Glioblastoma Multiforme: Multidisciplinary Care and Advances in Therapy

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Approximately 20,500 new cases of primary brain tumor are diagnosed annually.[1] Causing an estimated 13,000 deaths each year, primary brain tumors are responsible for more deaths than Hodgkin's lymphoma, cervical cancer, and melanoma combined.[1] Of these primary brain tumors, approximately 50% are gliomas, and 50% of these are glioblastoma multiforme (GBM).[2] GBM is the most common and aggressive primary brain tumor, with a mortality that nears 100%[3] and a median survival of less than 1 year. Physician-scientists have had limited success in prolonging survival since the introduction of postsurgical radiation therapy in the late 1970s.[3–9] The challenge in treating GBM lies in the unique environment of the central nervous system (CNS). Unlike other organ systems, the CNS has no regenerative capacity, leading to devastating consequences if disturbed. Additionally, the blood-brain barrier (BBB) renders many conventional chemotherapeutics ineffective.[2]

Fortunately, a new era in the care of GBM patients is emerging in which the efforts of neurosurgeons, neurooncologists, neuropathologists, radiation oncologists, neuroradiologists, and palliative care specialists are coordinated. This approach facilitates collaboration and translational research and has led to recent advances in care. This article provides a brief overview of GBM, including established diagnostic and therapeutic options, and discusses recent progress in the disciplines involved in the care of patients diagnosed with GBM.

TAKE HOME POINTS

- Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor, with a mortality of nearly 100% and a median survival of less than 1 year.
- The presenting symptoms of GBM can be focal based upon brain location or generalized due to increases in intracranial pressure and mass effect; headache, seizure, and change in mental status occur most frequently.
- Contrast-enhanced magnetic resonance imaging is the standard diagnostic modality for intracranial malignancies, while standard therapy for GBM includes gross total resection of the tumor followed by postoperative external beam radiotherapy.
- Routine seizure prophylaxis with an antiepileptic drug provides no benefit in patients with brain tumors who do not have a history of seizures.
- Areas of development in the management of GBM include using pathologic analysis of tumor specimens to select patients for adjuvant chemotherapy and use of agents and systems that facilitate local delivery of chemotherapeutic agents or radiation to tumors or the postresection tumor bed.

CLASSIFICATION

Brain tumors are a heterogeneous group of malignancies derived from tissues of different origins (**Table 1**).[10] It is important to differentiate between primary brain tumors—those originating in the CNS—and metastatic tumors.[10] Among primary tumors of malignant potential are the gliomas, which are divided into astroglial and oligodendroglial tumors[10] and further classified by degree of aggressiveness as either low grade (World Health Organization [WHO] grade II) or high grade (WHO grades III and IV).[3] The tumors commonly known as astrocytomas are astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), and GBM (WHO grade IV).[10]

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Table 1. Common Brain Tumors

Benign primary tumors
Acoustic neuromas
Choroid plexus papillomas
Colloid cysts
Craniopharyngiomas
Epidermoid tumors
Hemangioblastomas
Meningiomas
Pilocytic astrocytomas
Pituitary adenomas
Malignant primary tumors
Chordomas
Choroid plexus carcinomas
Germ cell tumors
Gliomas
Astroglial neoplasms
Low-grade astrocytomas
Anaplastic astrocytomas
Glioblastoma multiforme
Ependymomas
Gangliogliomas
Mixed gliomas
Oligodendrogliomas
Medulloblastomas
Pineal cell tumors
Pituitary carcinomas
Primary central nervous system lymphoma
Primitive neuroectodermal tumors
Metastatic tumors
Meningeal carcinomatosis
Single or multiple metastases

Adapted with permission from Black PM. Brain tumors. Part 1. N Engl J Med 1991;324:1471–6.

The high-grade astrocytomas (WHO grades III and IV) account for the majority of astrocytic tumors and are collectively referred to as malignant gliomas.[11] The WHO classification has significant implications in both treatment and prognosis.[3] The progression in astrocytomas from WHO grade II to IV is based on the histopathologic features of nuclear and cellular pleomorphism, degree of cellularity, mitotic activity, microvascular proliferation, and presence of necrosis.[3,11] Accordingly, as the most aggressive of these tumors, GBM is characterized by marked endothelial proliferation and cellular heterogeneity as well as broad zones of necrosis with peripheral palisades of tumor cells and numerous mitotic figures (**Figure 1**).[12]

PATHOGENESIS

GBM can occur as a primary or secondary neoplasm: a primary lesion transforms directly from normal astroglial cells, whereas a secondary lesion progresses from a lower grade malignancy to a grade IV malignancy.[13] Primary GBM tends to occur in an older patient population (> 55 yr), while secondary GBM tends to occur in younger adults (< 45 yr).[13] Although phenotypically similar, these 2 types of GBM occur through the accumulation of different mutations (**Figure 2**).[13] Inactivation of tumor suppressor genes and activation of oncogenes leads to altered transcription of proteins involved in normal cellular homeostasis, cell-cycle regulation, and interaction with other cells in the CNS.[11] These changes allow the tumor cells to forgo apoptotic processes and assume a malignant phenotype capable of growth, proliferation, and infiltration.[11] From an etiologic standpoint, environmental factors such as smoking, diet, and alcohol intake have not been linked to GBM,[10] although it is suggested that high doses of cranial irradiation and occupational exposure to some toxins may be linked to increased incidence of gliomas.[10,14,15] Glioma risk attributable to inheritance has been estimated at 4%[16,17] and is most commonly associated with neurofibromatosis, tuberous sclerosis, Turcot's syndrome, and Li-Fraumeni syndrome.[3,10]

CLINICAL PRESENTATION

Given the rapid progression of GBM, the importance of a keen diagnostic acumen and a low threshold of suspicion among primary care physicians cannot be over emphasized. The presenting symptoms of GBM are varied (**Table 2** and **Table 3**)[18,19] and can be focal based upon location in the brain, or generalized due to increases in intracranial pressure and mass effect.[20] The 3 common phenomena of headache, seizure, and change in mental status merit further discussion as their occurrence is nearly universal in the natural history of GBM.[18] Headache is the most common presenting symptom in patients with malignant glioma.[18] In general, the pain is ipsilateral to the hemisphere containing the tumor[19] and is described as intermittent, dull, and nonthrobbing.[21,22] These symptoms are similar to common tension headache and can be differentiated by eliciting a history of recent change in headache quality, new-onset headache in an adult patient, or an association with symptoms indicative of increased intracranial pressure (ICP).[19,21,22] Symptoms of increased ICP include pain that wakes the patient at night, is worse with activity, is exacerbated by cough or the Valsalva maneuver, or is accompanied by nausea and vomiting. Symptoms of increased ICP are indications for

