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Recurrent glioblastoma multiforme: a review of natural history and management options

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✓ Glioblastoma multiforme (GBM) is one of the most aggressive primary brain tumors, with a grim prognosis despite maximal treatment. Advancements in the past decades have not significantly increased the overall survival of patients with this disease. The recurrence of GBM is inevitable, its management often unclear and case dependent. In this report, the authors summarize the current literature regarding the natural history, surveillance algorithms, and treatment options of recurrent GBM. Furthermore, they provide brief discussions regarding current novel efforts in basic and clinical research. They conclude that although recurrent GBM remains a fatal disease, the literature suggests that a subset of patients may benefit from maximal treatment efforts. Nevertheless, further research effort in all aspects of GBM diagnosis and treatment remains essential to improve the overall prognosis of this disease.

Key Words • treatment planning • recurrent brain tumor • progressive disease • survival • resection • outcome

Glioblastoma multiforme is a World Health Organization Grade IV tumor that represents 15 to 20% of all primary intracranial tumors.[2] It is the most malignant astrocytic tumor, with histopathological features that include cellular polymorphism, brisk mitotic activity, microvascular proliferation, and necrosis. Despite advances in imaging techniques and multimodal treatment options, the overall prognosis of patients with GBM remains grim. The median duration of patient survival is estimated to be between 12 and18 months with maximal treatment, but those without any intervention die soon after diagnosis.[23,46] To date, very few cases of curative outcome or long-term survival have been reported.[55,58,72] In a large retrospective study, Scott, et al.,[58] estimated that 2.2% of the cohort survived for more than 2 years. Overall, the 5-year survival rate is less than 10%, with a final mortality rate of close to 100%.[24,38]

Glioblastoma has an unfavorable prognosis mainly due to its high propensity for tumor recurrence. It has been suggested that GBM recurrence is inevitable after a median survival time of 32 to 36 weeks.[1,19] The natural history of recurrent GBM, however, is largely undefined for the following reasons: 1) lack of uniform definition and criteria for tumor recurrence; 2) institutional variability in treatment philosophy; and 3) the heterogeneous nature of the disease, including location of recurrence and distinct mechanisms believed to contribute to known subtypes of GBM. For this report, we performed a PubMed-based literature search focusing on the terms "recurrent glioblastoma" and "management." We summarize various published studies to provide insight into the currently used surveillance algorithm and treatment strategies for recurrent GBM (Fig. 1). Furthermore, we discuss novel research that may potentially aid in preventing or controlling GBM progression and recurrence.

Abbreviations used in this paper: AA = anaplastic astrocytoma; BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea (carmustine); CBV = cerebral blood volume; Cho = choline; Cr = creatine; GBM = glioblastoma multiforme; KPS = Karnofsky Performance Scale; Lac = lactate; MR = magnetic resonance; NAA = *N*-acetyl aspartate; PET = positron emission tomography; PFS = progression-free survival; QOL = quality of life; SRS = stereotactic radiosurgery; TMZ = temozolomide; VEGF = vascular endothelial growth factor.

