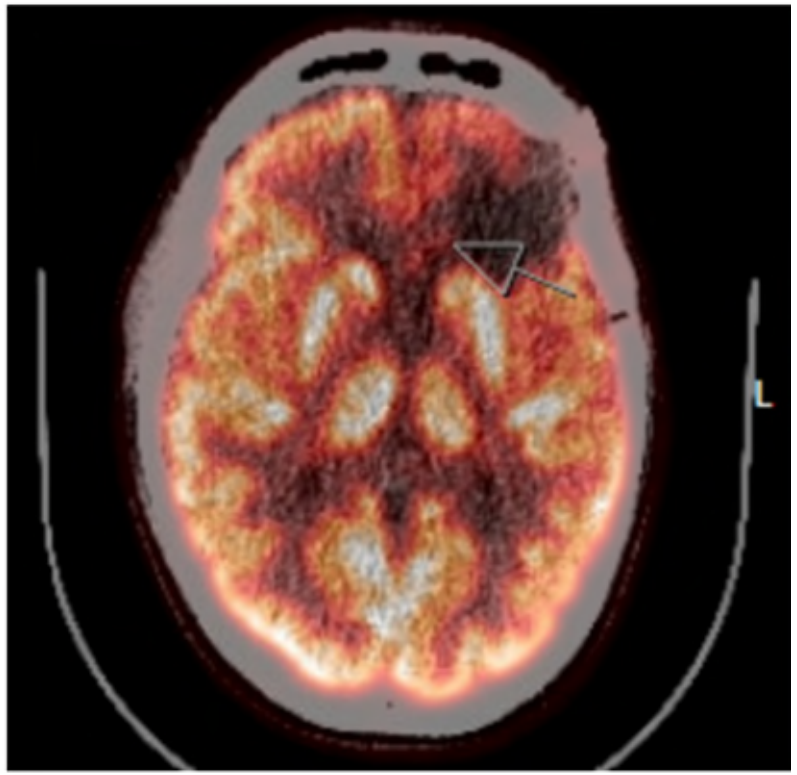
	Sensitivity	Specificity	Accuracy
MR Spectroscopy	79-97%	65-99%	80-81%
18F-PET/CT	73-86%	22-56%	77-88%

Aseel et al., J Neuroimaging 2023

Mixed radiographic findings over time

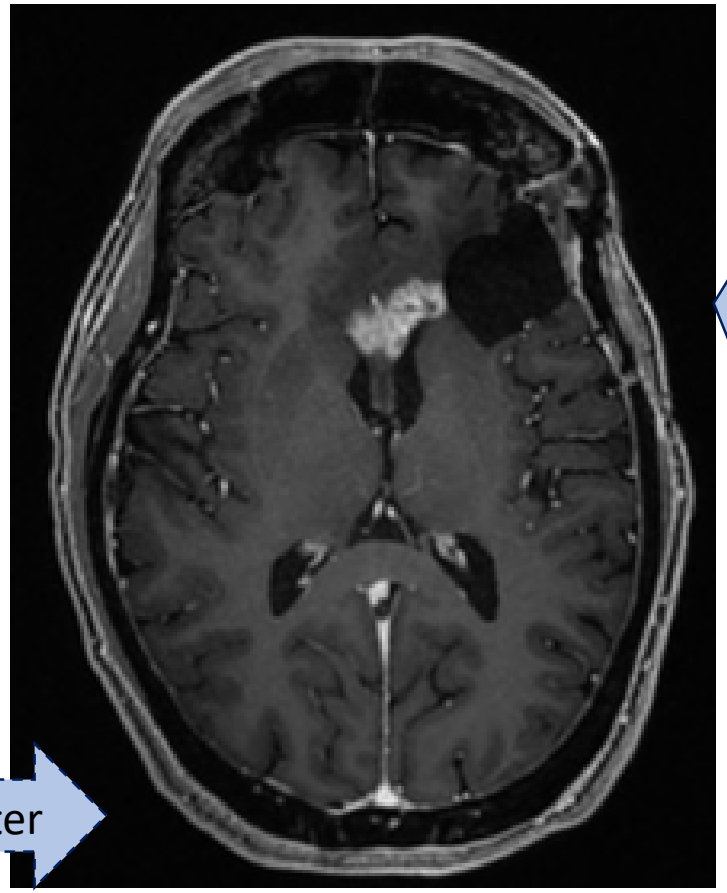
PET/CT showed that the *enhancing area on MRIs had mild uptake consistent with radiation necrosis*

