Neurosurg Focus 20 (4):E3, 2006

Management of malignant glioma: steady progress with multimodal approaches

LYNN S. ASHBY, M.D., AND TIMOTHY C. RYKEN, M.D.

Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona; and Departments of Neurosurgery and Radiation Oncology, University of Iowa Hospitals and Clinics, Iowa City, Iowa

✓ Despite recent successes in the treatment of cancer with multidisciplinary multimodal treatment approaches, the duration of survival for patients with malignant glioma remains limited. Malignant gliomas represent a class of infiltrative, aggressive neoplasms that are generally resistant to combination therapies. The basic approach to treatment has involved a combination of surgery and radiotherapy. The use of chemotherapy has been met with skepticism because of its limited efficacy and the significant side effects demonstrated in clinical trials. Nevertheless, based on findings in randomized trials of new agents, it has been suggested that further evaluation of the role of chemotherapy is warranted. Temozolomide and Gliadel (carmustine wafers) are generally well tolerated due to their limited systemic toxicity. These agents appear particularly well suited for incorporation into multimodal treatment strategies. Proposed investigations and ongoing clinical trials will be conducted to assess the use of these agents in novel combination therapies. Future treatment strategies may include a wide variety of biological response modifiers, but will need to continue to address local control with surgery, radiation, and adjuvant chemotherapy.

KEY WORDS • glioma • temozolomide • Gliadel wafer • radiotherapy • chemotherapy • surgery

Tumors of the CNS

Epidemiological Features

Primary tumors of the CNS, from high-grade malignant gliomas and primitive neuroectodermal tumors to relatively benign meningiomas, neuromas, and adenomas of the pituitary gland, exhibit a range of behavior. In the most recent report from the Central Brain Tumor Registry of the US, researchers estimate that 7.3 new cases of primary malignant tumors of the CNS are diagnosed per 100,000 person-years.[1,18] In 2005, there were 21,690 new cases of primary brain tumors, with 12,760 deaths recorded in the annual report of the Central Brain Tumor Registry of the US (2005–2006).[18] Gliomas account for 42% of all primary CNS tumors and 77% of all malignant primary CNS tumors. Gliomas develop from diverse histological lineages, including but not restricted to oligodendroglioma, astrocytoma, and mixed oligoastrocytoma. Of these, low-grade and high-grade variants occur, but all have the potential to become highly malignant neoplasms that are recalcitrant to treatment, with GBM (World Health Organization Grade IV astrocytoma) being the most common and aggressive primary brain tumor in adults (Fig. 1).

Prognostic Factors

The prognosis for patients with CNS tumors is influenced by the histological features of the neoplasm, the age of the patient, and the neurological condition or functional status of the individual. In general, the effect of treatment on the overall prognosis has been surprisingly limited. Primary brain tumors, specifically gliomas, are difficult to treat and are generally considered incurable. Even the slower-growing tumors have the potential to recur and progress. Survival time is limited, and neurological morbidity from disease progression is high.[2,34,56,90] Investigators participating in the GO Project reported on a large cohort (788 patients) with malignant glioma who underwent biopsy sampling or resection; the median duration of survival was 48 weeks for the overall population and only 40.9 weeks for patients with GBM.[68]

Limitations of Current Treatments

Despite the efforts of research scientists and clinical investigators, progress in the treatment of malignant glioma has been limited until recent years. In the past, treatment for malignant gliomas frequently included resection or biopsy procedures followed by radiotherapy. The role of chemotherapy has been controversial; patients with malignant glioma typically have been treated at major brain tumor centers by medical and neurooncologists with special

Abbreviations used in this paper: BBB = blood–brain barrier; BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea; CI = confidence interval; CNS = central nervous system; FDA = Food and Drug Administration; GBM = glioblastoma multiforme; GO = Glioma Outcomes; MGMT = O^6-methylguanine–DNA methyltransferase; PCV = procarbazine, lomustine, and vincristine; TMZ = temozolomide.

