Update on the current management of glioblastoma

Caroline Chung*[1] & Normand Laperriere[1]

Practice Points

- Glioblastoma is the most common primary brain tumor in adults.
- Clinical prognostic factors for patients with glioblastoma include age, performance status, tumor size and extent of resection.
- For young patients with good performance status, maximal safe tumor resection followed by 6 weeks of radiation with concurrent and adjuvant temozolomide is the recommended treatment.
- For patients who are older or who have compromised performance status, shorter courses of radiotherapy over 2–3 weeks are typically recommended after surgical resection. There are ongoing studies to investigate whether the addition of temozolomide to a shorter course of radiotherapy will improve outcome in this subset of patients.
- Following combined therapy, patients can present with pseudoprogression, a self-limited reaction to the therapy that radiologically and clinically mimics tumor progression.
- Management of recurrent tumor is highly individualized and can include repeat surgery, radiation and/or systemic therapy (i.e., chemotherapy/targeted agents).

SUMMARY Glioblastoma is the most common primary brain tumor in adults, with a rising incidence, predominantly in the older population. Aggressive treatment involves maximal safe resection followed by radiation with concurrent and adjuvant temozolomide. The added benefit of temozolomide in subsets of patients who were not included in the landmark, randomized study is under investigation. Despite multimodal treatment, median survival ranges between 12 and 18 months. The majority of patients suffer local tumor progression or recurrence, for which management is highly personalized, considering the patient's clinical presentation, performance status and the extent of tumor recurrence in order to optimize each patient's

[1]Princess Margaret Cancer Centre, 610 University Avenue, Toronto, Ontario, M5G 2M9, Canada
*Author for correspondence: caroline.chung@rmp.uhn.on.ca

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outcome. Advances in surgical techniques and radiotherapy have decreased treatment-related morbidity at initial treatment and enabled consideration of repeated local therapies in selected situations. Ongoing research into the underlying molecular and cytogenetic pathways responsible for tumor growth and progression are facilitating the development and investigation of targeted therapies.

Glioblastoma (GB) is the most common primary brain tumor in adults, classified as a WHO grade IV astrocytoma. The incidence is currently six per 100,000 people per year and has been rising [1]. The greatest increase in incidence has been in patients diagnosed at the age of 65 years or over, who now make up nearly half of all patients diagnosed with GB [2,3]. Despite aggressive treatment with surgery, radiation and chemotherapy for those who can tolerate this regimen, the prognosis remains poor with median survival ranging between 12 and 18 months in recent reports of multimodality therapy [4]. In patients who cannot tolerate combined modality therapy, median survival is shorter.

Clinical presentation

Symptoms & signs

The clinical presentation of GB can vary widely, depending on the particular location of the tumor. Presenting symptoms can be categorized into three main types: raised intracranial pressure, seizures and specific neurologic losses progressing over several days to weeks. Symptoms associated with raised intracranial pressure include headaches, nausea and vomiting, ataxia, confusion and decreasing level of consciousness. Patients can present with either or both partial and generalized seizures. Focal neurological deficits, including deficits in motor and sensory function, speech disturbance, cognitive changes and visual deficits can develop over days to weeks, depending on which particular regions of brain are involved with tumor infiltration and peritumoral edema.

Imaging

The imaging modality of choice to evaluate intracranial tumors is MRI, which includes a gadolinium-enhanced T_1-weighted sequence to evaluate the enhancing tumor and a noncontrast, T_2-weighted sequence to evaluate the extent of nonenhancing tumor and peritumoral edema. GB is characterized by extensive breakdown of the blood–brain barrier, leading to a contrast-enhancing lesion on gadolinium-enhanced T_1-weighted sequences. Furthermore, their rapid proliferation rate can result in outgrowth of their vascular supply leading to central necrosis. On T_2-weighted, fluid-attenuated inversion recovery images, a diffuse, hyperintense infiltrative pattern is commonly observed. GB can present as a solitary lesion or with multifocal involvement **(Figure 1)**. A solitary lesion with the described appearance on MRI would have a differential diagnosis that includes an abscess, metastasis, lymphoma and subacute ischemia. Additional magnetic resonance (MR) acquisitions such as diffusion-weighted imaging can be useful to differentiate tumor versus ischemia, but there is no definitive diagnostic imaging test and histological confirmation of the diagnosis of GB is recommended prior to initiation of therapy.

