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Case-Based Review: newly diagnosed glioblastoma

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Glioblastoma (WHO grade IV astrocytoma) is the most common and most aggressive primary brain tumor in adults. Optimal treatment of a patient with glioblastoma requires collaborative care across numerous specialties. The diagnosis of glioblastoma may be suggested by the symptomatic presentation and imaging, but it must be pathologically confirmed via surgery, which can have dual diagnostic and therapeutic roles. Standard of care postsurgical treatment for newly diagnosed patients involves radiation therapy and oral temozolomide chemotherapy. Despite numerous recent trials of novel therapeutic approaches, this standard of care has not changed in over a decade. Treatment options under active investigation include molecularly targeted therapies, immunotherapeutic approaches, and the use of alternating electrical field to disrupt tumor cell division. These trials may be aided by new insights into glioblastoma heterogeneity, allowing for focused evaluation of new treatments in the patient subpopulations most likely to benefit from them. Because glioblastoma is incurable by current therapies, frequent clinical and radiographic assessment is needed after initial treatment to allow for early intervention upon progressive tumor when it occurs.

Keywords: chemotherapy, glioblastoma, radiation, surgery, temozolomide.

Clinical Case Presentation

A 73-year-old man presented to his local emergency department after experiencing a generalized seizure. He had moderate left-sided weakness in the initial postictal period which quickly resolved. In retrospect, the patient had noted subjective left-hand "clumsiness" for a month prior to the seizure, but had not reported it to his family or physician. A CT scan was obtained in the emergency room and was followed shortly by an MRI (Fig. 1). The patient was then referred to our institution for further care.

Initial Supportive Care

The presentation of high-grade glioma is variable, depending on the location of the lesion within the brain. Headaches, seizures, and subacutely progressive neurological deficits are all common presenting symptoms.

Antiepileptic Therapy

Patients who present with seizure should be treated with antiepileptic drug (AED) therapy. An optimum AED choice would have rapid efficacy, few side effects, and no drug–drug interactions. In clinical practice, levetiracetam is often chosen as the first-line agent in this setting.[1] Studies have suggested that some AEDs may have direct antitumor effects. For example, valproic acid is a histone deacetylase (HDAC) inhibitor,[2] while levetiracetam is an MGMT inhibitor.[3] However, no impact of AED choice on survival has been proven, so AED choice should be based on efficacy and tolerability.

In patients with high-grade glioma who have not had a seizure, there is no proven role for long-term prophylactic AED therapy, and the American Academy of Neurology recommends against the routine use of prophylactic AEDs outside of the immediate perioperative period.[4] As previous studies of prophylactic AED therapy evaluated older agents in mixed patient populations, some experts question their applicability to current practice. A large trial of lacosamide vs placebo for seizure prophylaxis in patients with high-grade gliomas is ongoing to address this issue.[5]

Corticosteroid Therapy

In patients presenting with headaches or focal neurological deficits, symptoms may be due to peritumoral vasogenic edema, which

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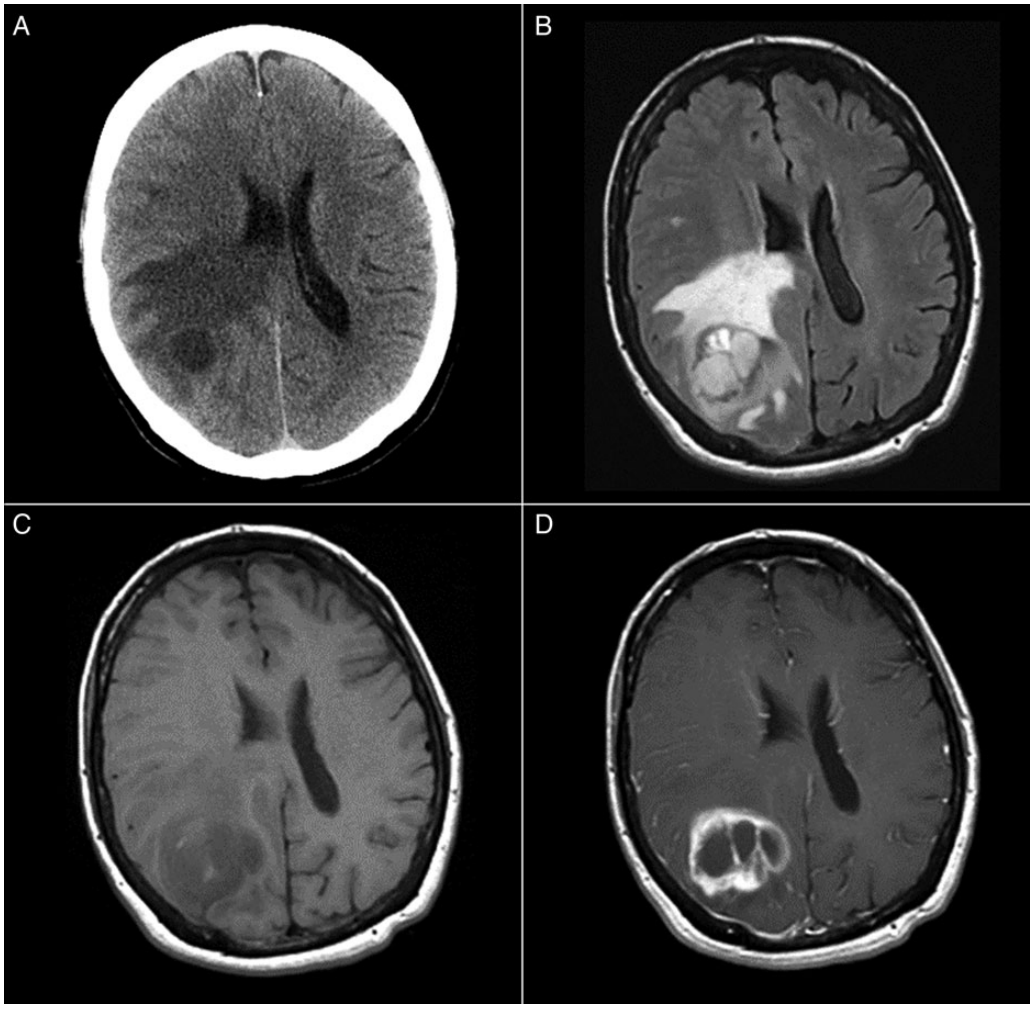

Fig. 1. (A) Unenhanced CT, (B) T2-weighted FLAIR, (C) gradient echo T1-weighted, and (D) post-gadolinium spin echo T1-weighted images depict a relatively circumscribed mass in the left superior temporal lobe with both solid, enhancing components and some cystic or necrotic areas. Moderate edema signal surrounds a portion of the mass.

may respond to corticosteroid therapy. Dexamethasone is often started at 16 mg daily in 4 divided doses, and tapered down to the lowest effective dose or discontinued altogether. While this dosing schedule is widely used based on the short pharmacologic half-life of dexamethasone, the biological half-life is in excess of 36 hours, and daily or twice-daily dosing is effective and more convenient for maintenance therapy in most patients. Gastrointestinal prophylaxis and pneumocystis prophylaxis should be considered in patients in whom long-term corticosteroid treatment is anticipated.

