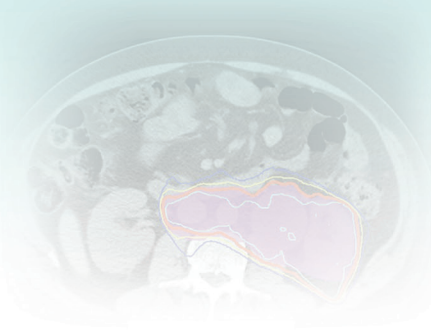
CHAPTER

27 High-Grade Gliomas



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INCIDENCE

There are approximately 68,000 new cases of brain tumors diagnosed in the United States each year. Gliomas now account for nearly 80% of malignant brain tumors. Glioblastoma (GBM) is the most common primary malignant brain tumor.[1]

BIOLOGIC CHARACTERISTICS

A better prognosis is associated with grade III tumors (as classified by the World Health Organization [WHO]) when compared with grade IV tumors (i.e., GBM) and for oligodendrogliomas when compared with astrocytomas. A better response to therapy and higher rates of survival are associated with oligodendroglial tumors manifesting 1p19q codeletions and IDH mutations. Methylation of the promoter for the *MGMT* gene predicts for increased sensitivity to DNA alkylating agents such as temozolomide and is prognostic for overall survival (OS) in patients with GBM, especially older patients.

STAGING EVALUATION

Optimal imaging is carried out with contrast-enhanced magnetic resonance imaging (MRI). Computed tomography (CT) scans are primarily used as an infrastructure for radiation treatment planning before fusion with MRI images. On the first postoperative day, an MRI study should be obtained to evaluate the extent of resection and as a basis for radiation treatment planning.

PRIMARY THERAPY AND RESULTS

The standard of care for the definitive treatment of newly diagnosed GBM in patients aged 18 years to 70 years is the delivery of approximately 60 Gy of fractionated partial brain radiotherapy following maximal safe surgical debulking. Irradiation (most commonly administered with conformal strategies) should be accompanied by concurrent temozolomide chemotherapy. Adjuvant temozolomide is also administered for at least 6 months following the end of radiotherapy unless disease progression occurs.

Temozolomide has not been established as a component of standard therapy for newly diagnosed WHO grade III gliomas; ongoing trials are investigating this issue.

Prospective randomized trials could not define a role for either brachytherapy or radiosurgery in the initial management of high-grade gliomas.

LOCALLY ADVANCED DISEASE AND RECURRENCE

Bevacizumab has been approved for salvage of failures following definitive therapy for GBM. If chemotherapeutic options are not available in the setting of recurrence, creative radiotherapeutic strategies (e.g., radiosurgery, intensity-modulated radiation therapy [IMRT], brachytherapy) may be considered.

High-grade gliomas are almost universally fatal. Although recently discovered combined-modality approaches have prolonged survival, many patients succumb relatively quickly, and cure remains elusive for the majority.

New protocols have recently emerged after decades of limited progress in the management of these tumors. New chemotherapeutic drugs, such as temozolomide, have found application in GBM. Bevacizumab is effective in recurrent disease and prolongs radiographic disease control in first-line regimens. In the future, molecular profiling may also allow tailoring of specific treatment to the patients most likely to benefit.

ETIOLOGY AND EPIDEMIOLOGY

Most malignant brain tumors are high-grade gliomas, and most of these are GBM, a WHO grade IV tumor. The remainder are WHO grade III tumors such as anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma. Men are more commonly affected than women. The peak incidence occurs in the age range of 65 years to 75 years, and the median survival time is inversely proportional to age; these findings have prompted a redoubling of efforts in elderly subpopulations.[1]

There has been concern for cancer development following exposure to electromagnetic fields, but definitive evidence is lacking. More recently, the use of cellular telephones has been studied extensively in Europe,[2] but its importance as a risk factor has not been established. In terms of chemical exposure, nitrosamines have long been regarded as culpable, but causality is far from proven.[3] Brain tumors have also been linked with previous exposure to therapeutic ionizing radiation.[3] However, the absolute risk is low.

Most gliomas are sporadic, but genetic susceptibility is suspected based on the occurrence of multiple brain tumors in families with germline mutation of the *TP53* suppressor gene and patients with neurofibromatosis type I as well as the rare patients who have been diagnosed with Turcot's syndrome. A heritable syndrome contributes to less than 5% of GBMs.[4]

PREVENTION AND EARLY DETECTION

No viable strategy for screening or early detection of glial tumors has been developed. There is also no convincing evidence demonstrating either improved survival when high-grade gliomas are found early, or a clear rationale for prophylactic strategies to reduce the incidence of these aggressive tumors.[3]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Investigators around the world are searching for the molecular biologic characteristics of gliomas in an effort to improve therapy. For example, work by the Cancer Genome Atlas Research Network[5] and others[6,7] suggests that at least three molecular subclasses of GBM exist with potential therapeutic and prognostic implications. Mouse modeling has also demonstrated the oncogenic importance of abnormalities in receptor signaling (e.g., epidermal growth factor receptor [EGFR] and platelet-derived growth factor receptor [PDGFR]), signal transduction cascades (e.g., RAS and AKT), and cell cycle regulation.[8]

In the early 1990s, it was recognized that deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) occurs in most oligodendrogliomas.[9] Codeletion of 1p and 19q is prognostic for longer survival,[10-12] although until recently controversy existed as to whether this finding should alter therapy.[13] It is now recognized that an unbalanced chromosomal translocation underlies 1p/19q codeletion,[14,15] but the specific genes involved and their mechanism of action remain elusive. More recently, mutations in the isocitrate dehydrogenase 1 and 2 *(IDH1* and *IDH2)* genes, occurring most often in low-grade gliomas but also in a minority of WHO grades III and IV tumors have been described,[16,17] and are prognostic for longer survival.[12,16,18,19] Methylation of the *MGMT* promoter (see the section on chemotherapy) is emerging as a potential but imperfect predictive and prognostic factor in the treatment of newly diagnosed GBMs.

With the exception of 1p19q codeletion in anaplastic tumors, it is not yet clear how to best incorporate molecular data into the treatment of individual patients. Detailed discussions of the biologic characteristics of glioma and their clinical relevance are beyond the scope of this chapter and can be found elsewhere.[20]

PATHOLOGY AND PATHWAYS OF SPREAD

The WHO classification system[21] is derived in part from the correlation between pathologic findings and survival rates observed by Bailey and Cushing[22] and published in the early 1900s. In current parlance, *low grade* refers to WHO grades I to II tumors and *high grade* to WHO grades III to IV tumors (Figure 27-1). However, the WHO grade I gliomas (e.g., juvenile pilocytic astrocytomas) are biologically different tumors from the others, infrequently occur in adults, and may be amenable to surgical cure. *Anaplastic* in the context of gliomas refers to WHO grade III tumors such as anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas. GBM is a WHO grade IV astrocytoma, although the most recent WHO classification scheme does account for other rare subtypes, including GBM with oligodendroglial components.

WHO grades II to IV gliomas are characterized by a tendency to directly infiltrate adjacent brain tissue. Lesions with direct access to the corpus callosum may extend across the midline and configure themselves in a classic "butterfly pattern" (Figure 27-2). MRI underestimates the extent of invasive disease, and the diffusely infiltrative nature of these tumors makes complete removal of all tumor cells impossible. This "misleading appearance of enucleability" was described more than 80 years ago.[22] Leptomeningeal spread occurs occasionally (Figure 27-3). Hematogenous and lymphatic spread are exceedingly uncommon.[23]

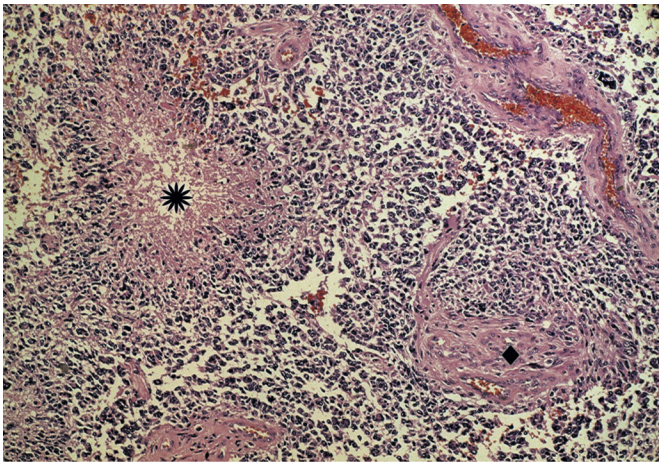

Figure 27-1 Highly cellular astrocytic glioma with foci of microvascular proliferation *(asterisk)* and pseudopalisading necrosis *(diamond)* consistent with glioblastoma.

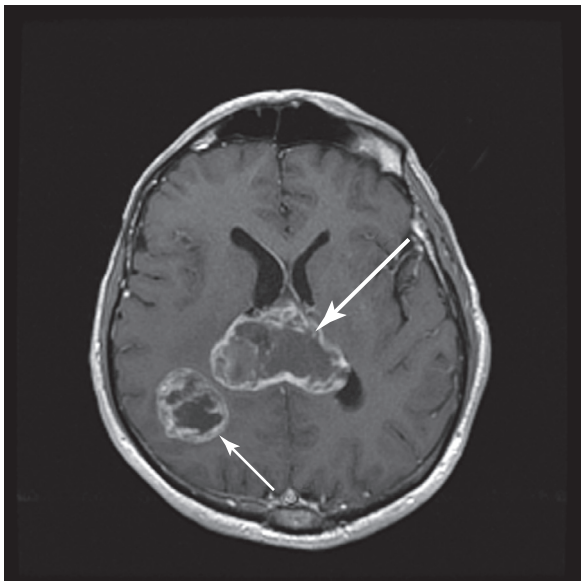

Figure 27-2 "Butterfly" glioblastoma *(long arrow)*; a separate satellite lesion in the right parietal lobe *(short arrow)* is also apparent. The contrast enhancement with central necrosis is classic for a glioblastoma, which was histologically confirmed by biopsy.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

No specific symptom constellation is pathognomonic of high-grade glioma. Typically, patients present with some combination of headaches, neurologic deficits, nausea, and vomiting, depending on tumor size and location. It is not unusual for patients to present with or subsequently develop seizures. Tissue for pathologic diagnosis can be obtained via stereotactic biopsy, open biopsy, or gross resection in the context of craniotomy. More complete resection improves diagnostic accuracy, provides additional tissue for molecular analyses, and is increasingly thought to improve OS.