18F-PET

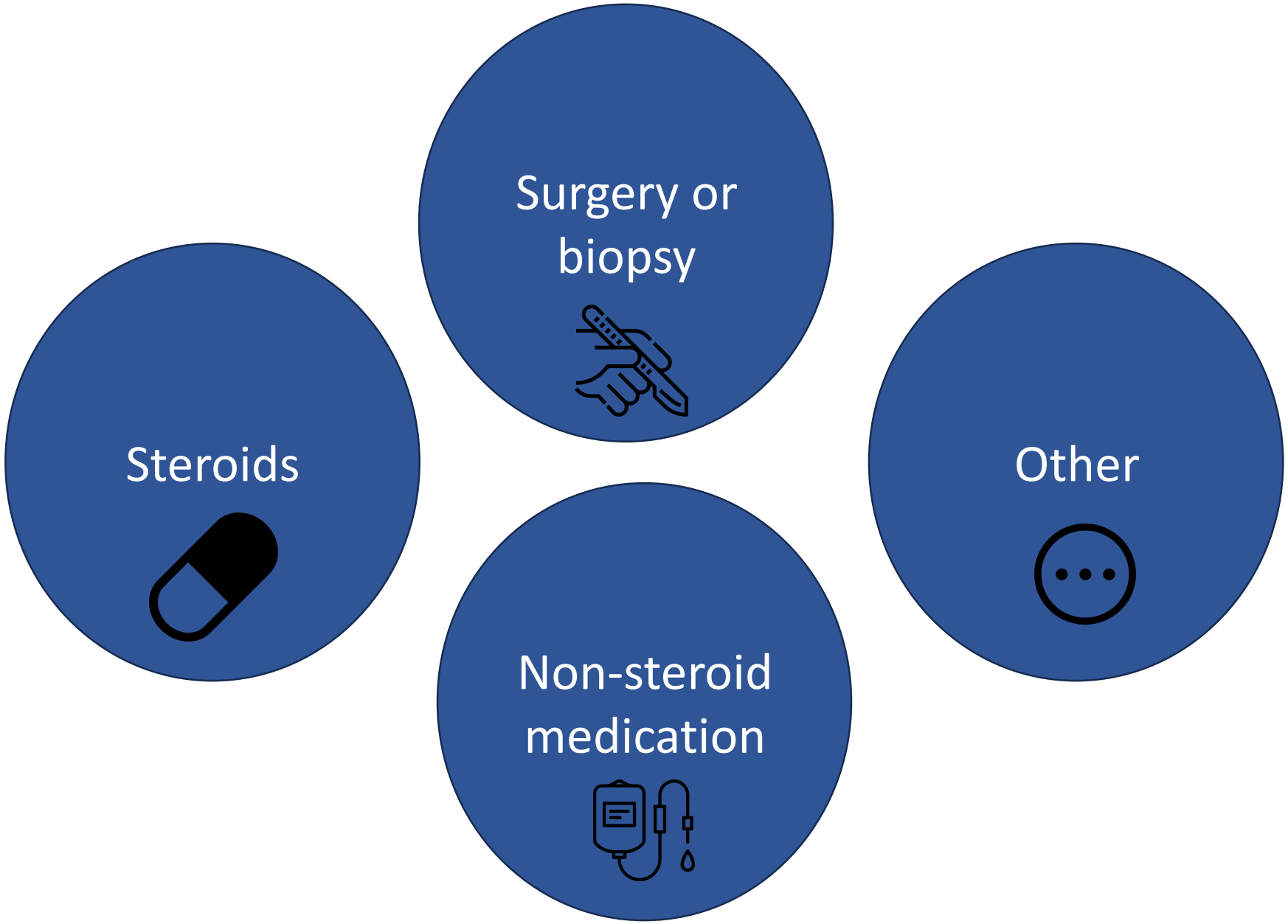


1 month later

T1 + contrast



Repeat MRI Brain one month later continued to show *enhancing lesion in left corpus callosum increased in size concerning for tumor progression*


