1 ■ GLIOBLASTOMA

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QUICK HIT ■ GBM is the most common primary brain tumor in adults. GBM has a poor prognosis with a median survival of ~14 months. Treatment is maximal safe resection with neurologic preservation followed by adjuvant chemoRT. The standard RT dose is 60 Gy with TMZ given 75 mg/m^2 daily concurrently and 150 to 200 mg/m^2 adjuvantly for days 1 to 5 of a 28-day cycle for 6 to 12 months as tolerated. RT field is typically 46 Gy to T2/FLAIR edema and then additional 14 Gy boost to resection cavity and T1 contrast enhancement, generally with a 2-cm CTV expansion. The most common site of treatment failure is local progression. For older or frail patients, options include palliative care, short-course RT ± TMZ, or TMZ alone (particularly for MGMT methylated patients).

EPIDEMIOLOGY: Most common (80%) primary malignant brain tumor in adults.[1] Incidence: Three to four cases per 100,000 or about 10,000 cases/year in the United States. Median age at diagnosis is 64 and the male-to-female ratio is approximately 1.5:1.[2]

ANATOMY: Diffusely infiltrative tumor that grows along white matter tracts. Location is dependent on amount of white matter: 75% are supratentorial (31% temporal, 24% parietal, 23% frontal, 16% occipital), <20% multifocal, 2% to 7% multicentric, 10% present with positive CSF cytology.[3]

PATHOLOGY: Cell of origin is the supporting glial cells of CNS. WHO 2016 update[4] now defines three distinct types: glioblastoma, IDH-wild-type; glioblastoma, IDH-mutant; and glioblastoma, NOS (see the Genetics section for details on IDH1). Other rare variants include giant cell glioblastoma, gliosarcoma, or epithelioid glioblastoma. Diagnosis of a WHO grade IV glioma requires the pathognomonic finding of "pseudopalisading" necrosis OR at least three MEAN criteria: high **m**itotic index, **e**ndothelial proliferation, nuclear **a**typia, or **n**ecrosis.

GENETICS

MGMT Gene Methylation: O^6-methylguanine-DNA methyltransferase is located on chromosome 10q26. Its purpose is to repair alkylation of guanine at the O^6 position. When the promoter undergoes epigenetic silencing by methylation, the gene is downregulated. The Hegi study (see Evidence-Based Q&A) defined its prognostic and predictive value.

IDH1 Mutation: Present in ~10% of GBM and associated with increased age and secondary tumors that developed from previous low-grade gliomas.[4] IDH1 mutation is an independent positive prognostic factor (MS 27.4 months for IDH1-mutant vs. 14 months for IDH1-wild-type).[5]

EGFRv3 Variant: In-frame deletion of exons 2 to 7 of the *EGFR* gene affecting 801 base pairs and is an independent predictor of a poor prognosis with standard chemoRT.[6]

BRAF V600E Mutation: Same variant as in melanoma, but seen commonly in giant cell and epithelioid glioblastomas and lower grade gliomas.[7]

ATRX: Alpha-thalassemia/mental retardation syndrome x-linked gene (*ATRX*) is a gene that is involved in chromatin regulation. A mutation in ATRX is frequently seen in patients with grade II/III astrocytomas as well as patients with secondary GBM.[8–10]

See Chapter 3 for a discussion of 1p19q codeletion.

CLINICAL PRESENTATION: Headache, cognitive changes, seizure, motor weakness, nausea/vomiting, visual loss, sensory loss, language disturbance, dysphagia, papilledema, gait disturbance, intracranial bleed.

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WORKUP: H&P with neurologic exam. Fundoscopic exam (if suspicious of increased intracranial pressure).

Labs: CBC to establish baseline for CHT.

Imaging: MRI brain with and without gadolinium (heterogeneous enhancement, central necrosis, surrounding edema; T1 hypointense and T2 edema hyperintense).

Biopsy: Stereotactic or open biopsy with genetic assessment as earlier.