The typical imaging appearance of a GBM is a ring-enhancing or heterogeneously enhancing lesion. The differential diagnosis may include stroke, brain metastasis, primary central nervous system lymphoma, demyelination, and even infectious or other inflammatory diseases. If a brain metastasis

is suspected, it is prudent to perform an appropriate extracranial evaluation to identify the primary malignant tumor. If there is a high index of suspicion for primary central nervous system lymphoma, such as in multifocal, periventricular, or homogenously enhancing lesions,[24] corticosteroids should be withheld preoperatively unless herniation is imminent because their use may confound the histologic diagnosis.

Nearly all GBMs demonstrate contrast enhancement. However, up to 10% of anaplastic gliomas will not manifest such a pattern on imaging. Background uptake in the brain (an organ with an inherent avidity for glucose) significantly compromises the use of glucose-based positron emission tomography (PET) as a diagnostic tool for high-grade gliomas.

An algorithm for the evaluation and management of patients with GBM is shown in Figure 27-4.

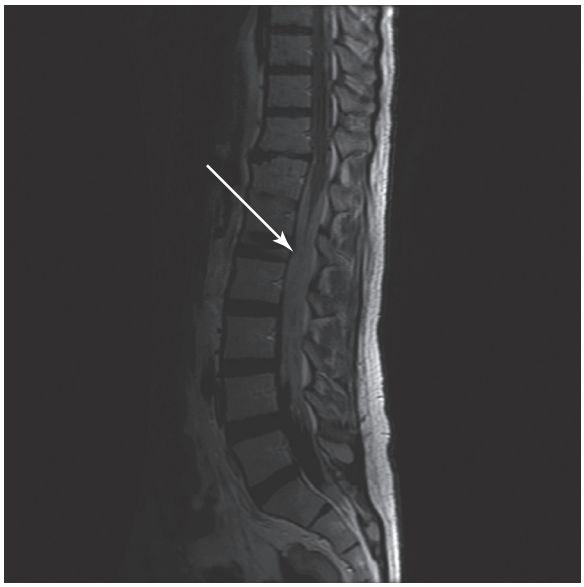

Figure 27-3 T1 contrast-enhanced sagittal view from a magnetic resonance imaging showing rare leptomeningeal spread from a glioblastoma surrounding the spinal cord.

PRIMARY THERAPY

Prognostic and Predictive Factors

Historically, all high-grade gliomas were lumped together in most clinical trials, thereby confounding results because of maldistribution of patients with differing prognoses. In 1993, Curran et al[25] published a landmark paper describing a prognostic classification scheme based on clinical variables. Data from three Radiation Therapy Oncology Group (RTOG) trials that enrolled nearly 1600 patients with high-grade glioma from 1974 to 1989 were used. This recursive partitioning analysis (RPA) methodology builds decision trees to model predictors by examining all possible "cut points" for all variables included in the model. Patients were segmented into six distinct groups with different survival outcomes. The key variables included patient age, performance status, histologic tumor type (i.e., anaplastic astrocytoma versus GBM), mental status, symptom duration antecedent to diagnosis, extent of resection, neurologic function, and radiotherapy dose. Median survival ranged from 4.6 months for class VI patients to almost 5 years for class I patients, underscoring heterogeneity. The European Organization for Research and Treatment of Cancer (EORTC) demonstrated that the prior RTOG RPA classification remained valid among patients in a more recent Phase III trial.[26] An RPA for anaplastic oligodendroglial tumors has also been proposed.[27]

One of the more controversial factors in the setting of high-grade gliomas has been the extent of surgical resection. Bailey and Cushing observed longer survival following resection in their 1926 publication,[22] as did others in the 1960s.[28] Numerous series since then also support more complete resection as a prognostic factor.[29-33] One of the largest involved more than 400 patients at the M. D. Anderson Cancer Center and demonstrated improved median survival (13 versus 8.8 months; $p < 0.0001$) following at least 98% resection, as defined by postoperative MRI scans.[34] One small randomized study of 30 patients older than 65 years demonstrated improved survival rates following resection versus biopsy alone.[32] Use of 5-aminolevulinic acid fluorescence intraoperatively improves the likelihood of gross total resection,[29] but the effect on survival is debated.

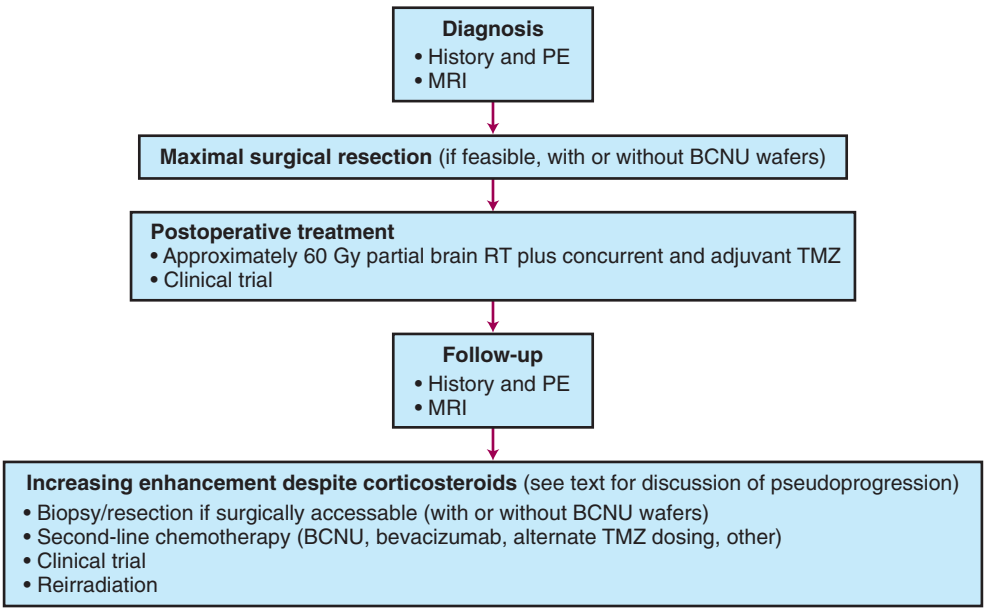

Figure 27-4 Algorithm for diagnosis and treatment of glioblastoma. See text for details. *BCNU,* Carmustine; *MRI,* magnetic resonance imaging; *PE,* physical examination; *RT*, radiotherapy; *TMZ,* temozolomide.

Surgery

Patients can often undergo a craniotomy where the goal is the safe removal of the largest possible volume of tumor to establish a diagnosis and relieve mass effect. High-grade gliomas are not surgically curable because of their extensive infiltration.

If biopsy rather than resection is pursued, choices include stereotactic options with CT or MRI guidance or open craniotomy and biopsy. Some have employed metabolic imaging such as magnetic resonance spectroscopy (MRS) to better select the biopsy sites most likely to contain the most aggressive portions of the tumor, but this is not widely used. Usually, stereotactic biopsy can be performed using either frame-based or frameless neuronavigation systems. The pathologist can review the frozen section to make an immediate preliminary diagnosis and confirm tissue adequacy.

When craniotomy is contemplated, meticulous planning is invested in the scalp incision and flap design. Special care must be taken to preserve the vascular supply of the scalp. The bony opening is devised to be sufficiently large to facilitate resection without needlessly exposing adjacent brain to the risk of injury. After opening the scalp, burr holes are placed and connected with a craniotomy. The bone flap is removed and the dura mater is opened. As a rule, the bone flap is reattached at the end of the resection, although some surgeons prefer not to reattach the bone flap.

Although tumors on the brain surface are immediately visible after exposure, subcortical lesions are harder to discern. Frameless image-guided neuronavigation systems are employed to localize subcortical tumors along with intraoperative ultrasound and MRI. Tumors that are situated near "eloquent" areas of cortex, such as those harboring motor and speech function, are mapped intraoperatively via electrical cortical stimulation to achieve maximal tumor debulking without operative morbidity. Resection of gliomas in the dominant hemisphere is often carried out under local anesthesia with supplementary sedation to allow speech mapping.

Occasionally, tumors may be removed en bloc via circumferential dissection, but more frequently, resection is effected in piecemeal fashion. A cavitational ultrasonic surgical aspirator (CUSA) facilitates removal of a firm, adherent, or calcified tumor.

Patients are routinely monitored in an intensive care unit following a craniotomy. The first MRI is obtained within 24 hours to 48 hours after surgery before postoperative changes set in. The extent of resection can be determined in this manner.

External Beam Irradiation

External beam irradiation (EBRT) has historically been the cornerstone of the therapeutic approach to GBM (and anaplastic astrocytoma) for the past half-century, and its use in brain tumors was already described by the 1920s.[35] In the 1970s and early 1980s, categorical level I data became available from several studies,[36] including prospective Phase III trials conducted by the Brain Tumor Study Group (BTSG)[37,38] (Table 27-1).

The radiotherapeutic approach to high-grade glioma has evolved. Initially, large opposed lateral fields were employed to cover the entire brain volume. In 1989, Shapiro et al[42] published data from Brain Tumor Cooperative Group trial 80-01, in which the randomization was altered during the trial to compare partial brain irradiation with whole-brain radiotherapy (WBRT). No difference in OS or change in the patterns of failure was seen. Accordingly, WBRT is generally not advocated, except perhaps in the scenario of a widespread intracranial process such as gliomatosis cerebri.[43]

Several lines of evidence have influenced the trend to treat the gross tumor volume along with a margin of approximately 2 cm. In a classic paper published in 1980, Hochberg and Pruitt[44] used CT scans to determine that nearly 90% of GBM recurrences occurred within 2 cm of the primary tumor site (although this may be changing with the use of bevacizumab). Wallner et al[45] assessed the patterns of recurrence in 32 patients with unifocal malignant gliomas who were treated with primary surgery and postoperative irradiation. Nearly 80% of patients manifested recurrence or progression within 2 cm of the original tumor. Even when 80 Gy of partial brain irradiation was used in a prospective Phase I trial,[46] 90% of patients failed within the high-dose region.