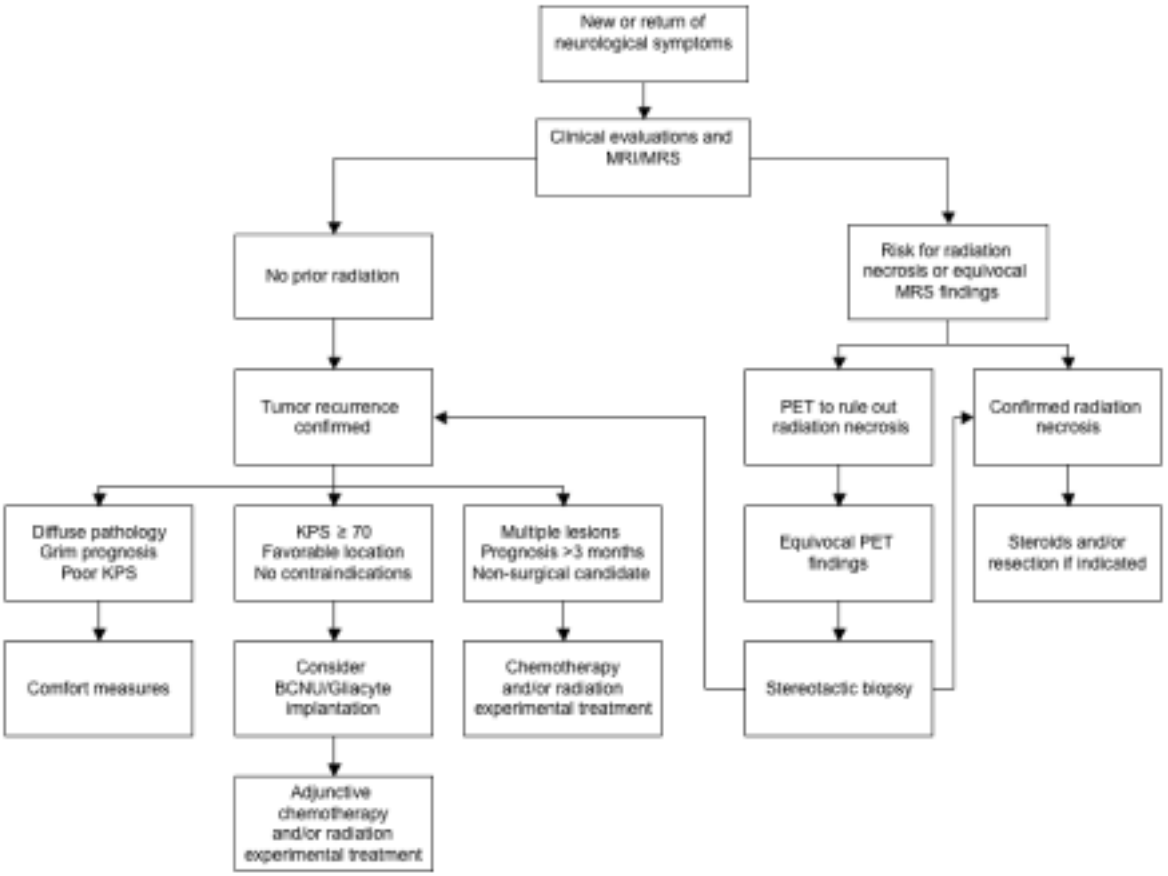

FIG. 1. Management algorithm for recurrent GBM. MRS = MR spectroscopy.

Definition of Recurrent GBM

The criteria used to define recurrent GBM remain ambiguous due to the varied presentation of new lesions. First, the infiltrative nature of GBM cells makes it difficult to eliminate microscopic disease despite macroscopic gross-total resection. Studies have shown that GBM recurrence most often occurs in the form of a local continuous growth within 2 to 3 cm from the border of the original lesion.[27,30,42] Choucair, et al.,[19] reported that more than 90% of patients with glioma showed recurrence at the original tumor location and that multiple lesions developed in 5% after treatment. Second, although less common, GBM may also recur through the development of new parenchymal lesions that fail to exhibit continuous growth patterns, intraventricular spread, or dissemination.[43] Bauman, et al.,[7] have shown that uncommon relapse patterns are more prevalent in midline tumors and tumors that infiltrate both hemispheres. Finally, in an attempt to preserve neurological function and maintain patient QOL, subtotal resections are sometimes performed when tumors infiltrate eloquent areas of the brain. Tumor recurrence is also defined by the appearance of residual tumor growth on imaging studies or the manifestation of new clinical symptoms. The term "tumor recurrence" is frequently used synonymously with "tumor progression" because of the spectrum from which new lesions can develop. Thus, researchers and clinicians often define GBM recurrence as a change from a previous interval of tumor absence or a loss of prior complete tumor control. Despite this, variability exists among different studies, institutions, and practices. Certain authors define tumor progression from a residual tumor as a 25% increase in the cross-sectional area of the tumor in the slice with the greatest amount of tumor or as a 25% increase in contrast-enhancing volume,[67] although recurrence has also been defined as a greater-than-50% growth in the time between two successive imaging studies.[5] Therefore, it is important to note that the following results summarized from various studies reflect inherit differences in selection criteria. However, the significance of such differences may have a minimal impact in terms of overall prognosis of recurrent GBM.