PROGNOSTIC FACTORS: Clinical factors as established by Li et al.[11]: KPS, age, extent of resection. MGMT status, IDH1 status. See Table 1.1 [12] for RTOG RPA.

Table 1.1: RPA Classification for Glioblastoma Multiforme

RPA Class	Defining Variables	MS (mos)	OS at 1, 3, and 5 Yrs
III	<50 y/o and KPS ≥90	17.1	70%, 20%, 14%
IV	<50 y/o and KPS <90 ≥50 y/o, KPS ≥70, resection, and working	11.2	46%, 7%, 4%
V + VI	≥50 y/o, KPS ≥70, resection, and not working ≥50 y/o, KPS ≥70, biopsy only ≥50 y/o, KPS <70	7.5	28%, 1%, 0%

Source: From Li J, Wang M, Won M, et al. Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. *Int J Radiat Oncol Biol Phys*. 2011;81(3):623–630. doi:10.1016/j.ijrobp.2010.06.012; Walker MD, Alexander E, Jr., Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: a cooperative clinical trial. *J Neurosurg*. 1978;49(3):333–343. doi:10.3171/jns.1978.49.3.0333

TREATMENT PARADIGM

Surgery: Primary treatment is maximal safe surgical resection with neurologic preservation. For technically unresectable tumors, a biopsy is warranted to obtain tissue. Various tools may be applied to improve safety of resection such as intraoperative ultrasound/MRI, functional mapping (phase reversal, direct brain stimulation, awake anesthesia). To evaluate the extent of resection, obtain a contrast-enhanced MRI within 72 hours of surgery (ideally 24–48 hours) to avoid confounding with subacute blood products.

Chemotherapy: As established in the Stupp trial, daily use of TMZ 75 mg/m^2 concurrently during RT course, including weekends. This is followed by adjuvant TMZ for d1–5 of 28-day cycle for 6 to 12 months, starting at 150 mg/m^2 and escalated as tolerated to 200 mg/m^2. Major side effects of TMZ are constipation, thrombocytopenia, and neutropenia. Patients treated with TMZ require prophylaxis against pneumocystis pneumonia and can be given daily DS trimethoprim/sulfamethoxazole or alternatively, two pentamidine inhalation treatments during the RT course. TMZ is a prodrug converted to MTIC, which alkylates DNA. Only 5% to 10% of methylation events yield the O^6-methylguanine, but if the methyl group is not removed prior to cell division, the adducts are highly cytotoxic (see MGMT earlier).

Radiation

Indications: Adjuvant RT improves OS vs. observation or CHT alone after surgery (see the following studies) and is indicated in all patients of sufficient functional status to tolerate treatment.

Dose: 60 Gy/30 fx is standard. For older or frail individuals, various hypofractionated schemes have been investigated (see the following studies). In the palliative setting, RT is superior to best supportive care in terms of OS.

Toxicity: Acute: Fatigue, headache, exacerbation of presenting neurologic deficits, alopecia, nausea, cerebral edema. Late: Cognitive changes, radiation necrosis, hypopituitarism, cataracts, vision loss (rare and location-dependent).

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapter 3.[13]

EVIDENCE-BASED Q&A

What is considered optimal surgery for glioblastoma?

Lacroix, MDACC (*J Neurosurg 2001*, PMID 11780887): RR showing improved OS with ≥98% resection in better prognostic patients (young, good KPS, no MRI evidence of necrosis). GTR also limits chance of cerebral edema during RT. **Conclusion: GTR improved OS in select patients compared with no clear benefit to STR**.

What are the contraindications to GTR?

Eloquent/inaccessible areas involved (brainstem, motor cortex, language centers, etc.), significant infiltration past midline, periventricular or diffuse lesions, medical comorbidities.

How did we arrive at the current standard RT dose?