It has been demonstrated on biopsy and autopsy studies that the abnormality detected on T2 or fluid-attenuated inversion-recovery (FLAIR) images harbors microscopic tumor extension. Accordingly, 45 Gy to 50 Gy is generally delivered, in 1.8-Gy to 2-Gy fractions, to the T2/FLAIR abnormality seen

TABLE 27-1 Positive Phase III Trials Evaluating the Role of Irradiation, Chemotherapy, or Chemoradiation in the Treatment of Malignant Gliomas

Study	No. Patients	Treatment Arm	Median (mo)	18 mo	24 mo	5 yr
BTSG 69-01*[37]	VSG		—			
	31	Observation	3.2	0	0	0
	51	Carmustine	4.3	4	0	0
	68	Radiation therapy	8.3	4	1	NA
	72	Radiation therapy plus carmustine	7.9	19	5	NA
BTSG 72-01†[38]	VSG		—			
	81	Semustine	4.8	10	8	NA
	94	Radiation therapy	8.3	15	10	NA
	92	Radiation therapy plus carmustine	11.8	27	15	NA
	91	Radiation therapy plus semustine	9.7	23	12	NA
EORTC/NCI-C‡[39-41]	286	Radiation therapy	12.1	21	11	2
	287	Radiation therapy plus temozolomide	14.6	39	27	10

BTSG, *Brain Tumor Study Group;* EORTC, *European Organization for Research and Treatment of Cancer;* NA, *not available;* NCI-C, *NCI Canada;* VSG, *valid study group;* yr, *year.*

*p = *0.001 for radiation therapy versus observation/supportive care and radiation therapy plus carmustine versus observation/supportive care.*

†p ≤ *0.003 for radiation therapy, radiation therapy plus carmustine, and radiation therapy plus semustine versus semustine alone.*

‡p < *0.0001. Most patients randomized to radiation therapy alone crossed over to temozolomide at time of relapse or progression.*

on the image, followed by a boost to raise the total dose to 60 Gy based on the T1-enhancing abnormality. The MRI abnormalities, however, remain quite nonspecific in terms of histopathologic confirmation, and even when novel strategies such as MRS are used for radiotherapy planning, there can be over or underestimation of the true extent of microscopic spread.[47]

A novel view of target definition has recently been proposed.[48,49] This approach posits that neuroprogenitor cells in the subventricular zone (SVZ) play a role in tumor recurrence. In retrospective analyses of dose distribution among patients with GBM, investigators found that the deposition of high dose (e.g., >40 Gy) in the ipsilateral SVZ was associated with a significantly improved progression-free survival (PFS) and OS in patients who also achieved gross total resection of their tumors. To validate this hypothesis, prospective clinical trials will need to be conducted to determine if cancer stem cells will need to be encompassed when delineating the targets for irradiation of high-grade glioma.

Rationale for Current Total Irradiation Dose

A pooled analysis of three successive randomized trials conducted by the Brain Tumor Study Group (BTSG 66-01, 69-01, 72-01, respectively) generated data to support doses in excess of 50 Gy.[50] A stepwise improvement in survival was observed with doses ranging from less than 45 Gy to 60 Gy, consistent with dose response. A comparison of 70 Gy versus 60 Gy demonstrated no survival or local control advantage for the 70-Gy dose.[51,52] These results established 60 Gy as the standard of care.

Dose escalation has remained an important investigational option because there is still a pattern of failure characterized by local progression or recurrence. There are now multiple techniques for dose escalation, including three-dimensional conformal irradiation, radiosurgery, and brachytherapy, but these have not yielded higher rates of disease control or survival. Increasing the radiotherapy dose or reirradiation with radioprotective or antiangiogenic agents may be a useful strategy in the future.[53]

Altered Fractionation

The RTOG has systematically and rigorously studied hyperfractionation for high-grade gliomas. In RTOG 83-02, patients were randomized to one of four dose arms (64.8 Gy, 72 Gy, 76.8 Gy, or 81.6 Gy) using twice-daily fractions of 1.2 Gy. Initial results suggested the superiority of 72 Gy,[54] but a subsequent Phase III trial demonstrated no improvement.[55] Prados et al[56] used an elegant randomization to assess not only a hyperfractionation schedule, but also to determine the activity of difluoromethylornithine (DFMO), a compound that inhibits sublethal and potentially lethal damage repair. Unfortunately, neither intervention improved survival.

Stereotactic Irradiation

Two provocative small-scale experiences prompted the design of Phase III trials to formally evaluate radiosurgery for high-grade gliomas.[57,58] Loeffler et al[57] reported on 37 patients treated with 59.4-Gy fractionated radiotherapy followed by a stereotactic radiosurgery (SRS) boost to a median dose of 12 Gy. After a median follow-up period of 19 months, a 76% survival rate was reported. Sarkaria et al[58] described 115 patients with high-grade glioma who received conformal radiation therapy and a SRS boost; median survival time was 96 weeks. These results called into question whether they represented a benefit from SRS or simply selection bias.

RTOG 93-05 compared conformal irradiation plus carmustine with or without a SRS boost for newly diagnosed GBM. No differences were observed in terms of OS (median, approximately 13 months in each arm) or quality of life.[59]

SRS may still have a role in the treatment of recurrent disease, particularly if a focal region of recurrence can be defined.[53] However, this has not been tested in prospective trials.

Brachytherapy

Brachytherapy, the use of implanted radioactive material at the site of the tumor offers a mechanism for focal dose escalation. Both permanent and temporary radioactive implants have been used. Early positive results by Gutin et al[60] suggested a potential survival benefit in a Phase II trial. These findings were not reproduced in subsequent randomized trials.[61,62]

Interest in this modality was rekindled when the GliaSite radiation therapy system (Proxima Therapeutics, Alpharetta, Georgia) received approval by the Food and Drug Administration (FDA) in 2001. This intracavitary device is implanted at the time of tumor debulking, and a solution of iodine-125 (^{125}I) is injected into an expandable closed-catheter balloon. A retrospective study suggested reasonable safety and promising efficacy.[63] A Phase I study was conducted.[64] However, the implant induces changes in imaging that complicate determination of disease progression.[65]

Chemotherapy: Concurrent with EBRT, Maintenance, and Other

Early randomized trials of chemotherapy were individually negative, but meta-analysis of these trials showed that 15% to 20% of patients treated with radiation therapy (RT) and nitrosoureas survived at least 18 months versus 5% treated with radiotherapy alone (Table 27-1).[37,38,66,67] Nitrosoureas, especially carmustine, were the most commonly used drugs, although procarbazine was also used extensively.[68] The combination of procarbazine, lomustine (CCNU), and vincristine (PCV)[69] had no clear benefit (yet much greater toxicity) versus carmustine for anaplastic astrocytoma,[70] and this regimen has been largely abandoned for nonoligodendroglial tumors.

Intratumoral delivery of chemotherapy for residual postoperative disease is most commonly in the form of carmustine-eluting (Gliadel) wafers. Patients undergoing wafer implantation during surgery for recurrent GBM survived approximately 2 months longer than patients without wafers in one study ($p = 0.02$).[71] Treatment of newly diagnosed disease also yielded a 2-month prolongation of average survival.[72,73] However, this was not statistically significant when the analysis was restricted to patients with GBM histology. Of note, wafer delivery of carmustine versus systemic administration has not been compared for safety or efficacy. Gliadel does, however, carry an FDA label for implantation during resection of recurrent GBM and newly diagnosed malignant glioma. Attempts to treat residual visible or microscopic disease with other local chemotherapies delivered through implanted catheters and using convection-enhanced migration of drug have generally failed.[74]

Currently, the most widely used chemotherapeutic agent is temozolomide. Whether it is more effective than nitrosoureas has not been investigated, but it is unquestionably better tolerated with significant myelosuppression in less than 20% of patients.[39,40] Temozolomide was first approved for use in the United States in recurrent anaplastic astrocytomas following a phase II study.[75] A randomized study also demonstrated superior efficacy to procarbazine in recurrent GBM.[76]

Temozolomide for newly diagnosed GBM has been studied both when given before RT[77] and when combined with RT in various dosing schedules.[78,79] Its role for newly diagnosed GBM was established by Stupp et al[39,40] on the basis of the EORTC 26981/22981 and NCIC CE.3 trial (Figure 27-4). In

this Phase III multicenter study, 573 patients with newly diagnosed GBM received RT alone or RT with concurrent temozolomide followed by six adjuvant cycles of temozolomide. The patients who received the combined-modality regimen had significantly longer OS and PFS without significantly more toxicity (Table 27-1). The 5-year OS was 10% among those receiving temozolomide versus 2% among those receiving RT alone ($p < 0.0001$).[39] Patients in the most favorable RPA class had a 5-year OS rate of 28% following combined therapy.[39] In a companion paper, Hegi et al[41] reported that methylation of the promoter for the O_6-methylguanine DNA methyltransferase *(MGMT)* gene, which encodes the DNA repair enzyme O_6-alkylguanine DNA alkyltransferase (AGT or AGAT, but now commonly also referred to as MGMT), was correlated with prolonged survival and patients with *MGMT* methylated tumors benefited the most from temozolomide.