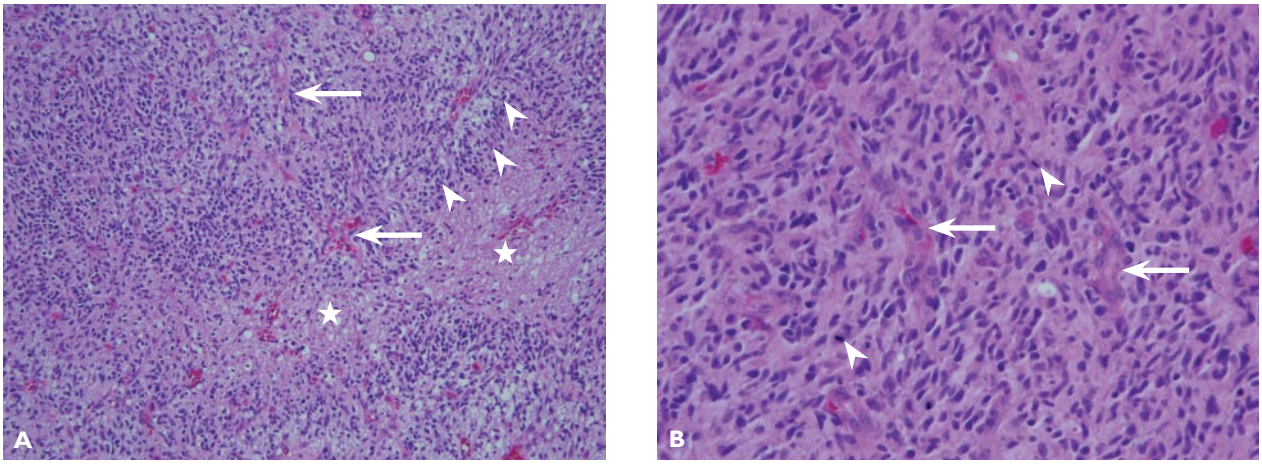

Figure 1. Histopathologic sections of glioblastoma multiforme. (**A**) Pseudopalisading cells (*arrowheads*) are seen organized around areas of necrosis (*stars*) with adjacent prominent vascular channels (*arrows*). (Hematoxylin-eosin × 50). (**B**) Both vascular hyperplasia (*arrows*) and abundant mitotic figures (*arrowheads*) are recognized in a highly cellular and pleomorphic background. (Hematoxylin-eosin × 200).

immediate neuroimaging.[19,22,23] Another indication for neuroimaging is new-onset seizure in patients without a history of epilepsy,[7] as seizure is the presenting symptom in 32% of malignant glioma patients[18] and 10% to 20% of adults with new-onset seizures will eventually be diagnosed with some form of CNS malignancy.[24] Often more subtle in nature, an alteration in mental status is the presenting symptom in 16% to 34% of malignant glioma patients.[18] Family members or patients may describe alterations in concentration, memory, affect, personality, or initiative.[19] These changes are typically much less insidious than the changes seen in patients with dementia and should prompt further evaluation.[18]

STANDARDS OF CARE AND GLIOMA OUTCOMES

With few exceptions, studies aimed at the management of malignant glioma have been retrospective in nature, leading to controversy over standards of care.[25] Prior to publication of the Glioma Outcomes (GO) Project study in 2003, there had never been a comprehensive resource from which to draw evidence-based treatment guidelines for the management of this disease.[18] This groundbreaking study enrolled 788 patients at 52 clinical sites between October 1997 and July 2000 and made available practice pattern and outcomes data for 565 newly diagnosed malignant glioma patients. The goal was to delineate standards of care from diagnosis until death and to pinpoint areas in need of further research. The GO Project elucidated trends in clinical presentation that emphasize the critical importance of primary care physicians in facilitating early diagnosis and also served to establish current trends in therapeutics and supportive care.[18] The mainstays of contrast-enhanced magnetic resonance imaging (MRI) for diagnosis, surgical craniotomy with attempt at gross total resection, and postoperative external beam radiotherapy (EBRT) are applied in the management of nearly all newly diagnosed cases of GBM.[18] Supported by the National Comprehensive Cancer Network (NCCN),[26] these therapeutic recommendations have remained unchanged since the late 1970s.[4–9]

Magnetic Resonance Imaging

Used for diagnosis of 92% of malignant gliomas,[18] contrast-enhanced MRI has emerged over the past 2 decades as the gold standard for imaging of intracranial malignancies.[3] Coupled with high clinical suspicion, there are several key characteristics on contrast-enhanced MRI suggestive of GBM (**Figure 3**). On a T1 pulse sequence, GBM appears as a poorly defined, heterogeneous lesion[27] displaying ring enhancement.[3] GBM tumors are frequently located in the frontal or temporal lobes of the cerebral hemispheres, sparing the more superficial cortex and infiltrating deep structures.[28] The heterogeneous signal intensity is due to cysts, hemorrhage, calcification, and necrosis and is often accompanied by surrounding vasogenic edema best seen as a hyperintensity on T2 pulse sequences.[28] In addition, the combination of mass effect[27] and characteristic spread across the corpus callosum to the contralateral cerebral hemisphere to form a characteristic "butterfly" lesion[28] are findings virtually pathognomonic for GBM. While MRI has advantages such as precision in detecting tumor extent with low sensitivity to bony artifacts, there are instances in which computed tomography is the preferred modality,[29] such as defining bony landmarks for craniotomy, when MRI