Clinical Case Relevance

The patient was started on antiepileptic therapy at the time of his original emergency department visit. He had no further seizures. His exam was pertinent for a Karnofsky Performance Score of 90, and subtle left-sided pronator drift and slowing of rapid hand and foot movements on the left side were his only findings on physical exam. Dexamethasone was not initiated as he did not have symptoms of elevated intracranial pressure, such as headache or papilledema.

Initial Diagnostic Imaging

Because the symptomatic presentation of brain tumors is nonspecific, the presumptive diagnosis of brain tumor is often made only after imaging. Glioblastoma may be initially imaged with CT, particularly in the emergency department setting, but MRI provides more diagnostic information.

The typical CT appearance of glioblastoma is a mass lesion, often iso- to hyperattenuating (bright) in comparison to normal gray matter, with surrounding hypoattenuation due to infiltrating tumor and vasogenic edema. Contrast-enhanced CT classically reveals a centrally necrotic enhancing mass. Given that vascular proliferation is a hallmark of glioblastoma, intratumoral hemorrhage is common and may be visualized on CT, though it is more frequently identified as microhemorrhages on MR susceptibility-weighted imaging (SWI). Calcification is uncommon in glioblastoma, but can occasionally be seen.

On MRI, nearly all glioblastomas enhance with gadolinium contrast, usually showing a thick, irregular rind of tumor surrounding a necrotic cavity. Heterogeneity of signal intensity and

contrast enhancement within glioblastomas and irregularity in shape are expected. Vascular hyperpermeability contributes to surrounding vasogenic edema visible as high signal intensity on T2-weighted images. Hemorrhage may complicate the appearance of glioblastoma, with acute and early subacute hemorrhage appearing hypointense on T2-weighted images and iso- to hyperintense on T1-weighted images. This intrinsic T1 hyperintensity of blood is similar in appearance to gadolinium enhancement, so it is crucial to always compare T1-weighted postcontrast images with T1-weighted precontrast images to ensure accurate judgment of enhancement.

The infiltrative nature of glioblastoma is generally more apparent on MRI than on CT. Mass-like signal abnormality infiltrating along white matter tracts is suggestive of glioma as opposed to other entities. However, distinguishing between nonenhancing infiltrative glial tumor with edema and vasogenic edema from any other etiology can be difficult or impossible. Frequently, glial infiltration and thickening of the cerebral cortex can be appreciated on T2-weighted and T2-weighted FLAIR images, which may help to distinguish gliomas from other neoplasms. Multifocality, distant, or diffuse disease may be seen initially in approximately 13% of glioblastoma cases, with some areas sometimes looking less aggressive than the primary mass.[6] It is also well established that microscopic glial tumor cell infiltration is expected to extend beyond visualized signal abnormality on MRI.

The differential diagnosis of glioblastoma often includes metastasis and CNS lymphoma. Generally speaking, glioblastoma tends to be more irregularly shaped than metastases because of its predilection for spread along white matter tracts,[7] but there is overlap at least in qualitative analysis. Primary CNS lymphoma (PCNSL) in the immunocompetent patient is most often homogeneous in signal intensity and enhancement, though exceptions do occur; while heterogeneity and central necrosis are more common in CNS lymphoma in the immunocompromised.

Advanced MRI techniques including perfusion imaging techniques such as dynamic susceptibility contrast (DSC) imaging, diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), SWI, and MR spectroscopy may help to distinguish glioblastoma from other tumors. Given the histological hallmark of neovascularity in glioblastoma, increased blood volume (often expressed as rCBV, or relative cerebral blood volume) is expected within at least portions of a glioblastoma.[8–10] On MR spectroscopy, glioblastoma typically has the nonspecific findings of elevated choline and decreased N-acetylaspartate (NAA) and may have elevated lipid and lactate resonances. Generally speaking, the choline:NAA ratio increases with astrocytoma grade.[11] Due to the infiltrative nature of glioblastoma relative to metastases, one may expect greater CBV[12,13] and greater choline:creatine[14,15] in the peritumoral areas of glioblastoma relative to metastases. rCBV also tends to be greater in enhancing tumor and peritumoral areas of glioblastoma than in CNS lymphoma.[12] Apparent diffusion coefficient tends to be lower in CNS lymphoma than in glioblastoma, given the great hypercellularity of lymphoma.[12] Microhemorrhages on SWI are found in most glioblastomas but rarely in CNS lymphoma.[16,17] Differentiation of glioblastoma and lymphoma using multiparametric advanced MRI has also been suggested.[18] Imaging genomic mapping is a burgeoning area of research that has begun to discover associations between MRI features and glioblastoma genotypes and clinical phenotypes.[19]

Many published reports using advanced MRI techniques have relied on quantitative analyses, which are currently difficult to standardize across imaging platforms and institutions. For example, with perfusion imaging, there exists great variability in all steps from IV gadolinium bolus injection to scanner platforms used to MRI scan parameters chosen to post-processing software and analysis techniques used.[20] Given the technical variabilities of advanced MR techniques and expected glioblastoma heterogeneity, there are limits to the sensitivity and specificity of these techniques. The standardization of advanced MRI is well recognized as a pressing clinical and research need.

Clinical Case Relevance

The initial imaging obtained for this patient included a CT and contrast-enhanced MRI, shown in Fig. 1. Both of these images, and the MRI in particular, were concerning for glioblastoma, and metastasis and non-neuroplastic entities such as infection or demyelination were thought to be significantly less likely.

Surgery

Surgical resection is the primary treatment for glioblastomas. The goals of surgery are tissue diagnosis, including molecular and genetic tumor analysis, as well as cytoreduction for alleviation of presenting symptoms and improved tumor control. As previously discussed, in the appropriate context imaging can be very suggestive of glioblastoma. However, tissue diagnosis is the standard of care and only in cases of truly inaccessible tumors (such as brainstem lesions) or grave infirmity of the patient, precluding surgical candidacy, should treatment be undertaken without pathological confirmation of disease.

The surgical approach of choice is maximal safe resection. Over the past several years, significant data have accumulated supporting the idea that maximizing the extent of tumor resection positively impacts survival for patients with newly diagnosed glioblastoma.[21,22] In a single institution study of 949 patients with high-grade gliomas, more than half of whom were operated on for the first time, the extent of resection was shown to be an independent predictor (gross total resection [GTR] vs near total resection [NTR], NTR vs subtotal resection [STR]) of prolonged survival (median OS 11 months GTR, 9 months NTR, and 5 months STR).[23]

The association between extent of resection and survival benefit holds true even for tumors that are difficult to resect. In a study of multicentric high-grade glioma, resection of a dominant lesion was strongly predictive of improved overall survival when compared with biopsy only (12 months vs 4 months).[24] In the setting of insular high-grade gliomas, one of the most technically difficult eloquent cortical areas to access surgically, extent of resection $\geq$90% of the tumor provided 2-year overall survival of 91% compared with 75% for volumetric resection $<$90% of the tumor, in addition to improved progression-free survival.[25] The beneficial effect of maximal resection has also been suggested to extend to elderly patients without an increase in mortality or complications.[26]

Several technical intraoperative adjuncts have been developed in an effort to maximize the extent of safe resection.[27,28] Use of frameless stereotactic guidance, which allows for optimal patient positioning, accurate tailoring of the craniotomy, and safe access trajectory to the tumor, has become standard for resection of

glioblastomas. Recent advances have made it possible for intraoperative guidance to integrate imaging tools such as tractography, which allows for identification of motor, speech, and visual pathways, as well as MR spectroscopy to facilitate accurate targeting of presumed higher-grade areas within a heterogeneous tumor.[29] In cases where only a biopsy is planned, such imaging integration allows targeting of regions likely to optimize diagnostic yield and accuracy.