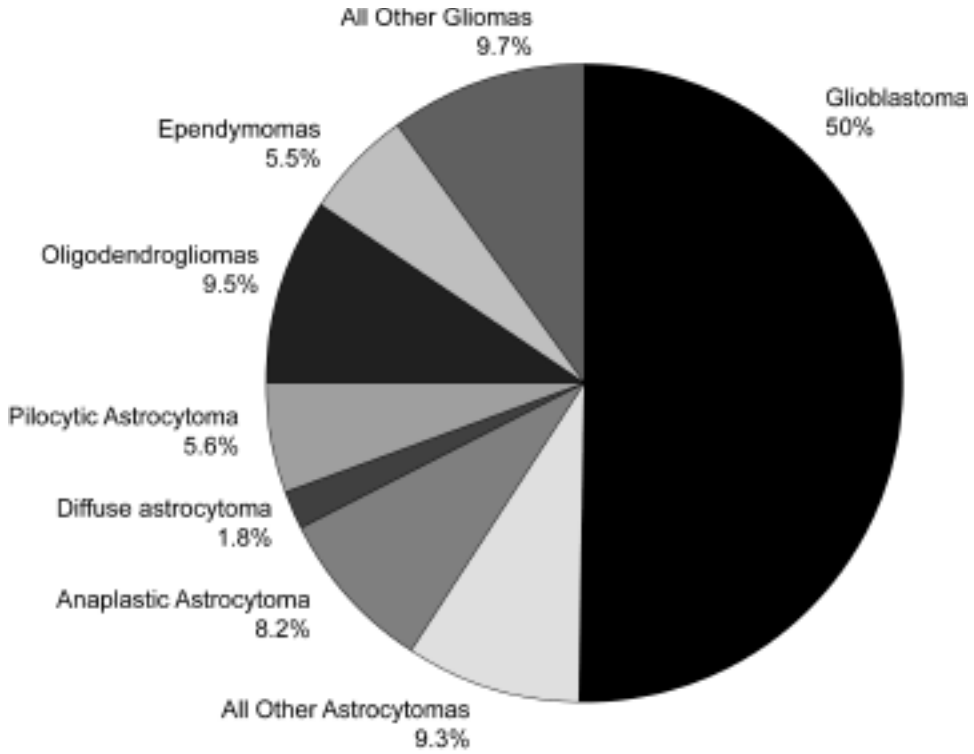

FIG. 1. Pie chart showing the relative incidence of primary brain gliomas by type. Adapted from CBTRUS: Statistical Report: Primary Brain Tumors in the United States, 1997–2001, Hinsdale, IL: Central Brain Tumor Registry of the United States, 2004. No Permission needed.

training and interest in cancer of the CNS or as participants in clinical trials. Even with advances in neuroimaging, neurosurgical stereotactic navigation systems, and improved tumor control with targeted radiotherapy, recurrence is still nearly universal and survival duration is limited by the inevitable relapse and disease progression (Fig. 2). In the GO Project, half of the middle-aged patients (41–60 years old) with diagnoses of GBM and non-GBM lesions died within 53 and 85 weeks, respectively, post-treatment.[68]

Historically, to achieve successful treatment of other more common cancers, clinicians had to overcome similar challenges to those presented by malignant gliomas. For example, the median survival time for patients with recurrent metastatic breast cancer has improved over the past few decades, from 15 months (1974–1979) to 58 months (1995–2000).[42] It appears that this can be largely attributed to the advent of multimodal treatment strategies in which resection, radiotherapy, chemotherapy, and other bioactive agents are used. In the 1950s, surgery was the mainstay treatment for breast cancer with or without radiotherapy;[52,55,115] by the 1960s, adjuvant chemotherapy was introduced as single-agent therapy and then in multiagent combinations.[35–37,99] Today, the addition of biological response modifiers, immune modulators, and targeted receptor blockers has resulted in better overall and disease-free survival rates for patients with breast cancer.[8,9,30,44,98,123] The experience with advances in breast cancer treatment demonstrates that multimodal and multiagent treatment strategies can substantially improve survival in patients with cancer. In this review we will discuss recent advances in multimodal approaches to the management of malignant glioma, with particular emphasis on the current status and future potential of the therapies for this disease that have been most recently approved by the FDA. These include the BCNU wafer (Gliadel wafer/implant; MGI Pharma, Bloomington, MN) in 1996 and 2003, and TMZ (Temodar in the US and Temodal globally; Schering-Plough Corp., Kenilworth, NJ) in 1997 and 2005.

Established Therapies for Malignant Glioma

Advances in the treatment of malignant gliomas have lagged behind the strides made in treating extraneural tumors. Several additions to the armamentarium over the past several decades have led to improved outcomes; however, significant changes in the overall treatment paradigms have remained elusive. Patients who receive "supportive care" only, usually corticosteroid and anticonvulsant drugs, have a median survival duration of approximately 14 weeks or less (Fig. 2). As multimodal treatment strategies that include surgery, radiotherapy, and chemotherapy have been developed and used, the median survival time has improved, but not to the extent observed in other cancers, such as breast cancer.[2]

Surgery and Radiotherapy. Historically, patients treated with surgery alone have a median survival duration of less than 6 months.[59,80] The addition of postoperative radiotherapy extended the median survival time to approximately 9 months.[63,124] In several studies, researchers have investigated various fractionation schedules, but none has demonstrated a significant benefit compared with stan-