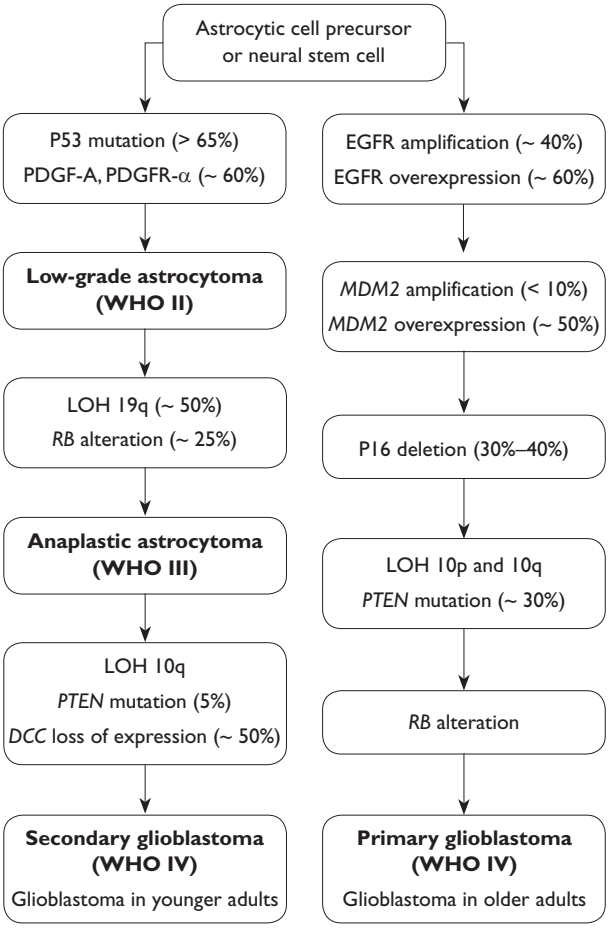

Figure 2. Progression of molecular pathophysiology in astrocytomas. *DCC* = deleted in colorectal cancer (gene on chromosome 18q21); EGFR = epidermal growth factor receptor; LOH = loss of heterozygosity; *MDM2* = oncogene located on chromosome 12q14•3-q15; PDGF(R) = platelet-derived growth factor (receptor); *PTEN* = phosphate and tensin homology (tumor suppressor gene located at chromosome 10q23•3); *RB* = retinoblastoma gene and protein (*RB1* gene maps to chromosome 13q14). (Adapted with permission from Kim L, Glantz M. Chemotherapeutic options for primary brain tumors. Curr Treat Options Oncol 2006;7:470.).

is contraindicated, or for immediate postoperative feedback of complications such as hemorrhage, infarct, or pneumocephalus.[29]

Supportive Care

Peritumoral edema can lead to functional compromise depending on location and, more importantly, the life-threatening sequelae of mass effect and herniation.[30] Accordingly, essentially all patients diagnosed with malignant glioma are treated with corticosteroids in the perioperative period.[18] It is critical, however, to consider the impressive dose-dependent side-effect profile of these drugs, which is of particular concern in an already compromised population. These side effects include gastrointestinal and hematologic complications, increased susceptibility to infections, glucose intolerance, steroid myopathy, and behavioral changes. Among corticosteroids, dexamethasone has the most favorable side-effect profile and is often used as a first-line agent.[31,32]

Table 2. Initial Presenting Signs and Symptoms in Patients with Malignant Glioma

Sign/Symptom	Frequency, %
Headache	56.0
Memory loss	35.5
Cognitive changes	34.4
Motor deficit	33.0
Language deficit	32.5
Seizure	31.9
Personality change	23.1
Visual problems	21.6
Other	17.4
Changes in consciousness	16.2
Nausea/vomiting	13.1
Sensory deficit	12.6
Papilledema	4.6

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Up to 60% of malignant glioma patients experience seizures during their disease course.[33] However, 2 independent meta-analyses have shown that routine prophylaxis with an antiepileptic drug (AED) provides no benefit in brain tumor patients who do not have a history of seizures.[34,35] Practice parameters from the American Academy of Neurology concur that AEDs should not be administered routinely to patients with GBM.[34] Common AEDs, including phenytoin, carbamazepine, and benzodiazepines, are known to induce hepatic microsomal enzymes and have a profound effect on the metabolism of steroids and chemotherapeutic agents.[36] Accordingly, because of the lack of benefit for prophylaxis and the undesirable side-effect profile, treatment with AEDs is reserved for cases of documented seizure. Data suggest that second-generation AEDs such as levetiracetam may have greater utility in this unique population due to an improved pharmacodynamic and side-effect profile.[37]

Resection

Supported by the NCCN and confirmed by the GO Project, standard therapy for newly diagnosed GBM

begins with an attempt at gross total resection.[18,26] Resection serves to establish a pathologic diagnosis and to alleviate increased ICP and compression of adjacent cortex.[8] Survival advantage has been confirmed in retrospective studies for resection of 98% of tumor mass, although this projected benefit must be balanced with potential harm to adjacent eloquent cortex, which often limits the extent of resection.[8] With thorough preoperative planning and the utilization of intraoperative technologies such as neuronavigation and awake craniotomy with cortical mapping (*see* Neurosurgery), it is possible to minimize postoperative morbidity and increase the precision of tumor resection.[38]

External Beam Radiotherapy

Postoperative EBRT is standard of care for malignant gliomas.[18] This trend was pioneered in the 1960s by Bouchard and Pierce,[39] who first reported survival benefit in GBM patients receiving radiation therapy. By the late 1970s, a randomized trial had shown that the human brain could safely tolerate a fractionated dose to 60 Gy, with improvement of median survival from 14 to 36 weeks over supportive care alone.[4] Subsequent attempts at increasing this total dose have failed to add survival benefit,[40,41] and accordingly, standard recommendations for GBM have remained essentially unchanged.[9] Most recently, a comprehensive review of radiation therapy for newly diagnosed malignant glioma by Laperriere et al[9] established that the preferred schedule is postoperative fractionated dose radiotherapy of 60 Gy in 30 fractions focused in a field that encompasses the enhancing lesion plus a 2 cm margin. Moreover, there is no apparent benefit to whole brain radiotherapy, radiation dose intensification schedules, or radiation sensitizers.

RECENT ADVANCES AND FUTURE DIRECTIONS

The most alarming statistic uncovered by the GO Project was that the median length of survival at diagnosis for GBM was 41 weeks,[25] with a 32% 1-year survival rate, a rate which has remained unchanged since the 1980s.[42] This section reviews advances in each discipline involved in GBM management and discusses future prospects for changing this disheartening statistic.

Neurooncology

In the care of patients with GBM, neurooncologists take on the challenge of instituting chemotherapy targeted at a malignancy that historically has shown only modest response to chemotherapy.[43] Neurooncologists are also responsible for managing often life-threatening issues in supportive care, such as cerebral edema, antiepileptic prophylaxis, cancer fatigue, depression, and venous thromboembolism.[31] Unfortunately, the GO Project uncovered mismanagement of these important issues,[18] findings that likely reflect the inadequate supply of neurooncologists nationally.