Surgery or biopsy
Steroids
Other
Non-steroid medication

Non-steroid medications

International Journal of Radiation Oncology*Biology*Physics
Volume 79, Issue 5, 1 April 2011, Pages 1487-1495

Clinical Investigation

Randomized Double-Blind Placebo-Controlled Trial of Bevacizumab Therapy for Radiation Necrosis of the Central Nervous System

Victor A. Levin M.D. *, Luc Bidaut Ph.D. †, Ping Hou Ph.D. †, Ashok J. Kumar M.D. ‡, Jeffrey S. Wefel Ph.D. *, B. Nebiyou Bekele Ph.D. §, Sujit Prabhu M.D. *, Monica Loghin M.D. *, Mark R. Gilbert M.D. *, Edward F. Jackson Ph.D. †

MDACC: **14 patients with radiation necrosis** (confirmed by biopsy or on imaging). Randomized to **bevacizumab 7.5mg/kg q3 weeks x 4 doses vs saline placebo.**

Results All participants had improvement in neurologic symptoms and imaging findings on MRI. All patients who progressed on placebo responded to bevacizumab at crossover.

Non-steroid medications

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 101, Issue 5, 1 August 2018, Pages 1087-1095

Clinical Investigation

Bevacizumab Monotherapy Reduces Radiation-induced Brain Necrosis in Nasopharyngeal Carcinoma Patients: A Randomized Controlled Trial

Yongteng Xu MD * †, Xiaoming Rong MD, PhD * †, Weihan Hu MD ‡, Xiaolong Huang MD * †, Yi Li MD, PhD * †, Dong Zheng MD, PhD §, Zhaoxi Cai MD ‖, Zhiyi Zuo MD, PhD ¶, Yamei Tang MD, PhD * † #

112 pts randomized to: **bevacizumab (5 mg/kg Q2 weeks x 4) or methylprednisolone/prednisone**

Results Bevacizumab vs steroids

Higher response rate (66% vs 32%)

Increased clinical improvement (62% vs 43%)

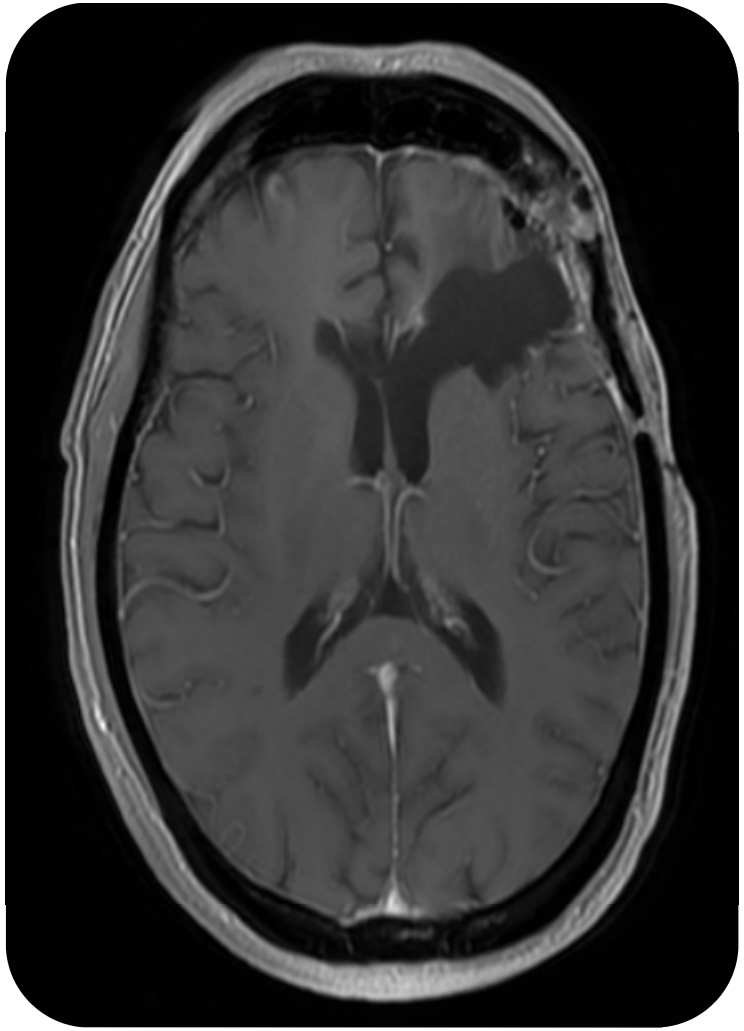
Recurrence rate at 6 months follow up: 29% vs 27%

