



ACRODeck

Glioblastoma Multiforme

Qateeb Khan, M.D.

Introduction to ACRODeck



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

Table of Contents

1. Clinical Presentation and Differential Diagnosis
2. Initial Workup
3. Staging
4. Treatment Summary
 - Surgery
 - Chemotherapy
 - Radiation
 - Tumor Treating Fields
5. Prognosis
6. Review Questions

Clinical Presentation and Differential Diagnosis

Presentation with seizures can be a positive prognostic factor

- As with any CNS lesion, the location of the lesion will determine the clinical presentation
 - Symptoms may include neurologic deficits, headaches, altered mental status, seizures, motor and sensory deficits, nausea and vomiting
- Differential Diagnosis:
 - Glioma
 - Ependymoma
 - Lymphoma
 - Brain metastasis
 - Intracranial abscess
 - Empyema
 - Multiple sclerosis

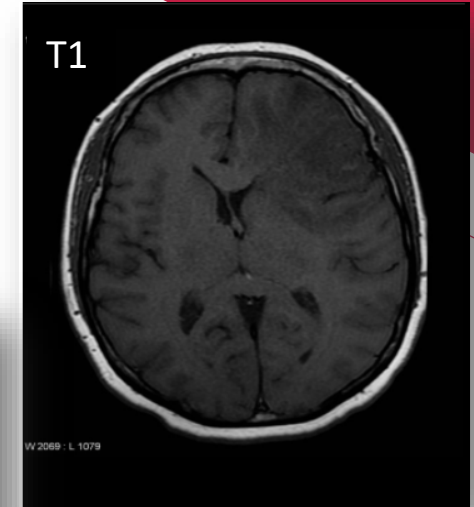
Initial Workup

- H/P
- CBC and CMP
- MRI brain with and without contrast (obtain one within 24-48 hours of resection as well)
 - Classic findings: heterogeneous enhancement, central necrosis with surrounding edema

MRI Sequence	Appearance	Visualization of ...
T1	Hypointense	Anatomy
T1c	Ring-Enhancing Lesion	Tumor
T2 / FLAIR	Hyperintense	Edema

- Consider steroids and anti-epileptics
- Maximal safe resection
 - Test for IDH and MGMT methylation status

For moderate/severe edema, can use:
- 10 mg loading dose of dexamethasone
- Followed by 4 mg q6hrs



Radiopaedia



Staging

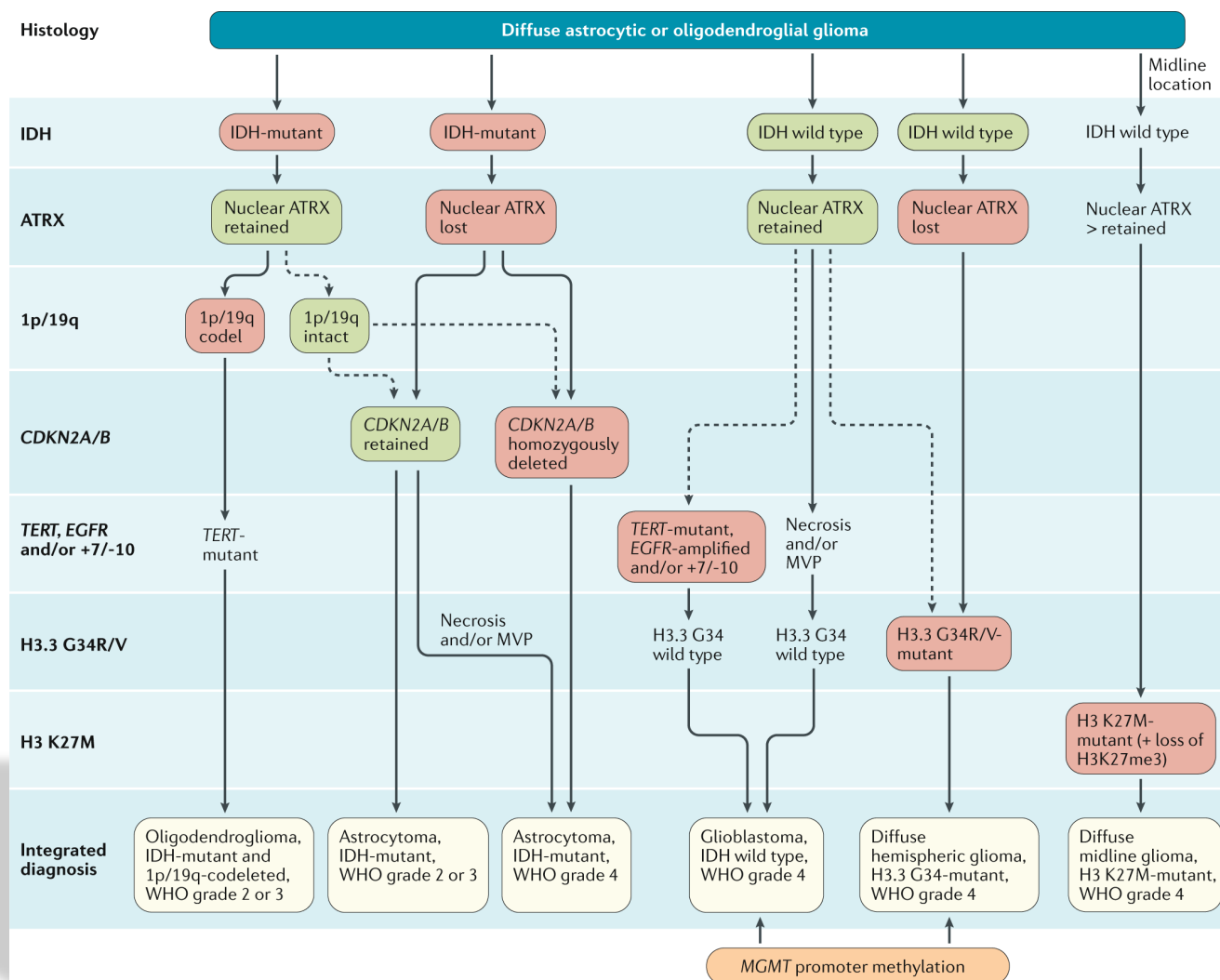
- Primary CNS tumors are graded, not staged