The BTCG 69-01[12] and 1981 SGSG[14] studies demonstrated a doubling of survival with adjuvant RT over best supportive care. Dose escalation was beneficial to 60 Gy/30 fx, but there was no benefit to escalating to 70 Gy. A subsequent University of Michigan experience[15] showed that escalating to 90 Gy still resulted in 90% in-field failures and increase in toxicity. Thus 60 Gy/30 fx is considered the standard dose for GBM. A recent single-arm phase I study from the University of Michigan has shown promising median OS of 20.1 months with safe dose escalation to 75 Gy/30 fx along with concurrent and adjuvant TMZ.[16] This has raised the question again about the potential benefit of dose escalation in the TMZ era and has in part led to the ongoing NRG BN001 trial.

What chemotherapies have been used after surgery?

Historically, nitrosoureas were utilized, until a meta-analysis of PRTs of RT vs. RT + nitrosoureas showed only modest 1-year OS benefit.[17] BCNU was the RTOG standard of care for many years. BCNU wafers (Gliadel) were investigated in a phase III trial of RT ± BCNU wafers: MS improved to 13.9 months vs. 11.8 months.[18] However, the survival advantage was possibly driven by grade III patients, and a subsequent 2007 meta-analysis suggested BCNU wafers are not effective or cost-effective for glioblastoma.[19]

What trial defines the current standard of care in GBM management?

RT + concurrent and adjuvant TMZ is the standard of care based on the Stupp trial.

Stupp, EORTC 26899/NCIC (*NEJM* 2005, PMID 15758009; *Lancet Oncol* 2009, PMID 19269895): PRT of 573 patients with GBM, ages 18 to 70 with ECOG PS 0 to 2. All patients received EBRT 60 Gy/30 fx, and were randomized to RT alone or chemoRT with concurrent TMZ 75 mg/m^2 d1–7 q1week and then adjuvant TMZ 150 to 200 mg/m^2 d1–5 q4weeks × 6C. 80% received full course; 40% received full 6 cycles of adjuvant TMZ. OS and PFS were significantly improved (see Table 1.2) with the benefit holding across all subgroups and MGMT status as the strongest prognostic and predictive factor. **Conclusion: Concurrent chemoRT and adjuvant TMZ established as standard of care for GBM.**

Table 1.2 : Stupp Trial Results, Including 2009 Update (All Differences Are Statistically Significant)

	MS	2-Yr PFS	2-Yr OS	5-Yr OS
RT	12.1 mos	1.8%	10.9%	1.9%
RT + TMZ	14.6 mos	11.2%	27.2%	9.8%

What is the impact of MGMT status on the prognosis for GBM and their response to TMZ?

MGMT silencing is both prognostic (better outcome regardless of treatment) and predictive (better response to a specific treatment—TMZ in this case) for GBM.

Hegi (*NEJM* 2005, PMID 15758010): Subset analysis of 206 GBM patients in the Stupp trial, 45% of whom had epigenetic silencing of MGMT by methylation. Regardless of TMZ use, MGMT methylation was associated with improved OS (MS 15.3 vs. 11.8 months). Survival in methylated patients

treated with RT + TMZ vs. RT alone was 21.7 months vs. 15.3 months (p = .007) and 2-year OS was 46% vs. 23% (p = .007). In nonmethylated patients, MS difference between the groups was NS (12.7 vs. 11.8 months); however, 2-year OS was significant (13% vs. 2%). **Conclusion: MGMT methylation is both prognostic and predictive for response to TMZ.** *Comment: The use of TMZ in unmethylated patients is controversial; some feel the subset was underpowered and patients may still benefit.*

Is there any benefit to increasing the dose density of TMZ?