Prognostic factors

A number of clinical factors have been associated with outcome for patients with GB including age, performance status, tumor size and extent of resection [5–7]. Lamborn *et al.* reported a recursive partitioning analysis of these clinical prognostic factors for 832 patients with GB enrolled onto one of eight clinical trials of adjuvant radiation and chemotherapy [8]. They identified four risk groups:

- Group 1 (the lowest risk group): young patients (<40 years old) with tumor in the frontal lobe only;
- Group 2: young patients (<40 years old) with tumors beyond the frontal lobe;
- Group 3: patients aged between 40 and 65 years with Karnofsky performance status (KPS) >70 following subtotal or total resection;
- Group 4 (the highest risk group): all patients over 65 years of age, patients between 40 and 65 years who had KPS less than 80 or patients of any age who only had a biopsy only.

Median survival differed significantly between groups: 132 weeks for group 1; 71 weeks for

group 2; 63 weeks for group 3; and 37 weeks for group 4 [5].

In recent years, a growing number of pathogenetic and molecular features have been associated with prognosis, leading to the identification of at least two subtypes of GB: primary and secondary GB. In general, primary GB tends to present in older patients (>55 years of age) and is associated with a worse prognosis than secondary GB. Primary GB is characterized by genetic loss on chromosome 10, alteration of p16 or p19, overexpression or mutation of EGF receptor, or loss of the tumor suppressor protein phosphatase and tensin homolog [9–12]. Secondary GB is more commonly seen in younger patients, typically arises from a pre-existing lower-grade astrocytoma and has a much better prognosis than primary GB. Secondary GB tends to have a *TP53* mutation and/or overexpression of the PDGF receptor [9]. These specific findings are driving further investigation of potential targeted therapies along these molecular pathways.

Two additional pathogenetic features have shown promise as prognostic and predictive factors. *IDH1* mutation has been found to be an age-correlated prognostic marker that is commonly present in secondary GB, as well as in 50–80% of grade II/III gliomas in younger patients. It is virtually absent in elderly patients [5–7,9]. A second feature found in GB is the methylation status of O_6-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme that can reverse the DNA damage introduced by alkylating agents such as temozolomide. Methylation of the promoter of MGMT prevents transcription of the MGMT gene and thereby prevents repair of the DNA damage caused by temozolomide, making it more effective [12]. Patients with MGMT promoter methylation are more likely to respond to temozolomide and appear to have a longer survival, regardless of their age at diagnosis [10,11].

Management

Management of patients with GB typically involves multidisciplinary care from a neurosurgeon, radiation oncologist and neuro-oncologist. In general, management of individual patients is highly personalized based on the patient's age, clinical presentation, overall performance status, medical comorbidities and social supports, in order to optimize each patient's survival and quality of life.