MGMT repairs DNA damage induced by temozolomide, and methylation of the *MGMT* promoter silences expression of the protein, thereby accentuating the antineoplastic effects of temozolomide. However, the mechanism by which *MGMT* promoter methylation leads to an improved outcome is more complex. For example, some patients with tumors that did not demonstrate MGMT methylation also benefited from temozolomide although it is increasingly recognized that the initial test probably scored some "methylated" tumors as either "unmethylated" or "unknown."[39-41] Accordingly, it remains unclear whether MGMT analysis should categorically alter treatment, although this situation remains somewhat fluid. In addition, patients with tumors harboring methylated *MGMT* survived longer following treatment with RT alone than patients who did not have tumors harboring methylated *MGMT* treated identically.[39,40] Others reported similar findings in GBM[80] and other malignant gliomas.[81] Moreover, MGMT protein expression by immunostaining does not predict outcome.[82]

Several groups have explored intensifying the temozolomide dosing schedule in an attempt to overcome *MGMT*-mediated resistance.[83,84] The intensified regimens are designed to deplete MGMT activity as suggested by previous studies.[85] RTOG 0525 was a Phase III randomized placebo controlled study that compared standard temozolomide dosing following completion of radiotherapy (150 mg/m^2 to 200 mg/m^2 body surface area days 1 to 5 of 28) versus an intensified regimen (75 mg/m^2 to 100 mg/m^2 body surface area days 1 to 21 of 28). This prospectively validated that *MGMT* promoter methylation is a favorable prognostic factor regardless of treatment.[86] However, "dose-dense" temozolomide was more toxic than standard dosing and did not significantly alter PFS or OS regardless of *MGMT* status.[86]

Therefore, *MGMT* promoter methylation is prognostic but the mechanism remains unclear. In addition, there are now several different methodologies to test for *MGMT* promoter methylation, which may lead to discordant results.[87] It is possible that *MGMT* is a marker of more global hypermethylation and is only one of multiple genes mechanistically involved in resistance to alkylator chemotherapy and prognosis in tumors harboring the recently described Glioma CpG island methylator phenotype (G-CIMP).[88,89]

Another major area of investigation has been the use of vascular endothelial growth factor receptor (VEGFR) signaling inhibitors. Bevacizumab (Avastin) is a monoclonal antibody against VEGF that competitively inhibits binding of the ligand to VEGFR and targets tumor vascularity. It is the most widely studied of these antiangiogenic strategies.

Based on encouraging response rates and prolongation of PFS in recurrent GBM, two major Phase III studies, RTOG 0825 and Avastin in Glioblastoma (AVAglio) sponsored by F. Hoffmann La Roche, were launched nearly simultaneously. Following maximal safe surgical resection, both randomized patients to receive RT and temozolomide plus either bevacizumab or placebo. Although there were subtle differences in trial design with respect to extent of resection (e.g., biopsy-only patients not permitted in RTOG 0825 but allowed in AVAglio, timing of treatment, etc.), both demonstrated prolongation of PFS (median 10.7 versus 7.3 months, $p = 0.007$ for RTOG 0825; median 8.4 versus 4.3 months, $p < 0.001$ for AVAglio).[90,91] However, neither demonstrated a difference in OS (median 15.7 versus 16.1 months, $p = 0.21$ for RTOG 0825; median 16.8 months versus 16.7 months for AVAglio, $p = 0.10$). Both permitted cross-over from placebo to bevacizumab that was offered as part of the study design to participants in RTOG 0825 and permitted but not offered routinely in AVAglio.

These results have not categorically settled the issue of whether bevacizumab should be used for newly diagnosed GBM. In RTOG 0825, the prolongation of PFS did not meet the prespecified statistical level (30% reduction in hazard, $p = 0.004$ required for significance), whereas it did for AVaglio (23% improvement, $p = 0.01$ required for significant difference in PFS). In addition, quality of life measures in RTOG 0825 did not demonstrate a "Net Clinical Benefit," in fact it was worse for those who received bevacizumab, whereas improvement was observed in AVAglio.[90,91] In the context of these results, some practitioners consider using bevacizumab for patients with unresectable large deep tumors with surrounding edema, and especially patients with poor performance status, but such patients would have been excluded from the Phase III trials.

Other antiangiogenic therapies also have not improved survival. For example, the EORTC in collaboration with the Canadian Brain Tumor Consortium conducted the Phase III CENTRIC (CilENgitide in combination with Temozolomide and Radiotherapy In newly diagnosed glioblastoma Phase III randomized Clinical trial) study to evaluate the integrin inhibitor cilengitide that has reported antiangiogenic properties.[92] Based on encouraging Phase II results among the subset of patients with *MGMT* methylated tumors,[93] CENTRIC randomized such patients with newly diagnosed GBM to standard RT and temozolomide with or without cilengitide.[94] Median survival was unchanged (26.3 months in both arms, hazard ratio [HR] 1.02, $p = 0.86$).[94] There was also no significant improvement in PFS (13.5 months versus 10.7 months, HR 0.93, $p = 0.48$) as evaluated by the treating investigator.[94] A study of cediranib for newly diagnosed GBM (RTOG 0837) is ongoing; however, the failure of cediranib to demonstrate meaningful efficacy in recurrent GBM is concerning.

Two studies have evaluated antiangiogenic therapy in particular for patients with *MGMT* unmethylated tumors. The ongoing CORE (Cilengitide in patients with newly diagnosed glioblastoma multifoRme and unmethylated *MGMT* genE promoter) randomized such patients to RT and temozolomide with or without cilengitide. Results are not available yet. The German GLARIUS Phase II trial randomized cases with ummethyalted *MGMT* 2:1 to RT and concurrent bevacizumab followed by maintenance temozolomide for six cycles.[95] The primary endpoint was 6-month PFS determined by central review (generally considered somewhat unconventional), with 80% power to detect an increase from 40% to 60%. Results favored the bevacizumab arm (79.6% versus 41.3%, $p < 0.0001$). Median PFS (9.7 versus 6.0 months, HR 0.3, $p < 0.0001$) and OS (16.6 versus 14.8 months, HR 0.60, $p = 0.031$) also significantly favored the experimental arm.[95] These results require maturation and further validation, but begin to suggest a subgroup of patients who may benefit from addition of bevacizumab containing chemotherapy in lieu of temozolomide for newly diagnosed GBM. Notably, OS did not favor the bevacizumab group in RTOG 0825 or AVAglio,[90,91] but these trials were not intended for comparison.

Anaplastic Gliomas

Anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas represent the most common WHO grade III tumors.[1,21] In anaplastic gliomas, resection appears to improve survival relative to biopsy, as it does for GBM.

Anaplastic Astrocytic Neoplasms

It is generally accepted that RT should be administered postoperatively for astrocytomas. In a German study (NOA-04), early analysis demonstrated that survival was equivalent whether chemotherapy or RT was used first among patients with anaplastic astrocytomas, oligodendrogliomas, and mixed tumors.[12] However, time to progression following RT was longer than after chemotherapy, and initial radiation therapy achieved more complete and partial responses than initial chemotherapy, suggesting the superiority of RT.[96] In addition, the data were relatively immature at initial publication, and longer follow-up may demonstrate the importance of primary RT more fully among anaplastic astrocytomas, or mixed oligoastrocytomas without 1p19q codeletion.

Regarding chemotherapy, Combs et al[97] reviewed the outcome of 191 patients with grade III astrocytic tumors treated at the University of Heidelberg with either RT alone or RT in combination with temozolomide during a 20-year period (from 1988 to 2007). In this retrospective study, no significant advantage in rates of OS or PFS could be attributed to the combination. RTOG trial 9813 randomized patients with anaplastic astrocytomas (or oligoastrocytomas) to RT with concurrent nitrosourea (carmustine or lomustine) or with temozolomide, and results are pending.

The ongoing Concurrent vs. Adjuvant Temozolomide for NON 1p19q co-deleted anaplastic gliomas, also called EORTC 26053-22054 (CATNON) Intergroup trial randomizes patients to receive postoperative RT alone, concurrent temozolomide and RT without adjuvant temozolomide, RT (without concurrent temozolomide) followed by adjuvant temozolomide, or RT with both concurrent and adjuvant temozolomide (Figure 27-5). Although technically this study allows any WHO grade III glioma without 1p/19q codeletion, the majority of the tumors will be anaplastic astrocytomas.

Anaplastic Oligodendroglial Tumors

Long-term follow-up is now available for patients enrolled on RTOG 94-02[10,98] and EORTC 26951.[11,99] In these studies, radiation was compared to radiation with PCV chemotherapy. The RTOG trial entailed administration of chemotherapy before irradiation (intensified PCV[100] for up to four cycles in the combined-modality arm) whereas the reverse sequence (i.e., RT alone versus 59.4 Gy followed by up to six cycles of standard dose PCV) was used in the EORTC trial. With median follow-up in excess of 10 years in both studies, there was a dramatic improvement in OS associated with combined chemotherapy and radiotherapy (irrespective of sequence) among patients with anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma whose tumors contain allelic loss of chromosomes 1p and 19q, compared with radiation alone. For example, in RTOG 9402, median survival was 14.7 years versus 7.3 years ($p = 0.03$, HR 0.59 for chemoradiotherapy) and in EORTC 26951 median survival was not reached versus 9.3 years ($p = 0.0594$, HR 0.56 for chemoradiotherapy). In addition, patients with *IDH* mutant but not 1p19q codeleted tumors also benefited from chemotherapy, although the magnitude was lower than for those with tumors that harbored both codeletion and *IDH* mutation.[101] Those with *MGMT* promoter methylation[87] or ATRX expression[101] may also benefit regardless of 1p19q deletion status.

The applicability of these findings in an era where PCV is no longer popular remains debatable, especially because temozolomide has almost entirely replaced PCV in routine practice[102] despite the lack of a clear efficacy equivalence. What is clear, however, is that RT alone is inadequate for treatment of patients with codeleted tumors, and likely those with *IDH1* or *IDH2* mutated tumors, regardless of deletion status.