Surgery or biopsy

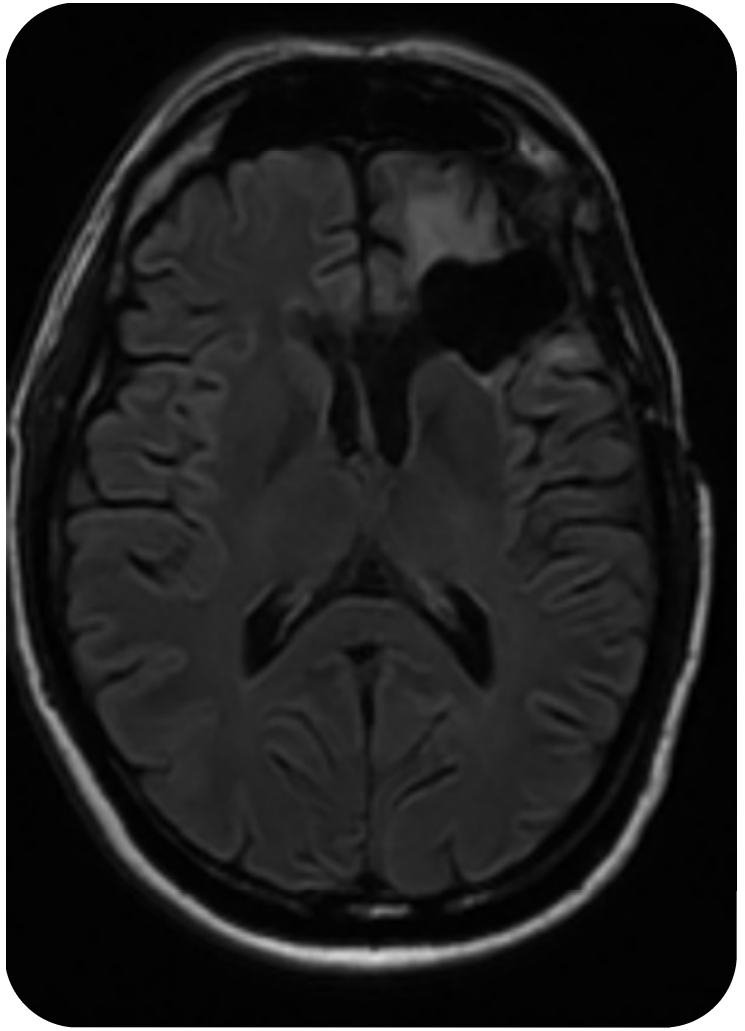
When to consider biopsy or surgical resection?

Case 2

- Patient underwent another resection ~2 years after adjuvant radiation for definitive tissue diagnosis
    - Pathology report: **radiation necrosis**
- Currently 4.5 years out from definitive treatment. He remains asymptomatic and feeling well.



