SA–CME Information

CHEMORADIATION TREATMENT OF GLIOBLASTOMA MULTIFORME: TREATMENT GUIDELINES AND CONSIDERATIONS

Description

Authors review the North American and European guidelines for chemoradiation of GBM created as a result of the new 2016 WHO classification system, focusing specifically on age, performance status, molecular markers, and disease recurrence. They also discuss factors such as socioeconomic and insurance status that impact radiation treatment compliance and GBM outcomes.

Learning Objectives

After completing this activity, participants will be able to:

1. Learn about radiation treatment indications for glioblastoma and the factors impacting treatment recommendations.
2. Apply radiation volume determinations and varying radiation schedules based on patient age, performance status, and methylation status.
3. Expand arsenal of adjuvant treatment modalities to include tumor-treating fields (TTFields), proton beam therapy (PBT), and dendritic cell vaccines.
4. Define social determinants of health and socioeconomic status.
5. Adopt a better understanding of the impact of social determinants of health on radiation treatment and glioblastoma outcomes.

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Chemoradiation treatment of glioblastoma multiforme: Treatment guidelines and considerations

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Glioblastoma (GBM) is the most common primary malignant neoplasm of the brain, with an incidence of 3.19 per 100,000 persons in the US.[1] Standard of care includes maximal surgical resection and radiation therapy (RT) with concomitant temozolomide (TMZ) chemotherapy. The median 3-year survival rate for a newly diagnosed patient with this aggressive cancer remains a dismal 10.1%.[2] Nevertheless, recent advancements in the use of alternating electric field therapy, also known as tumor-treating fields (TTFields), and dendritic cell vaccines are beginning to challenge the status quo with initial results yielding a median overall survival of 20.9 months.[3,4] Moreover, molecular characterization of primary brain tumors has had a substantial impact on the stratification of central nervous system (CNS) neoplasms. This includes a more nuanced characterization of GBM molecular markers, thus leading to the creation of an integrated diagnosis.[5] In this review, we highlight the North American and European guidelines for chemoradiation of GBM created as a result of the new 2016 World Health Organization (WHO) classification system. Specifically, we focus on the factors of age, performance status, molecular markers, and disease recurrence as the main components for the clinical application of the guidelines. Furthermore, we highlight factors, such as socioeconomic and insurance status, that impact radiation treatment compliance and GBM outcomes.

Standard of Care

Therapy for GBM is divided into multiple strata of treatment modalities including surgery, radiation and chemotherapy. Tumor molecular markers may be used as a guiding prognostic factor to optimize a personalized treatment plan.[6,7] These molecular features confer a survival advantage in GBM, as they predict a favorable treatment response. Markers screened for after a histologic diagnosis of GBM may include: O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status and isocitrate dehydrogenase (IDH) mutation.[7] In this article, however, we will focus on MGMT promoter methylation status. Furthermore, tumor resectability, Karnofsky Performance Score (KPS), and patient age are important components of the clinical-care decision-making process (**Table 1**).[8]

Patients Age < 70

For patients age < 70 years and a KPS ≥ 60, guidelines recommend maximal surgical resection followed by adjuvant therapy.[7-11] The type of adjuvant treatment is dictated by postresection KPS and MGMT promoter status. For patients < 70, postresection KPS ≥ 60, and methylated MGMT promoter status, guidelines recommend standard brain RT, concurrent plus adjuvant temozolomide (TMZ), and TTFields.[7] Recommendations remain the same for patients with the same age and KPS bracket but an unmethylated/indeterminate MGMT promoter.[7] However, standard brain RT alone is an option for this second group. According to the American Society for Radiation Oncology (ASTRO) guidelines, standard brain RT entails partial-brain RT of 60 Gy in 2-Gy fractions (30 total fractions) delivered throughout 6 weeks.[8] Similarly, the European Association for Neuro-Oncology (EANO) guidelines recommend focal

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Table 1. Overview of Adjuvant Treatment According to Age, KPS, and Recurrence

	KPS 60 ± methylated MGMT promotor status	KPS < 60
Patients < 70 years	Standard brain RT + concurrent & adjuvant TMZ ± alternating electric fields therapy	Hypofractionated brain RT ± concurrent & adjuvant TMZ or TMZ alone or Palliative care
Patients > 70 years	Standard brain RT + concurrent & adjuvant TMZ ± alternating electric fields therapy or Hypofractionated brain RT ± concurrent & adjuvant TMZ or Hypofractionated brain RT alone or TMZ alone (unmethylated only)	Hypofractionated brain RT ± concurrent & adjuvant TMZ or TMZ alone or Palliative care
Recurrent Glioblastoma	Palliative care or Consider systemic chemotherapy or Consider reirradiation	