Direct cortical mapping allows identification of motor pathways and, when combined with awake craniotomy used for mapping of language areas, is an important adjunct to surgical resection of lesions in eloquent cortex.[25,30] A systematic review of the literature showed that direct cortical mapping decreases late severe neurological deficits from 8.25% to 3.4% and increases the rate of GTR from 58% to 75%.[31]

Intraoperative MRI has been used in an attempt to maximize extent of surgical resection and identification of residual resectable tumor.[32] In a study including both high-grade and low-grade tumors, use of intraoperative MRI increased the volumetric extent of resection from 76% to 96%.[33] However, the high installation cost of an intraoperative magnet as well as the complexities involved in its intraoperative use have led to research into alternate ways to identify residual tumor during surgical resection. The utilization of fluorescence guidance has been recently advocated. The use of fluorophores such as 5-aminolevulenic acid (5-ALA) or fluorescein, which accumulate in areas of blood brain disruption, can be a powerful adjunct that allows for the accurate identification of tumor borders and possible residual disease at the time of resection.[34–36] In a systematic review of 10 studies, patients who underwent surgery utilizing 5-ALA for maximizing resection had improved 6-month progression-free survival and overall survival.[37] A multicenter, randomized, phase III trial of 5-ALA-guided surgery found higher rates of gross total resection and 6-month progression-free survival in the 5-ALA group without any increase in adverse events.[38]

Following the initial multicenter, randomized trial of implantable carmustine polymer wafers in the treatment of recurrent high-grade glioma, Attenello et al reported their experience with their use during surgery for newly diagnosed high-grade gliomas and found an overall median survival of 13.5 months without any increased incidence of complications.[39,40] Although the use of chemotherapy implants appears to be safe in the setting of primary glioblastoma, the relative lack of improved survival and the fact that much of the data regarding the use of chemotherapy wafer implants predates the use of temozolomide (TMZ), has limited enthusiasm for this approach.

Surgery for high-grade gliomas is in general associated with relatively low rates of major complications. In an analysis of the patients in the Glioma Outcomes Project, an overall complication rate of 24% was reported for surgical treatment of newly diagnosed high-grade gliomas. In decreasing frequency, major complications included: depression (11%), worsened neurological status (8.1%), seizures (7.5%), adverse drug reaction (5.2%), DVT (4.2%), intracranial bleeding (1.6%), and pulmonary embolism and wound infection (0.5% each). Perioperative mortality was reported as 1.5%.[41] These results were similar to an earlier study that reported 13% major complications and 1.7% mortality in patient undergoing craniotomy for intraparenchymal tumors.[42] In an analysis of the California Inpatient Database, Marcus et al reported a 30-day readmission rate of 13.2% for patients who underwent surgical treatment for a glioma who were originally discharged home. The most common presentations at readmission were seizures (20.9%) and surgical infection (14.5%).[43]

In summary, surgery remains the first and very important treatment modality for a newly diagnosed glioblastoma. Its effectiveness for optimizing overall survival is related to the extent of resection and its safety is dependent on various intraoperative adjuncts that allow for accurate localization of the tumor as well as eloquent cortical areas.

Clinical Case Relevance

The patient underwent resection of his tumor without use of awake craniotomy or intraoperative MRI. Following surgery, his left-sided weakness was transiently worse but it then improved back to the presurgical baseline. His extensive resection placed him in a more favorable prognostic group than biopsy alone would have. Preoperative and postoperative MRI images are displayed in Fig. 2.

Pathology

The histological diagnosis in this case was WHO grade IV astrocytoma (glioblastoma). It was an infiltrative astrocytoma showing areas of high cellularity and brisk mitotic activity (Fig. 3A), tumor necrosis (Fig. 3B), and microvascular proliferation (Fig. 3C). The diagnostic criteria from the WHO (2007) include presence of cytological atypia, mitotic activity, microvascular proliferation, and/or tumor necrosis.[44] Briefly, an infiltrative astrocytoma exhibiting cytological atypia alone, including elongated, irregular and hyperchromatic nuclei, is considered WHO grade II (diffuse astrocytoma). The presence of increased cellularity, nuclear atypia, and mitotic activity warrant a WHO grade III (anaplastic astrocytoma) designation. Tumors that additionally show microvascular proliferation and/or necrosis are WHO grade IV (glioblastoma). Classic microvascular proliferation has the appearance of "glomeruloid tufts," consisting of multilayered, mitotically active endothelial cells admixed with smooth muscle cells/pericytes (as represented in Fig. 3C). Although necrosis surrounded by pseudopalisading tumor cells is most characteristic of glioblastoma (Fig. 3B), both geographic and pseudopalisading tumor necrosis can be present and are associated with similarly dismal prognoses. Astrocytoma grading is based on the highest histological grade. Since infiltrative astrocytomas can have considerable regional heterogeneity, especially toward their infiltrative border into surrounding parenchyma, it is important to assess whether a biopsy sample is representative of the entire tumor by correlating histological, clinical, and radiological findings. A biopsy taken at the periphery of a ring-enhancing mass could well show a low to moderately cellular tumor (as seen in Fig. 3D) with/without mitoses, prompting an inaccurate diagnosis of diffuse or anaplastic astrocytoma (WHO grade II or III) rather than glioblastoma (WHO grade IV).

Historically, glioblastomas have been distinguished based on their clinical presentation as primary (de novo) or secondary glioblastomas that develop in progression from a lower grade astrocytoma. Primary glioblastomas, the most common (>90%), develop with a short clinical history without clinical or pathological evidence of a lower grade precursor, and are typically seen in older patients. There are no definite histological features to

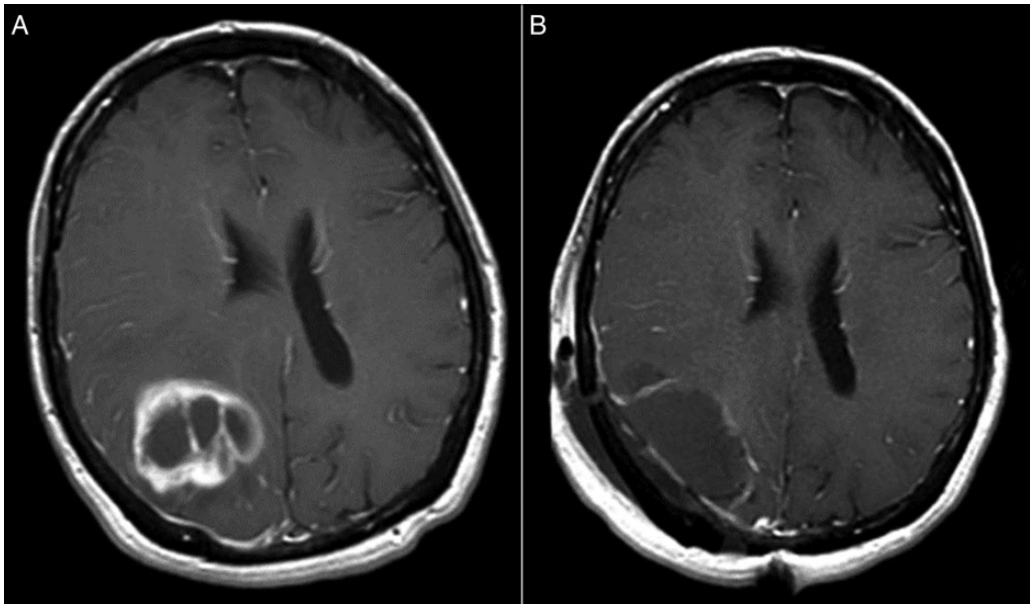

Fig. 2. Post-gadolinium spin echo T1-weighted images (A) before and (B) after surgery.