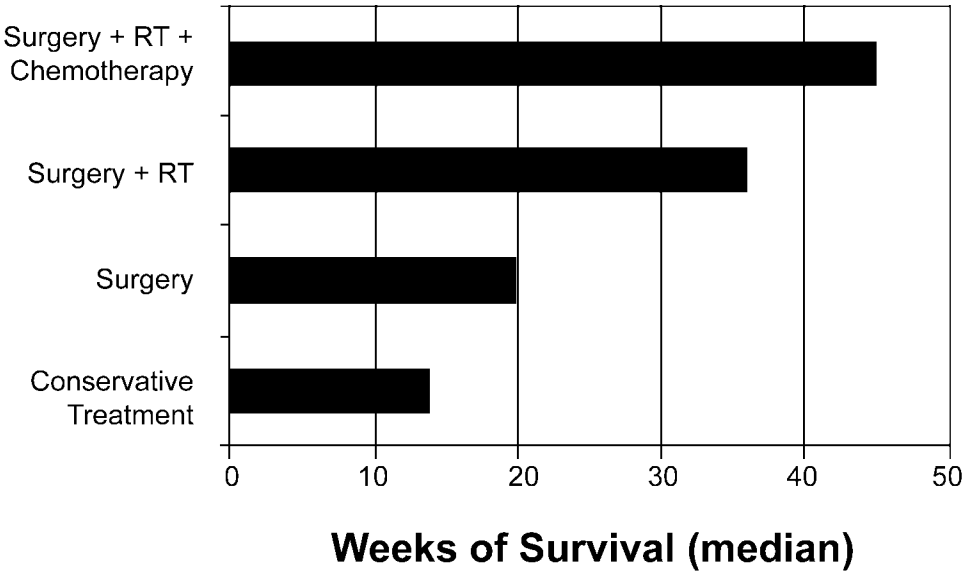

FIG. 2. Bar graph showing improvement in survival for malignant glioma. Graph was created from data presented in Avgeropoulos NG, and Batchelor TT: New treatment strategies for malignant gliomas. **Oncologist 4:** 209–224, 1999.

dard dose schedules.[63] Efforts to increase radiation doses to the local tumor region have included new techniques such as radiosurgery[104] and brachytherapy,[102] which have also met with limited success.

Systemic Chemotherapy. Historically, several factors have been proposed to explain the limited success of chemotherapy for malignant glioma, including the following: 1) intrinsic drug resistance; 2) tumor heterogeneity; and 3) failure to cross the BBB in sufficient amounts to reach and maintain therapeutic levels of cytotoxicity.[7,62,84]

Various chemotherapy agents and combinations have been tested in randomized clinical trials over the past few decades. Stewart[109] combined a total of 3004 patients from 12 studies performed between 1969 and 1991 to perform a metaanalysis to determine the overall efficacy of several agents, mostly nitrosoureas: carmustine, lomustine, nimustine, procarbazine, dacarbazine, and others. As a result of this analysis, found a significant prolongation of survival with the addition of chemotherapy ($p < 0.0001$), representing an increase in the 1-year survival rate from 40 to 46%, with an associated mean increase in survival of 2 months for those receiving chemotherapy compared with those treated with radiotherapy alone. Additionally, clinical trials testing chemotherapy for brain tumors have consistently confirmed that numerous factors, including patient age, performance status, and tumor grade, contribute to survival and likely influence the response to treatment.[58,68,94] Recent pivotal work refining the classification of gliomas based on molecular genetic "signatures" has better defined the chemosensitive compared with chemoresistant subgroups of otherwise histologically identical tumors. These include 1p19q allelic analysis in oligodendroglioma[17,57] and the DNA repair enzyme MGMT promoter methylation status in GBM.[54]

Therapeutic Response to Nitrosoureas. Nitrosoureas such as BCNU have been widely studied in primary brain tumors because they have shown activity against gliomas in preclinical studies[94] and have excellent BBB penetration.[71] However, these agents have substantial hematopoietic, pulmonary, and renal toxicity, which limits their therapeutic utility.[10] Adjuvant intravenously delivered nitrosoureas provided a slight benefit[34,108] or no benefit[124,125] when compared with radiotherapy alone. Fine, et al.,[34] performed a metaanalysis of 16 studies that were conducted over 15 years and involved more than 2350 patients with malignant glioma treated with radiotherapy with and without adjuvant chemotherapy. Nitrosoureas were used in most of these trials. These investigators estimated that the addition of chemotherapy following radiotherapy provided some benefit, prolonging survival from a median of 9.4 months to 12 months. Similar results were observed in a more recent metaanalysis that included 3004 patients, indicating a survival advantage of 2 months with the addition of chemotherapy to radiotherapy.[109]

Combination Chemotherapy With Nitrosoureas. Efforts to reduce drug resistance and improve efficacy led to combination therapy with PCV. Initially, PCV was shown to have some activity against anaplastic oligodendroglioma,[120] but in a recent Medical Research Council study of 674 patients with malignant glioma, investigators failed to demonstrate a survival advantage when PCV was added to radiotherapy compared with radiotherapy alone following resection.[74] Despite the widespread assumption that PCV is well tolerated, significant myelosuppression and other adverse events often prevented completion of the full six-cycle course of recommended treatment.[120]

Response to Platinum-Based Regimens. Several attempts to use platinum-based regimens (carboplatin and cisplatin) have failed to demonstrate an overall survival advantage over BCNU alone, despite an initial objective radiographically confirmed response.[2,29,76] Specifically, the use of concurrent infused BCNU and cisplatin has not resulted in demonstrably improved survival over standard systemic BCNU in patients with GBM.[45]

Despite the limited efficacy of chemotherapy in most patients with malignant glioma, we have inferred from some studies that the use of chemotherapy in multimodal regimens may be a contributing factor to long-term survival. Our review of clinical studies by Chamberlain and Kormanik[19] leads us to suggest that the addition of chemotherapy to surgery and radiation improves long-term survival, particularly for patients with GBM, with a 5-year survival rate of 18% for patients receiving surgery, radiotherapy, and chemotherapy compared with 0% for those receiving surgery and radiotherapy alone. Furthermore, in an additional population-based study, it was suggested that the use of aggressive surgery and adjunct chemotherapy may improve the likelihood of long-term survival in selected patients with GBM.[94] As recently as 2001, conventional management of malignant glioma in some centers still consisted of surgery and radiotherapy only.[74] In 2005, researchers working on the GO Project reported that the use of chemotherapy in the management of malignant glioma was infrequent,[22] despite the evidence that the addition of chemotherapy is associated with longer survival.[68]

New Emphasis on Tumor Control With Local Treatment

In recent years, highly focused radiation and locally administered chemotherapy modalities have been developed to deliver aggressive antitumor treatment directly to the lesion site while minimizing exposure to adjacent areas of the brain and reducing systemic toxicity.