Gilbert, RTOG 0525 (*JCO* 2013, PMID 24101040): PRT of 833 patients treated 60 Gy/30 fx with daily TMZ (75 mg/m^2) randomized to adjuvant Stupp regimen (150–200 mg/m^2 × 5 days) vs. adjuvant TMZ 75 to 100 mg/m^2 × 21 days q4w × 6 to 12 cycles. Increasing the number of days that patients received TMZ did not improve OS or PFS, regardless of methylation status. However, the study did confirm the prognostic significance of MGMT methylation, with improved OS (21.2 vs. 14 months, p < .0001). **Conclusion: MGMT methylation is prognostic, but dose-dense TMZ was not beneficial.**

Is there any role of hyperfractionation in GBM?

RTOG 8302[20] and RTOG 9006[21] examined this question and showed no benefit to hyperfractionated RT compared to standard fractionation in patients with malignant glioma.

Does a radiosurgery boost improve disease control for GBM patients?

Souhami, RTOG 9305 (*IJROP* 2004, PMID 15465203): PRT of GBM patients with KPS ≥70 and unifocal, enhancing, well-demarcated, ≤4 cm lesion randomized to RT + BCNU ± upfront SRS (15–24 Gy, depending on size). MS was 13.5 months in SRS arm vs. 13.6 months in standard arm. **Conclusion: There is no role for an upfront SRS boost in GBM.**

Is there a role for a brachytherapy boost in malignant gliomas?

Two PRTs showed no improvement in overall survival with brachytherapy boost including using I-125 implant prior to EBRT or after EBRT in malignant gliomas.[22,23]

What is the role of WBRT in GBM?

WBRT can be considered for multifocal disease/subependymal spread, or poor performance patients (KPS <60), with comparable outcomes (MS ~7 months) to limited volume RT.[24,25]

What is the basis for the treatment volumes used during standard chemoRT?

After standard treatment, over 80% of recurrences occur within a 2-cm margin of the contrast-enhancing lesion seen on CT or MRI at original diagnosis.[26] *Thus high-dose treatment volume typically includes a 2-cm CTV expansion of the resection cavity and any residual enhancing tumor, as used in RTOG protocols. Though peritumoral edema seen on T2 and FLAIR MRI sequences is typically targeted in the low-dose PTV, retrospective single-institution reviews have suggested that there are no increased rates of local recurrence when peritumoral edema is not specifically targeted during radiation treatment.*[27] *In fact, EORTC protocols for GBM do not include targeting of edema volumes.*[26]

Is there a benefit to the addition of bevacizumab to TMZ?

Gilbert, RTOG 0825 (*NEJM* 2014, PMID 24552317): PRT in 637 GBM patients treated with the Stupp regimen with or without bevacizumab 10 mg/kg q2 weeks × 12 cycles after RT. Patients stratified by MGMT methylation status. Prespecified coprimary end points were OS and PFS. Use of bevacizumab did not improve MS (15.7 vs. 16.1 months). Although PFS was increased with use of bevacizumab (10.7 vs. 7.3 months, p = .007), this did not meet the prespecified end point of p < .004. Bevacizumab group was also associated with increased hypertension, VTE events, intestinal perforation, and neutropenia. **Conclusion: No improvement in OS with addition of bevacizumab to standard RT + TMZ; there was a modest PFS benefit, but this did not reach predefined target for statistical significance.**

Chinot, AVAGLIO Study (*NEJM* 2014, PMID 24552318): PRT of 921 patients with GBM treated with Stupp regimen with or without biweekly bevacizumab 10 mg/kg q2 weeks. OS was not statistically

improved 16.8 vs. 16.7 months. PFS was statistically improved to 10.6 from 6.2 months with addition of bevacizumab. However, higher grade III toxicity was observed in the bevacizumab arm 66.8% vs. 51.3%.

What are TTF and is there a benefit in GBM?

Polarization occurs in cells during the spindle formation process in mitosis. Alternating electric fields can be used to disrupt this normal polarization, thus inhibiting cell division. The FDA-approved NovoTTF-100A (Optune) is a device a patient wears on their head along with an attached portable battery pack that emits alternating electric fields.