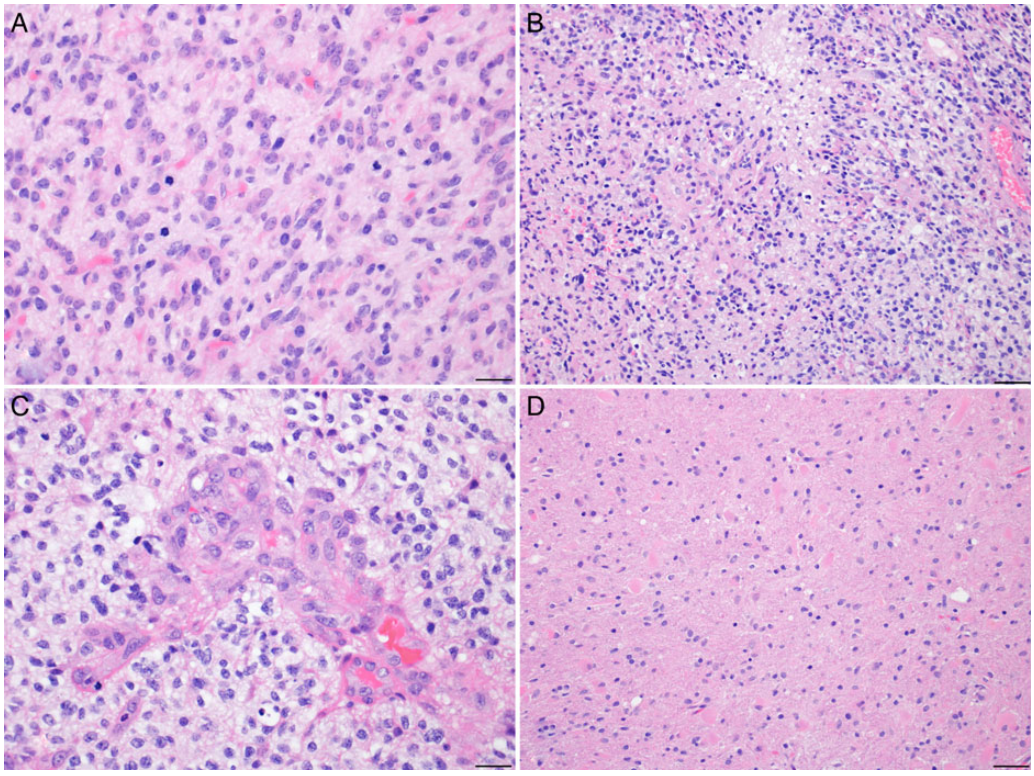

Fig. 3. The biopsies demonstrated an infiltrating population of atypical astrocytic cells, showing (A) brisk mitotic activity, (B) tumor necrosis, and (C) microvascular proliferation, consistent with a diagnosis of glioblastoma. A biopsy from the periphery of this mass may show (D) a low-to-moderately cellular tumor, with or without mitoses, corresponding to a lower histological grade. In images (A) and (C), photographed at 400× magnification, the scale bars on the bottom right represent 20 μm. In images (B) and (D), photographed at 200× magnification, the scale bars represent 50 μm.

distinguish primary and secondary glioblastomas. With advancing molecular information, however, it is clear that primary and secondary glioblastoma are two different diseases.

Mutation of isocitrate dehydrogenase (IDH) is frequently seen in low-grade glioma, and is also found in approximately 12% of glioblastomas.[45] The presence of IDH mutation within a

glioblastoma is suggestive of secondary glioblastoma, regardless of any previous history of low-grade glioma.[46–50] In glioblastoma, mutations almost exclusively involve residue 132 (R132) of *IDH1* resulting in the substitution of arginine.[46,51] The presence of *IDH1* mutation in glioblastoma has been associated with younger age and relatively longer survival.[52–56] Alterations in receptor tyrosine kinase pathways have also been frequently identified in glioblastomas.[57] Epidermal growth factor receptor (EGFR) activation, either by amplification of wild-type *EGFR* or by deletion of exons 2–7 that encode the extracellular domain (the variant III mutation) resulting in ligand-independent constitutive activation of EGFR,[47–49] is more commonly seen among primary glioblastomas. Mutations of the *TP53* gene are frequent in, but not exclusive of, secondary glioblastomas.[50,58,59] On the other hand, mutations in the promoter region of the telomerase reverse transcriptase (*TERT*) gene are predominantly found in primary glioblastomas that lack *IDH1* mutations, and appear to be associated with worse prognosis.[49,60–62]

The gene for the DNA-repair enzyme O(6)-methylguanine-DNA methyltransferase (*MGMT*) has a promoter region that is rich in CG dinucleotide (CpG) sites that are normally unmethylated. However, in glioblastomas, the cytosine in these CpG sites may become methylated, resulting in transcriptional silencing of *MGMT* and subsequent impairment of the DNA-repair process.[63–65] Glioblastomas with *MGMT*-promoter hypermethylation are unable to repair the DNA damage caused by alkylating agents (such as TMZ), and carry a more favorable prognosis than tumors without methylation of *MGMT*.[66–69] Tumors with *IDH* mutation frequently have *MGMT* promoter methylation.[70]

Integrated genomic analysis has revealed subsets of high-grade astrocytomas based on the differential expression of prognostic markers.[71,72] Three to four major subgroups are generally well recognized, and their distinction appears to be relatively robust on meta-analysis.[73] At one end of the spectrum is the proneural subgroup, characterized by alterations in markers associated with neurogenesis, strongly associated with *IDH1* mutations, and tending to have more favorable outcomes. The mesenchymal subgroup is at the other end of the spectrum, expressing markers usually associated with mesenchymal tissue and increased angiogenesis, associated with loss and/or mutation of the *NF1* gene, and tending to have relatively worse outcomes. These expression-based subgroups were also distinguished by their CpG island methylation status.[74] Glioblastomas in the proneural subgroup were more frequently found to show widespread CpG island hypermethylation, termed a glioma CpG island methylator phenotype (G-CIMP), which was not usually seen in tumors of the mesenchymal subgroup.

At present, the diagnosis of glioblastomas per the 2007 WHO guidelines is based on well-established histological features. However, testing for *MGMT* status is becoming accepted as a standard of care for newly diagnosed glioblastomas, as is screening for *IDH1* mutations. As newer therapeutic modalities emerge, there is increasing recognition for the need to communicate the status of prognostically and therapeutically relevant genomic markers to help guide clinical decisions for patient management. In a preliminary attempt to address this, consensus guidelines suggested at an international meeting of neuropathologists recommended that pathologists to provide an integrated diagnosis that incorporates the histological diagnosis and relevant molecular information.[75] For example, the diagnosis of glioblastoma, WHO grade IV, might also include the results of the *IDH1* mutation status, *MGMT* status, and other relevant markers.