Epidemiology

Although the epidemiology of GBM is well established, the heterogeneity in defining recurrence and the variability of treatment algorithms that are used at different institutions result in a vague profile of recurrent GBM. In a multicenter trial that included 222 patients with recurrent GBM to evaluate intraoperative placement of a biodegradable Gliadel wafer, the patient cohort was predominantly men (64.5%) in the fifth decade of life (median age 48 years). The median interval from

initial diagnosis to evidence of tumor recurrence was 12 months, but most patients (> 80%) were noted to have undergone less than 75% tumor resection during initial surgery. In this study, patients with a KPS score less than 60 were excluded.[12] Among a cohort of 301 patients with GBM, Barker, et al.,[5] identified 223 with tumor recurrence. Without selection bias, 64% of patients had a KPS score less than 70 at time of recurrence. These predominantly male patients (63%) had a mean age of 54 years. The median interval from initial diagnosis to clinical or radiographic evidence of tumor recurrence was 4.9 months.

The recurrence of GBM is detected during imaging surveillance or by the development in the patient of new or recurring symptoms and signs. In a questionnaire-based study by Osoba, et al.,[49] patients with recurrent GBM or AA with a KPS score less than 70 self-reported the following symptoms: fatigue, uncertainty about the future, motor difficulties, drowsiness, communication difficulties, and headaches. In addition, the patients also complained of pain and visual deficits. Although most symptoms were likely due to tumor recurrence, the authors stated that confounding factors such as radiation necrosis and steroid treatments may have contributed to generalized fatigue, whereas pain and uncertainty of the future may have been nonspecific for brain cancer. Difficulties in motor function, vision, leg strength, and pain were reported more frequently by patients with recurrent GBM than by those with recurrent AA, providing evidence that disease aggression may be directly related to degree of neurological deficit.

Imaging Studies

Gadolinium-Enhanced MR Imaging

Gadolinium-enhanced MR imaging remains the gold-standard imaging modality for the assessment of all intracranial neoplasms. However, standard guidelines do not exist in determining the timing and frequency of obtaining posttreatment imaging studies for surveillance of recurrent GBM.[67] Generally, postoperative contrast-enhanced MR images are obtained within 24 to 48 hours to assess the extent of resection and minimize potential confounding factors, such as gliosis, which can develop as early as postoperative Day 3. After the initial baseline study, variability exists in follow-up surveillance. Factors in determining the frequency of imaging include different adjunctive therapy regimens, clinical trial enrollment, onset of new symptoms, patient compliance, and health status. Serial imaging at 2- to 3-month intervals is believed to be sufficient for adequate monitoring.[67]

Positron Emission Tomography

Although not used for initial diagnosis of GBM due to its relatively inferior image resolution compared with MR imaging and CT, PET still plays an important role in the management of recurrent GBM, which is often determined by the detection of further growth of residual tumors, based on imaging studies. When the extent of tumor growth does not meet institution-specific criteria, PET may be used to demonstrate increased regional glucose metabolism, which has been shown to correlate with tumor cellularity and patient survival.[34] In a study in which surgical outcomes of recurrent GBM were evaluated, Barker, et al.,[5] included four patients whose PET images suggested proliferation despite an MR imaging indication of a less than 50% increase in size of a residual tumor. Therefore, the use of PET may aid in the early detection of recurrent GBM in cases with unclear MR imaging findings.

Another key role of PET is in the delineation of radiation necrosis resulting from tumor recurrence.[34] As part of standard GBM adjunctive therapy, injury due to radiation and brachytherapy is well described. Patients with radiation necrosis and associated edema can present with symptoms identical to those of tumor recurrence, such as headaches, seizures, and new or recurrent neurological deficits. Although radiation necrosis mimics tumor recurrence on MR images, it is readily detectable with PET due to its low metabolic characteristics. Therefore, PET imaging can play an important role in the treatment of patients who had undergone radiotherapy in whom new lesions or symptoms develop.

Magnetic Resonance Spectroscopy

The use of serial proton MR spectroscopy is becoming a standard protocol in the imaging of brain tumors. This imaging technology, which can supplement current conventional MR imaging protocols, allows serial monitoring of biochemical changes in various intracranial pathological entities, including tumors, stroke, infections, epilepsy, and neurodegenerative diseases. In MR spectroscopy, each metabolite has its own signature, is measured as parts per million, and reflects specific cellular and biochemical processes. The most commonly examined metabolites include the following: NAA, a neuronal marker that decreases with neuronal disease or loss of integrity; Cr, which is used as a measure of energy stores; Lac, a product of anaerobic metabolism; and Cho, a cell membrane marker that is readily elevated in tumors and inflammatory processes, reflecting rapid cell turnover. Through analysis of changes in various metabolite ratios, pathological processes, including neoplasm, can be interpreted with strong specificities. Generally, in highly metabolic tumors, including GBM, the levels of NAA and Cr are decreased, and the rapid growth results in elevated Cho and Lac levels. Thus, in comparison with normal tissues, GBM demonstrates an increase in Cho/Cr and Cho/NAA peak ratios, an increased Lac/Cho peak ratio, and a decreased NAA/Cr ratio (Table 1).