Table 3. Focal Presenting Signs of Malignant Glioma and Localization in the Central Nervous System

Location	Clinical Findings
Brainstem	Ataxia, cranial nerve palsies, motor deficits, nausea/vomiting, sensory loss, vertigo
Frontal lobe	Gait disturbance, gaze preference, impaired judgment, motor deficits, personality change, seizure, urinary symptoms
Cerebellum	Ataxia, headache, nuchal rigidity, nystagmus, occipital headache, vertigo
Occipital lobe	Seizures with visual manifestations, visual field deficits
Parietal lobe	Anosognosia (inability to acknowledge deficits), aphasia, apraxia, hemineglect, motor deficits, sensory loss
Periventricular areas	Headache with postural change or Valsalva maneuver, hypothalamic and autonomic dysfunction, nausea/vomiting, syncope
Temporal lobe	Aphasia, memory disturbance, seizure, tinnitus, visual field deficits
Thalamus	Cognitive impairment, motor deficits, sensory loss

Data from Wen and Black.[19]

Systemic chemotherapy. Beginning in the 1970s, randomized trials were conducted to investigate chemotherapy as treatment for malignant glioma in the adjuvant setting.[43] The majority of studies focused on the lipid-based nitrosureas to facilitate crossing of the BBB.[43] Subsequent meta-analysis confirmed a modest improvement in survival: an approximate 6% survival increase at 1 year and a 2-month increase in median survival time.[43] Despite these suggestions of efficacy, the GO Project revealed that only 54% of eligible patients with malignant glioma are receiving chemotherapy.[18] Although reasons behind this trend are speculative, many patients and physicians alike may be unable to justify the morbidity associated with chemotherapy (eg, myelosuppression, pulmonary fibrosis, and fatigue) in light of the modest survival benefit.[18] However, recent advances in the delineation of GBM pathogenesis have led to clinical trials of the chemotherapeutic agent temozolomide, a drug that has shown great promise.[44]

To understand the motivation for selecting temozolomide as a chemotherapeutic agent, it is important to understand the molecular genetics of GBM. The O^6-methylguanine–DNA methyltransferase (*MGMT*)

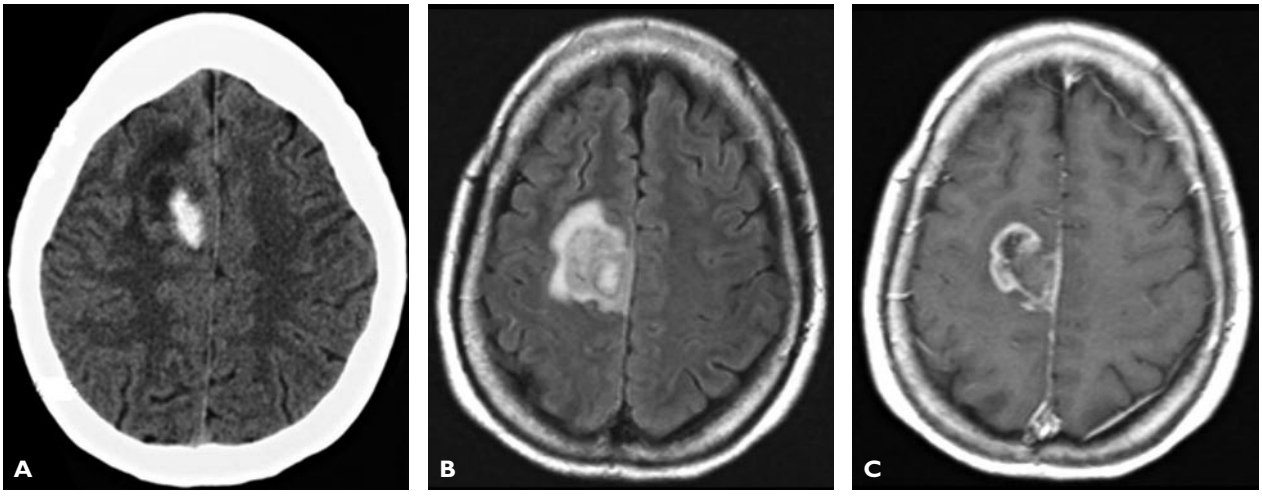

Figure 3. (**A**) Noncontrast axial computed tomography image of the head reveals an isodense ringed lesion associated with surrounding hypodense edema and hyperdense hemorrhage. (**B**) T2/FLAIR–weighted magnetic resonance image in the same patient displays a heterogeneous mass with surrounding hyperintense edema. (**C**) Ring enhancement on a T1–weighted magnetic resonance image with intravenous contrast. FLAIR = fluid attenuation inversion recovery.

DNA-repair gene is found on chromosome 10q26 and codes for the DNA repair enzyme O^6-alkylguanine–DNA alkyltransferase (AGT).[45] *MGMT* is expressed in both normal and neoplastic cells, where it provides a protective effect through repair of DNA alkylation and prevention of erroneous transcription.[46] The mechanism of alkylating chemotherapeutics is to induce cell death by causing mismatched DNA base pairs which cannot be repaired.[46] A high level of AGT activity in tumor cells creates a chemoresistant phenotype that is seen in high-grade gliomas and consequently limits their response to nitrosurea-based chemotherapy.[46,47] Likewise, a low level of AGT activity in glioma tissue is associated with longer survival in patients receiving chemotherapy.[48]

Temozolomide is an orally administered alkylating agent with 100% bioavailability[49] that has the unique ability to deplete the DNA repair enzyme AGT.[50] Based on preclinical data,[51,52] it was theorized that temozolomide and radiation therapy could act synergistically,[53] with temozolomide rendering tumor cells more radiosensitive.[54] A phase II trial in 2002[47] established the safety and tolerability of postoperative concomitant temozolomide and radiation therapy. Shortly thereafter, the first ever prospective phase III trial of chemotherapy in GBM was undertaken, with 573 GBM patients from 85 treatment centers randomized to 2 postsurgical groups: radiation therapy alone (60 Gy) or radiation therapy (60 Gy) plus continuous temozolomide, followed by 6 cycles of temozolomide alone.[44] The study showed a significant difference in favor of the treatment group in both median survival (14.6 versus 12.1 mo) and 2-year survival rate (26.5% versus 10.5%).[44] Furthermore, the study supported the minimal toxicity profile of combined therapy[44] and led to an US Food and Drug Administration (FDA)–endorsed indication.[55] Since publication in 2005,[44] this combination therapy has been gaining widespread use in the management of newly diagnosed GBM.[26]