Clinical Case Relevance

Pathology revealed glioblastoma, *MGMT* methylated. The *MGMT* methylation status is prognostic of better survival, relative to patients with unmethylated *MGMT*, and it also may predict response to treatment in some situations, to be discussed later.

Epidemiology

Glioblastoma is the most common primary brain tumor in adults. In the United States, the age-adjusted incidence rate is 3.19 (95% confidence interval 3.16–3.21) per 100 000 persons.[76] The lifetime risk of being diagnosed with an invasive cancer of the nervous system, most of which are either glioblastoma or glioblastoma precursors, is approximately 1 in 161, with the risk of dying from an invasive cancer of the nervous system being approximately 1 in 222.[77] Thus, while glioblastoma remains a relatively rare tumor, many patients will be aware of one or more acquaintances or relatives with this condition purely by chance, sometimes raising concern of clustering of tumors by geography or within a family.

Glioblastoma is more common in men than women, as are all infiltrating gliomas. Incidence rises with age, peaking in the 75–84 age range. Thus, though the overall age-adjusted incidence rate of glioblastoma does not appear to be rising, the raw number of tumors diagnosed each year is expected to climb in coming decades due to aging of the population at large. In the United States, glioblastoma is more common amongst non-Hispanic whites than in black, Asian/Pacific Islander, or American Indian/Alaskan native groups.

Ionizing radiation remains the only proven exposure risk factor for glioblastoma. Typically, radiation-induced glioblastoma is seen years after therapeutic radiation for another tumor or medical condition. Diagnostic radiation, for example from CT scanning or even dental X-rays may theoretically confer increased risk of glioma, but this has not yet been confirmed in large-scale epidemiological studies. Nonionizing radiation, specifically related to the use of cellular telephones, has not been convincingly linked to glioma incidence, but this is an area of active investigation. Asthma and atopic disease are associated with lower risk of glioblastoma in multiple studies, with one meta-analysis showing a reduction in glioma risk of 40% in patients with allergies.[78]

Many patients with glioblastoma are concerned about possible genetic risk factors, and ask about the advisability of screening for relatives. A heritable component to glioblastoma risk has long been demonstrated by the association between glioblastoma and Mendelian cancer syndromes including the Lynch and Li-Fraumeni syndromes. Recently, genome-wide association studies have revealed single nucleotide polymorphisms (SNPs) associated with glioblastoma risk. These SNPs have been identified within the candidate genes *TERT* (chromosome 5p15.33), *EGFR* (7p11.2), *CDKN2B* (9p21.3), *TP53* (17p13.1), and *RTEL1* (20q13.33).[79] Other SNP associations such as those within *CCDC26* (8q24.21) and *PHLDB1* (11q23.3) are mainly associated with IDH-mutant tumors and thus risk of secondary glioblastoma. Most of the currently identified risk SNPs confer only a modest

increase in risk of glioma, and thus the absolute risk of glioma remains low even in individuals carrying the risk SNPs.

Clinical Case Relevance

The patient came from a large family with a history of a number of different tumor types, but no first or second degree relatives with primary brain tumors. He was reassured that his family members were at low risk of primary brain tumor, and no screening studies were recommended.

Standard-of-Care Treatment

Glioblastoma is an infiltrative tumor, with residual disease present after surgery, even in cases of radiographic gross total resection. Additional treatment to address this residual tumor is thus necessary as soon as the operative site has healed appropriately. This additional treatment may take the form radiation therapy (RT), chemotherapy, or both, depending on the clinical scenario.

Current Standard-of-Care Therapy

The current standard-of-care treatment for newly diagnosed glioblastoma was established by a landmark trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada Trials Group (NCIC).[80] In this trial patients were randomized to RT alone (the previous standard of care) vs RT with concurrent and adjuvant oral TMZ chemotherapy. In this trial, median survival was 12.1 months in the radiation-only arm and 14.6 months in the TMZ arm. More importantly, combined chemoradiotherapy significantly increased the proportion of relatively long-term survivors from 10.9% to 27.2% at two years and from 1.9% to 9.8% at five years. Patients whose tumors had methylation of the promoter for the *MGMT* gene (*MGMT* methylated) had greater benefit from the addition of TMZ (46% 2-year survival vs 27% for the *MGMT* unmethylated patients), but *MGMT* unmethylated patients still had incremental benefit from the addition of TMZ (14% 2-year survival vs $<2\%$).[69]

Numerous studies have indicated a benefit to using RT in the treatment of gliomas.[81,82] A dose of 60 Gy in 2 Gy fractions is the recommended dose based on prior studies indicating that doses up to but not exceeding 60 Gy impact survival.[83,84] Despite agreement of a standard dose recommended in both clinical trials and practice, there is tremendous variability in the volume of tissue irradiated. A common approach endorsed by the Radiation Therapy Oncology Group and other cooperative groups is to target the tumor edema with a 2.5-cm margin to a dose of 46 Gy followed by a cone down to the resection cavity and contrast-enhancing tumor with similar margin to a dose of 60 Gy.[85] Other cooperative groups also recommend a staged approach initially including tumor edema with a cone down to the enhancing tumor, but only add a 1-cm margin. Additional strategies include treating the enhancing tumor and resection cavity with a 2–3-cm margin to a total dose of 60 Gy without a staged volume reduction.[80] The volume of brain irradiated in each of these scenarios is substantially different. While studies have demonstrated comparable outcomes comparing conformal radiation to whole brain irradiation, similar comparisons have not been made between these varied radiation approaches.[86]

Typically, TMZ is given daily during RT at a dose of 75 mg per square meter of surface area each day, followed by a rest period of approximately a month at the end of radiation. TMZ is then resumed at the dose of 150 mg per square meter on days 1–5 of a single 28-day cycle, and subsequent 28-day cycles are dosed at 200 mg per square meter on days 1–5 if the first adjuvant cycle was well tolerated. In the clinical trial that proved the efficacy of this approach, a total of 6 adjuvant cycles were given.[80] In practice, some physicians recommend more than 6 cycles, though there is currently no definitive data demonstrating that more prolonged regimens are associated with superior survival.

Side Effect Management

The most common symptomatic side effects of treatment are mild fatigue, nausea, and constipation. All patients receiving TMZ should be provided with antiemetic therapy, both to take prior to each TMZ dose to prevent nausea and also for as-needed use. Antiemetics of the serotonin 5-HT3 receptor antagonist class, such as ondansetron and granisetron, are often used for this purpose. TMZ often causes mild thrombocytopenia, but severe thrombocytopenia, neutropenia, and anemia are much less common. Asymptomatic leukopenia is very common in patients on TMZ. Prophylaxis against *Pneumocystis jiroveci* pneumonia with trimethoprim/sulfamethoxazole or an alternative agent is recommended for the full duration of TMZ therapy.