Historically, the MEAN criteria (mitotic index, endothelial proliferation, nuclear atypia, necrosis) was the cornerstone of CNS tumor grading

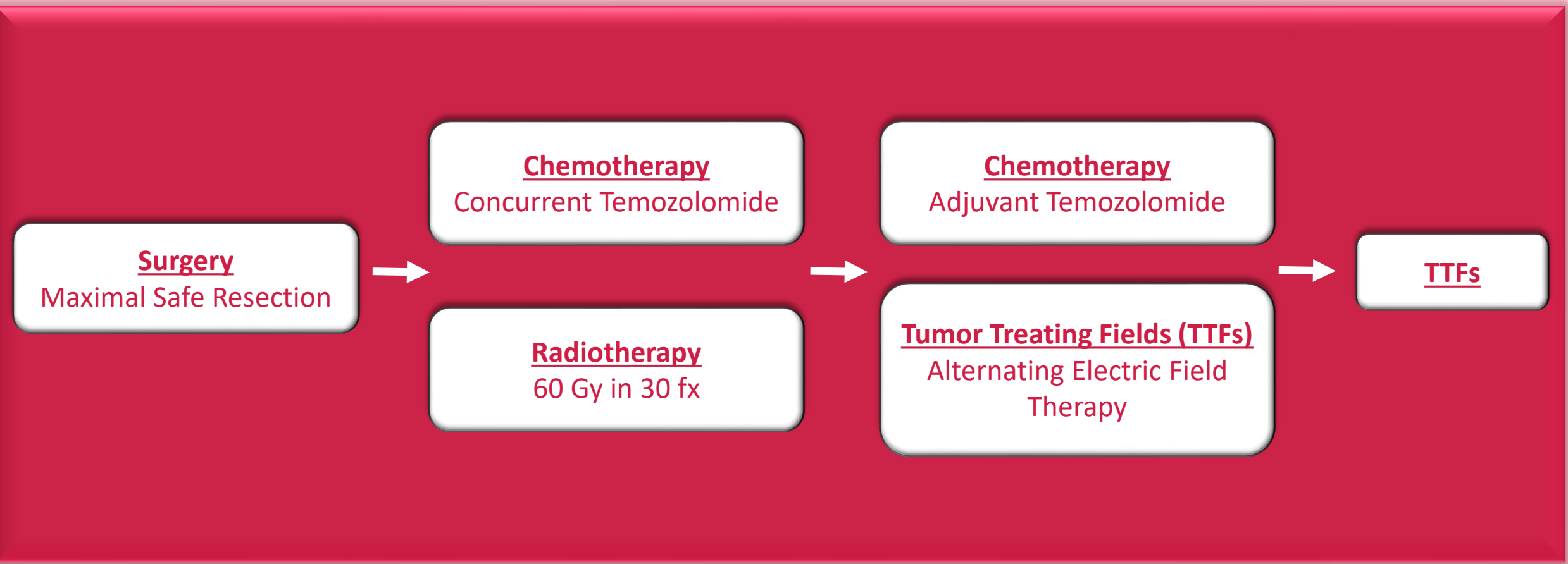
Tumor	WHO Grade
Pilocytic astrocytoma (and others)	1
Diffuse low-grade glioma	2
Anaplastic glioma	3
Glioblastoma Multiforme	4