As mentioned previously, the increasing administration of local radiotherapy has led to a concern about the growing incidence of radiation necrosis and an interest in developing noninvasive diagnostic tools to distinguish this pathological entity from tumor recurrence. Research has shown that, because it has the ability to characterize abnormal processes based on their metabolic activity, MR spectroscopy can be used to discriminate between localized radiation necrosis and recurrent tumor that shows elevated Cho levels after brachytherapy.[69] In a recent study of 29 patients, Weybright, et al.,[70] found that both tumor recurrence and radiation necrosis demonstrated increased Cho/Cr and Cho/NAA

TABLE 1

*Imaging modalities to distinguish tumor from radiation necrosis**

Aspects	MRI (w/ Gd)	MRS	Perfusion MRI†	PET
tumor	hyperintense	↑↑ Cho/NAA ↑↑ Ch/Cr ↓↓ NAA/Cr	↑ relative CBV (>2.6) ‡ enhancement rate (ΔI/tΔ)	↑ metabolic activity (↑ glucose uptake)
radiation necrosis	hypointense	↑ Cho/NAA ↑ Ch/Cr ↑ NAA/Cr	↓ relative CBV (<0.6) ↓ enhancement rate (ΔI/tΔ)	↓ metabolic activity (↓ glucose uptake)
limitations	nonspecific, cannot differentiate tumor progression from therapy-related changes	heterogeneous areas of increased metabolic activity	heterogeneous areas of relative CBV	low image resolution, expensive, time intensive

* Single arrows indicate increase or decrease; double arrows indicate a relatively higher or lower ratio. Abbreviations: ΔI/tΔ = change in intensity/change in time.

† Measurements in parentheses are given as milliliters of blood per gram of tissue.

ratios and a decreased NAA/Cr ratio when compared with normal brain. However, the changes appear significantly greater when comparing tumor recurrence with radiation necrosis (Cho/Cr: 2.52 compared with 1.57; Cho/NAA: 3.48 compared with 1.31; NAA/Cr: 0.79 compared with 1.22). Similarly, Rock, et al.,[52] were able to correctly predict the histopathology of a subsequently resected specimen in a case of pure radiation necrosis or pure tumor recurrence. However, it was noted that in specimens with mixed necrosis and neoplasm, the spectral patterns were less definitive. Thus, although MR spectroscopy can be a practical noninvasive screening technique, certain limitations exist at this time.

Perfusion MR Imaging

Perfusion MR imaging provides a noninvasive assessment of the physiological features of vascular tissue. Recent interest in antiangiogenic therapy for highly vascular tumors, including GBMs, has led to the evaluation of the efficacy of perfusion MR imaging. Contrast-enhanced T_2-weighted, echo planar imaging has been evaluated for use in determining treatment response of recurrent malignant gliomas, specifically to thalidomide and carboplatin.[13] Abnormal enhancement of gliomas on conventional, contrast-enhanced, T_1-weighted MR images is nonspecific and cannot be used to differentiate tumor progression from therapy-related changes. Dynamic, contrast-enhanced, T_2-weighted, echo planar MR imaging has been shown to be helpful in assessing tumor vascularity.[3,39] Cha, et al.,[13] found that tumor response to treatment did not correlate well with conventional imaging findings and that relative CBV values decreased significantly in all patients in the study group between the start of therapy and the first follow up. The authors concluded that dynamic contrast-enhanced MR imaging is a valuable supplement to conventional MR imaging in assessing tumor activity during therapy and that it correlates better than conventional studies with clinical status and treatment response.