In addition, the role of RT for newly diagnosed anaplastic oligodendroglioma is becoming the subject of controversy because of the tumor's reported sensitivity to chemotherapy,[100] especially tumors with 1p/19q codeletion.[103] Neither RTOG 9402 nor EORTC 26951 used chemotherapy alone, which was recommended by 42% of clinicians (typically with temozolomide)[13] and used in 55% of patients from 2005 to 2007 in a retrospective series of codeleted tumors, without prospective data supporting such usage.[102] The ongoing CODEL (for 1p/19q CO-DELeted tumors) trial now randomizes patients to RT followed by PCV versus RT plus concurrent and adjuvant temozolomide, versus temozolomide alone (Figure 27-6).

The CATNON and CODEL study designs are premised on the belief that the 1p/19q chromosomal status may be more important than the histologic subtype for WHO grade III lesions. However, scientific advances in the interim may outpace the questions posed by these trials as it becomes apparent that *MGMT* promoter methylation[81,87] and *IDH* gene mutation[12,18,101] are also powerful markers of outcome in anaplastic gliomas. There is a clear need to move beyond histologic information (e.g., WHO subtyping) because important advances in prognostication have been made.[104]

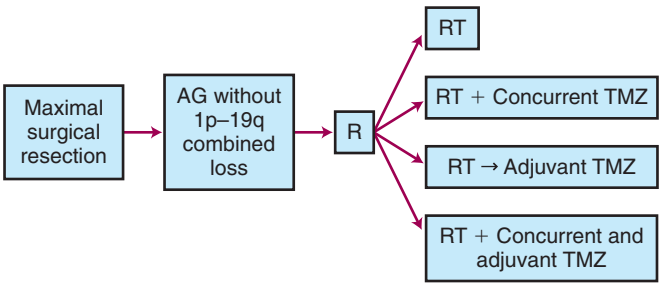

Figure 27-5 Schema from the CATNON study (Intergroup phase III, EORTC 26-53, RTOG 0834). *AG*, Anaplastic glioma; *R*, randomization; *RT*, radiotherapy; *TMZ*, temozolomide.

Special Topics

Toxicities of Radiation Therapy

Acute and late effects of irradiation, including brain necrosis are discussed in a subsequent section on Irradiation Techniques and Toxicities.[45,97,105-107]

Elderly Patients with GBM

More than 44% of GBMs occur in patients older than 65 years of age,[1] but prospective trials often exclude elderly patients.[39,40]

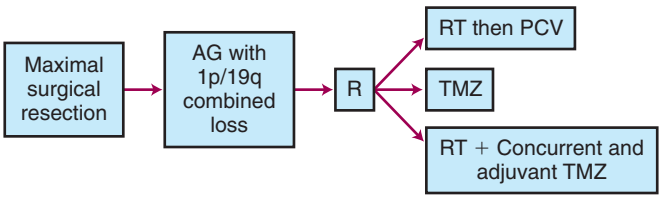

Figure 27-6 Schema from the CODEL trial (NCCTG NO0557/RTOG 0670). *PCV*, Procarbazine; *TMZ*, temozolomide.

Because these patients often have a worse outcome than younger patients, there has been some uncertainty with regard to the aggressiveness of treatment, and the definition of "elderly" is highly variable.

A Finnish randomized study of 30 patients older than age 65 years with imaging consistent with malignant gliomas demonstrated longer median survival following craniotomy than following biopsy (5.7 versus 2.1 months; $p = 0.035$).[32] The Association of French-Speaking Neuro-Oncologists[106] conducted a randomized trial comparing RT alone (50 Gy in conventional fractionation) versus supportive care among patients older than 70 years of age. The trial was discontinued after 85 patients were registered when it became apparent that RT was associated with a statistically advantageous outcome (median survival time, 29 versus 17 weeks; $p = 0.002$).

Efforts to abbreviate the duration of RT have been conducted. For example, a randomized study in patients older than age 60 years demonstrated that 40 Gy in 15 fractions was not inferior to 60 Gy in 30 fractions.[107]

A Phase II study of temozolomide alone in 32 patients older than age 70 years with newly diagnosed GBM demonstrated a response rate of 31%, median PFS time of 5 months and median survival time of 6.4 months, comparable to RT alone.[108,109] A single-arm 77-patient Phase II study for those older than age 70 with poor performance status (Karnofsky Performance Status [KPS] <70)[110] demonstrated median survival of approximately 6 months, with 26% becoming functionally independent (KPS at least 70).[111] Among those with *MGMT*-promoter methylated tumors (13 of 31 tested) median OS was approximately 7 months, and *MGMT* status was a statistically significant prognostic factor.[111]

In the NOA-08 trial conducted by the German Neuro-Oncology Working Group,[112] 373 patients older than age 65 with KPS of at least 60 with anaplastic astrocytoma or GBM (in 89%) were treated following randomization with RT (60 Gy) or an intensive schedule of temozolomide (100 mg/m^2 days 1 to 7 and 15 to 21 of every 28) without RT. If patients did not tolerate treatment or if they demonstrated progression, then cross-over (or surgical intervention) was triggered. Survival was slightly shorter following chemotherapy alone (8.6 months versus 9.6 months), but did not reach the prespecified statistical endpoint for declaring it inferiority (i.e., it was noninferior, based on accepting a certain level of survival loss designated as "noninferior"). Among patients with *MGMT* unmethylated tumors, RT was statistically superior (4.6-month versus 3.3-month event-free-survival). In addition, in *MGMT*-methylated cases, treatment with temozolomide was superior (8.4-month versus 4.6-month event-free survival). Analyzed differently, *MGMT* status did not influence event-free survival following RT (4.6 months regardless of *MGMT* status). However, *MGMT* status clearly and strongly influenced event-free survival following temozolomide alone (8.4 months versus 3.3 months for methylated versus unmethylated). Accordingly, among those with *MGMT*-methylated tumors, RT alone was an inferior treatment to temozolomide, and similarly, temozolomide alone was an inferior treatment to RT in those with unmethylated tumors. Many have presumed by implication that temozolomide in lieu of RT could be considered a reasonable treatment strategy in the elderly, but this supposition does not take into account the fact that results with combination RT and temozolomide are superior in almost all trials, and in the U.S. trials, even patients in their 80s were enrolled. Accordingly, monotherapy should be reserved for patients with poor KPS. Further, the intense schedule of temozolomide was excessively toxic and more standard schedules of temozolomide, commonly used in the United States were not studied in this trial,[112,113] and as eluded to previously, the combination of RT and temozolomide (the standard of care for patients younger than age 70 in Europe, and no age limit imposed in U.S. clinical trials, including enrollment patients, even in their 80s, as long as KPS was >70)[39,40] was not studied. It must further be underscored that NOA-08 had a noninferiority design, which included a definition of inferiority of temozolomide as a greater than 25% difference in survival endpoints, which arguably represents too much latitude and insufficient statistical rigor to allow clinicians to conclude that a new standard of care has emerged, especially given that there are few other comparable scenarios in oncology, where 25% loss of survival is accepted as noninferior.

In a Phase III trial from the Nordic Clinical Brain Tumour Study Group, 291 patients were randomized to standard dose temozolomide, standard (60 Gy) RT, or hypofractionated RT (10 fractions of 3.4 Gy each), and similar to the NOA-08 trial, there was no combined-modality therapy arm.[114] The trial has been criticized for its inclusion criteria of 60-year-olds under the rubric of "elderly" in view of the fact that the median age for the diagnosis of GBM is closer to 65 in the contemporary era.[115] Nonetheless, in an unplanned posthoc subset analysis of patients older than 70 years of age ($n = 123$), standard irradiation was associated with inferior survival in comparison to the other therapeutic arms; there was no difference in outcome between temozolomide and short-course RT, with fewer cytopenic toxicities in the short-course RT arm. The Nordic trial, much like the German study, revealed that *MGMT*-promoter methylation predicted for better outcomes in those treated with temozolomide alone, and once again it must be noted that the trial was not initially powered for this assessment as a primary observation. These trials are still open to interpretation at this juncture. The case could be made that for those patients in whom for reasons of poor performance status or inability to commute for long-course RT, temozolomide alone or short-course RT without temozolomide is an acceptable alternative; for patients who might be at higher risk of infection, short-course RT would induce fewer cytopenic episodes and might actually be preferred over temozolomide. For *MGMT*-methylated tumors in patients for whom daily radiation treatments for 6 weeks or so may impose unacceptable burden, temozolomide alone could be considered. This is not to say that RT is not an effective option for elderly patients, especially for patients with unmethylated-promoter *MGMT*. Indeed, an important next step will be to investigate chemoradiation strategies using a shortened course of irradiation, especially in the elderly poor KPS subset of patients; this is the subject of an ongoing trial by the EORTC and NCI Canada (NCT00482677).

It should also be noted that intravenous temozolomide has recently became available as an option for elderly or otherwise impaired patients who cannot swallow capsules or comply with an oral regimen.[116]

Pseudo-Progression

Pseudo-progression confounds interpretation of imaging performed in the first several months following completion of RT. Descriptions of "pseudo-progression" appeared as early as 1979, when Hoffman et al[117] described patients treated with RT and carmustine. Among patients thought to have experienced disease progression immediately following irradiation, nearly half were shown to have improvement or at least stabilization on subsequent brain imaging.

A report in 2004 described that approximately one third of patients with gliomas stabilized or improved with no change in management.[118] Chamberlain et al[119] reported histologically proven treatment injury rather than disease progression in approximately 50% of patients with symptomatic resectable lesions felt to represent worsening disease

following concurrent RT and temozolomide. The incidence of pseudo-progression has been reported to be as high as 75%, in selected subsets of patients with GBM.[84,120,121] Pseudo-progression rather than "true" progression may also correlate with *MGMT*-promoter methylation,[120] although this has not yet been prospectively validated.