T1 + contrast



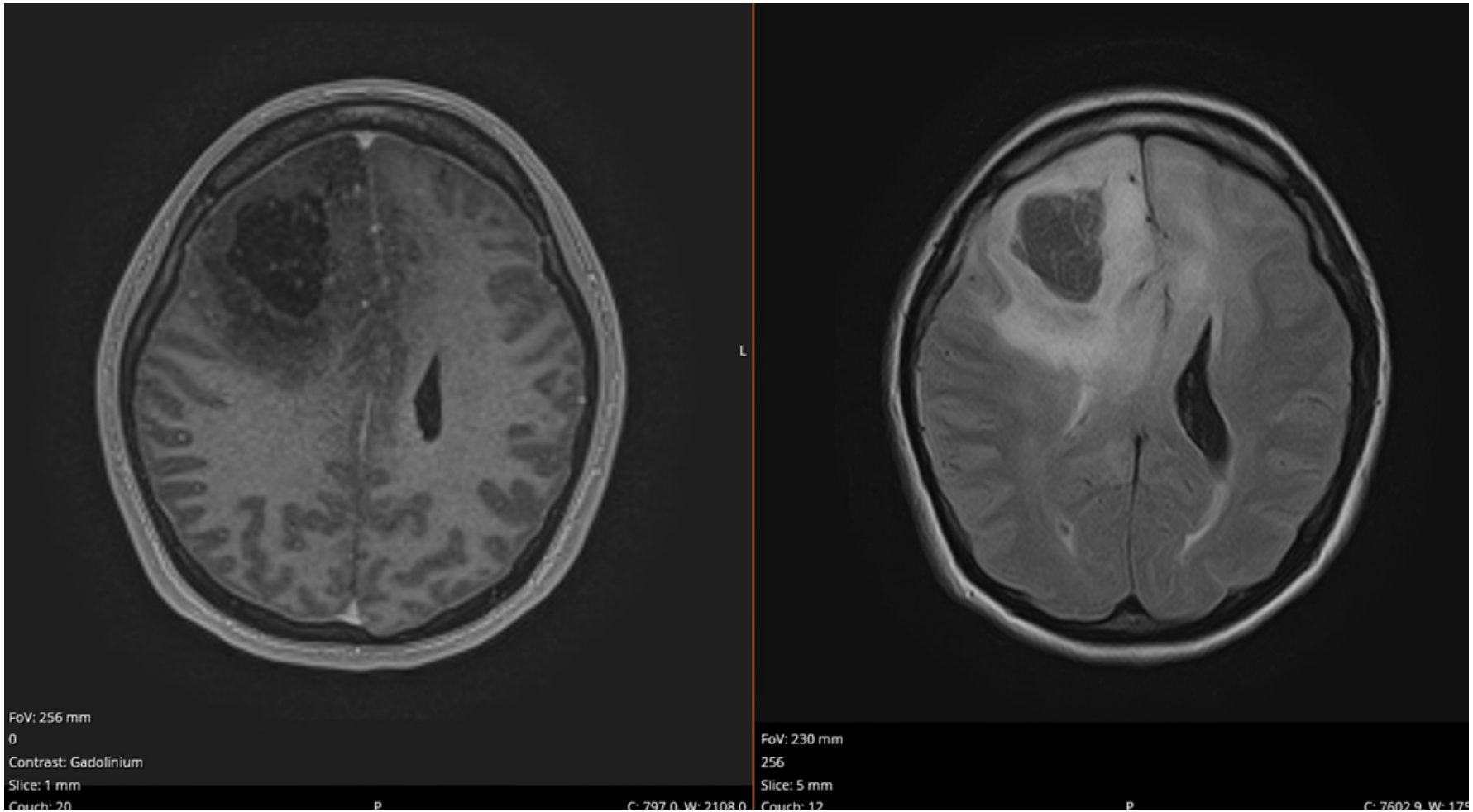
T2/FLAIR

Case 3

Diagnosis and Management of High Grade Glioma

Case 3

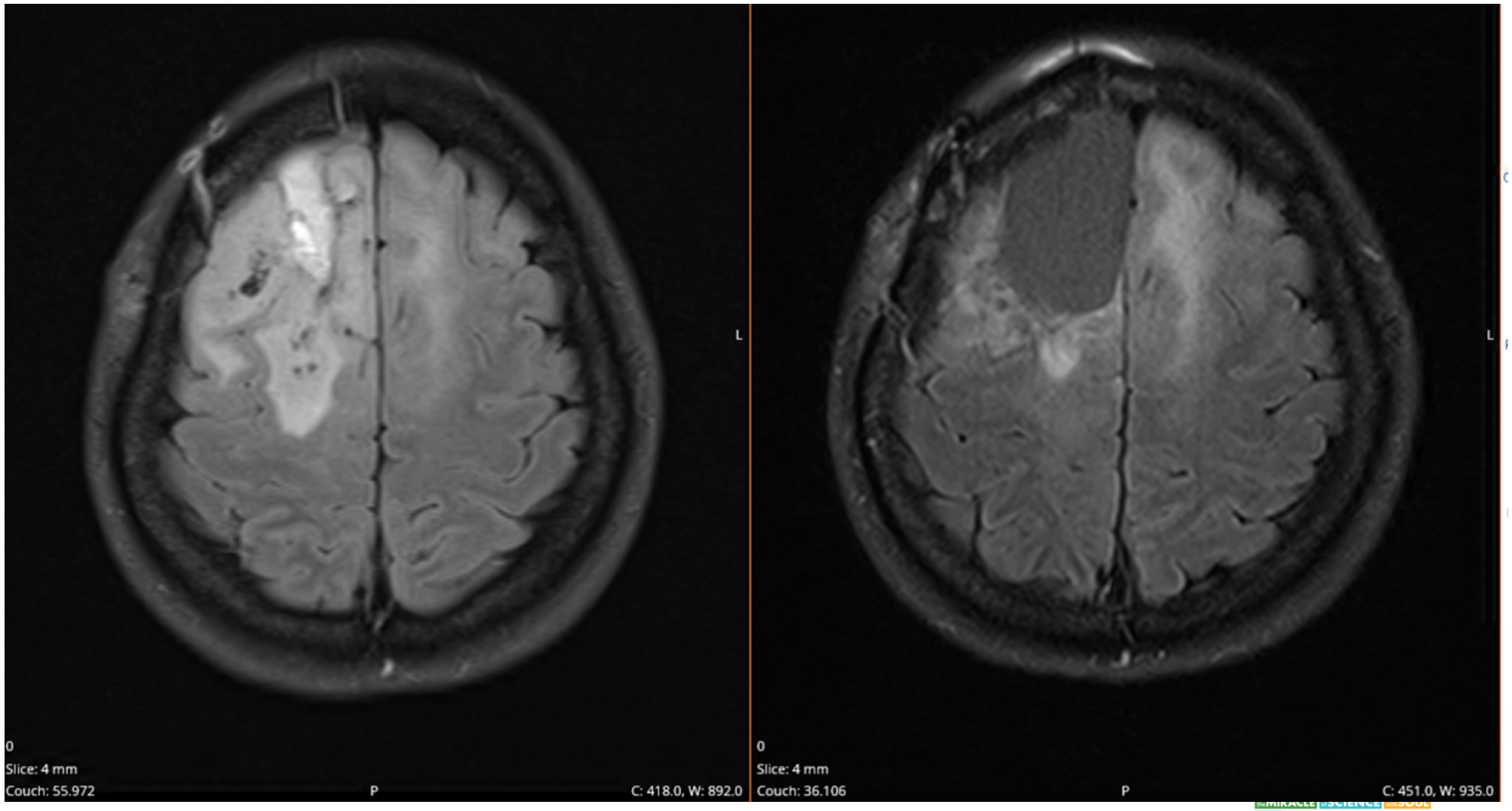
35 year old woman presented with worsening headaches and associated nausea for several months.



Case 3

Post-op MRI from 1st surgery

Post-op MRI from 2nd surgery



City of Hope

2021 WHO Updated Classification of Gliomas

Low-Grade (1, 2)
(MRI: non-enhancing tumor)

High-Grade (3, 4)
(MRI: enhancing tumor)

Grade 2 oligodendroglioma → Grade 3 oligodendroglioma
(IDHmut; 1p19q co-del) (IDHmut; 1p19q co-del)

Grade 2 astrocytoma → Grade 3 astrocytoma
(IDHmut) (IDHmut)

↓

Grade 4 astrocytoma
(IDHmut, homozygous CDKN2A/B deletion)

Glioblastoma
(IDH wildtype, TERT promoter, +chr7/-chr10, EGFR amplified)

Case 3

Preliminary pathology report:
Grade 3 astrocytoma (IDH1 mutated)

"*Note: Despite the reported focal enhancement on imaging studies, definite micro-endothelial proliferation or necrosis is not seen."

Genomic Alterations Detected	Allele Frequency	Approved Therapies in patient's tumor*	Therapies in other tumor type*
ATRX Loss	N/A	None	None
CCND1 Amplification	N/A	None	None
CDKN2A Loss	N/A	None	None
CDKN2B Loss	N/A	None	None
FGF3 Amplification	N/A	None	None
FGF4 Amplification	N/A	None	None
FGF19 Amplification	N/A	None	None
IDH1 (c.395G>A p.R132H)	36%	None	Ivosidenib

Final integrated diagnosis (combined tissue-based histological and molecular diagnosis)