In addition to assessing tumor activity based on vascular physiology, perfusion MR imaging may also be useful in the identification of radiation necrosis. In general, radiation necrosis typically shows decreased relative CBV, whereas tumor recurrence results in high relative CBV.[4] For example, using gradient echo dynamic-susceptibility perfusion MR imaging, Sugahara, et al.,[66] found that lesions with relative CBV greater than 2.6 ml blood/g of tissue were indicative of tumor recurrence, and relative CBV of less than 0.6 was consistent with radiation necrosis. However, there was significant overlap between the groups, requiring other modalities such as PET or single-photon emission computerized tomography to allow differentiation. Using more delayed, T_1-weighted MR imaging permeability methods and an empiric model to study the rate of contrast enhancement, Hazle, et al.,[33] were able to reliably distinguish between tumor recurrence, radiation necrosis, or a combination of both factors. In that study of 95 patients, the authors found that radiation necrosis and tumoral tissue enhance at different rates, with recurrent tumor having the greatest mean maximal enhancement rates, mixed radiation necrosis and tumor having intermediate rates, and pure tumor necrosis having the slowest rates. More clinical experience and research with perfusion MR imaging are warranted, because they hold great potential in treating recurrent GBM with antiangiogenic therapy and local radiation therapy.

Molecular-Based Imaging

Molecular imaging provides the ability to noninvasively visualize and quantify potential critical molecular events and parameters in recurrent GBM in vivo as well as to determine the efficacy of treatment regimens. Molecular imaging can be used to investigate the transcriptional regulation, signal transduction, and protein/protein interactions involved in GBM, and it is essential to the future development of treatment strategies based on gene therapy.[36] Of particular interest in the imaging of GBM is the efficacy of monitoring angiogenesis and antiangiogenic therapies via αvβ3-integrin.

The feasibility of imaging αvβ3-integrin using MR imaging technology and antibody-coated paramagnetic liposomes was recently demonstrated in an animal model.[61] However, molecular antibodies have a number of disadvantageous characteristics due to vascularia-

tion requirements, barriers to antibody penetration, and intratumoral pressure. Therefore, the majority of studies have focused on radiolabeled small-RGD-peptide antagonists of integrin as radiopharmaceuticals for tumor imaging and therapy.

Chen, et al.,[16] have recently demonstrated the efficacy of optical-based fluorescence imaging using RGD-cy5.5 to monitor GBM angiogenesis in an animal model. A follow-up paper showed that cy5.5-conjugated monomeric, dimeric, and tetrameric RGD peptides were all suitable for integrin expression imaging and that the multimerization of RGD-peptide resulted in improved imaging characteristics of the tetramer.[18] In addition, longitudinal micro-PET imaging using [^{18}F]FB-RGD has been shown to provide the sensitivity and resolution to visualize and quantify anatomical variations during brain tumor growth and angiogenesis through interaction with integrins expressed on tumor cells and angiogenic tumor vessels.[17]

The combination of MR imaging and PET in the diagnosis and treatment of GBM should be useful in the future to assess tumor size, vascularity, and molecular profile. Recently, a clinical trial of gene therapy for recurrent GBM showed that integration of MR and PET imaging data into a three-dimensional stereotactic coordinate system resulted in the development of an efficient noninvasive spatiotemporal method using the antiglioblastoma *HSV-1-tk* gene for monitoring gene therapy in the brain.[35] With further improved molecular profiling of glioblastoma, there will be an increased number of potential targets for novel therapeutic agents such as the angiogenic markers VEGF and endothelial growth factor receptor.[10]

Treatment Options

Surgical Intervention

Surgical intervention is essential in the initial treatment of GBM. In addition to providing tissue specimens for histological confirmation, it is well documented that the extent of surgery, ranging from biopsy to subtotal resection to gross-total resection, can affect overall patient survival.[8,9,14,45] When faced with evidence of recurrent GBM, surgical intervention requires clear identification of short-term goals and a diligent consideration of overall prognosis, including potential treatment side effects. In patients without medical contraindications, surgery can confirm tumor recurrence, reduce intracranial pressure, improve neurological status, and possibly improve efficacy of adjunctive therapy.

Stereotatically guided biopsy procedures allow for the sampling of small, inaccessible, or even multiple lesions with minimal patient morbidity and mortality rates (estimated to be 2–5% and $< 1\%$, respectively).[67] This is particularly relevant in treatment decisions for patients whose imaging studies fail to differentiate between radiation necrosis and tumor recurrence. Stereotactic approaches expand potential treatment options. For example, patients with mass effect secondary to tumor-associated cysts may receive short-term relief from shunt placement or stereotactically guided fluid drainage. Although uncommonly used, chemotherapy or radioactive agents for interstitial brachytherapy may also be introduced. Although stereotactically guided biopsy sampling is frequently performed in relatively low-risk patients, clinicians must be aware of potential complications associated with small sampling. Multiple-pass sampling may improve overall sensitivity but must be weighed against the increased risk of infection and hemorrhage.