Multiple imaging techniques have been explored to delineate radiographic pseudo-progression from true progression.[120,122-126] However, at this time, histologic analysis is the only validated method of distinguishing the two diagnoses, and even that has its limitations because of sampling issues, and difficulty in interpreting tumor cell viability posttreatment.[127]

It is presumed that the incidence of pseudo-progression is higher following concurrent RT and temozolomide than that following RT alone, although supportive evidence is equivocal.[128] As chemoradiotherapy is now the accepted standard of care for newly diagnosed GBM, no prospective study is likely to study this definitively. One approach to dealing with this issue involves using the MRI study done following RT as a new baseline, unless there is surgical documentation of recurrent disease or clear worsening outside of the RT portal. This remains an area of active study.[129] It is also worth noting that the "stabilization" of the peritumoral vasculature induced by antiangiogenic agents can possibly lead to a reduction in the pseudo-progression event rate, and has sometimes been used to manage florid imaging changes, with or without clinical deterioration.

RECURRENT DISEASE

Chemotherapy

Efforts to treat recurrent disease with single agents, either cytotoxics or molecular-targeted agents, have generally been unsuccessful, at least in part because of the innate resistance, poor drug penetrability, and molecular complexity of the disease.[130] Some studies suggest the key may lie in identifying the patients most likely to respond based on molecular profiling of tumor tissue at recurrence.[131]

An exception is the use of agents that target vascular endothelial growth factor (VEGF) or VEGFRs. Bevacizumab, a monoclonal antibody against VEGF, is the most widely studied of these antiangiogenic strategies.

The "BRAIN" trial was a noncomparative Phase II study for recurrent GBM that randomized 167 patients to either bevacizumab alone or bevacizumab combined with irinotecan,[132] the latter regimen adopted from activity of that combination in colon cancer.[133] The 6-month PFS was 43% with bevacizumab and 50% with bevacizumab plus irinotecan.[132] Similar results were seen in a single-arm Phase II study conducted by the NCI.[134] None of these trials however provided categorical evidence of improved OS.

These results are far superior to those of prior available therapies. For example, the 6-month PFS following carmustine is approximately 15% to 20%.[135] Emerging data from the randomized Dutch BELOB (BEvacizumab vs. LOmustine in glioBlastoma, Or Both) study demonstrate the superiority of bevacizumab (10 mg/kg days 1 and 15 of 28) combined with lomustine (90 mg/m^2 to 110 mg/m^2 every 6 weeks) versus either alone in terms of 6-month PFS (16% for bevacizumab, 13% for lomustine alone, >40% for lomustine with bevacizumab).[136] Based on these results, EORTC 26101 has been redesigned to compare lomustine alone (110 mg/m^2) versus bevacizumab with lomustine (90 mg/m^2), specifically seeking a survival benefit in a Phase III context for recurrent GBM.

Trials of other VEGF/VEGFR inhibitors have been negative. For example, REGAL (Recentin in Glioblastoma Alone and With Lomustine) was a Phase III trial[137] that tested efficacy of Recentin (cediranib), a direct oral pan-VEGFR inhibitor after a prior promising Phase II study.[138] An interim analysis demonstrated median PFS was longer following cedirinib (92 days) or cedirinib and lomustine (125 days) than lomustine (plus placebo, 82 days). However, median OS was not longer with cediranib (8.0 months versus 9.4 months versus 9.8 months), and the PFS benefit did not reach the prespecified improvement goal; accordingly, the trial was declared negative and accrual terminated.[137]

Therefore, despite increased response rates and improved PFS, to date there are no data clearly demonstrating a survival advantage for the use of bevacizumab, and its major potential toxicities include thromboembolic disease, hemorrhagic consequences, and hypertension. In addition, almost all salvage treatments following progression on bevacizumab are ineffective,[41,139] and therefore, the timing of bevacizumab for either first or later recurrence remains controversial. Recent data suggest that deferring bevacizumab to a second or later recurrence does not shorten survival.[140] The potential toxicity, as well as the fear of inducing a more invasive tumor phenotype also tempers enthusiasm for use of this agent in newly diagnosed disease, especially in light of lack of survival benefit from the RTOG 0825[90] and AVAglio trials.[91]

Alternating Electric Fields

Finally, one nonchemotherapy approach has been explored using alternating electric fields, tumor treatment fields (TTF) generated by a current source on the scalp (NovoTTF). This therapy is hypothesized to affect the mitotic spindle and thereby reduce proliferation. A Phase III trial suggested noninferiority when compared to any one of several possible physician-chosen chemotherapy regimens (median survival 6.6 months versus 6.0 months, HR 0.86 [95% CI, 0.66 to 1.12], $p = 0.27$; 6-month PFS 21.4% versus 15.1%, $p = 0.13$) with less toxicity than chemotherapy.[141]

Favoring a role for the device in treatment of glioblastoma, in addition to the similarly of survival and fewer side effects, more responses were seen in the TTF arm, although the difference was not significant and the response rate was low regardless of treatment. These results led to accelerated FDA approval. It should also be noted that 31% of patients received bevacizumab as the comparator chemotherapy during treatment on study, and approximately 20% of patients in both arms had a bevacizumab refractory tumor, suggesting benefit of the device in such patients.

However, it should be noted the trial was formally negative. The primary endpoint was improvement in survival. The statistical design had 80% power to detect a 60% increase in survival (HR 0.63, $p \leq 0.05$), and this was not achieved. The study was neither designed nor powered for a noninferiority endpoint, and the lack of a difference in survival in this study is not necessarily the same as true noninferiority.

In addition, the requirement for device approval is less stringent than for a drug, and the trial design and results have been heavily criticized. For example, there was no placebo device used as a control. One explanation is the questionable ethics of randomizing patients to no treatment whatsoever had the design been chemotherapy compared with NovoTTF compared with placebo device. However, that could have been ameliorated by randomizing patients to a specific chemotherapy (such as a nitrosourea or bevacizumab or both) in combination with either NovoTTF or placebo device.

Therefore, a clear interpretation remains elusive. The device appears reasonably safe, and it may well be that NovoTTF was noninferior to various chemotherapies. However, it is equally plausible that neither the device nor the chemotherapies were

beneficial to the patients. A Phase III study for newly diagnosed GBM (without placebo control) is ongoing, and a trial evaluating survival benefit in bevacizumab refractory GBM is being designed through the RTOG Foundation.

Reirradiation

Focal RT approaches are often employed with limited volume recurrences. In a retrospective analysis of 95 patients with recurrent gliomas treated with the GliaSite device, the median survival time was 36 weeks.[142,143] However, whether this is a function of true benefit or patient selection has not been determined.

Fractionated RT to treat larger-volume recurrent disease has also been employed. Although there has been speculation from animal studies that neural tissue will recover from previous irradiation to a large extent once some time has elapsed (e.g., 1 year to 3 years),[144] no firm data quantify the degree to which one can assume that a "dose discount" exists. It is most likely that the damage from reirradiation is underestimated because the majority of patients do not live long enough to express such damage. A small study showed good short-term tolerance to intensity-modulated radiation therapy (IMRT) delivered in six daily fractions of 5 Gy each.[145] A recent single-arm trial from the Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated reasonable safety and efficacy of combined bevacizumab and reirradiation using IMRT for small recurrent malignant gliomas.[50] No radionecrosis was observed and survival appeared to be prolonged relative to historic controls, suggesting that bevacizumab may not only treat radionecrosis[146] but might protect against it. Another approach was recently reported by investigators from Jefferson Medical College[147] who treated 147 patients with recurrent high-grade glioma to 35 Gy in 3.5-Gy fractions with stereotactic radiation therapy. This hypofractionated stereotactic radiation therapy (HSRT) approach was associated with a median survival time in excess of 10 months.

Based on the promising results from the MSKCC and Jefferson trials, RTOG 12-05 was recently opened for patients with recurrent GBM. The Phase II study, which will enroll approximately 180 patients who are bevacizumab-naive with recurrent disease, compares concurrent bevacizumab plus reirradiation (using a hypofractionated RT schema of 35 Gy in 10 fractions) to bevacizumab alone.

IRRADIATION TECHNIQUES AND TOXICITIES

Whole-brain radiation therapy (WBRT) has been replaced with partial brain techniques by consensus for almost all gliomas. Although the dose computation component of treatment planning requires CT imaging, effective image registration with MRI has made this the modality of choice for contouring. The notion of a dedicated MRI simulator has also been proposed as a valuable adjunct in the radiotherapeutic management of high-grade gliomas.[148] However, treatment plans based only on MRI are not able to take into account tissue electron-density variations, which may lead to slightly inaccurate dose calculations.

Patients are usually simulated after surgical wound apposition is reasonably stable and free of infection (generally, 10 days to 14 days after the operation). An immobilization mask is fashioned to reduce motion during and between fractions. The planning CT scan is extended to encompass the head and neck region to allow sufficient anatomic areas for proper image fusion and generation of high-quality digitally reconstructed radiographs (DRRs) and to permit the introduction of noncoplanar beams; ideally, the slice thickness should match that of the MRI used for fusion.

For high-grade gliomas, especially GBM, T1 contrast-enhanced sequences are used to define the gross tumor volume (GTV) and the T2 or FLAIR sequences plus a margin define the microscopic disease extent, or clinical target volume (CTV), which reflects the bulk of microscopic infiltration. To arrive at a planning target volume (PTV), both organ motion and setup error must be taken into account. Organ motion in the brain is quite minimal during therapy (e.g., <1 mm). The PTV may be further modified to exclude normal tissue in areas where gliomas are unlikely to infiltrate. Bokstein et al[149] recently demonstrated that when anatomic barriers such as the temporal bone can serve as a border to impede tumor spread, failure is likely to be seen in less than 5% of cases even when the customary 2-cm margins are *not added* to the abnormalities seen on MRI (Figure 27-7).

In general, there are two major schools of thought (with numerous institutional variations based on these) that provide guidance for the prescription of the radiation regimen. The RTOG approach is a biphasic technique that includes an initial PTV (PTV 1) followed by a second PTV (PTV 2) that represents the cone down. In the lexicon of the RTOG, the PTV 1 includes the T2 or FLAIR CTV with a margin and is treated to 46 Gy in 2-Gy fractions. The PTV 2 includes the T1-enhancing GTV with a margin and is treated to an additional 14 Gy. The EORTC recommends a single-phase technique using one treatment volume throughout the course of therapy. Table 27-2 shows the partial brain volumes advocated by several cooperative groups for the successive phases of partial brain irradiation.