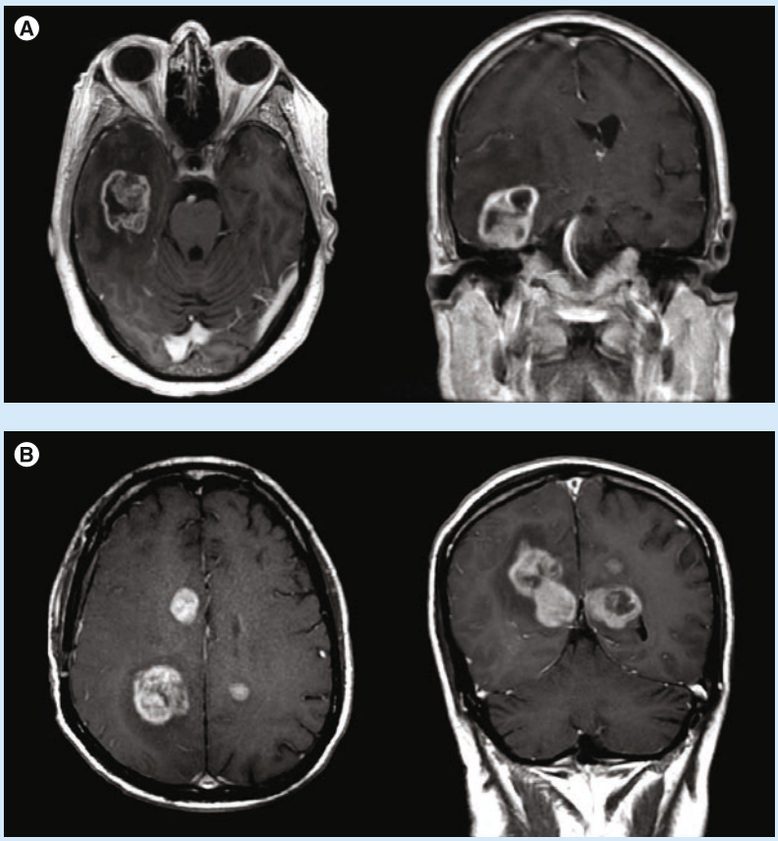

Figure 1. Representative axial slices of gadolinium-enhanced T1-weighted images. (A) A solitary glioblastoma lesion and **(B)** multifocal glioblastoma.

Surgery

As GB is a diffusely infiltrative tumor, it is virtually impossible to achieve a complete resection. Nonetheless, every effort should be made to achieve as close to a gross total tumor resection as possible, whenever feasible. In some cases, the extent of surgery is limited by tumor involvement of eloquent areas or by the sheer volume of tumor.

Patients who undergo a partial resection or biopsy have a worse prognosis compared with patients who have gross total resection [13,14]. Gross total resection may provide multiple therapeutic benefits: decompression of the brain to improve functional status, reduced steroid dosage, and reduction in tumor burden to delay tumor regrowth and increase the likelihood of response to radiation and/or chemotherapy [15,16]. The ability to achieve a gross total resection may also reflect the extent and involvement of the tumor preoperatively. Surgical advances, including the use of advanced intraoperative

imaging, neuronavigation tools and use of tissue fluorescence with 5-aminolevolinic acid to guide surgical resection are increasing the capability to achieve more extensive tumor resections while maintaining functional outcome in patients [17–19]. Although the extent of resection can depend on a number factors, including tumor location and surgeon experience, recent studies report promising results with complete resection of enhancing tumor on MRI in 89% of cases with low rates of postoperative neurological deficits [18].

Radiation therapy

Following surgery, the most common adjuvant therapy is external beam radiotherapy (RT). The specific RT treatment volume, dose and duration are highly dependent on the patient's clinical presentation and prognostic factors. In patients with KPS >70, RT is typically delivered to any residual contrast-enhancing tumor, in addition to the surgical cavity with a 1.5–2.0 cm margin that will encompass the majority of the surrounding T_2 signal hyperintensity and an additional margin for set-up variability for each radiation treatment fraction (Figure 2). The dose and fractionation used in young patients with good performance status is 60 Gy in 30 fractions delivered over 6 weeks, typically delivered with concurrent temozolomide, as per Stupp *et al.* [20]. For elderly patients with reasonable performance status, treatment with 40 Gy in 15 fractions delivered over 3 weeks has been shown to have similar outcomes to 60 Gy in 30 fractions [21]. In patients with poor performance status, a total of 30 Gy in ten fractions delivered over 2 weeks may be offered, but in some cases omission of RT and focus on supportive care may be discussed and recommended.