The efficacy and utility of repeated resection alone in cases of recurrent GBM remains controversial due to a lack of randomized clinical trials evaluating this intervention independently. The majority of studies are confounded by the inherent selection bias to perform surgery in patients with high functional status, favorable anatomical tumor locations, and lack of medical contraindications. The potential variability in the extent of resection combined with the absence of uniform treatments for the initial disease makes randomized control studies difficult both practically and financially. Despite these limitations, several studies in the literature provide anecdotal evidence and justification for repeated resection in a select subset of patients with recurrent GBM.

In a review of studies focused on repeated resection, Nieder, et al.,[47] showed that the median survival time after resection was 14 to 50 weeks.[1,5,12,62,65] The median survival from the time of initial GBM diagnosis among these patients was 13 to 22 months.[47] Rostomily et al.,[53] reported a prolonged PFS of 7 weeks in patients undergoing combined chemotherapy plus repeated resection compared with patients receiving chemotherapy alone (21 weeks compared with 14 weeks). However, the overall survival rate among this cohort of 51 patients was equivocal. Barker, et al.,[5] performed a retrospective review of 222 patients with recurrent GBM. In this study, the 46 patients who underwent secondary surgery and adjunctive therapy demonstrated a median survival time of 36 weeks following resection. In comparison, patients who received similar chemotherapy and/or radiation therapy had a median survival time of 23 weeks. Interestingly, 28% of patients in the repeated resection group had an improved KPS score, whereas 49% had similar functional status. The authors noted that although the results were likely secondary to selection bias, a subset of patients with recurrent GBM might potentially benefit from repeated resection.

In addition to decreasing mass effect, repeated craniotomy allows for the potential in situ delivery of chemotherapy or brachytherapy. In a randomized study evaluating the efficacy of BCNU implantation during repeated resection compared with placebo, Brem, et al.,[12] reported a 50% improvement in survival at 6 months following treatment (56% with BCNU compared with 36% with placebo). In this study, commonly discussed side effects such as serious intracranial infections (2.2%), postoperative seizures, and edema that required steroid medications were reported to be within accepted ranges for repeated surgery alone.

Overall, resection in cases of recurrent GBM may provide a modest benefit in survival and/or improvement in QOL within a subset of patients. Brem, et al.,[12] showed that preoperative performance status and age were significant prognostic factors. Similarly, in a multivariate analysis by Ammirati, et al.,[1] performance status was found to be a significant predictor of outcome,

although patient age appeared to be noncontributory. The extent of initial resection has also been shown to influence patient survival.[26] Although minor discrepancies exist among different studies, the general consensus among researchers is that resection should be seriously considered in those with a high KPS score (> 70) and whose lesions are in a favorable location.

Chemotherapy Treatment

Chemotherapy is the most common treatment option for recurrent malignant gliomas.[14,22] Although traditionally reserved for salvage treatment of recurrent GBM, chemotherapy agents have shown a wide range of efficacy, either when administered alone or as a supplement to cytoreductive surgery.[14] Chemotherapeutic agents such as TMZ, carboplatin, procarbazine, and imatinib mesylate are currently being examined for their potential in the palliative treatment of recurrent GBMs.[49] These drugs have been administered in a variety of formats, including single-agent, multiagent, interstitial, intrathecal, and combination therapies, and are hypothesized to decrease patients' risk of death by approximately 15%.[63] In a large, meta-analysis study by Stewart,[63] the 2-year survival rate for individuals with GBM increased from 9 to 13% when chemotherapy was used.

Treatment of recurrent GBM tumors with TMZ has shown promising antitumor efficacy with a favorable toxicity profile. In a study by Brandes, et al.,[11] patients who were treated for recurrent or progressive GBM with a TMZ regimen showed an overall response rate of 19% and a mean time to progression of 11.7 weeks. Similarly, it was found that treatment of recurrent GBM with a standard TMZ regimen (150–200 mg/m^2 for 5 days in 28-day cycles) resulted in 21% of patients showing PFS for 6 months compared with 8% of patients treated with procarbazine.[73] However, more recent studies have shown that a more rigorous regimen (150 mg/m^2 daily on a week on/week off cycle) may yield a PFS of 6 months as high as 48% with an overall survival for 12 months of 81%.[71] Various combinatorial strategies have been examined, including TMZ plus the matrix metalloproteinase inhibitor marimastat or 13-*cis*-retinoic acid, resulting in a PFS for 6 months of 39 and 32%, respectively.[37]