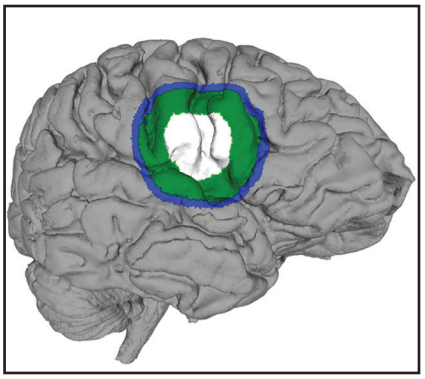

FIGURE 1. *Computer-generated rendition of targeted partial-brain radiation therapy of a right hemispheric glioblastoma (surface only). White represents gross tumor volume (GTV); surgical bed. Green shows clinical target volume (CTV); GTV + 1 to 2.5 cm margin. Blue is the planning target volume (PTV); CTV + 0.3 to 0.5 cm margin. Note: For illustration purposes only; dimensions not drawn completely to scale.*

RT of 50-60 Gy in 1.8-2.0 Gy fractions following surgical resection or biopsy in patients < 70 years of age and a KPS ≥ 70. Gross total resection has been shown to improve outcomes and is therefore recommended for clinically eligible patients.[6] Both ASTRO and EANO guidelines recommend targeted delivery of radiation against whole-brain therapy to minimize toxicity to structures such as the optic nerves, optic chiasm, retinas, brainstem, pituitary, cochlea, hippocampus and other sensitive structures.[6-8]

Determining the tumor volumes is an important consideration when conducting partial-brain RT in GBM patients (**Figure 1**). The gross tumor volume (GTV) includes the surgical bed and any area of postsurgical or postbiopsy T1 MRI enhancement. The clinical target volume (CTV) is defined as the GTV and any residual T2W or fluid-attenuated inversion recovery (FLAIR) signal abnormalities plus an additional margin of 1 to 2.5 cm. Finally, the planning target volume (PTV) of 0.3 cm to 0.5 cm is added onto the CTV to account for daily setup error.[6] Radiation may be administered using 1- or 2-phase radiation target volume strategies. The 1-phase target volume approach encompasses the CTV and margin without targeting edema.[8] In contrast, the 2-phase target volume method includes the CTV, margin, and edema measured using hyperintense T2 and FLAIR MRI regions as a guide. This is subsequently narrowed down to target only the gross residual tumor and resection cavity in the second phase.[8]

In addition to surgery and radiation, chemotherapeutic agents are the mainstay of treatment. Concurrent and adjuvant TMZ is recommended as its addition to radiation in the treatment of newly diagnosed GBM has been shown to provide a survival benefit.[12,13] A study by Ballhausen et al demonstrated improved survival with daily concurrent TMZ administration (15.7 months) during radiation treatment compared to TMZ administration for 5 out of 7 days (12.6 months).[14] Currently, the Radiation Therapy Oncology Group (RTOG) / NRG, National Comprehensive Cancer Network (NCCN), EANO, and the Medical Oncology Spanish Society (SEOM) guidelines recommend 75mg/m^2 daily concurrent TMZ throughout radiation treatment followed by maintenance therapy of 150-200mg/m^2 for 5 days every 4 weeks for 6 cycles.[6]

Finally, the inclusion of TTFields as part of the treatment plan is improving the overall survival of patients with GBM. This noninvasive antimitotic therapy consists of low intensity, 200 kHz frequency, and alternating electrical currents delivered via 2 transducer arrays on a shaved scalp (**Figure 2**). The device is worn ≥ 18 hours/day on the same days as administrations of TMZ.[3] When used at a monthly compliance of > 90% TTFields have resulted in a statistically significant improvement in the median overall survival to 24.9 months.[15] TTFields, however, are an option only for patients with supratentorial disease.[7]

Patients Age > 70

For patients > 70 years old, performance status and MGMT status are important considerations when choosing the treatment regimen with the utmost benefit in survival and quality of life. Treatment remains controversial and attempts are underway to understand the role of TMZ and hypofractionated RT in the elderly, especially in those