The role of postoperative RT as the mainstay adjuvant treatment for GB is supported by multiple randomized studies [22]. The target volume for RT in most centers is the primary tumor site (surgical cavity and residual enhancing tumor) with a 1.5–2.0 cm margin microscopic extension. This is based on evidence that more than 90% of recurrences occur at the primary tumor site and peritumoral region following surgery and radiation with and without temozolomide [23,24]. Furthermore, studies comparing local RT alone with whole brain RT and local RT boost failed to demonstrate any survival benefit [25,26]. The accepted standard dose of RT is 60 Gy in 30 fractions and attempts at dose escalation beyond 60 Gy have resulted

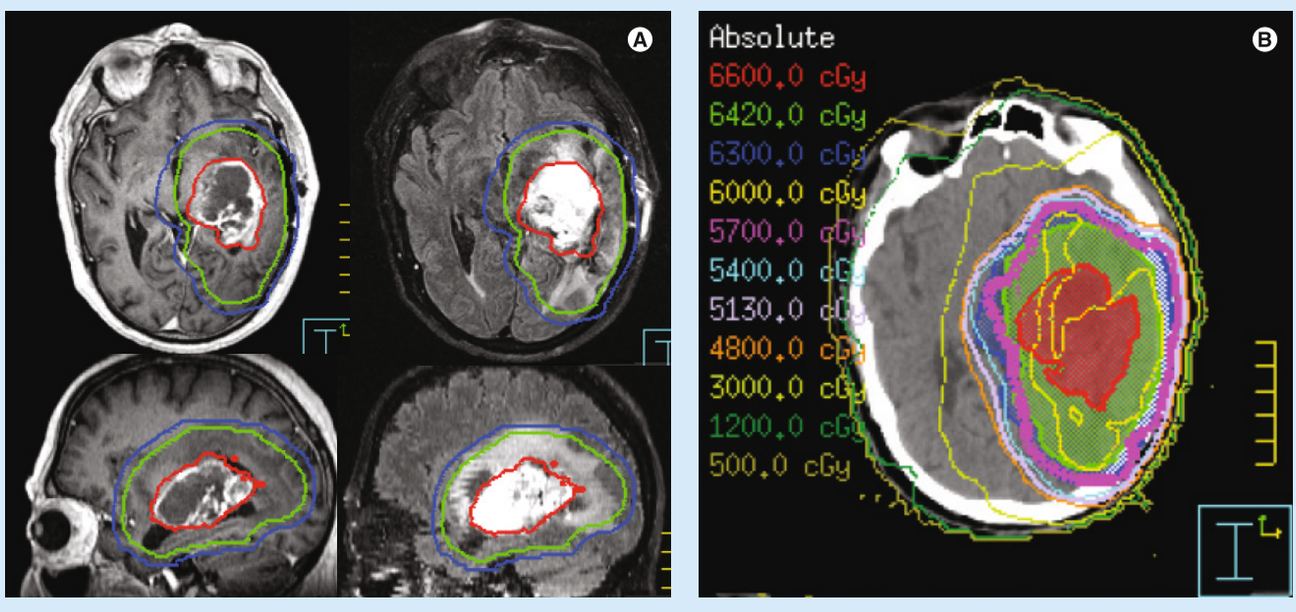

Figure 2. Representative images of an intensity-modulated radiation therapy plan. (A) The contours of the gross tumor volume (including surgical cavity; red), the clinical target volume that encompasses most of the fluid-attenuated inversion recovery abnormality (green) and the planning target volume that accounts for small variations in treatment set-up (blue). **(B)** The radiation doses encompassing the target volumes but sparing the surrounding brain tissue.

in greater toxicity with no evidence of improved tumor control or survival [27,28].

Systemic therapy

The primary systemic therapy used at initial diagnosis of GB is currently temozolomide. Concurrent temozolomide 75 mg/m^2 daily is administered during RT and adjuvant temozolomide (150–200 mg/m^2 daily for 5 days every 28 days for 6–12 cycles after completion of RT) is the current standard of care for patients aged <65–70 years with a good performance status (ECOG score: 0–2) [20]. Patients are monitored with weekly complete blood count during the concurrent treatment and monthly during the adjuvant treatment, as there is a risk of hematological toxicity. The most common hematological toxicity is thrombocytopenia but lymphopenia can also occur. Prophylaxis for thrush, herpes and pneumocystis should be considered, particularly in patients with lymphocyte counts of less than 400 per mm^3.