The cytotoxicity of TMZ and related alkylating agents depends on several possible drug-resistance mechanisms, primarily the suppression of DNA repair mechanisms. In the case of TMZ, the most commonly considered resistance mechanism is the repair of TMZ-induced methyl adducts at the O^6-guanine in DNA that are repaired by the O^6-methylguanine-DNA methyltransferase cytoprotective repair protein.[74] In several studies the authors have administered O^6-benzylguanine to aid in the suppression of such DNA-repair pathways and have found a substantial increase in the cytotoxicity of TMZ in preclinical models.[50] Because such chemotherapy treatments are designed to relieve neurological stress and prolong survival rather than cure the underlying lesion, it is important to consider QOL standards when choosing a multimodality treatment option. Osoba, et al.,[49] revealed that patients suffering from recurrent GBM were more satisfied and reported a higher health-related QOL when treated with TMZ than with procarbazine. Such data may influence physicians in their decisions to treat with chemotherapeutic agents. Hence, the administration of chemotherapy should be based on a consideration of health-related QOL, increased hospitalization, cost of therapy, and chemotoxicity.

The further application of chemotherapeutic interventions beyond initial recurrence treatment does not significantly increase duration of patient survival or pose any benefit to warrant their use.[32] Furthermore, the use of multiagent chemotherapy does not suggest any significant benefit over the use of single-agent chemotherapy.[47] Rather, studies show an increase in hematological toxicity with the application of more complex combinatorial agents.[1,51,56]

Antiangiogenic Treatment

Targeting tumor angiogenesis is an experimental method for tumor control and stabilization. Signaling pathways related to VEGF, bone morphogenetic protein–2, and angiopoietins are examples of systems that contribute to the formation of tumoral neovasculature. Thus, the use of antiangiogenic therapy has been the topic of much discussion and experimentation. Researchers have shown that independent antiangiogenic treatment, known as monotherapy, produces limited clinical effects. Due to their delayed onset, current antiangiogenic therapies allow tumor progression, which reduces their use for end-stage disease.[48] However, the use of antiangiogenic agents in combination with other therapies may provide better results.[6] Often coupled with a chemotherapy agent, antiangiogenic therapies have been shown to be effective in primary GBM tumors, producing a patient survival time of 16 months.[68] Similarly, as to which chemotherapy agent to use, it has been shown that PTK-787 (a VEGF receptor inhibitor) combined with TMZ produced a median time to progression of 15.1 weeks compared with PTK-787 combined with lomustine, which resulted in a median time to progression of 10.4 weeks.[74]

Radiation and Brachytherapy

Stereotactic radiosurgery is a noninvasive method of localized irradiation, particularly for smaller recurrent GBM lesions.[22] It has gained widespread popularity in part because of its use as an outpatient procedure and its relatively decreased recovery period. In a study by Combs, et al.,[22] the median survival of patients undergoing single-fraction SRS (median dose of 15 Gy) for recurrent GBM was 10 months. This finding is consistent with several other studies that report similar survival times.[44,60]

The risks associated with SRS include the possibility of radiation-induced necrosis, edema, hydrocephalus, worsening of preexisting symptoms, and radiation toxicity. Specifically, the application of SRS to larger tumors has been avoided because of an increased risk of radiation-induced toxicity and mass effect.[59]

The efficacy of SRS is similar to that of brachytherapy. In a study by Shrieve, et al.,[60] in which they compared outcomes in patients treated with SRS with outcomes in those treated by brachytherapy, the authors reported an overall survival time of 10.2 months for SRS-treated patients and 11.4 months for brachythera-

py-treated patients. It was also documented that SRS-based therapy allowed the delivery of targeted radiation to inoperable recurrent tumors and avoided an increased risk of infection, hemorrhage, and personnel radiation exposure.