Staging: 2021 WHO CNS5 Update

Now, molecular markers play a dominant role in tumor grading:
all GBMs are IDH-WT



Treatment Summary: Glioblastoma Multiforme



Surgery

As with other gliomas, a maximal safe resection is indicated

- A gross total resection is prognostic

The eloquence of the involved brain parenchyma often determines the extent of resection

Chemotherapy

Must give TMP-SMZ
(Bactrim) with TMZ, as
PCP prophylaxis

- Temozolomide (TMZ):
 - Concurrent TMZ
 - 75 mg/m² daily including weekends
 - Adjuvant TMZ
 - 6 cycles, each for 28 days
 - Dosed between 150 – 200 mg/m² daily
- Side effects of TMZ include diarrhea/constipation, development of a rash, mouth sores, edema, hair thinning, nausea, and thrombocytopenia
 - Ondansetron (Zofran) is often prescribed
 - Weekly CBC and CMP are obtained
 - Pregnant and nursing women should not use TMZ

Radiation

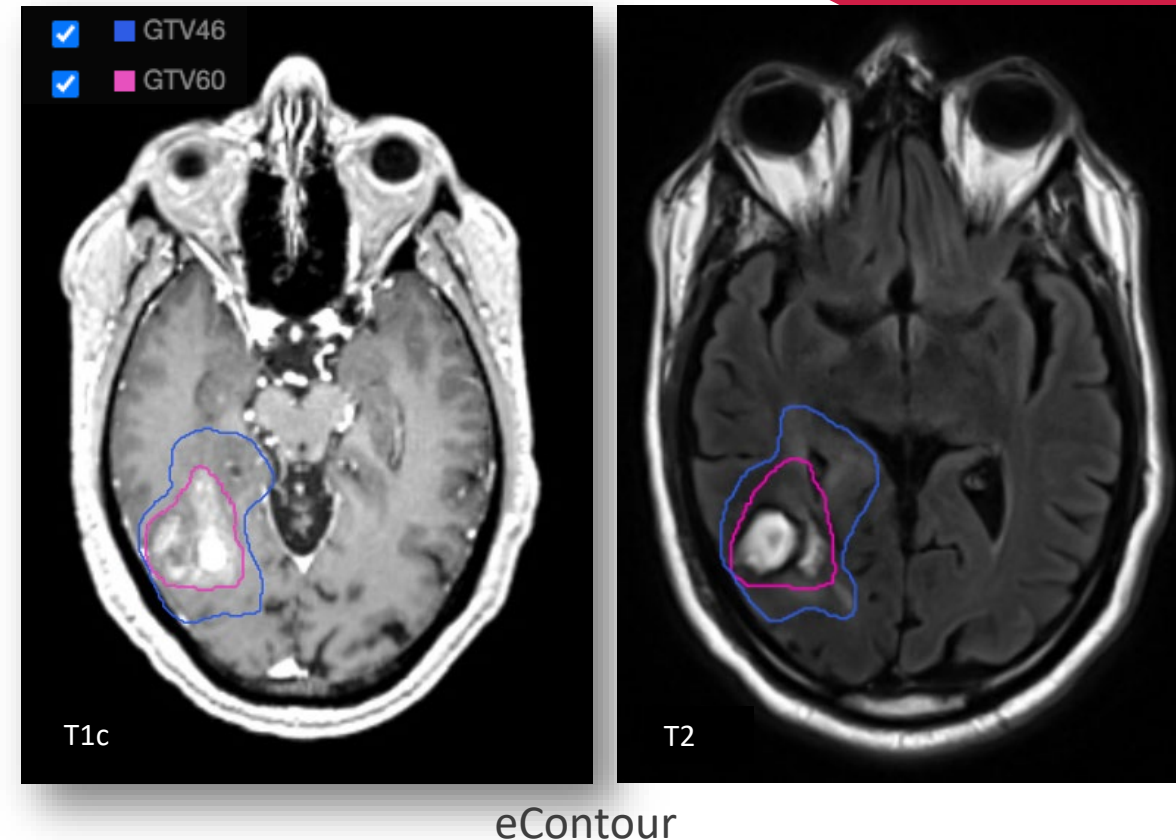
Radiotherapy
60 Gy in 30 fx

Simulation

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

Treatment

- 60 Gy in 30 fx is standard per Stupp regimen
 - PMID: 29260225
- For elderly patients with poor performance status, hypofractionated regimens can be considered:
 - 40 Gy in 15 fx, 34 Gy in 10 fx, 25 Gy in 5 fx
 - Can be administered with or without chemotherapy, based on the performance status of the patient



Radiation Treatment and Volumes: EORTC and RTOG

Please note there is considerable variation between institutions

Table 1

Guidelines for target delineation of glioblastoma, according to the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG).