Common acute radiation side effects include headaches, nausea, exacerbation of presenting symptoms, hair loss, skin reaction at the site of radiation, and fatigue. Less common acute side effects can include dry mouth or altered taste, hearing impairment or seizures. Possible late side effects of radiation include decreased pituitary hormonal production, cataract formation, secondary cancers, and nerve damage. Radiation necrosis can occur and cause symptoms similar to tumor recurrence or stroke. Necrosis is initially managed with steroids but may require more intensive options such as surgery or bevacizumab therapy.[87]

Neurocognition can be altered during initial therapy secondary to inflammation, anxiety, and medications, but radiation can also cause cognitive impairment months to years after it is completed, even in the absence of tumor progression. Learning and memory are the most commonly impaired cognitive domains. The extent of impairment may be related to patient-specific factors, but also related to volume of tissue irradiated and location of the radiation field. For example, dose to hippocampal structures has been found to influence extent of neurocognitive dysfunction.[88–90]

Elderly Patients and Patients with Poor Performance Status

The pivotal trial that demonstrated the efficacy of TMZ for newly diagnosed glioblastoma did not include patients over the age of 70, leaving unanswered the question of whether this regimen is effective and well tolerated in elderly patients.[80] Moreover, a number of trials have been conducted that suggest, at least in some circumstances, abbreviated or less intensive treatments may be effective in older patients. In a randomized, phase III trial conducted by the Nordic Clinical Brain Tumor Study Group, patients age 60 or older with glioblastoma were randomized to the typical 6 weeks of RT, 2 weeks of hypofractionated RT, or TMZ without RT.[91] The trial demonstrated that both the hypofractionated RT and TMZ monotherapy were superior to 6 weeks of RT

with respect to overall survival. Similarly, in the German NOA-08 trial, patients over 65 years of age were randomized to dose-dense TMZ or standard 6-week RT, with similar outcomes in each group.[92] Both the Nordic and NOA-08 trials demonstrated that *MGMT* methylation was predictive of response to TMZ therapy. Patients whose tumors demonstrated methylation of *MGMT* had better survival when treated with regimens that contained TMZ, whereas patients with unmethylated *MGMT* did better when treated with RT. Although both these studies were randomized phase III studies, there are significant limitations in interpreting the data. Notably, 6 weeks of RT with concurrent and adjuvant TMZ was not an arm in either study, so direct comparisons of these alternative approaches to the current standard of care are not possible. In addition, the definition of elderly varied across these trials and across other, retrospective analyses.

Currently, as no therapy has been proven superior or equivalent to standard combined chemoradiotherapy in elderly patients, this therapy is a reasonable option for patients of any age with good performance status who are felt likely to tolerate intensive treatment. In patients with poor performance status or those in whom treatment tolerability is a concern, treatment choice should be informed by *MGMT* methylation testing. In patients with *MGMT* methylation, TMZ monotherapy is reasonable, whereas RT monotherapy is an option for patients without *MGMT* methylation. Given the results of the Nordic trial, as well as a previous trial that demonstrated that abbreviated RT was not inferior to 6-week RT, hypofractionated RT is preferable to the standard six-week schedule in this patient group if not combined with chemotherapy.[93]

Optune (NovoTTF-100A)

Recently released information, in the form of a press release and a presentation at a neuro-oncology specialty meeting, suggests that the addition of therapy with alternating electric fields via the Optune device (NovoCure) may prolong both progression-free and overall survival by several months when combined with standard chemoradiotherapy for newly diagnosed glioblastoma.[94] In the trial for which data were presented, Optune therapy was initiated at the time of initiation of adjuvant TMZ therapy and continued until tumor progression. While this result is cause for optimism, the results presented were from an interim data analysis, and publication of the full trial data in a peer-reviewed journal will be necessary before Optune therapy can be critically evaluated for possible inclusion in a new standard of care for glioblastoma.

Recent Clinical Trial Results

After combined chemoradiotherapy became the standard of care, more aggressive dosing of TMZ was tested in hopes that it might provide additional efficacy. RTOG 0525, a large phase III study, compared a dose-dense schedule of TMZ after RT with the standard 5-day schedule. No difference in survival was noted in either *MGMT* methylated or *MGMT* unmethylated patients.[85] Cilengitide, a targeted drug that inhibits integrins, was added to standard RT and TMZ in two separate clinical trials, a phase III study in *MGMT* methylated patients[95] and a phase II study in *MGMT* unmethylated patients,[96] but did not show improvement in survival in either case. The addition of the anti-angiogenic agent bevacizumab, an antibody against VEGF, to standard RT and TMZ was tested in two large phase III trials. While there was some improvement in progression-free survival, no improvement in overall survival was noted in either of these trials.[97,98] As such, bevacizumab has not at this time been approved for use in initial treatment of glioblastoma.

Important Ongoing Clinical Trials

There are numerous phase I and II trials around the world testing the addition of other drugs to standard therapy, including targeted agents, cytotoxic agents, and a variety of immune-targeting approaches. In addition, there are trials in progress testing alternative radiation techniques such as proton therapy or imaging-guided radiation dose escalation, and trials testing metabolic approaches against cancer such as variations on the ketogenic diet.

With regard to phase III trials, a randomized, placebo-controlled trial is currently ongoing that tests the addition of an autologous vaccine made from a patient's own tumor and their own dendritic cells (DCVax-L) to initial adjuvant TMZ.[99] Another glioblastoma immunotherapy approach, using the EGFRvIII-targeted experimental cancer vaccine rindopepimut (CDX-110), is being evaluated in the ACT IV trial.[100] Within the elderly population specifically, a randomized, phase III trial comparing hypofractionated RT alone or in combination with TMZ has completed accrual in Canada, Europe, and Japan[101]; the results are eagerly awaited to further inform whether combination therapy is effective in this patient population.

Clinical Case Relevance

The patient had excellent performance status and was felt to be a candidate for standard chemoradiotherapy, despite his age of 73. He developed mild nausea and moderate fatigue during chemoradiotherapy, but no life-threatening toxicities. He likewise tolerated adjuvant TMZ well from a symptomatic standpoint, though several cycles had to be briefly delayed due to mild thrombocytopenia. He discontinued TMZ therapy and moved to an observational phase following the sixth adjuvant cycle. Had he not been judged a good candidate for standard therapy, a TMZ-only approach, sparing radiation, would have been an acceptable alternative for an elderly man with an *MGMT*-methylated tumor.

Follow-up Imaging

Initial Postoperative Imaging

Postoperative imaging is strongly recommended within the first 48 hours following surgical resection in order to establish a post-operative baseline. If MRI is obtained, it is important to compare precontrast T1-weighted images with post-contrast T1-weighted images in order to detect true residual enhancement, as blood products in or around the surgical bed are usually present and may cause T1 shortening on both pre-gadolinium and post-gadolinium images. It is also crucial to perform DWI in order to detect any perioperative infarction, which may subsequently gain enhancement in the subacute phase, lose restricted diffusion, and present as a troubling, new enhancing lesion on subsequent MRI follow-ups.[102]

Long-term Follow-up

Generally, patients undergo monthly clinical evaluation and blood work during adjuvant TMZ, with MRI every other month. After the completion of TMZ, imaging is recommended every 2 to 3 months until 2 years from the end of treatment. After this time, MRI can be performed less often, provided the patient and physician are comfortable with this approach. Regardless of duration of disease-free survival, clinical evaluation and imaging should take place on at least an annual basis.