Stupp (*JAMA* 2017, PMID 29260225): PRT of 695 patients with GBM treated with chemoRT (Stupp regimen) and then randomized to either conventional adjuvant TMZ or TTF + TMZ. MFU 40 months, minimum follow-up 24 months. TTF significantly improved OS (20.9 months vs. 16.0 months, $p < .001$) and PFS (6.7 m vs. 4.0 m, $p < .001$) with use of TTF + TMZ. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTF vs. no patients who received TMZ alone. **Conclusion: NovoTTF + adjuvant TMZ as part of Stupp protocol is associated with a 5-month OS benefit.**

MANAGEMENT OF OLDER/FRAIL PATIENTS WITH GBM

What is the role of RT over best supportive care?

Radiation therapy improves OS over best supportive care in older patients with good KPS.

Keime-Guibert, France (*NEJM* 2007, PMID 17429084): PRT of 81 patients ≥age 70 (all KPS ≥70) with newly diagnosed AA or GBM randomized to RT 50.4 Gy/28 fx vs. best supportive care after biopsy/resection. MS improved with RT (29.1 vs. 16.9 weeks, $p = .002$). No difference between the arms in terms of QOL or cognition. Trial closed early after interim analysis demonstrated improved OS with use of RT. **Conclusion: RT plays an important role in improving OS in GBM patients even in the older population, without decline in QOL or measured cognitive function.**

Is hypofractionation comparable to standard fractionation for older-adult/poor performance status GBM patients?

Multiple trials have demonstrated the efficacy of hypofractionated, shortened regimens for select patients who are not receiving systemic therapy. An important caveat is that these trials generally have not taken into account genetic markers and thus it is unknown what the durability of control is compared to standard therapy for those with favorable genetic profiles. Prospectively validated regimens include 40 Gy/15 fx, 34 Gy/10 fx, and 25 Gy/5 fx.

Roa, Canadian (*JCO* 2004, PMID 15051755): PRT of 100 patients ≥60 y/o randomized to 60 Gy/30 fx vs. 40 Gy/15 fx (no CHT), MS was 5.1 months for standard vs. 5.6 for shorter course RT (NS); shorter course arm required less steroid use at end of treatment (49% vs. 23%); 26% patients stopped long-course RT vs. 10% in short-course arm. **Conclusion: In patients older than 60 who are not receiving systemic therapy, there is no difference in OS between 40 Gy/15 fx and standard fractionation.**

Roa, IAEA (*JCO* 2015, PMID 26392096): PRT of 98 older/frail patients (age ≥50 and KPS 50–70 or age ≥65 with KPS ≥50) with GBM randomized to 25 Gy/5 fx vs. 40 Gy/15 fx. No CHT given. Patients receiving 25 Gy/5 fx had noninferior OS compared to those receiving 40 Gy/15 fx, and no difference in PFS or QOL. **Conclusion: Short-course RT delivered in 1 week (25 Gy/5 fx) is a treatment option for older and/or frail patients with newly diagnosed GBM.**

Can TMZ be substituted for RT in elderly patients?

TMZ alone is a noninferior option compared to standard RT in older patients and may be preferred over RT alone in patients with MGMT promoter methylation.

Wick, NOA-08 (*Lancet Oncol* 2012, PMID 22578793): PRT of 373 patients with AA (11%) or GBM (89%), age >65 and KPS ≥60 randomized to (a) TMZ alone (100 mg/m^2 for 7 days, alternating with 7 days off, for as long as tolerated) vs. (b) standard RT alone (60 Gy/30 fx). OS for patients receiving TMZ alone was noninferior to those receiving standard RT (8.6 months vs. 9.6 months). Patients with MGMT promoter methylation had improved OS compared to unmethylated patients. Patients

with MGMT methylation had significantly improved EFS with receipt of TMZ compared to RT. Patients without methylation had significantly improved EFS when receiving RT compared to TMZ. **Conclusion: TMZ alone is noninferior to standard RT alone in this older patient population. MGMT promoter methylation is an important prognostic factor and may be predictive for appropriate treatment regimen.**