Previous studies have suggested that methylation of the promoter region of the *MGMT* gene and subsequent silencing leads to increased susceptibility to alkylating chemotherapeutics.[48,56] To test this theory and look for evidence of survival benefit, pathologic analysis of 206 available GBM specimens from the phase III trial of temozolomide were undertaken.[45] Among patients demonstrating methylation of the *MGMT* promoter, there was a 6.4-month median survival benefit with the combination therapy (21.7 versus 15.3 mo) but insignificant benefit in patients without a methylated promoter.[45] The 2-year survival rate in patients with promoter methylation treated with combination therapy was 46% versus 13.8% in the unmethylated group.[45] These results have significant implications. If methylation status in patients is determined during pathologic analysis of surgical specimens, patients can be selected for suitability of adjuvant chemotherapy based on likelihood of response,[45] avoiding unnecessary morbidity. The potential befefits of basing therapeutics on the unique pathophysiologic fingerprint of a patient's malignancy has basic scientists and clinicians hopeful for the future of GBM chemotherapeutics.[2,57]

Therapies targeting aberrant signal transduction. With an increased understanding of molecular pathogenesis

in malignant glioma, there has been a surge in the development of targeted therapies, agents that focus on aberrant signal transduction.[58] Signal transduction is the interaction between cell surface receptors and intracellular effector proteins, eventually leading to gene transcription in the nucleus and control over cellular processes.[59] Although gliomas are genetically heterogeneous, they share common alterations in these pathways that lead to the malignant phenotype.[59] Different therapeutic approaches have been evaluated, including the inhibition of growth factor ligands or their intracellular effector proteins.[60] One approach that has elicited particular enthusiasm is the inhibition of growth factor receptors. Ligand binding to these often amplified,[61] overexpressed,[61] or mutated[62] receptors initiates intrinsic tyrosine kinase activity and pathway activation.[59] The orally administered receptor tyrosine kinase inhibitors (RTKIs), which have proven utility in malignancies such as chronic myelogenous leukemia[63] and lung cancer,[64] compete with receptor ATP-binding and subsequently inhibit activation.

The epidermal growth factor receptor (EGFR) is amplified in up to 50% of GBM cases,[65] and among these nearly 40% express the mutant receptor EGFR vIII.[62] This receptor displays constitutive activation and has been shown to independently predict poor survival.[66] Accordingly, the EGFR-focused RTKI gefitinib (Iressa, ZD1839 [AstraZeneca, Wilmington, DE]) and erlotinib (Tarceva, OSI-774 [Genentech, San Francisco, CA]) are rational approaches to therapy.[59] Unfortunately, clinical trials of these drugs in unselected malignant glioma patients have shown only modest effects on survival.[67–72] However, it has been shown that radiographic response to these drugs can be predicted based on evaluation of biopsy tissue for the receptor and specific effector proteins.[73,74] Coexpression of EGFR vIII and normal *PTEN* (phosphatase and tensin homolog)[73] as well as overexpression of EGFR and low levels of PKB/Akt (protein kinase B)[68] have been shown to serve as predictors of drug response. In a similar fashion, imatinib (Gleevec, STI-571 [Novartis, Basel, Switzerland]), an RTKI of the platelet-derived growth factor receptor (PDGFR), shows survival benefit as monotherapy only in malignant glioma patients selected for tumor expression of PDGFR.[75,76]

To date, the majority of single-targeted agents in monotherapy have been associated with poor clinical response in unselected malignant glioma patients.[59] It is postulated that a reason for failure is the genetic heterogeneity typical of the disease and a lack of common reliance on a specific survival pathway among unique tumors.[77] As such, the future of targeted therapy may also lie in individualized tumor analysis with therapeutics tailored accordingly. Another consideration is the presence of compensatory pathways that are activated when another is blocked.[77] To address this possibility, multitargeted RTKIs are under investigation as are combinations of single-targeted RTKI to block multiple targets in the same pathway.[59] Given the sophisticated pathogenesis in malignant gliomas, no "magic bullet" may ever be found. However, as basic science continues to identify novel pathogenic biomarkers and targeted therapeutics are refined, small gains will continue to be made.[59]

Neuroradiology

A skilled neuroradiologist is instrumental in each phase of care of GBM patients, including diagnosis, perioperative assessment, and monitoring for recurrences. Although MRI is the standard modality in assessment of GBM, it has limitations.[27,28] Recent advances in radiologic technology include perfusion MRI (pMRI) and magnetic resonance spectroscopic imaging (^{1}H MRSI), which give radiologists an increased ability to differentiate tumor from other confounding intracranial processes, monitor response to chemotherapy, and distinguish tumor recurrence from radiation necrosis.[78] Accordingly, the potential exists for more efficient treatment planning, optimization of therapy, and the avoidance of unnecessary morbidity.

Perfusion MRI. Traditional MRI is limited by the relative nonspecific nature of contrast enhancement, which represents a disruption of the BBB.[79,80] While active tumor enhances, so does the post-therapy tumor bed and areas of radiation necrosis.[79] In the past, differentiation between these processes in a noninvasive manner was difficult. Perfusion-sensitive, contrast-enhanced MRI is a novel technique that allows for assessment of tumor microvascularity by taking advantage of a characteristic that sets active tumor apart.[79] pMRI is a calculation of relative cerebral blood volume (rCBV) in the area of interest relative to an analogous area in the contralateral cerebral hemisphere (**Figure 4**).[78] The proangiogenic environment of active tumor results in a high rCBV, differentiating it from more ischemic processes such as necrosis, which can be indistinguishable clinically and radiographically.[78,81] Thus, pMRI can prevent premature surgical intervention and unnecessary morbidity. In addition, in diagnosis of malignant glioma, it is essential to sample tissue of the highest histopathologic grade, which generally also has the greatest vascularity and perfusion.[82,83] pMRI allows for precise presurgical mapping before stereotactic biopsy, ensuring that subsequent therapies are appropriate.[82] Similarly, with the emergence of new options in chemotherapy targeted at antiangiogenic pathways, pMRI technology allows