With the advent of functional imaging tools (e.g., functional MRI [fMRI]) it may be possible to specifically modify irradiation doses to functional brain areas. Figure 27-8 displays a treatment plan wherein the region governing motor control (e.g., finger tapping) is delineated to enable an accounting for dose deposition. In this case, this region in the right hemisphere (i.e., governing tapping by the left upper extremity) is included in the high-dose region but the contralateral side is well spared; a major caveat here is that the dose-response relationships for various functional subvolumes in the brain are largely unknown, and therefore, this

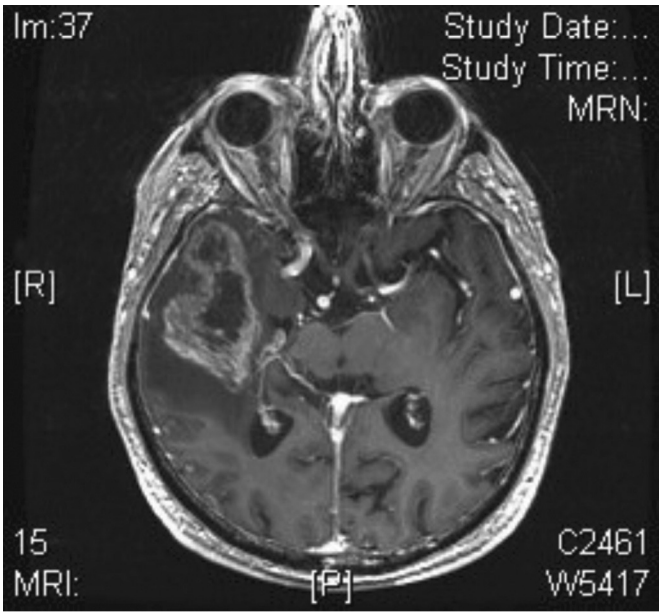

Figure 27-7 Lesion that could be treated without a full complement of margins because of anatomic barrier of the temporal bone.

information is of little practical dosimetric usefulness at this point in time.

In RTOG 08-25, it was noteworthy that approximately 80% of patients, irrespective of treatment arm, received IMRT. Lorentini et al[150] performed meticulous comparison of IMRT and three-dimensional (3D) conformal irradiation among patients treated for GBM. The IMRT plans consistently provided better target coverage than their 3D-conformal counterparts and yielded a statistically significant dose reduction to the healthy brain. The authors suggested that IMRT represents the superior technique when there are more than two regions of overlap between organs at risk (OAR) and the PTV.

Table 27-3 summarizes the tolerance of various OAR according to the new Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines. Lawrence et al[151] postulated that the original estimates of Emami et al,[152] suggesting a 5% risk of chronic brain damage at 5 years when one third of the brain is irradiated to 60 Gy, were overly conservative. Instead, they hypothesized (Figure 27-9) that the dose correlated with a 5% risk of damage at 5 years following conventionally fractionated irradiation to the partial brain is 72 Gy, but data regarding subvolume and substructure sensitivity are not included in the QUANTEC assessment.

TABLE 27-2 Radiotherapy Volume Used in Current Clinical Trials

RT Dose	Block Edge Dosimetry Margin*	Source for RT Dose
46 Gy 14 Gy	T2 + 2 cm T1 + 2.5 cm	RTOG
60 Gy†	T1 + 2-3 cm	EORTC
50 Gy 10 Gy	T2 + 2 cm T1 + 2 cm	NCCTG

3D, *Three-dimensional;* EORTC, *European Organization for Research and Treatment of Cancer;* Gy, *Gray;* NCCTG, *North Central Cancer Treatment Group;* RT, *irradiation dose;* RTOG, *Radiation Therapy Oncology Group.*
**Both RTOG and EORTC prescribe dose to block edge (geometric) margin, whereas NCCTG prescribes dose to dosimetry (3D) margin.*
†CENTRIC studies: either RTOG or EORTC volumes and RT doses are used, at individual physician discretion.

There may sometimes be a tendency to overlook structures that, if damaged, would have led to noncatastrophic sequelae. For instance, although it is true that radiation-induced cataracts are easily repairable,[156] avoidance of entrance and exit dose to the eye may be a relatively simple means of preventing not only cataracts but also conjunctivitis and a dry eye, by sparing the lacrimal gland. Similarly, when one contours the ear canals, there is now a greater awareness of the risks of developing otitis externa as well as otitis media.

There are reports of cytopenias arising from cranial irradiation even among patients who have not received chemotherapy.[157] The hypothesized mechanism of this is either irradiation of circulating blood within the radiation portals, injury to marrow in the cranium, or the use of vertex beams that exit through the spinal axis. The latter mechanism has also been invoked to explain radiation-induced fatigue by some investigators.[158]

For tumors located in the temporal lobes, the exit dose to the parotid gland may cause xerostomia. Tumors in such locations may be best treated with IMRT because one of the success stories of the application of IMRT to the head and neck region is indeed the elimination of this bothersome side effect.

Overall, the aim is to achieve the treatment plan that most closely approximates the defined volumes and thereby produces the most conformal plans. Relatively low energy beams (e.g., 6 MV) are typically employed. In contrast to the irradiation of varying organs containing primary tumors, it is

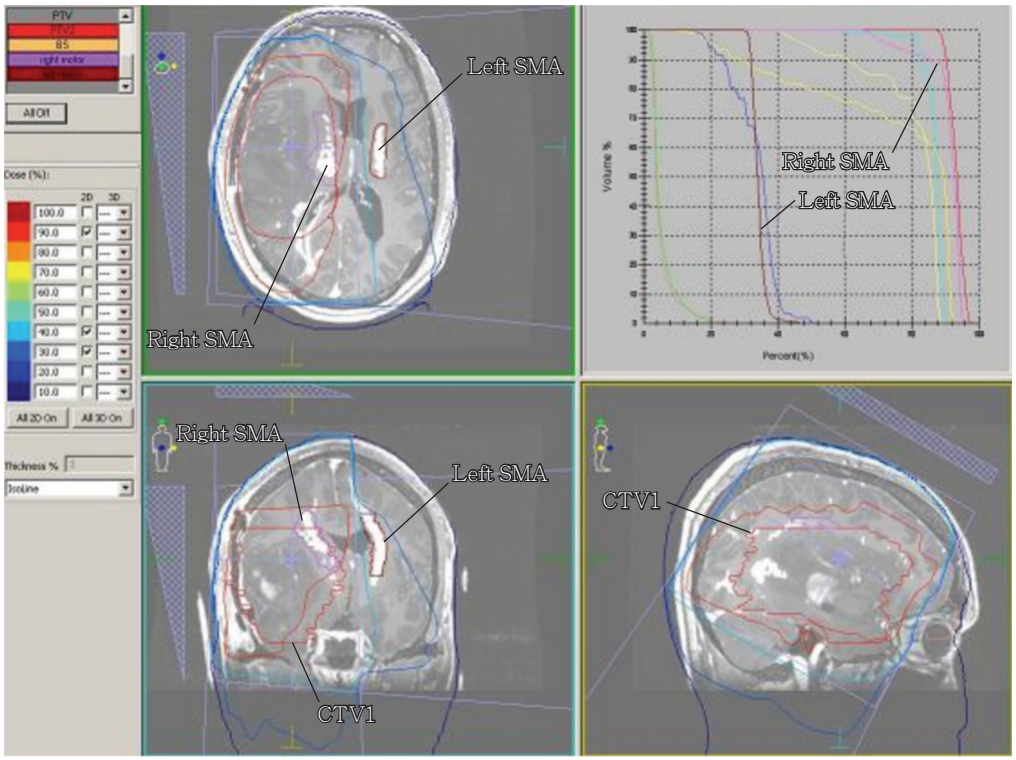

Figure 27-8 Treatment planning based on a functional MRI. Note delineation of the clinical target volume *(CTV)* as well as left and right somatomotor areas *(SMA)* controlling hand movements of the right and left upper extremities, respectively.

TABLE 27-3 Selected Organs at Risk for Treatment Planning of Malignant Glioma

Organ	Dose Limit	Comments
Brain parenchyma[151]	72 Gy	Brain appears to be more sensitive to fraction size > 2 Gy and to twice-daily radiation therapy
Optic apparatus[153]	60 Gy	12 Gy for single-fraction radiosurgery
Brainstem[154]	54 Gy	59 Gy if small volumes (i.e., 1-10 mL)
Parotid gland[155]	20 Gy 25 Gy	Severe xerostomia vis-à-vis sparing of one parotid gland Severe xerostomia vis-à-vis sparing of both parotid glands