Astrocytoma, IDH mutant, WHO grade 4

RT + TMZ followed by TMZ + TTF

An option for Newly Diagnosed MGMT methylated GBM Patients

Phase 3 study of TMZ + lomustine vs standard TMZ in MGMT methylated GBM patients (CeTeG/NOA-9)

***Herrlinger and Tzaridis et al., Lancet* 2019**

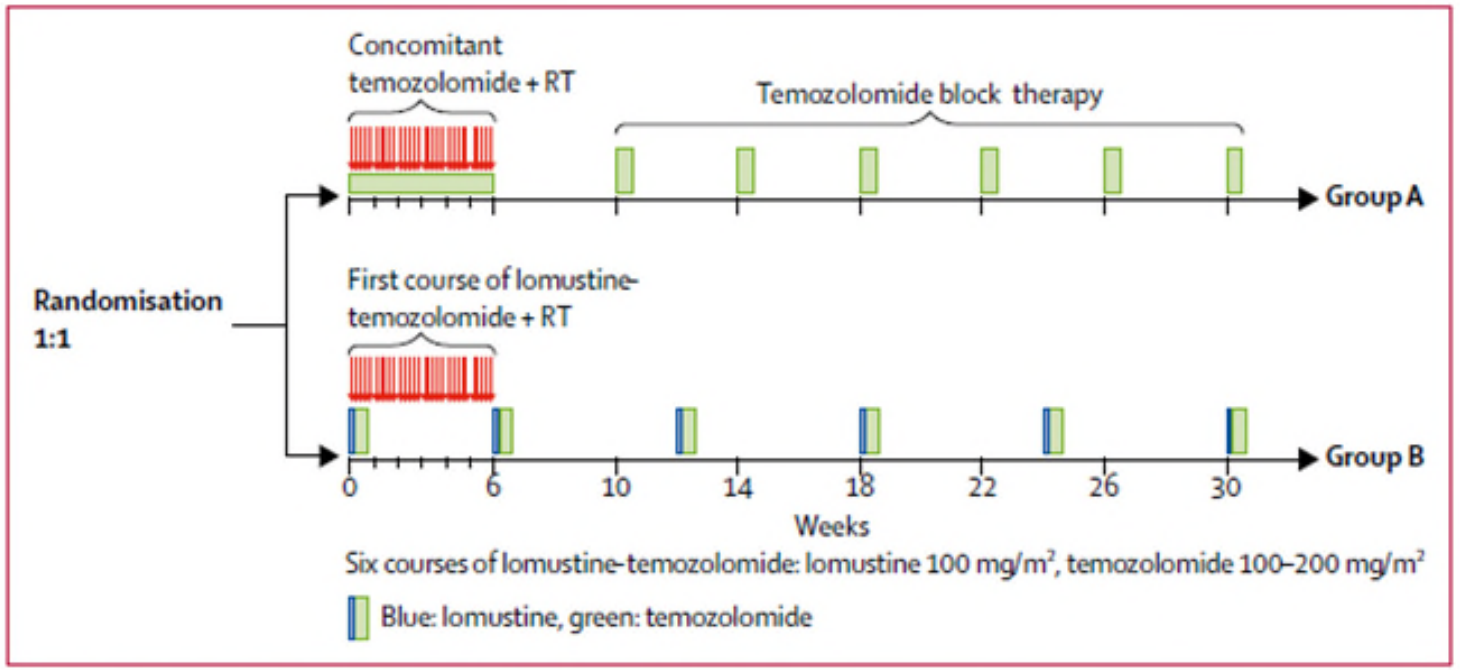


***Figure 1*: Schematic overview of the CeTeG/NOA-09 trial**

CeTeG/NOA-9: Phase 3 Study in Newly Diagnosed MGMT Methylated GBM Patients

Standard RT + TMZ arm	vs	RT +TMZ + lomustine arm
63 pts		66 pts
mOS: 31.4 months		mOS: 48.1 months
(83% IDH wt; 8% IDH mut)		(77% IDH wt; 5% IDH mut)