Radiosurgery and Brachytherapy. In general, the results of investigations in which the focal radiation dose is increased by numerous fractionation schedules or focal boost techniques, even to total doses of 120 Gy, have been disappointing.[24,63,64,78,95,104,118] The ongoing failure of dose escalation to affect survival in this disease has been a sobering disappointment. The most popular methods of adding radiation doses are stereotactic radiosurgery and brachytherapy (with or without hyperthermia) with seed implants or the implantation of a novel brachytherapy device called the GliaSite Radiation Therapy System (Cytyc Corp., Marlborough, MA).

Radiosurgery. The initial enthusiasm for the use of stereotactically guided radiosurgery to provide a technique for increasing the focal radiation dose as an adjunct in glioma management appears to have lost momentum after publication of a large Phase III study conducted by the Radiation Therapy Oncology Group. In this study, patients with newly diagnosed malignant glioma were randomized to receive either fractionated radiotherapy plus BCNU or fractionated radiotherapy plus BCNU plus radiosurgery (either a linear accelerator–based system or the Gamma Knife was allowed).[104] This study failed to demonstrate a survival advantage for the patients who received an additional radiosurgical boost as part of the initial management strategy.

Brachytherapy. Two large Phase III trials have been conducted in which standard radiotherapy alone was compared with standard radiotherapy plus low-activity iodine-125 seeds, with no significant survival advantage demonstrated by the addition of brachytherapy.[64,95] Smaller Phase II studies yielded variable results.[41,50,67,82,101] The addition of hyperthermia to brachytherapy demonstrated a statistically significant survival advantage in two small patient cohorts, but despite the favorable results, no large-scale, randomized study has been published to confirm these findings.[103,107] The implantation of permanent iodine-125 seeds has also become popular and is favored by some radiation oncologists. Permanent, low-activity seeds appear to be favored in these trials because of the lower rate of radiation necrosis[41,50,67,82] compared with that resulting from implantation of temporary, high-activity seeds.[6,102,126] A novel approach to brachytherapy is the GliaSite Radiation Therapy System, a balloon catheter system implanted in the surgical cavity that includes a reservoir to hold an aqueous solution of organically bound iodine-125 (Iotrex [sodium 3-(^{125}I)-iodo-4-hydroxybenzenesulfonate]) to deliver low-dose radiation through a subcutaneous port.[114] Although this approach has been shown to be feasible and safe in patients with recurrent malignant glioma, it has yet to achieve widespread use because of the lack of large-scale, randomized clinical data; the inconvenience to the patient, who needs to be isolated during treatment; and the necessity of a second surgery to remove the delivery system once treatment is completed.

The first efficacy study was recently published in which GliaSite brachytherapy was assessed in 24 patients with recurrent GBM.[20] The median survival duration following GliaSite treatment was 9.1 months, and appeared comparable to historical data. Patients with a Karnofsky Performance Scale score of at least 70 survived longer than those with a score less than 70 (9.3 compared with 3.1 months; $p < 0.003$). GliaSite is a very attractive device for patients with small, superficial lesions that are considered resectable, but large, randomized trials will be needed to test any meaningful efficacy. We hope that the results will not prove as disappointing in analysis as have those in previous radiosurgery[104] and brachytherapy trials.[95]

Recent Advances

New FDA-Approved Treatments for Malignant Glioma

Although only incremental success has been observed for use of radiation therapy and chemotherapy in malignant glioma in the past 20 years, two agents introduced since 1996 have demonstrated clinical benefit in extending survival in patients with malignant glioma. Recently, the FDA approved these treatments for brain tumors; novel local therapeutic methods (Gliadel wafer) and systemic chemotherapy (TMZ) were included. These therapies have set new benchmarks for success in treating malignant gliomas. Despite the popularity of PCV and the preference of many clinicians for this form of multiagent chemotherapy, the gold standard in measuring efficacy of any new adjuvant treatment has been radiotherapy alone or radiotherapy plus intravenously delivered BCNU.

The Gliadel Wafer. Gliadel is a biodegradable polymer wafer impregnated with BCNU. The wafer is a 1.4 cm × 1 mm disc fashioned from polifeprosan 20 (20:80 poly [bis](p-carboxyphenoxy) propane/sebacic acid) containing 3.85% (7.7 mg) of BCNU. At the time of resection, up to eight wafers are implanted into the surgical cavity (Fig. 3). Water in the interstitial fluid causes the polymer slowly to degrade.[69] The BCNU is thus released in a controlled

manner over several days to weeks and diffuses into the brain parenchyma at a high dose density.[27,31,38] Concentrations as high as 1200 times more than those achieved by intravenous infusion have been observed, with minimal systemic exposure.[40] Gliadel remains the only FDA-approved local chemotherapeutic agent indicated as a surgical adjunct for newly diagnosed malignant glioma and recurrent GBM. (See Gliadel prescribing information [Baltimore, MD: Guilford Pharmaceuticals Inc.; 2003]. Available at http://www.gliadel.com/pdf/PI_03_01_04.pdf. Accessed 8 September 2004.)