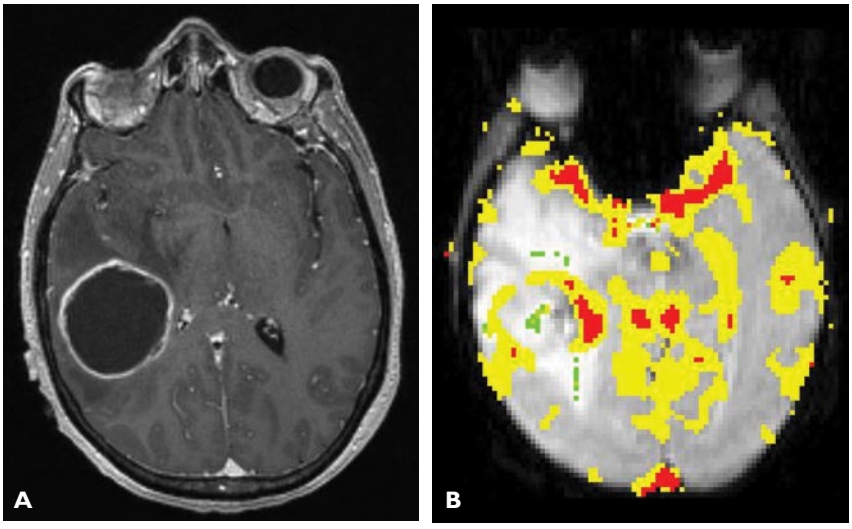

Figure 4. (**A**) Post-contrast T1-weighted axial magnetic resonance image (MRI) of a patient who underwent resection of a right temporal glioblastoma multiforme tumor and adjuvant radiotherapy. (**B**) Perfusion-sensitive, contrast-enhanced MRI displaying hyperperfusion and high relative cerebral blood volume at the margin of the resection cavity, which allow active tumor to be differentiated from radiation necrosis.

for noninvasive monitoring of response.[79] With prompt discontinuation of ineffective approaches and redirection, physicians can avoid morbidity and make the most of limited time.

Magnetic resonance spectroscopic imaging. ^{1}H MRSI is another relatively new modality available to neuroradiologists that has emerged as an adjunct to traditional MRI.[84] ^{1}H MRSI can detect biochemical compounds and quantify the metabolic processes in which they are involved, lending chemical specificity to the spatial localization of MRI.[83] Through analysis of metabolite ratios, pathologic processes specific to GBM can be interpreted.[84] Examples of common metabolites with utility in GBM are shown in **Table 4**.[83] In practice, GBM is distinguished from normal parenchyma by decreased N-acetylaspartate (NAA) and creatinine; elevated choline and lactate; increased ratios of choline/creatinine, choline/NAA, and lactate/choline; and a decreased ratio of NAA/creatinine.[84] Further applications for ^{1}H MRSI include precision in biopsy site selection, monitoring response to therapy, and distinguishing tumor progression from radiation necrosis.[78] Outside the realm of CNS malignancy, this technology also has utility in cerebrovascular disease, infection, and neurodegenerative processes.[84]

pMRI[85] and ^{1}H MRSI[86] are not yet considered routine in clinical management but offer a promising adjunct to anatomical imaging of malignant gliomas. Focused studies are anticipated to further elucidate the utility of these noninvasive technologies in diagnosis, treatment planning, and monitoring response to multimodality therapy.

Intra-arterial chemotherapy. Intra-arterial chemotherapy is an intervention in which a drug is directly delivered to the tumoral arterial supply under angiographic guidance.[87] This approach avoids metabolism of the drug before it reaches its target, allowing for a tenfold increase in tissue drug concentration as compared with intravenous administration.[87] Despite theoretical promise, intraarterial chemotherapy has never reached widespread acceptance for treatment of malignant gliomas due to reports of significant vascular and neurologic toxicity, a labor-intensive protocol, and a paucity of supportive randomized clinical data.[87,88] However, a resurgence in popularity of the technique is underway with the important addition of osmotic BBB disruption. Though BBB is compromised in malignant gliomas, this disruption may be too inconsistent for reliable drug penetration, as regions of infiltrating tumor can rely on existing normal brain vasculature.[89] To enhance tumor penetration, intra-arterial mannitol is administered prior to chemotherapy to cause a transient interruption in the tight junctions that compose the BBB.[90] In addition, drugs such as carboplatin are being utilized, which have a more favorable side-effect profile than nitrosureas when used for arterial infusion.[87] A recent phase II trial of intra-arterial chemotherapy with BBB disruption revealed a response rate of 58% in the subset of malignant astrocytoma patients.[90] These results are encouraging, and we await a phase III trial for definitive results of this reinvented technology.

Neurosurgery

Neuronavigation and cortical mapping. Frameless stereotaxy, or neuronavigation, has come into routine use in neurosurgical practice over the past 20 years.[91,92] This technology allows the surgeon to view the position of his instrument in the surgical field on a computer screen

relative to computed tomography or MRI images collected preoperatively, acting as a tool for localization in real time.[92] Although variations in the protocol exist, typically skin markers, or "fiducials," are applied to the scalp and established within preoperative imaging.[92] In the operating suite, infrared input to a digitizer correlates the scalp markers with their corresponding match on the data set of acquired preoperative images.[92] Through this process of point matching, the relationship between patient space and image space is established.[93] Little prospective data exists, but subjective accounts by neurosurgeons report use of neuronavigation in over 85% of GBM cases, and retrospective assessments suggest that neuronavigation improves the extent of resection and survival time.[94] However, the benefits must be balanced with sources of error such as "brainshift," changes in anatomy that occur relative to preoperative imaging. Accordingly, utilization remains at the discretion of the surgeon until evolving technologies such as intraoperative MRI can further refine this technology.[94]