The current standard treatment that combines temozolomide with RT for GB is based on the results of the Stupp *et al.* study, a landmark Phase III randomized control trial conducted by the European Organization for the Research and Treatment of Cancer and the National Cancer Institute of Canada [20]. This trial randomized 573 patients aged 18–70 years old with newly diagnosed GB to RT alone (60 Gy total in 2 Gy fractions delivered 5 days per week over 6 weeks) or RT with concurrent temozolomide (75 mg/m^2 daily was administered during RT) and adjuvant temozolomide (150–200 mg/m^2 daily for 5 days every 28 days for six cycles after completion of RT). The combined treatment arm had a significantly longer median survival of 14.6 months compared with 12.1 months with RT alone, and a significantly higher 2-year survival of 26.5% with combined therapy compared with 10.4% with RT alone. Progression-free survival for combined therapy was 11.2% at 2 years and 4.1% at 5 years compared with 1.8% at 2 years and 1.3% at 5 years for RT alone [20]. Based on this evidence that the addition of temozolomide improved survival with minimal increase in toxicity, RT with concurrent and adjuvant temozolomide for 6-monthly cycles was accepted as the new standard of care for good performance patients with a new diagnosis of GB.

With promising clinical responses to bevacizumab in the recurrent setting, there are two randomized clinical trials investigating whether adding bevacizumab to standard therapy will improve patient outcomes. The Radiation Therapy Oncology Group has completed accrual to a randomized study of standard therapy plus bevacizumab or placebo during chemoradiation followed by maintenance therapy in which patients in the placebo arm can crossover to receive bevacizumab at the time of progression. The second trial sponsored by Roche, called AVAglio, had a similar design but likely had fewer crossovers to bevacizumab as many of the participating European countries did not have access to bevacizumab outside of the study context. The preliminary result of the AVAglio study has demonstrated a progression-free survival benefit with the addition of bevacizumab although the impact on overall survival is yet to be seen [29]. Based on the current data, bevacizumab has not been US FDA approved for use in newly diagnosed patients and the pending results of these randomized studies will imminently guide whether bevacizumab is added to the standard therapy regimen for newly diagnosed GB.

Treatment of specific patient groups: the elderly and poor performance status

Although the Stupp study has established a standard of care for young patients who have good performance status, the recommended therapy for the growing proportion of elderly patients who did not meet the eligibility criteria for this study is still uncertain. There is an ongoing randomized clinical trial conducted by the National Cancer Institute of Canada Clinical Trials Group, the European Organization for the Research and Treatment of Cancer, the Trans Tasman Radiation Oncology Group and some selected Japanese centers of short-course RT (40 Gy total delivered in 15 fractions over 3 weeks) compared with this short course RT with concurrent and adjuvant temozolomide. Two recent studies have suggested a possible role of temozolomide monotherapy for elderly patients with GB, where results of temozolomide monotherapy versus 6 weeks of radiation monotherapy have yielded similar survival. These studies have suggested that MGMT promoter methylation has a higher predictive value for response to temozolomide, and this biomarker may play a role in guiding treatment decisions in elderly patients with GB [30,31].