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FIGURE 2. *(A) Optune Device, an FDA-approved medical device for delivering alternating electric field therapy via 4 transducers. (B) Patient with transducers placed on scalp. ©2019 Novocure. All rights reserved.*

with unmethylated MGMT promoters and those with poor performance status.[16] Nonetheless, there is surmounting evidence that RT in those >70 improves survival when compared to supportive care alone with similar quality of life and cognitive evaluations between groups.[17] In addition, hypofractionated RT has been shown to reduce steroid utilization and decrease early RT termination when compared with standard-length RT.[18]

According to EANO guidelines, treatment decisions should be based on MGMT status for patients >70 who are not eligible for radiation with concurrent or maintenance TMZ. Patients with MGMT methylation status are recommended to receive TMZ alone for 5 consecutive days every 28 days. Patients with non-MGMT/indeterminate methylation status should undergo hypofractionated RT of 40 Gy in 15 fractions using a similar T2W abnormality plus a 2-cm margin for planning tumor volumes.[6] ASTRO guidelines recommend a similar radiation schedule (40 Gy in 2.66 fractions) in addition to TMZ in elderly patients with good to reasonable performance status.[8] In contrast, SEOM recommends treatment with TMZ alone for patients with poor performance status and MGMT methylation.[19] In addition, the Nordic randomized phase III clinical trial found similar median survival when comparing TMZ alone to hypofractionated RT (34 Gy in 10 fractions) in patients > 60 years.[20] Results from Perry et al on elderly patients with GBM, however, have led to the consideration of short-course RT (40 Gy in 15 fractions) plus TMZ as standard of care.[21] CTV determinations for patients > 70 receiving hypofractionated RT should be made as described above for patients < 70 years old.[6]

In elderly patients with GBM, a KPS > 70, and MGMT promotor methylation, a study by Palmer et al reported that 49% of physicians surveyed recommended a standard course of radiation and chemotherapy while 39% recommended a short course of radiation and chemotherapy.[22] In elderly patients with KPS > 70 and non-MGMT methylation status, 51% of physicians recommended a short course of radiation alone. In patients with KPS < 50, 57% of physicians recommended supportive care. Although more studies are needed to elucidate optimal treatments in elderly patients with GBM, evidence suggests improved outcomes with use of hypofractionated RT and TMZ. A clinical trial by Perry et al showed improved median overall survival and median progression-free survival in elderly patients age > 65 who received hypofractionated RT (40 Gy in 15 fractions) and TMZ compared with those who received hypofractionated RT alone.[21]

Finally, despite advantages seen in patients < 70 years, and calls from the medical community and several medical governing bodies worldwide, the EANO and ASTRO have yet to include the use of TTFields in this patient cohort. However, 1 randomized clinical trial demonstrated a survival benefit in patients > 70 with a good performance status (KPS ≥ 70).[3]

Recurrent Glioblastoma

Unfortunately, most patients experience GBM recurrence despite maximal surgical resection, radiation and chemotherapy. Typically, recurrence of GBM occurs locally, most commonly within approximately 2 cm of the surgical resection cavity.[23,24] One study found a median progression-free survival of 7 months after local tumor recurrence.[24] The median overall survival rate after diagnosis of recurrence is still an estimated 22-44 weeks.[25] Nonetheless, maximal safe surgical resection can be done in clinically eligible patients; however, no consensus exists regarding maximal safe resection or dosage or type of chemoradiation therapy for tumor recurrence; the treatment plan remains the choice of the physician and patient.[23,24] To date, Scoccianti et al provides the most comprehensive effort to create a treatment protocol for recurrent GBM combining various approaches used in the US and Europe.[26] The results of their retrospective analysis suggest that radiation-only therapy as a salvage treatment has the likelihood of a relatively good outcome.[26] Patients are stratified according to the CTV of the recurrent neoplasm. Moreover, to minimize neurotoxicity patients should be treated using different fractionation and differentiated total dose in 2 Gy fractions. If the CTV is < 12.5 ml, then < 65 Gy with radiosurgery should be administered; if > 12.5 ml and < 35 ml, then <50 Gy with hypofractionated stereotactic RT should be administered; and if > 35 ml and < 50 ml, then < 36 Gy with conventionally fractionated RT should be administered.[26] Furthermore, newer technologies such as proton beam therapy may be a promising mo-