Another significant contribution to neurosurgical oncology over the past 2 decades is the technique of awake craniotomy with cortical mapping. This technology allows for intraoperative functional assessment of peritumoral cortex involving motor or language areas that might otherwise be limited to biopsy.[95] Accordingly, a more aggressive resection can occur while minimizing morbidity.[96–98] Though variations in current protocol exist, the procedure is still based upon the groundbreaking work of such prominent neurosurgeons as Berger,[96] Ojemann,[96] and Black.[97] Commonly during scalp incision and craniotomy, the patient is maintained in a state of conscious sedation, able to maintain spontaneous ventilation and follow commands.[99] Using adequate local anesthetic to avoid discomfort, the dura is incised and then sedation is held.[99] The patient is awake and cooperative to allow for functional assessment, and general anesthesia is reserved for emergency use only.[99] Tumor-infiltrated and potentially eloquent cortex is then subjected to electrical stimulation.[99] With concomitant observation and assessment by a neurologist or speech pathologist, cortex is mapped as either eloquent or resectable.[99] As resection continues into subcortical white matter regions, serial functional assessments are performed, and resection continues until complete or neurologic deficit appears.[89] This technique has been shown in a number of studies to be well tolerated, and it allows for a substantial reduction of tumor burden in eloquent areas.[95,99,100]

Local chemotherapy systems. As we have seen, the trend in GBM therapeutics is toward use of tumor-specific agents. It is theorized, however, that systemic chemotherapy cannot cross the BBB in sufficient concentration to render a tumoricidal effect.[101] To circumvent this phenomenon, the concept of local therapy to the postresection tumor bed is an attractive alternative.[102] In terms of pathogenesis, GBM invades by migrating along myelinated white matter tracts and small blood vessels, seeding cells beyond the tumor mass accessible to the surgeon and preventing a clean margin postresection.[102,103] Local chemotherapy can target micrometastases by taking advantage of the expression of tumor-specific proteins and rapid tumor cell turnover while minimizing toxicity to the postmitotic normal brain.[103–105] Local chemotherapy is also desirable because GBM rarely has systemic metastases, eliminating the necessity of systemic delivery with its associated toxicity.[103]

Table 4. ^{1}H MRSI Metabolites with Utility in Glioblastoma Multiforme and Associated Biochemical Processes

Metabolite	Process
Choline	Marker of membrane synthesis and turnover
Creatinine	Marker of cellular energy stores
Lactate	Marker of anaerobic metabolism
N-acetylaspartate	Neuron-specific marker directly related to normal neuronal function

^{1}H MRSI = magnetic resonance spectroscopy imaging.

Data from Nelson and Cha.[83]

Gliadel (MGI Pharma, Bloomington, MN) represents an early attempt at local therapy. It is a system for the delivery of carmustine via biodegradable polymer wafer and is FDA approved for the treatment of newly diagnosed and recurrent malignant gliomas.[106] Allowing for controlled drug release over 2 to 3 weeks, up to 8 wafers are placed at the time of surgery in the resection bed.[107] Local carmustine therapy offsets the short half-life of the drug and increases the local concentration at the most likely site of recurrence while avoiding the toxicity of systemic delivery.[103,108] Although in a phase III trial Gliadel in adjunct to conventional therapy did not achieve statistical significance for median length of survival in GBM patients (13.5 versus 11.4 mo, $P = 0.10$),[107] the trend indicates that local therapy may have a role in treatment. Pharmacokinetic studies have revealed that the Gliadel wafer has a penetration distance limited to several millimeters.[109] Given that GBM is known to recur at a margin 2 cm from the resection cavity,[110] it is possible that the modest gains seen in the Gliadel trial are not due to drug failure but rather the inability of the drug to reach its target in sufficient concentration.

Most chemotherapy agents are relatively large, on the order of 50,000 daltons or greater,[111] limiting diffusion to 1 mm per day and leading to a small penetration distance and interstitial spread.[111] In addition, intact BBB has intrinsic mechanisms to expel foreign chemicals from the CNS,[112] leading to lower drug concentrations. To circumvent these limitations, convection-enhanced delivery (CED) has been investigated as a means to improve upon drugs such as Gliadel. Postsurgically, a catheter is implanted into the resection cavity under image guidance.[111] With an infusion pump to drive flow, a continuous positive pressure injection is forced through the interstitial space, with subsequent dilatation of target tissues.[111] As the drug permeates, therapeutic concentrations are reached by bypassing the limitations imposed by the BBB and simple diffusion.[111] CED is effective in a hypoxic environment in which malignant cells are radioresistant[113] and provides high drug concentrations locally that may be toxic if administered systemically.[114] Accordingly, CED is an area of active research in the delivery of a wide range of CNS-active agents with applicability to GBM, ranging from RTKI[115] to targeted toxins[116] (discussed below).

As previously described, gliomas overexpress proteins not prevalent in normal brain, such as transferrin receptor,[117] vascular endothelial growth factor receptor,[118] and receptor of interleukin (IL)-13,[119] which can also serve as docking sites for tumoricidal agents, such as targeted toxins. Targeted toxins are recombinant polypeptides derived from bacteria such as *Pseudomonas aeruginosa.*[120] These potent peptide toxins are truncated to eliminate native toxicity and coupled to a tumor selective ligand, making them highly selective tumoricidal agents. Several targeted toxins have recently advanced from the preclinical stages of development to clinical trial, and 2 have recently completed phase III evaluation.[121,122]

Cintredekin besudotox (IL13-PE38 [NeoPharm, Lake Forest, IL]) is a chimeric toxin of human IL-13 fused to a mutated form of *Pseudomonas* exotoxin.[120] Capitalizing on the limited expression of the IL-13 receptor in non-neoplastic cells and overexpression in malignant gliomas,[119] early clinical trials in the setting of tumor recurrence offered promising results.[123–126] CED-based therapy was well tolerated, with evidence of response on both neuroimaging and histologic samples. This early success prompted the recently completed PRECISE trial, a phase III randomized open-label study of CED-mediated delivery of IL13-PE38 versus Gliadel in the postresection setting of recurrent GBM.[127] Similarly, TransMID (Tf-CRM107 [Xenova Group, Berkshire, UK]) is a conjugate of human transferrin and a mutant form of diphtheria toxin.[128,129] Transferrin receptor is a transmembrane glycoprotein that mediates the cellular uptake of iron. Its expression is limited to the luminal surface of brain capillaries in normal parenchyma,[130] but it is overexpressed on hematopoietic and neoplastic cells such as GBM.[117] Phase I and II trials proved the drug to be well tolerated with statistically significant tumor response in the setting of recurrence.[128,131] In addition, a phase III trial comparing TransMID with conventional treatment for unresectable recurrent GBM has been completed.[132] Unfortunately, these drugs failed to offer significant survival benefit beyond established therapies, likely secondary to variable expression of protein targets. However, while this application of CED was unsuccessful, it represents only 1 of limitless applications of this safe and well-tolerated novel approach to CNS drug delivery. With the limitations of the BBB and systemic toxicity removed, novel targeted therapies as well as drugs resurrected from failed trials of systemic delivery will continue to build on this established foundation.