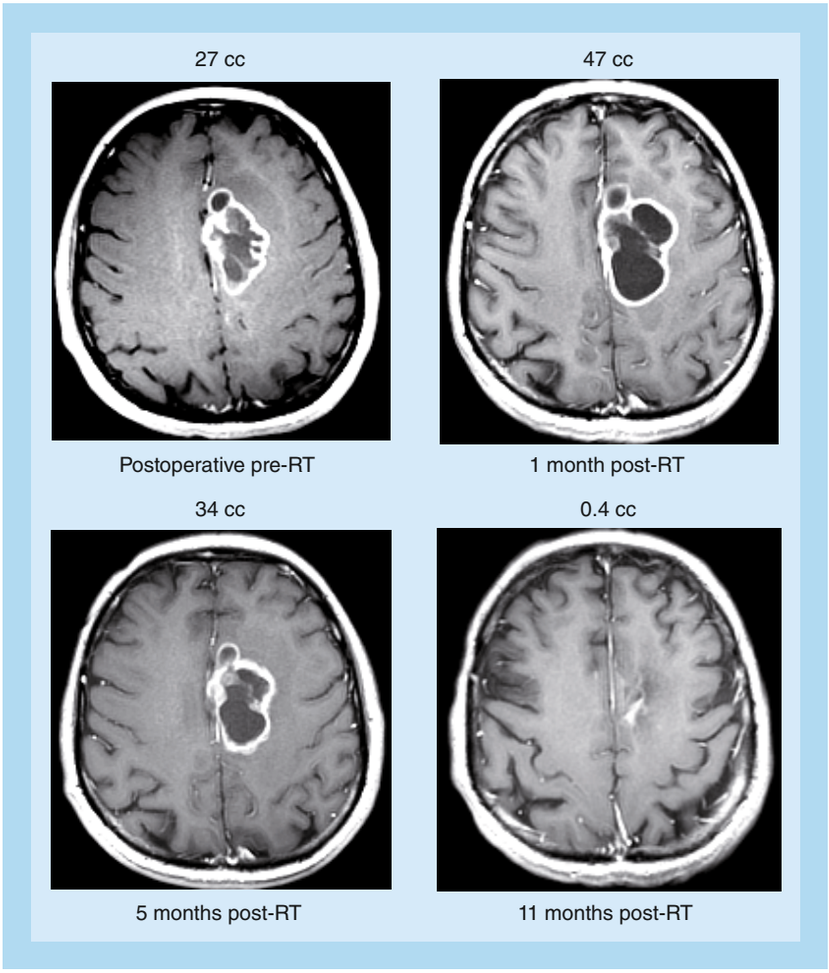

Figure 3. Case example of a patient treated with a standard 6-week course of radiotherapy with concurrent temozolomide who developed pseudoprogression. Note that the tumor volume increased at 1 month following completion of RT and subsequently decreased over time as the patient continued on the standard adjuvant temozolomide therapy.
RT: Radiotherapy.

Pseudoprogression

Soon after therapy with concurrent RT and temozolomide, a new phenomenon called pseudoprogression has been recognized **(Figure 3)**. This is typically a reaction to the therapy that radiologically and clinically mimics tumor progression but is invariably self-limited. Recent studies reported an incidence of 20–30% of pseudoprogression following concurrent radiation and temozolomide and rates as high as 92% of pseudoprogression in patients with MGMT methylated tumors compared with only a 40% chance of pseudoprogression in patients with unmethylated tumors [10,32]. There are ongoing research efforts aimed at differentiating pseudoprogression from true tumor progression in order to avoid offering patients salvage treatment in the setting of pseudoprogression, yet offer timely salvage treatments for those with true tumor progression. Clinically, patients who are symptomatic have been found to be 1.6-times more likely to have true progression over pseudoprogression [33]. Radiologically, efforts to incorporate advanced imaging such as perfusion MR, MR spectroscopy and PET have shown some promise, but the ability to differentiate true tumor progression from pseudoprogression remains a challenge with the imaging methods available to date [34].

Treatment options for tumor recurrence

In the case of true tumor progression or recurrence, repeated local therapies including surgical resection and repeat RT may be considered in selected cases. Treatments are typically individualized based on the clinical presentation and prognostic factors, including patient age, performance status and ability to obtain effective further resection. Repeat resection can provide rapid palliation of symptoms by debulking the tumor and decompressing the brain, and can also provide histological confirmation of the clinical and radiological suspicion [35–38]. As patients are typically treated with a full course of radiation at the time of their initial diagnosis, only highly selected patients are considered for repeat irradiation at the time of tumor recurrence. These patients typically have good performance status and present with focal disease recurrence after a durable period of tumor control. Repeat irradiation has been delivered using fractionated intensity modulate RT, as well as radiosurgery with varying dose and fractionation schedules. Accounting for this highly selected group patients, prior studies have reported a median survival of 26–47 weeks after repeat irradiation with highly conformal RT techniques, with a radionecrosis rate of 6–8% [39].