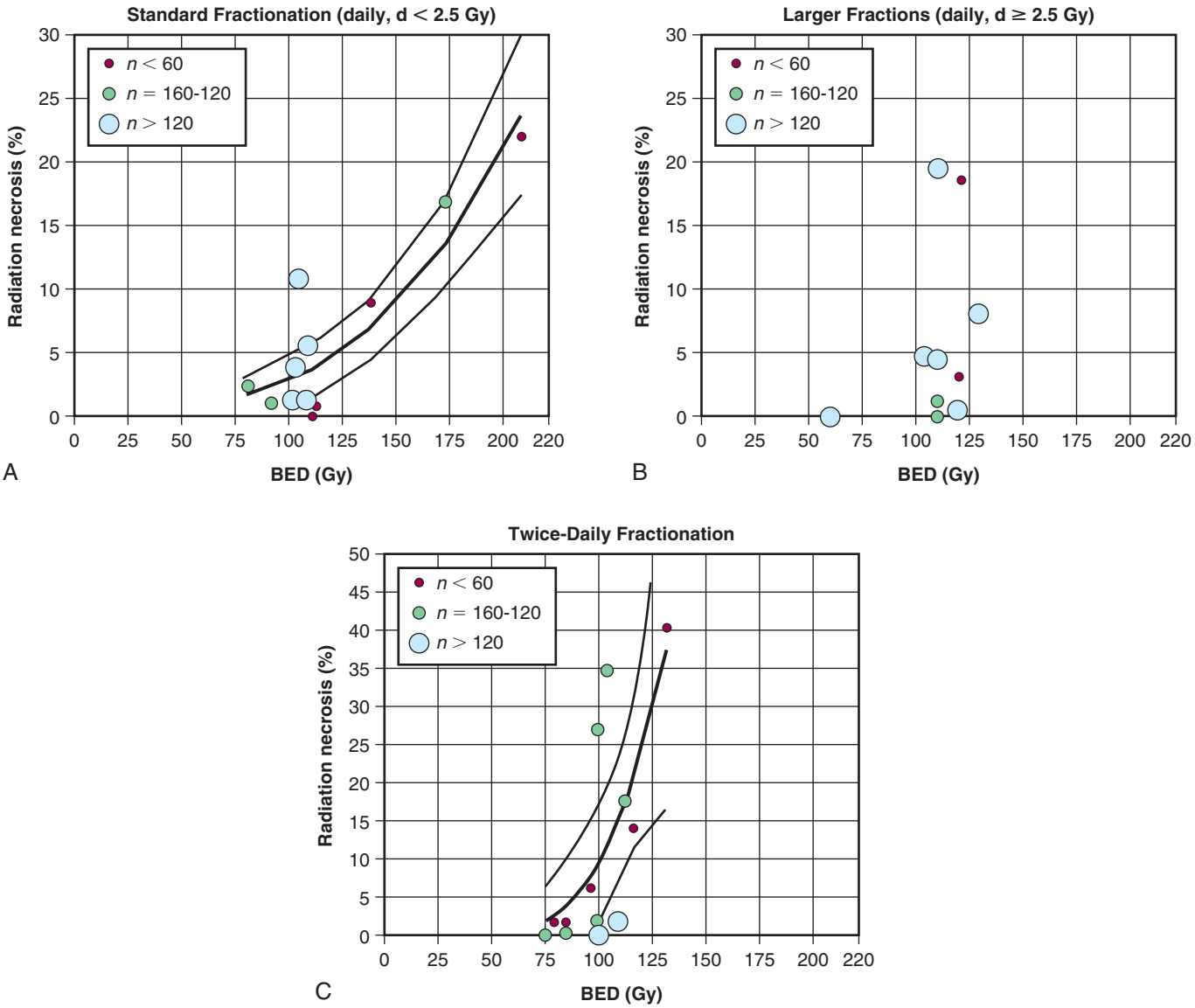

Figure 27-9 QUANTEC data for central nervous system tolerance based on the study in Lawrence et al. Relationship between biologically effective dose (BED) and radiation necrosis after fractionated radiotherapy. The Lawrence figure was done with a nonlinear least-squares algorithm using MatLab software (MathWorks, Natick, Mass.). The nonlinear function chosen was the probit model (similar functional form to the Lyman model). Dotted lines represent 95% confidence levels; each dot represents data from a specific study (Lawrence Table 2); *n* = patient numbers as shown. **A,** Fraction size less than 2.5 Gy. **B,** Fraction size 2.5 Gy or larger (data too scattered to allow plotting of "best-fit" line). **C,** Twice-daily radiotherapy. *Redrawn with permission from Lawrence YR, Li XA, Naqa I, et al: Radiation dose-volume effects in the brain. Int J Radiat Oncol Biol Phys 76:S20–S27, 2010.*

impossible to recommend a single idealized beam arrangement for high-grade gliomas. In this context, the role of proton therapy is being explored to further reduce dose to surrounding tissue distal to the tumor.

Miscellaneous Technique Issues

Despite the absence of level I evidence, IMRT is increasingly used, sometimes to escalate the dose and at other times to spare surrounding tissues or to explore the concomitant boost concept. However, clinical data supporting improved outcomes from IMRT in high-grade gliomas are essentially nonexistent.

Guidelines for tumor delineation and dose selection for WHO grade III gliomas are less well developed. In general, the FLAIR and T2 compartments are regarded as containing microscopic disease and therefore constitute the CTV. The typical dose is 59.4 Gy or 60 Gy in 1.8-Gy to 2-Gy fractions.

Toxicities of Radiation Therapy

Acute radiation morbidity includes fatigue, erythema, alopecia, headache, and rarely, nausea with or without vomiting; these are generally not severe and are usually self-limiting.[45] Some have cautioned that the combination of cranial RT and phenytoin as well as other anticonvulsants could give rise to the Stevens-Johnson syndrome,[159,160] but this dermatologic emergency is an exceedingly rare event, and the causal association between the two has not been established.

Late effects of radiation (e.g., somnolence and, especially, cognitive impairments) are more worrisome and may become manifest many years later.[161] The impact of partial brain irradiation on neurocognitive decline continues to be a hotly debated topic. The confounding factor is always the extent to which there is baseline cognitive impairment or decreased mentation secondary to tumor. Hippocampal sparing may emerge as a method to reduce the risks of neurocongnitive injury as it appears to do in the treatment of brain metastases with WBRT.[162]

Brain necrosis is a serious and uncommon late toxicity, and recently bevacizumab has been explored as a treatment.[146] In a small trial, all patients showed improvement of MRI abnormalities as well as a reduction in corticosteroid requirements following treatment with bevacizumab.[163]

We currently estimate the risk of normal tissue damage based on the most sensitive 5% of the population. Accordingly, we bias our recommendations in a manner that is not germane to most individuals, and preliminary efforts at predicting the likelihood of toxicities based on risk are ongoing.[164,165]

TREATMENT ALGORITHM, CONTROVERSIES, CHALLENGES, AND FUTURE POSSIBILITIES

Treatment Algorithm

For adults up to age 70 years with newly diagnosed GBM, the current standard of care is safe maximal surgical resection (with or without Gliadel wafer implantation) followed by concurrent EBRT (approximately 60 Gy in 30 fractions) with temozolomide and followed by at least 6 months of adjuvant temozolomide (Figure 27-4). For suspected progression that occurs within 3 months of completing RT, the possibility of pseudo-progression should be strongly considered.[166] Relapsed disease may be treated with re-resection, second-line chemotherapy, or experimental therapy in a clinical trial. Reirradiation is also a possibility but is used infrequently. Bevacizumab is approved for relapsed disease, as are carmustine wafers and Gliasite brachytherapy.

For newly diagnosed anaplastic gliomas, RT is typically administered as part of the initial therapy. Some advocate chemotherapy first, especially in 1p19q codeleted anaplastic oligodendroglial tumors.[12,13] Based on randomized trials, RT before and after PCV chemotherapy is clearly superior to RT alone for patients with 1p19q codeleted anaplastic oligodendroglial tumors.[98,99]

Controversies

Treatment for elderly patients (variably defined as older than 60, 65, or 70 years of age, depending on the study) remains controversial. Patients with a good performance status and few comorbidities are often treated according to the same algorithm used for younger patients. However, abbreviated radiotherapy courses appear to be noninferior[107] and are often employed. Temozolomide alone using standard rather than intensified dosing is a reasonable treatment strategy for elderly patients with *MGMT*-methylated tumors based on comparisons to RT alone, specifically in patients for whom combined-modality therapy is a significant challenge.[112,114] Definitive studies of combined RT and temozolomide restricted only to "elderly" patients have not been completed, and whether chemoradiation using a rapid course of RT is superior to RT or temozolomide alone is under investigation, but it must be borne in mind that the U.S. trials included patients even in their 80s when using combined-modality approaches.

Bevacizumab does not prolong survival when added to RT and temozolomide for newly diagnosed GBM.[90,91] Emerging data suggest that combining bevacizumab with nitrosourea therapy may be superior to bevacizumab or nitrosurea alone for recurrent GBM[136] and this is being further tested in Phase III study by the EORTC.

Treatment of anaplastic gliomas is an area of extreme controversy, with astrocytomas often treated as GBMs and a more variable approach used for oligodendrogliomas. Ongoing trials will attempt to define a standard algorithm based on the 1p/19q deletion status.

Challenges

Local control of high-grade gliomas remains a vexing problem. In addition, the increased recognition of pseudo-progression as an entity and the possibility of pseudo-response to antiangiogenic therapy such as bevacizumab[167] complicate matters further. A revised set of consensus criteria were recently developed in part to address some of these issues.[129,166] Certainly, correlative clinical follow-up to provide the proper perspective on the health status of the patient will never be abandoned, because imaging will always represent an imperfect surrogate for survival. Although new developments in diagnostic imaging continue to hold out promise for resolution of the diagnostic dilemmas faced by the neurooncology team, to date even the most sophisticated imaging studies (e.g., FDG PET, MRS) have not provided a consistently reliable solution to these and other vexing problems.

Future Possibilities

Prior dose-escalation trials for GBM, all conducted in the pre-temozolomide era, have been uniformly negative beyond 60 Gy. However, it is conceivable that the notion of dose escalation now needs to be revisited in the backdrop of control of microscopic disease by temozolomide enhancing the effect of focal dose-escalation, as well as the potential radioprotection offered by bevacizumab.[53]

The 5-year OS from the EORTC-NCIC study of patients with GBM treated with RT and temozolomide was approximately 10%, and for patients with favorable prognostic factors it approached 30%.[39] Moreover, a patient who lived more than 20 years following the diagnosis of GBM was described, perhaps the longest documented survivor.[168] He had been treated with surgery and partial brain irradiation with no concurrent or maintenance chemotherapy (59 Gy of 6-MV photons in conventional fractionation delivered via a shrinking-field technique). The authors speculated that the outcome may have stemmed from the fact that he had a favorable molecular profile (e.g., methylated *MGMT* promoter, *PTEN* wild-type, and *p53* positive, which the authors termed "triple positive," similar to the nomenclature of breast cancer). Whether this explained the long survival time is unclear. More importantly, these observations prove that one may strive to create and sustain hope for patients diagnosed with high-grade glioma.

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