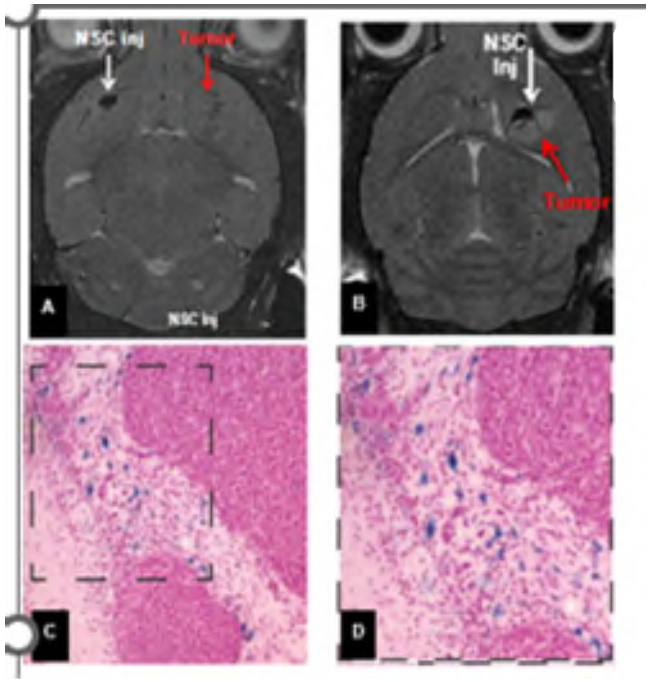
Stay tuned: NRG-BN011 started in 2021

- Same trial design and patient population
- Plan to randomize 306 pts
- Stratify by intent to use Tumor Treating Fields
- 2025: anticipated results for the primary endpoint (mOS)

NCT05139056 Phase 1 Study of Intracerebrally Administered Weekly Doses of NSC/CRAd in Recurrent GBM Patients

Neural stem cell based oncolytic virotherapy

- **NSCs are tumor-tropic and can be used as delivery vehicles.**
- **NSCs protect the virus from neutralizing antibodies** en route to tumor sites
- **NSCs improve distribution of the oncolytic virus** delivering it to multiple invasive tumor sites (*across normal brain tissue*).



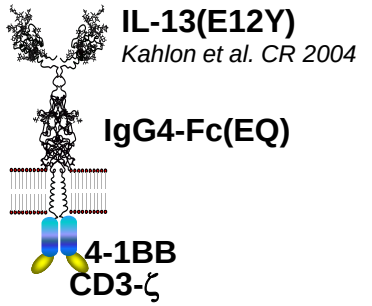
Multi-center study: City of Hope, Stanford, Northwestern, Wake Forest

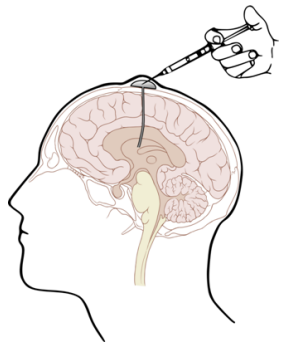
Funding: California Institute of Regenerative Medicine (PI: Portnow)

Chimeric Antigen Receptor (CAR) T cell Brain Tumor Clinical Trials at City of Hope

NCT03696030 A Phase 1 Cellular Immunotherapy Study of Intraventricularly Administered Autologous HER2-Targeted Chimeric Antigen Receptor (HER2-CAR) T cells in **Patients with Brain and/or Leptomeningeal Metastases from HER2 Positive Cancers** (PI: Portnow)
NCT04003649 A Phase 1 Study to Evaluate IL13Rα2-targeted Chimeric Antigen Receptor (CAR) T Cells Combined with Checkpoint Inhibition for Patients with Recurrent Glioblastoma (PI: Badie)
NCT04214392 A Phase 1 Study to Evaluate Chimeric Antigen Receptor (CAR) T Cells With a Chlorotoxin Tumor-targeting Domain for Patients with MMP2+ Recurrent or Progressive Glioblastoma. (PI: Badie)
NCT04661384 A Phase 1 Study to Evaluate IL13Rα2-targeted Chimeric Antigen Receptor (CAR) T Cells for Adult **Patients with Leptomeningeal Glioblastoma, Ependymoma or Medulloblastoma.** (PI: Feldman)

IL13Rα2-targeted CAR





How we can help you with your glioma patients

- COH Brain Tumor Board: Fridays 8:15-9:15 am
    - Join by televideo to present your case or send patient information/MRIs to vsainz@coh.org
- 2nd opinions
- Clinical trial options
- Happy to co-manage patients with you!

Thanks for your attention!

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