Used in this manner, Gliadel has been one of the few treatment modalities to demonstrate a statistical benefit in patients with malignant glioma, both in prolonging survival and in maintaining neurological function and performance status.[13,119,127] Originally approved by the FDA in 1996 for use in recurrent GBM, Gliadel was approved in 2003 for initial treatment of all high-grade malignant glioma histological types at first diagnosis. Currently, a number of ongoing studies are being performed to investigate the safety and efficacy of combining local therapies, such as Gliadel, with other systemic agents, biological response modifiers, immunotherapy, and chemotherapy as part of multimodal, multiagent strategies.[25,66,91,92,130]

Gliadel for Recurrent GBM. Table 1 summarizes key clinical trials in patients with recurrent brain tumors treated with Gliadel that led to its FDA approval. In recurrent malignant glioma, a Phase I/II dose-finding study in which BCNU wafer monotherapy was used in 21 patients resulted in 86% of them remaining alive for more than 1 year from initial diagnosis, and 38% lived more than 1 year from the time of implantation.[12] Subsequently, in a large, double-blind, placebo-controlled, multicenter study conducted at the member institutions of the Polymer Treatment Group, 222 patients with recurrent malignant glioma[13] were randomized to receive either Gliadel or placebo wafers at the time of repeated operation for recurrent or progressive disease. Numerous previous therapies had failed in the patients enrolled in this study, and they had undergone up to five previous craniotomies for resection. All patients had undergone previous radiation therapy with or without chemotherapy. In this heavily pretreated group, salvage therapy with Gliadel resulted in an 8-week net increase in median survival duration over that achieved with placebo for the intent-to-treat population (Fig. 4).[13] Among the 145 patients with GBM, the addition of Gliadel significantly improved the 6-month survival rate, to 56%, compared with 36% for patients with GBM who received the placebo wafer ($p = 0.02$).

Gliadel for Newly Diagnosed High-Grade Malignant Glioma. A series of prospective studies were conducted in which BCNU polymeric chemotherapy was evaluated. Initially, a Phase I trial of 22 patients treated with Gliadel and postoperative radiotherapy indicated a median survival duration of 10.5 weeks and a 36% 1-year survival rate, with acceptable toxicity (Table 1).[11] Following this, Valtonen, et al.,[119] described the results of a Phase III randomized placebo-controlled trial of Gliadel used in conjunction with resection and radiotherapy in newly diagnosed malignant glioma. The intent was to enroll 100 patients, but due to unavailability of the Gliadel for a period of time, the study was closed early to enrollment. The

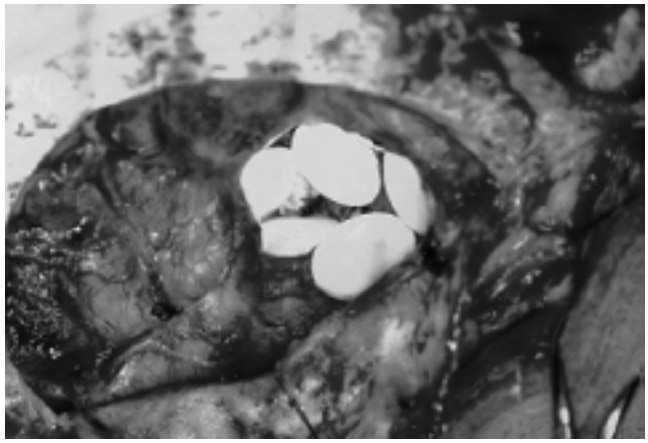

FIG. 3. Intraoperative photograph showing Gliadel wafer placement in the tumor resection cavity. Reprinted with permission from Sampath P, Brem H: Implantable slow-release chemotherapeutic polymers for the treatment of malignant brain tumors. **Cancer Control 5:**130–137, 1998.

patients continued to be followed in blinded fashion for 2 years. There were 16 patients in each group, but only 11 with GBM were in the Gliadel group compared with 16 in the control group. The median survival duration for patients with GBM in the two groups was 13.3 months for the Gliadel group compared with 10 months for control, which despite the limited numbers of patients was statistically significant ($p = 0.0008$). At 3 years, four patients with GBM were still living, three of whom were in the Gliadel treatment group.

More recently, Westphal, et al.,[127] completed a larger randomized placebo-controlled Phase III trial of nearly identical design to the earlier trial of Valtonen, et al. Two hundred forty patients with newly diagnosed malignant glioma were randomized into two groups: in one the treatment consisted of surgery and placement of the Gliadel wafer, followed by postoperative radiotherapy, and in the other the treatment included surgery, placement of a placebo wafer, and postoperative radiotherapy.