Radiation Oncology

Early attempts at local control. Although studies have shown no utility for EBRT beyond 60 Gy,[40,41] data also indicates that length of survival in malignant glioma patients is directly related to radiation dose.[40,133] It is suggested that radiation dose is limited by toxicity to normal brain and ensuing clinical sequelae.[134] Given that the majority of GBM tumors recur within 2 cm of the original tumor,[116] radiation oncologists have also begun to pursue the idea of "local control" in an attempt to minimize the exposure of normal brain and target micrometastases.[135] Historically, the 2 modalities that have received the most attention are brachytherapy and stereotactic radiosurgery.

Brachytherapy involves a radiation source, commonly a "seed implant," placed in direct contact with the tumor to emit a continuous dose of radiation.[134] With decades of proven utility in breast[136] and prostate[137] cancers, pursuit as an adjunct to therapy in malignant gliomas was intuitive and underwent intensive research beginning in the 1980s.[138–143] Brachytherapy follows the standard course of gross total resection and EBRT in newly diagnosed disease[138–140] or re-resection in the setting of recurrence[141–143] and is accomplished by stereotactic placement of radioactive seeds through burr holes in the cranium. Utilizing a radioactive isotope, typically iodine, seeds are placed along the axis of residual enhancing tumor. In theory, the continuous low-dose irradiation preferentially damages proliferating tumor cells, which are less efficient than normal brain at repairing sublethal damage.[135,144] Furthermore, given that hypoxic cells are radioresistant,[144] postoperative

stereotactic implantation allows for the reintroduction of oxygen to the seed environment.[135] Unfortunately, despite these theoretical advantages and promising data from phase II clinical trials,[138–143] 2 prospective randomized phase III trials of brachytherapy failed to show a survival advantage.[145,146] Analyses revealed that the benefit seen in earlier trials was likely secondary to selection bias towards younger patients with higher performance scores and more accessible tumors that underwent more extensive resection.[147] Furthermore, rates of reoperation from symptomatic radiation necrosis were reported as high as 64%.[146] Accordingly, the majority of support for the use of brachytherapy in malignant gliomas has passed.[135]

Stereotactic radiosurgery, a technique pioneered in the 1950s for use in trigeminal neuralgia,[148] has come into use in the treatment of CNS diseases such as vascular malformations, malignancies, epilepsy, and movement disorders.[149] This modality offers one-time precision delivery of focused high-dose radiation to the tumor, with the added advantages of a steep drop off of radiation dose outside of a precision target, leading to a favorable morbidity profile.[135] It has received much attention over the past 20 years as a promising adjunct to GBM management, and early prospective studies from the 1990s showed encouraging results.[150,151] Unfortunately, in 2004 a phase III trial of postsurgical radiosurgery as a boost prior to conventional therapy failed to show survival advantage or improvement in quality of life, with 93% of patients displaying local recurrence.[152] Again it has been suggested that earlier nonrandomized studies demonstrating survival advantage were secondary to selection bias.[153] Current recommendations by the American Society for Therapeutic Radiology and Oncology do not support the use of radiosurgery in the management of newly diagnosed malignant glioma, advising its use only as salvage therapy in recurrence.[154]

GliaSite system. The GliaSite Radiation Therapy System (Proxima Therapeutics, Alpharetta, GA) is a novel device for the local delivery of radiation to the postresection tumor bed that offers several improvements over older approaches.[155,156] This FDA-approved expandable balloon catheter is placed in the surgical cavity at the time of resection.[156] Acting as a spherical radiation source and designed to approximate the surgical cavity, it contains a subcutaneously accessible injection port brought through a cranial burr hole.[156] Within 1 to 3 weeks after placement, the apparatus is filled with liquid iodine to deliver a radiation dose up to 1 cm from the balloon surface over several days, after which the chemical is retrieved.[155,156] GliaSite has several advantages over traditional brachytherapy.[155,156] From a procedural standpoint, it eliminates the need for a separate invasive procedure, and the radiation source can be efficiently added or removed outside of the operating room.[156] From a therapeutic standpoint, the close approximation of the resection cavity delivers a homogeneous radiation dose to the most likely site of tumor recurrence, limiting exposure of healthy parenchyma, lessening the need for reoperation, and lowering associated morbidity.[116,155,156]

To date, results have been promising. In a phase I trial, Tatter et al[156] established the safety and feasibility of GliaSite in an open-label study of recurrent malignant glioma patients presenting for re-resection. The overall median survival postresection was 54.4 weeks and 34.3 weeks in the subset of patients with GBM.[156] In comparison, the median survival postresection in the control arm (re-resection alone) of a comparable prospective trial of Gliadel wafer in recurrence was 23 weeks for grades III and IV and 20 weeks for GBM alone.[157] Although survival was not a primary endpoint in this phase I study, the results are certainly suggestive of survival benefit. Additionally, no patients required reoperation for symptomatic radiation necrosis,[157] suggesting an appropriately targeted homogeneous dose of radiation. A subsequent phase II trial confirmed this,[133] and most recently, a 2006 retrospective multi-institutional analysis encompassing the work of 10 institutions in recurrence offered favorable results.[158] With a median postresection survival of 43.6 weeks for grades III and IV and 35.9 weeks for GBM,[158] this comprehensive study further supported the use of GliaSite as a promising adjunct to current standards of care. Currently, we await a phase III trial for recurrence as well as further research into the potential use of GliaSite in initial management of GBM. For now, however, GliaSite offers the possibility of survival benefit with minimal risk in patients with recurrent disease and few promising options.

CONCLUSION

The many disciplines that encompass care of the GBM patient are making slow but steady progress to impact survival. As the delineation of the molecular pathophysiology of GBM continues, the current trend in multidisciplinary care will continue to ensure the prompt transition of this science to patient care. It is the hope of clinicians and researchers alike that GBM will follow the trend of other complex malignancies such as recurrent breast cancer, which has seen survival rates rise fourfold over the past 30 years.[159] Through the continued pursuit of well-planned clinical trials and the coordination of care and research efforts in a

multidisciplinary fashion, the cure for this devastating disease may soon become a reality. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 36.

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