It is expected that the imaging appearance of a treated glioblastoma will evolve over time. One hopes for tumor regression after chemoradiation, but a temporary worsening of imaging findings, including increased contrast enhancement and edema signal with mass effect, is very common as a reaction to treated and dying tumor. This phenomenon is known as pseudoprogression, named so because the MRI appearance may be identical to tumor progression when, in fact, subsequent follow-up examinations with no change in therapy show regression of these imaging findings.[103] There is, unfortunately, often no basis on which to discriminate post-treatment related enhancement from enhancement related to viable tumor using standard morphological MRI.

Pseudoprogression may be more common with the combined use of TMZ with RT, it is more common in those with *MGMT* promoter methylation, and it has been associated with an improved clinical outcome in some cohorts.[104,105] The incidence of pseudoprogression is on the order of 30%,[106] depending on how it is judged, and most pseudoprogression occurs within 3 months of the end of RT. However, pseudoprogression occurring after this 3-month period but within the first year is not uncommon, particularly in those with *MGMT* promoter methylation.[107]

The Macdonald criteria has been used as a framework for judging glioblastoma progression or regression, relying mainly upon 2-dimensional maximal diameters of contrast-enhancing lesions.[108] In 2010, the Response Assessment in Neurooncology (RANO) criteria were published, updating the Macdonald criteria in several important ways, while maintaining a reliance upon the product of perpendicular diameters of contrast-enhancing lesions as an indicator of tumor size and status.[109] One very important caveat in the RANO criteria is that, because of the common occurrence of pseudoprogression with modern chemoradiation therapy, a radiographic diagnosis of tumor progression cannot be made within the first 3 months of the end of chemoradiation if an enlarging, enhancing lesion is within the high-dose field of RT. Any apparent tumor progression within the first 3 months after radiation must be closely followed to differentiate early tumor progression from pseudoprogression. Because pseudoprogression occasionally occurs beyond 3 months from the end of radiotherapy, some would advocate early follow-up scans to confirm or deny pseudoprogression if there is apparent radiographic progression occurring even beyond the 3-month window after radiotherapy. RANO also allows for the determination of progression when there is nonenhancing tumoral progression, as nonenhancing tumor progression is not uncommon.[6] New, discrete, masslike abnormalities or new cortical expansion with T2 lengthening suggest nonenhancing tumor progression per RANO criteria. Unfortunately, distinguishing nonenhancing tumor from other treatment-related effects and edema is often difficult or impossible.

Given the complexity of MRI interpretation, other means of glioblastoma treatment response assessment are needed. Estimates of tumor cell proliferation rates and invasion have been made through the analysis of MRI coupled with computational modeling as a means to monitor treated glioblastomas over time.[110,111] Physiologic or mechanistic imaging techniques such as dynamic susceptibility contrast (DSC) perfusion imaging, dynamic contrast enhanced perfusion imaging (DCE), DWI, spectroscopy, and PET with various tracers also may aid in distinguishing progressing tumor from treatment-related changes such as pseudoprogression and radiation necrosis, but their implementation has to date been so variable site-to-site that these techniques have not been included in the RANO criteria.

Generally speaking, it is expected that CBV will be elevated with viable high-grade glioma but not radiation necrosis, and possibly not elevated with pseudoprogression, though data for pseudoprogression are as yet less clear.[112–119] However, the variability in perfusion imaging has already been mentioned, there is often overlap between CBV in viable glioblastoma and radiation-induced changes, there is frequently an admixture of viable tumor and radiation-induced changes, and leakage of gadolinium into the interstitium breaks tracer-kinetic modeling assumptions and presents a challenge to accurate determination of CBV. In order to optimize CBV measurement, the use of a leakage-correction option is advised during image postprocessing. Many experts also recommend the use of a gadolinium preload prior to the acquisition of DSC images. Histogram and voxel-wise analyses of perfusion data hold promise for improving the differentiation between viable tumor and treatment-related changes, but they are postprocessing intensive.[120,121] Given the frequent admixture of residual glioma and radiation-related changes, determination of a residual/recurrent tumor fraction would be desirable and such a metric using CBV has been shown to correlate with overall survival.[122] Importantly, the relative change in lesion CBV over time may be crucial in judging tumoral stability or progression,[123] though it bears stating explicitly that uniformity in perfusion technique between time points is mandatory for the best chance at fair comparisons.

DCE perfusion imaging, which is generally more technically demanding than DSC perfusion imaging, also holds promise for differentiating recurrent glioblastoma from treatment-related changes, using metrics such as the volume transfer coefficient k_{trans} and initial area under the curve.[118,124–126] MR spectroscopy can be technically challenging to perform well and interpret, but after therapy choline and lipid and lactate levels have been shown to correlate with glioma outcomes.[119,127] More data on the value of MR spectroscopy in the glioblastoma post-treatment setting is needed. ADC values from DWI imaging, particularly when using advanced analysis techniques such as histogram analysis and functional diffusion maps (fDMs),[128–133] may also help to differentiate recurrent tumor from treatment-related changes. Amino acid PET may also aid in this discrimination better than with FDG PET but these techniques need further evaluation.[134–138] Finally, it is likely that multiparametric approaches with advanced MRI techniques will add to assessment of glioblastoma treatment response.[119]

Clinical Case Relevance

The first MRI following the completion of chemoradiotherapy, shown in Fig. 4A, demonstrated a rim of contrast enhancement around the resection cavity that had not been visible on the initial postoperative imaging (Fig. 2B). The patient was asymptomatic,

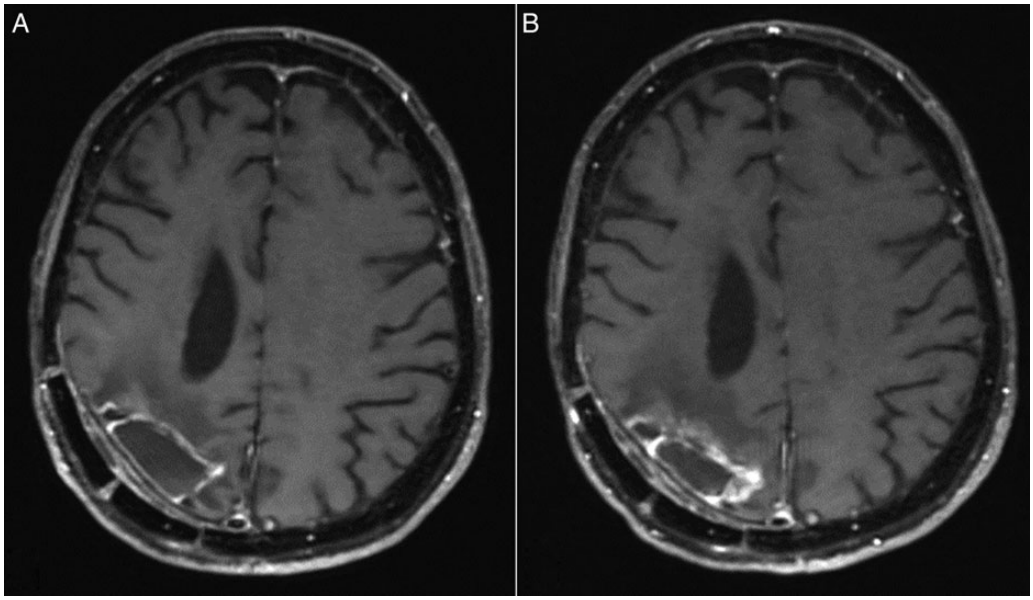

Fig. 4. (A) The first MRI following chemoradiotherapy and (B) MRI evidence of tumor progression approximately 2 years later. Both are post-gadolinium spin echo T1-weighted images.