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dality given its role in many skull base tumors and pediatric cancers; however, it has not yet established itself in the treatment of GBM. More research will be required to determine whether protons and other heavy particles offer an advantage in GBM dosimetry.[27]

In the US, several options are available to the patient. First, if the postresection KPS > 60, systemic chemotherapy can be considered. Recommended regimens include TMZ, bevacizumab, lomustine/carmustine, procarbazine, and/or vincristine. If there has been a long time between stopping TMZ and tumor progression, it is reasonable to restart the patient on TMZ—especially if the tumor is MGMT methylated.[28] Similarly, lomustine/carmustine is a reasonable second-line therapy for a tumor that is MGMT methylated.[29] Next, although bevacizumab has not demonstrated improved overall survival in recurrent GBM, it is still FDA-approved based on improved performance status.[30,31] Furthermore, evidence from the EF-11 randomized phase III clinical trial indicates the equivalence of chemotherapy and TTFields in treatment of recurrent GBM. TTFields were found comparable to chemotherapy in median survival and progression-free survival with improved quality of life seen in the TTFields cohort.[32]

Radiation Treatment and Social Determinants of Health

In recent years, social determinants of health—the circumstances in which people are born, grow up, live, work and age, and the systems put in place to deal with illness—have increasingly become a topic of research in the treatment of GBM.[33] One influential factor driving this exploration is the ever-rising cost of US healthcare, especially in neuro-oncology. As the use of TMZ, trial-combined chemotherapy (such as TMZ and bevacizumab), and TTFields has increased, so has the overall cost of the treatment course for newly diagnosed GBM. A recently published analysis evaluating the direct medical costs of GBM found that the mean total cumulative costs per patient from 3 months prediagnosis to 12 months, and to 5 years post diagnosis were $201,749 and $268,031, respectively.[34] Broken down further, the average per-patient per-month post-GBM diagnosis was $7,394.[34] Given these substantial costs, there is little surprise that the standard-of-care treatment course can be deemed cost-prohibitive. Rhome et al found that compliance with chemotherapy treatment was associated with male gender, white race, younger age (< 50 years), higher performance status (> 70), insurance status, higher income/education, and receipt of treatment at an academic center.[35] This can have an overwhelming negative effect on overall patient survival, especially when compliance with treatment such as TTFields is closely linked with overall rates of survival.[15]

Unfortunately, supporting evidence in this matter is only beginning to be discovered, despite the use of surgery, chemotherapy, and radiation in the treatment of GBM for more than 20 years. For example, a recent national survey of NCCN panel members showed that neither sexual orientation nor gender identity, which are part of social determinants of health, were thought to be relevant to the focus of the NCCN guidelines.[36] Moreover, 77% responded that their panels currently do not address LGBTQ issues, with no plans to address them in the future.[36]

Furthermore, socioeconomic status, which encompasses education, income, and occupation, has been shown to impact time to radiation treatment.[37] One study by Pollom et al showed that in patients who underwent gross total tumor resection, those who received radiation within 15 to 21 days had a statistically significant improved survival with a trend in improved survival in those receiving treatment within 22 to 35 days.[36] The study found that patients who had Medicaid, government insurance, were uninsured, or lived in metropolitan areas were less likely to receive radiation within 35 days compared to patients from higher income areas. Other studies have shown the impact of insurance on radiation treatment. A study by Brown et al demonstrated a significant association between insurance type and odds of receiving radiation treatment. Patients with Medicare had the highest odds of receiving radiation, Medicaid patients had lower odds, and uninsured patients had the lowest odds.[38] Lastly, a study by Chandra et al showed that uninsured patients had significantly lower rates of radiation and TMZ treatment.[39]

Conclusion

In this review, we provide a simple overview of the current state of radiation use for treatment of GBM. Some of the most important prognostic factors and guiding principles are based on age, performance status, and tumor molecular markers. Conventionally fractionated stereotactic RT for patients < 70 years old yields the best results for progression-free survival. Hypofractionated stereotactic RT for patients > 70 years old can also be considered for improved progression-free survival. Recent studies have elucidated the benefit of newer treatment modalities such as TTFields and their significant benefit in progression-free and overall survival. Lastly, recent literature has demonstrated the impact of socioeconomic status and insurance status on radiation treatment after GBM surgical resection.

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