Malmström, Nordic Trial (*Lancet* 2012, PMID 22877848): PRT of 342 patients with GBM and age >60 randomized to CHT alone (TMZ 200 mg/m^2 d1–5 of 28-day cycle for up to 6 cycles) vs. 60 Gy/30 fx vs. 34 Gy/10 fx. MS significantly improved for patients receiving TMZ alone (8 months) vs. standard RT (6 months) but not vs. hypofractionated RT (7.5 months). For patients >70, survival was improved in both the TMZ and hypofractionated arms compared to standard fractionation. **Conclusion: Older patients had a detriment in OS when receiving standard RT compared to TMZ alone. Use of TMZ alone or hypofractionated RT should be considered standard in the elderly population, especially if over age 70.**

■ Should TMZ be added to short-course RT?

Perry, EORTC 26062 (*NEJM* 2017, PMID 28296618): PRT of patients with age ≥60 with newly diagnosed GBM were treated with 40 Gy/15 fx and randomized to no systemic therapy vs. 3 weeks concurrent TMZ and monthly adjuvant TMZ up to 12 cycles. RT + TMZ significantly improved OS compared to RT alone (9.3 vs. 7.6 months, $p = .0001$). PFS was improved as well (5.3 vs. 3.9 months, $p < .0001$). OS improved in MGMT methylated (13.5 vs. 7.7 months, $p = .0001$) but not statistically significant in unmethylated patients (10 vs. 7.9 months, $p = .055$). **Conclusion: There is an OS benefit to the addition of TMZ to RT even for those receiving a hypofractionated regimen. Patients with MGMT methylation benefit most from RT + TMZ with a ~6-month improvement in OS.**

RECURRENT/PROGRESSIVE GBM

■ What are the options when there is disease recurrence?

Recurrence is common with 80% of recurrences within 2-cm of primary.[26] Options include re-resection, ± carmustine wafer placement, bevacizumab, and TTF.

■ Is re-irradiation an option for progression?

Fokas (*Strahlenther Onkol* 2009, PMID 19370426): RR of 53 patients with recurrent GBM. Demonstrated MS of 9 months after re-RT with median dose of 30 Gy in median dose/fx of 3 Gy; only KPS <70 predicted for poor survival. Well tolerated with no acute or late toxicity >2. **Conclusion: Hypofractionated RT is safe and feasible for re-irradiation of GBM.**

■ What is the role of pulsed-reduced dose-rate re-irradiation to minimize toxicity?

The inverse dose-rate effect may allow for reassortment of tumor cells while the treatment is delivered, perhaps leading to increased tumor kill with decreased toxicity due to normal tissue repair.

Adkison, Wisconsin (*IJROBP* 2011, PMID 20472350): RR of 103 patients (86 with GBM) with pulsed reduced dose-rate re-RT. RT was delivered slowly at 0.0667 Gy/min to a median dose of 50 Gy. Four of 15 patients had significant RT necrosis on autopsy. MS for GBM patients after pulsed reduced dose-rate RT was 5.1 months. **Conclusion: Pulsed-reduced dose-rate RT appears safe in the re-irradiation setting in order to treat larger volumes to a higher dose.**

■ Is bevacizumab effective for recurrent GBM?

Bevacizumab is beneficial in improving PFS as a second-line therapy with or without re-irradiation; however, it is associated with a higher rate of toxicity.

Wong (*JNCCN* 2011, PMID 21464145): Meta-analysis of 15 trials (mainly phase II data) with a total of 548 patients treated with bevacizumab at recurrence. MS was 9.3 months 6% complete response, 49% partial response, and 29% stable disease.

Friedman, BRAIN Trial (*JCO* 2009, PMID 19720927): A total of 167 patients with recurrent GBM were randomized to bevacizumab or bevacizumab + irinotecan. MS 9 months in each arm; however, significantly worse grade III toxicities with use of combination therapy.

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