Further systemic therapy is more commonly utilized and can range from temozolomide rechallenge alternative chemotherapy or targeted therapies. Historically, nitrosureas, *bis*-chloroethylnitrosourea and lomustine were used as first-line chemotherapy at the time of recurrence following surgery and radiation and this remains a reasonable option at the time of tumor progression in patients previously treated with radiation and temozolomide [40,41]. Temozolomide

rechallenge with a continuous 50 mg/m^2 daily schedule has shown some promise with a 6-month progression-free survival of 23.9% [42]. Subsequently, the RESCUE study evaluated this same temozolomide regimen in patients with early progression within their first 6 months of adjuvant temozolomide, late progression while on extended adjuvant temozolomide beyond 6 months and as a true rechallenge after completing their adjuvant temozolomide. In this study, the 1-year survival was 27.3% in the early progressors, 14.8% in the late progressors and 28.6% in the rechallenge subgroups. One hypothesis for the superior results in the early progressors compared with late progressors was the inclusion of patients with pseudoprogression in the early progressor group [43]. Other studies have explored combination therapy with temozolomide and various agents but none have been shown to be more effective than single-agent nitrosurea; multiagent therapy is associated with greater toxicity [44,45].

As our understanding of the underlying molecular and cytogenetic pathways responsible for glioma growth and progressive grows, targeted therapies that influence tumor angiogenesis, invasion, apoptosis and growth are being explored. Of these agents, bevacizumab, a monoclonal antibody to VEGF, has been FDA approved for recurrent and progression GB after initial therapy following Phase II trial evidence that bevacizumab with and without irinotecan resulted in remarkable 6-month progression-free survival rates of 42.6 and 50.3%, respectively [46]. Radiological responses have been reported based on changes in volume of the gadolinium-enhancing tumor [47,48]. However, several studies have demonstrated that increases in T_2- or fluid-attenuated inversion recovery hyperintensity can be seen suggesting tumor progression concurrently with dramatic reduction in volume of the enhancing tumor on T_1-weighted images. Due to the mechanism of action of these anti-VEGF agents, the reduction in enhancing tumor volume on T_1 in this setting may reflect reduced vascular permeability rather than true tumor volume reduction – termed pseudo-response [49]. Furthermore, although studies have demonstrated progression-free survival improvements, further definitive studies are needed to confirm that bevacizumab improves overall survival in the recurrent setting.

Future perspective

GB remains the most common primary brain tumor in adults and has a rising incidence, particularly with our aging population. The current standard of care for younger patients with good performance status is maximal safe tumor resection followed by 6 weeks of radiation and concurrent and adjuvant temozolomide. With the growing proportion of elderly patients, specific studies are aimed at addressing the optimal management of this subset of patients exploring treatment with surgery followed by RT, RT combined with temozolomide or temozolomide alone. Generally, treatment has been individualized to the patient based on their clinical presentation, clinical prognostic factors (age, performance status, extent of tumor resection and tumor size), social situation and patient preference. But with increasing understanding of the underlying molecular and pathogenetic features of the tumor, such as *IDH1* mutation and MGMT methylation status, such markers will be used as prognostic and predictive tools to stratify patients in clinical trials and guide treatment decisions in future. This potential for individualized therapy will grow substantially with discovery of additional targeted therapies moving forward.

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■ **Highlights important radiological findings that can follow treatment with concurrent radiation and chemotherapy, as well as bevacizumab, which can be misleading, if not appreciated as pseudoprogression or a pseudoresponse.**