Table 1. Survival by *MGMT* methylation status in recent phase III trials for newly diagnosed glioblastoma

Trial	*MGMT* Status	OS Median (95% CI)	PFS Median (95% CI)
EORTC 26981/22981 and NCIC trial CE.3[a, 69,141]	Unmethylated	12.6 (11.6–14.4)	5.3 (not reported)
	Methylated	23.4 (18.6–32.8)	10.9 (not reported)
RTOG 0525[85]	Unmethylated	14.0 (12.9–14.7)	5.7 (5.1–6.1)
	Methylated	21.2 (17.9–24.8)	8.7 (6.6–11.2)
RTOG 0825[98]	Unmethylated	14.3 (13.6–15.3)	8.2 (7.5–9.2)
	Methylated	23.2 (20.1–28.3)	14.1 (10.5–16.1)

[a]OS statistics from Stupp Lancet Oncology 2009; PFS statistics from Hegi NEJM 2005. All statistics regard the RT + TMZ trial arm.
Abbreviations: MGMT, O(6)-methylguanine-DNA methyltransferase; OS, overall survival; PFS, progression-free survival; EORTC, European Organisation for Research and Treatment of Cancer; NCIC, National Cancer Institute of Canada; RTOG, Radiation Therapy Oncology Group.

the changes were suspected to be treatment-related, and no change of plan was recommended. He remained clinically and radiographically stable for nearly 2 years until he had tumor progression along the medial margin of his resection cavity, as shown in Fig. 4B. His KPS at the time of progression was 80, due to increased left-sided weakness, but he was still able to live independently with his wife. After discussing options including continuing to focus on aggressive tumor treatment, potentially at the cost of short-term quality of life, vs prioritizing quality of life and supportive care with hospice, he chose to pursue salvage chemotherapy, the details of which are beyond the scope of this review.

Prognosis and Survivorship

Overall Survival

Survival after diagnosis of glioblastoma has been steadily improving over the course of the last decade, for reasons both known and unknown. The widespread adoption of TMZ for newly diagnosed glioblastoma in and after 2005 was associated with in an increase in population-level survival.[139] Likewise, though a survival benefit has yet to be demonstrated in a randomized prospective trial, population-based data suggest that survival also improved after the FDA approval of bevacizumab for recurrent glioblastoma.[140] Additional improvements in the survival of patients with glioblastoma may be due to incremental improvement in surgery, radiation, and supportive care.

The median survival figure of 14.6 months from the pivotal TMZ trial is often shared with patients with newly diagnosed glioblastoma, but clinical trial median survival numbers have little relevance when predicting the specific prognosis of an individual patient. Many factors can significantly impact survival, including but not limited to age at diagnosis, performance status, extent of resection, *MGMT* methylation status, and *IDH* mutation status. Median survival by *MGMT* methylation status in recent phase III trials is shown in Table 1. A number of survival prognostication systems have been published, but again these are more relevant to cohorts than patients as individuals. In the long-term

follow-up of the pivotal phase III TMZ trial, among patients treated with radiation and TMZ, 27.2% were still alive at 2 years, 16.0% at 3 years, 12.1% at 4 years, and 9.8% at 5 years.[141] Survival to 10 years or longer is very rare.

Because glioblastoma is an intrinsically fatal diagnosis, and treatment can cause significant side effects, most tumor treatment plans require the sacrifice of some quality of life in the short term in the hope of gaining duration of life in the longer term. Early in the course of disease, this is a trade-off that most patients readily accept, though some choose to forgo aggressive therapy. With each successive treatment, the expected duration of benefit tends to decrease and toxicity may increase, so the merits of focusing purely on quality of life should be readdressed regularly, for example at the time of clinical or radiographic progression. When the service is available, patients may benefit from speaking with a palliative care physician early in the course of their disease, and maintaining the relationship until the end of their lives. While death may occur precipitously as the result of a pulmonary embolism or intracerebral hemorrhage, most patients die after weeks or rarely months of progressive decline following the decision to discontinue aggressive tumor therapy, and hospice services can be extremely valuable to patients and their families in this situation.

Supportive Care (Long-term)

Antiepileptic Therapy

Most patients with glioblastoma who have experienced a seizure require lifelong AED therapy, particularly if seizures occur during or after initial tumor therapy. There is variability in practice regarding patients who experienced seizure at initial presentation and are seizure-free on anti-epileptic therapy following tumor treatment. Many neuro-oncologists recommend lifelong AED therapy in this situation as well, whereas others will consider tapering patients off of antiepileptic therapy after 1 to 2 years if he patient is interested in doing so and electroencephalogram (EEG) at that time does not demonstrate epileptiform discharges. Of course, freedom from seizures cannot be guaranteed, with or without continuation of antiepileptic therapy. Patients electing to attempt to discontinue AEDs should be counseled about seizure safety and avoiding high-risk activities.

Anticoagulation

Patients with glioblastoma are at significant risk of venous thromboembolism and related complications. There is no proven role for prophylactic anticoagulant therapy to prevent deep venous thrombosis (DVT).[142] Instead, patients should be educated about the symptoms of DVT and pulmonary embolism (PE), and physicians should have a low threshold for obtaining confirmatory testing if these symptoms occur. The diagnosis of glioblastoma is not a contraindication for treatment with systemic anticoagulation if a DVT/PE occurs, even in the setting of antiangiogenic therapy.[143] Treatment with low molecular weight heparin products has been shown to be more effective that oral anticoagulation with warfarin in patients with cancer.[144]

Psychological and Emotional Well-being

Symptoms of depression and anxiety are common and undertreated in patients with glioblastoma. Many factors may contribute to depression in patients with glioblastoma, including loss of independence and function, the adjustment to the idea of a significantly shortened life, and possibly a direct biological effect of the tumor on neurotransmitter signaling.[145] Many patients and their families find cancer support groups, or ideally brain-tumor-specific support groups, very beneficial both for practical advice and the knowledge that they are not alone in facing this diagnosis. Antidepressant therapy and/or referral to a mental health professional should be considered for patients with symptoms that extend beyond the range of normal adjustment and negatively impact the quality of their lives.

Conclusion

Despite recent progress, glioblastoma remains an incurable tumor with survival under a year and a half for most patients. Multidisciplinary care is necessary to maximize survival time and preserve quality of life. In appropriately selected patients, aggressive surgery may relieve symptoms and prolong survival. Medical oncologists, radiation oncologists, and neurologists work as a team to design and deliver the initial treatment plan, typically involving the combination of RT and TMZ chemotherapy. Radiologists with expertise in the complexities of glioblastoma imaging help make the initial diagnosis and monitor response to therapy.

For glioblastoma survival to continue to improve, advances in each of these specialties and collaboration between specialties will be required. Advances in neurosurgical technique aided by advanced imaging modalities will allow for more extensive safe tumor resection at time of diagnosis and at time of recurrence. Ongoing clinical trials may help refine the long-recognized role of RT for the treatment of newly diagnosed glioblastoma in general and also define its role relative to that of TMZ in elderly patients. Novel therapeutic strategies, recently with an emphasis on molecularly targeted therapies and immunotherapeutic approaches, also hold the potential to significantly change the care of glioblastoma.

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