EORTC treatment volumes (EORTC 22981/22961, 26071/22072 (Centric), 26981–22981, and AVAglio trials)	RTOG treatment volumes (RTOG 0525, 0825, 0913, and AVAglio trials)
Phase 1 (to 60 Gy in 30 fractions) GTV = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans). CTV = GTV plus a margin of 2 cm* PTV = CTV plus a margin of 3–5 mm	Phase 1 (to 46 Gy in 23 fractions) GTV1 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans) plus surrounding oedema (hyperintensity on T2 or FLAIR MRI scans). CTV1 = GTV1 plus a margin of 2 cm (if no surrounding oedema is present, the CTV is the contrast enhancing tumour plus 2.5 cm. PTV1 = CTV1 plus a margin of 3–5 mm Phase 2 (14 Gy boost in 7 fractions) GTV2 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans) CTV2 = GTV2 plus a margin of 2 cm PTV2 = CTV2 plus a margin of 3–5 mm

GTV = gross tumour volume; CTV = clinical target volumes; PTV = planning target volume.

MRI = magnetic resonance imaging.

* Margins up to 3 cm were allowed in 22981/22961 trial, and 1.5 cm in 26981–22981 trial.

Selected CNS Dose Constraints

Tumor coverage may sometimes be prioritized over OAR sparing

Organ at Risk (OAR)	Dose Constraint (Gy)
Optic Nerves and Chiasm	Max < 54 – 60
Brainstem	Max < 54 - 60
Cochlea	Mean < 45
Pituitary	Mean < 45
Hippocampus	Max < 16, D _{100%} < 9

Radiation Toxicities

Modern radiation techniques have greatly reduced treatment related toxicities

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

- Chronic:
 - Swelling
 - Radionecrosis
 - **Location-Dependent:** for example, if tumor is near the hippocampus, radiation can lead to memory issues

Tumor Treating Fields (TTFs)

This is a 2.7 lb device with
rechargeable batteries

- TTFs are alternating electric fields that function as a regional anti-mitotic treatment
- The patient's MRI is used to determine the transducer layout, utilizing a mapping software to optimize field intensity
- TTFs are used after chemoradiation, starting with adjuvant TMZ and are continued indefinitely thereafter



Prognosis

- Median survival ranges from 1.5 to 2 years
- The tumor will almost invariably recur; salvage options include:
 - Re-resection
 - Re-irradiation
 - 35 Gy in 10 fx (per RTOG 1205)
 - Stereotactic radiosurgery
 - Temozolomide, Nitrosoureas, Avastin



Review

In the 1920s,
hemispherectomies were
performed for GBMs

Review #1: The Correct Surgery

What is the correct oncologic surgery for a GBM?

- (A) Gross total resection
- (B) Stereotactic needle biopsy
- (C) Maximal safe resection
- (D) There is no role for surgery in GBM given the intensive chemoradiation treatments

Review #2: The Stupp Regimen

Which of the following treatment regimens is considered the standard of care for a newly diagnosed glioblastoma, with residual disease after surgery?

- (A) RT to 60 Gy with concurrent and adjuvant temozolomide + tumor-treating fields
- (B) RT to 60 Gy with concurrent and adjuvant temozolomide + bevacizumab
- (C) RT with a boost to 74 Gy with concurrent and adjuvant temozolomide + tumor-treating fields
- (D) RT with a boost to 74 Gy with concurrent and adjuvant temozolomide + bevacizumab

Review #3: Doses, Volumes, and Expansions

In 1978, WBRT to 60 Gy was found to double OS

Which of the following volumes and doses is correct for the treatment of a GBM, per the RTOG Guidelines?

- (A) A total of 46 Gy to the edema volume, seen best on the T2 MRI
- (B) A total of 60 Gy to the edema volume, seen best on the T2 MRI
- (C) A total of 46 Gy to the contrast enhancing volume, seen best on the T1c MRI
- (D) A total of 74 Gy to the contrast enhancing volume, seen best on the T1c MRI

There is less than 3% risk
of optic neuritis at this
dose

Review #4: Dose Constraints

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

- (A) Mean < 45 Gy
- (B) Max < 54 Gy
- (C) $V_{20} < 37\%$
- (D) Max < 45 Gy



Review #5: Follow-up

Note: Pseudoprogression
can be seen on post-
treatment imaging!

Per NCCN, which of the following is a correct follow-up timeline after treatment for a GBM?

- (A) Brain MRI q2 months indefinitely
- (B) Brain MRI q3 months indefinitely
- (C) Brain MRI at 1 month, and then q3 months indefinitely
- (D) Brain MRI at 1 month, and then q6 months indefinitely

Answer Key

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

NRG-BN007 is comparing
TMZ vs. Ipi/Nivo for
unmethylated tumors