In the intent-to-treat analysis, the Gliadel group had a statistically significant survival advantage (13.9 months compared with 11.6 months [$p = 0.03$]; see Table 1 and Fig. 5). Analysis of a variety of neurological performance measures indicated that the quality of life roughly paralleled survival duration. There was an imbalance in the number of patients with GBM between the two groups (101 compared with 106); however, evaluation with a Cox proportional hazards model indicated that the survival advantage was maintained in the GBM subgroup, with a risk reduction of 31% (95% CI 3–51%). In addition, more patients in the control group underwent a second operation, with a significant effect on overall survival. Censoring the groups for this second procedure yielded a significant effect on the analysis and indicated a median survival duration of 14.8 months compared with 11.4 months ($p = 0.02$).

A metaanalysis has also been reported, in which the two randomized studies were combined. Specifically, in the GBM group a survival benefit was noted (13.1 months for the Gliadel-treated groups compared with 10.9 months for placebo; $p = 0.03$), and in standard multivariate analysis

TABLE 1

*Literature review of studies of Gliadel wafer or TMZ in patients with recurrent or newly diagnosed brain tumors**

Authors & Year	Study Type	Tumor	Treatment†	Survival		RR (%)
				Median	Increase	
Brem, et al., 1991	Phase I/II	rec	BCNU wafers	46.0 wks	—	—
Brem, et al., 1995[13]	Phase III; DBPC	rec	Gliadel	31.0 wks	8.0 wks	33
			placebo	23.0 wks		
Brem, et al., 1995[11]	Phase I	initial	Gliadel + RT	42.0 wks	—	—
Valtonen, et al., 1997	Phase II; DBPC	initial	Gliadel + RT	58.1 wks	18.2 wks	73
			RT + placebo	39.9 wks		
Yung, et al., 1999	Phase II; open label	rec	TMZ	13.6 mos	—	—
Yung, et al., 2000	Phase II; open label	rec	TMZ	7.3 mos§	NS	—
			procarbazine	5.7 mos§		
Stupp, et al., 2002	Phase II; open label	initial	TMZ + RT	16.0 mos	—	—
Westphal, et al., 2003	Phase III; DBPC	initial	Gliadel + RT	13.9 mos	2.3 mos	28
			RT + placebo	11.6 mos		
Kleinberg, et al., 2004	retro review	initial	Gliadel + RT	12.8 mos‡	—	—
Stupp, et al., 2005	Phase III; randomized	initial	TMZ + RT	14.6 mos	2.5 mos	38
			RT alone	12.1 mos		

* DBPC = double-blind placebo-controlled; NS = not significant; rec = recurrent; retro = retrospective; RR = risk reduction; RT = radiotherapy; — = not applicable.

† All treatments with Gliadel include resection.

‡ For 39 patients with GBM.

§ Reported in Temodal product information (p = 0.33), and not in the study.

this benefit was associated with a 29% reduction in risk of death (hazard ratio 0.71, 95% CI 0.54–0.95%; p = 0.02). In March 2003, the combination of the results of these studies led to FDA approval of Gliadel in the treatment of patients with newly diagnosed malignant glioma.

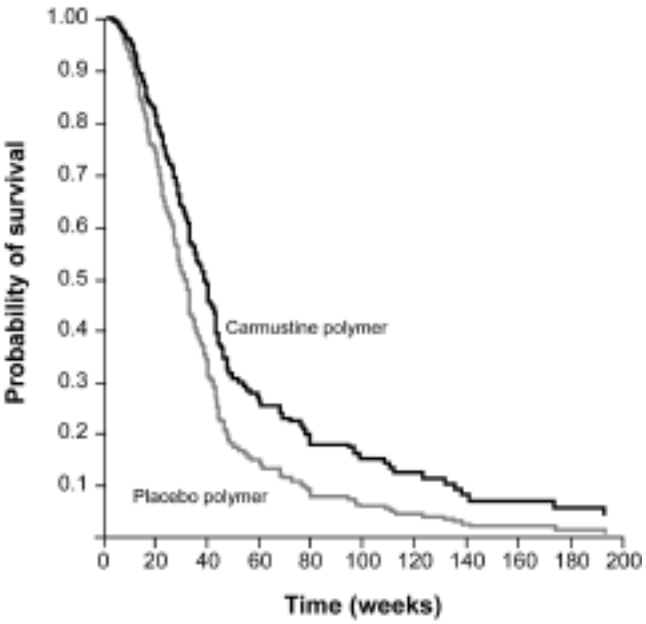

FIG. 4. Graph showing Kaplan–Meier survival curve of patients with recurrent GBM treated with Gliadel wafer and radiation therapy after adjustment for prognostic factors. Reprinted from The Lancet, vol. 345, Brem H, Piantadosi S, Burger PC, et al: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group, 1008–1012, copyright 1995, with permission from Elsevier.

Temozolomide. Historically, because of the marginal benefit of systemic chemotherapy in treating malignant glioma, medical oncologists did not commonly encourage its application except in a clinical trial, unless they were part of a neurooncology team at a major brain tumor center. Recently, however, TMZ has gained well-deserved popularity because of its indisputable efficacy, ease of oral administration, and modest side-effect profile. This agent is being considered as part of multimodal regimens in structured clinical trials to better define its appropriate use for anaplastic astrocytoma, oligodendroglioma, lymphoma, and brain metastasis.