The use of brachytherapy has evolved during the last decade. Primarily a treatment for recurrent GBMs, brachytherapy is associated with an increase in survival time. Interstitial brachytherapy is used to target greater radiation doses to tumor cells while limiting exposure to surrounding normal brain tissue. When using the latest brachytherapy techniques, physicians report a median survival time (postbrachytherapy) for patients with recurrent GBM of 9.1 months, a competitive figure when compared with repeated resection alone, chemotherapy, or repeated irradiation.[15] Similarly, it has also been shown that treatment of recurrent GBM with high-activity, removable ^{125}I interstitial brain implants elicits a long-term (3-year) survival rate of 15%.[57]

Unfortunately, the application of brachytherapy is limited. Only 20 to 30% of recurrent GBMs meet the morphological and focal criteria necessary for the surgical intervention associated with brachytherapy.[31,54] In some cases, posttreatment repeated operation is necessary to remove the therapeutic device or to address focal radiation necrosis. Possible complications associated with brachytherapy include the development of homonymous quadrantanopia, focal necrosis, edema, and neurological deterioration.[60]

Radiochemotherapy Treatment

The concept of "chemoradiosensitization" has led to the application of combined radiotherapy and chemotherapy (radiochemotherapy).[14] On March 15, 2005, the US Food and Drug Administration approved the user of TMZ in combination with radiotherapy for the treatment of adults with newly diagnosed GBM.[20] In a randomized trial of 573 patients with GBM of varying stages, the median survival time for those who received TMZ plus radiotherapy was 14.6 months compared with 12.1 months for those who received radiotherapy alone. Previously, in a Phase II clinical trial the concurrent administration of TMZ with radiotherapy was shown to elicit a median survival time of 15.7 months in patients with newly diagnosed GBM.[41] In a similar study, the use of postoperative TMZ radiochemotherapy resulted in a 4-year survival rate of 78% in a population of patients with both initial and recurrent malignant gliomas.[40] Patient health status and comorbidity must be weighed in the application of these multimodality treatments. However, it has been shown that the continuous application of TMZ and concomitant radiation is safe and efficacious.[64]

Novel Therapies

Another promising treatment modality lies in immunotherapy. Early-stage immunotherapeutic treatments can be divided into two major categories: targeted toxin therapy and anticancer vaccinations.[29] These two mechanisms use separate aspects of human immune response to targeted toxins or T cells, which are directed toward tumoral remnants. Authors of one study examined the effects of lymphokine-activated killer-cell implantation on recurrent GBMs. Of 40 patients in whom recurrent GBM was diagnosed, a median survival of 9 months and a 1-year survival rate of 34% were achieved.[25] Techniques involving gene therapy are producing comparable results. In a small study in which the authors examined the effects of an intratumoral injection of retroviral vector–producing cells combined with intravenous ganciclovir, they noted a 1-year patient survival rate of 25% with tumor response in 50% of the cases.[21] The future role of immunotherapies and gene therapies will become clearer as more Phase I and II clinical trials are completed. However, current experimental applications may provide a case-specific increase in survival time.

Conclusions

Despite advancement of all treatment aspects, patients with GBM continue to have poor prognoses. In patients who have completed first-line therapy, strict tumor surveillance with regularly scheduled imaging and clinical evaluations may enable early detection of tumor recurrence and allow for immediate treatments. With the frequent use of radiation therapy, potential radiation-induced injury or necrosis must be considered in patients who experience new or recurrent symptoms or radiographic lesions. Novel imaging techniques hold great promise in detecting the activation of tumor progression at molecular and cellular levels before changes can be seen using conventional radiographic methods.

Currently, limited evidence exists from randomized studies to explain the variable nature of the recurrent GBM and differences among institutional first-line treatment. Among patients determined to be favorable surgical candidates (those with high KPS scores, noneloquent location, and no medical contraindications), the addition of BCNU wafers appears to provide additional benefits. Regarding the administration of chemotherapy, either as the primary or an adjunctive therapy, the potential benefits appear to be independent of the number of agents used. Currently, TMZ is rapidly becoming the standard chemotherapy agent due to its ease of administration, minimal side-effect profile, and established improvement in survival rates.

Repeated resection should be considered in patients with high preoperative KPS scores or in those whose symptoms are secondary to mass effect from superficial noneloquent regions. The benefits of SRS and chemotherapy are similar and should be chosen based on their corresponding side-effect profiles. In general, improved outcomes are witnessed with combined radiotherapy and chemotherapy compared with each treatment alone.

Current trends indicate that the treatment of recurrent GBM will remain multimodal in nature. Further understanding of underlying tumor biology is essential in developing more effective strategies. Research in gene therapy, antiangiogenic antagonists, and immunotherapies holds great promise. With continual improvements in treatments and imaging techniques, it is the hope of clinicians, researchers, and patients that GBM may become a controllable disease with a favorable prognosis.

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