Temozolomide (3,4-dihydro-3-methyl-4-oxoimidazo [5,1-d]-*as*-tetrazine-8-carboxamide), is an orally administered systemic alkylating agent that crosses the BBB. Its bioavailability is essentially 100%, with peak plasma concentrations occurring at 1 hour after dosing. This drug is spontaneously hydrolyzed at physiological pH to 3-methyl-(triazen-1-yl)imidazole-4-carboxamide, which is further hydrolyzed to methylhydrazine, the active alkylating species.[77] The principal cytotoxic mechanism appears to be methylation of DNA. Although TMZ was originally tested and approved for a 5-day schedule every 28 days, extended-dose schedules continue to be studied. An extended dosing schedule is believed to deplete MGMT, an enzyme implicated in tumor resistance to alkylating agents.[3,15,75,106,116] Depletion of MGMT is associated with longer median survival times in patients who are receiving alkylating agents,[32,53,54] although this may be related to a subset of patients who demonstrate MGMT upregulation.

Temozolomide has shown single-agent activity against recurrent gliomas.[23,77,111,122,128] Additionally, in combination with standard fractionation radiation therapy, concurrent therapy followed by adjuvant TMZ showed effectiveness against newly diagnosed glioblastoma.[110,112]

Activity of TMZ for Recurrent Anaplastic Astrocytoma at First Relapse. A Phase II trial of TMZ was conducted at

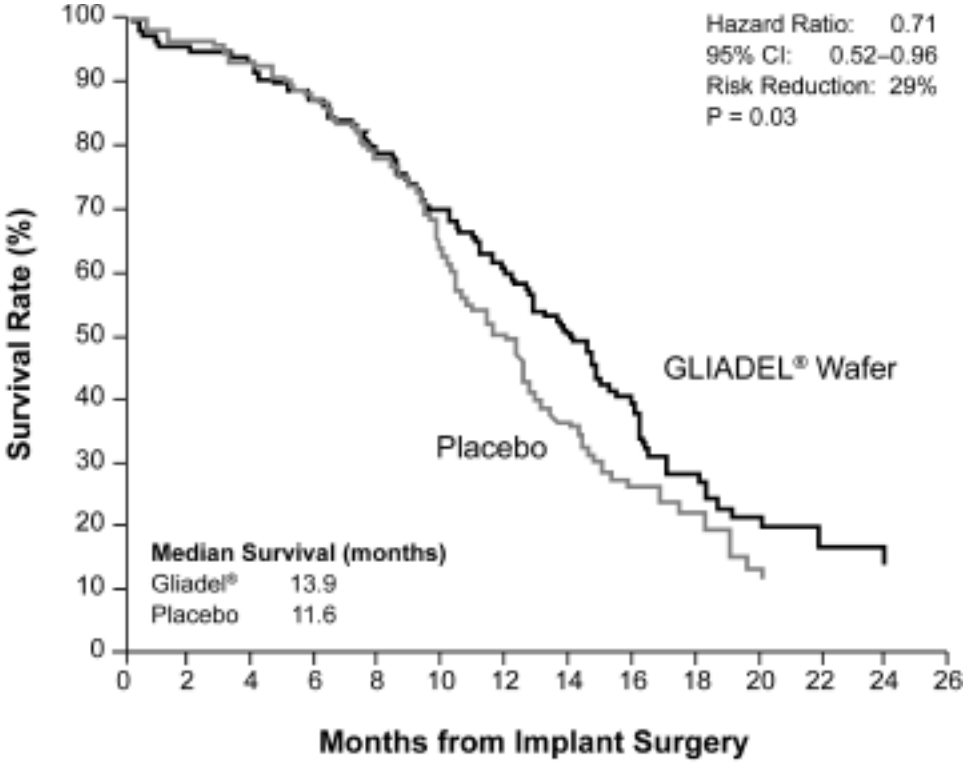

FIG. 5. Graph showing Kaplan–Meier survival curve of patients with newly diagnosed malignant glioma treated with radiation therapy and Gliadel wafer or placebo. (Numbers differ from those in the text because this was the intent-to-treat group, for which data were submitted to the FDA, whereas the text details the metaanalysis performed by Meldorf, Riddle V, Agarwal S et al: Long-term efficacy of the Gliadel wafer in patients with glioblastoma multiforme. Abstract presented at the Annual Meeting of the American Association of Neurological Surgeons, San Diego, CA, 2003. (http://www.aans.org/library/article.aspx?ArticleID=17769.) [Accessed January 11, 2006.] Reprinted with permission from Westphal M, Hilt DC, Bortey E, et al: A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. **Neuro-oncol 5:**79–88, 2003.

first relapse in 162 patients with malignant glioma, after treatment with radiotherapy and systemic nitrosourea (with or without procarbazine).[129] A histological review confirmed a diagnosis of anaplastic astrocytoma or anaplastic oligoastrocytoma in 111 of these patients. The median overall survival duration was 13.6 months and the median progression-free survival was 5.4 months; the 12-month survival rate was 56%. The investigators concluded that TMZ demonstrated good single-agent activity (Table 1).

In another Phase II trial, TMZ was compared with a standard procarbazine regimen at first relapse in 225 patients with confirmed recurrent GBM.[128] The median survival duration was 7.3 months for patients treated with TMZ compared with 5.7 months for those treated with procarbazine (p = not significant, Table 1). (See Temodal: Summary of product characteristics, 2005. Available at http://www.emea.eu.int/humandocs/PDFs/EPAR/Temodal/H-229-PI-en.pdf. Accessed 12 January 2006.)

The 6-month survival rate and median progression-free survival were different: 60% compared with 44% (p = 0.019) and 12.4 weeks compared with 8.32 weeks (p = 0.0063) in the TMZ and procarbazine groups, respectively. It was also noted that health-related quality of life measures were maintained in patients who were free of tumor progression at 6 months. Based on these and other studies, TMZ was approved in the US in 1999 for patients with recurrent anaplastic astrocytoma who have experienced disease progression after radiotherapy and initial treatment with a drug regimen containing a nitrosourea and procarbazine. (See Temodar product information, available at http://www.spfiles.com/pitemodar.pdf. Accessed 11 May 2005).

Use of TMZ in Newly Diagnosed GBM. The agent TMZ has also shown efficacy in newly diagnosed malignant glioma. In an open-label, Phase II study, 64 patients with newly diagnosed GBM were treated with concurrent TMZ and radiotherapy, followed by adjuvant TMZ administered for 5 days every 28 days for six cycles.[110] The median survival period for these patients was 16 months, with 1- and 2-year survival rates of 58 and 31%, respectively (Table 1). Based on the favorable findings in this preliminary Phase II study, the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group initiated a randomized, multicenter, Phase III trial to evaluate the benefit of adding TMZ to radiotherapy compared with radiotherapy alone for newly diagnosed GBM.[112] In this study, 573 patients were randomized to two treatment groups: 1) fractionated involved-field radiotherapy (2 Gy once daily, 5 days per

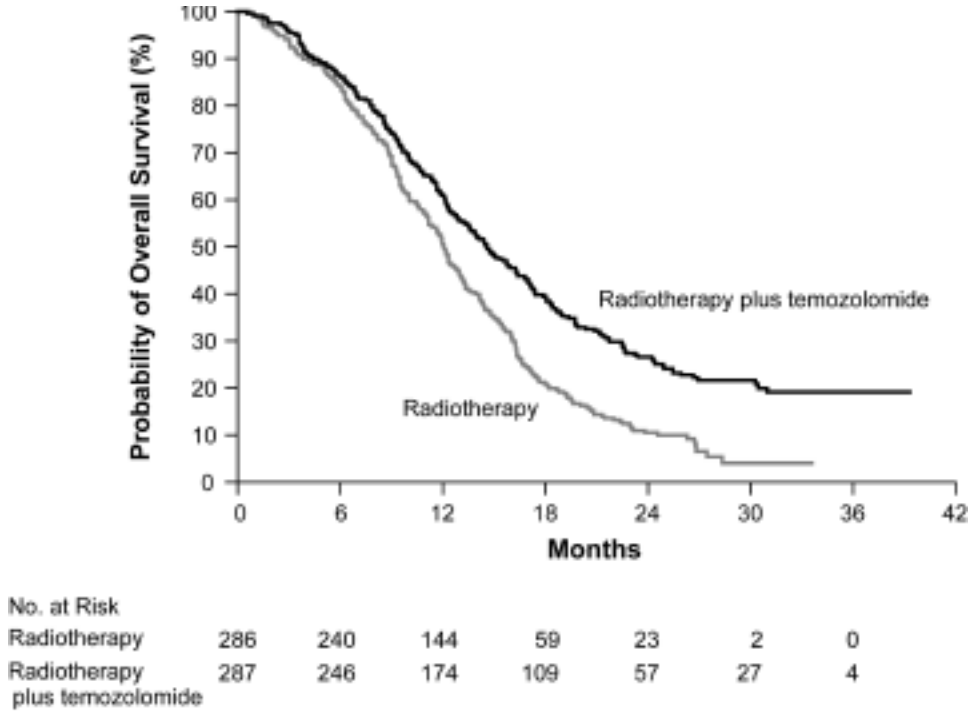

FIG. 6. Graph showing Kaplan–Meier estimates of overall survival in patients with newly diagnosed malignant glioma treated with radiation plus TMZ or placebo. Reprinted with permission from Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. **N Engl J Med 352:**987–996, 2005.

week for 6 weeks; 60 Gy total), or 2) the same radiotherapy schedule plus concurrent daily TMZ (75 mg/m^2/day) followed by up to six cycles of monthly adjuvant TMZ (150–200 mg/m^2/day for 5 days). The median survival duration was 14.6 months (95% CI 13.2–16.8 months) in patients who received radiotherapy plus TMZ, compared with 12.1 months (95% CI 11.2–13 months) in those who received radiotherapy alone, resulting in an increase in median survival duration of 2.5 months (Table 1, Fig. 6). The 2-year survival rate was 26.5% (95% CI 21.2–31.7%) for TMZ compared with 10.4% for radiotherapy alone (95% CI 6.8–14.1%). Grade 3 or 4 hematological toxicity occurred in 16% of patients in the TMZ group during concurrent or adjuvant treatment.[112]

Recently, a retrospective analysis of the European Organisation for Research and Treatment of Cancer–National Cancer Institute of Canada trial data was performed to assess the impact of resection on survival.[121] Prior to treatment with radiotherapy with or without TMZ, 39% of patients underwent complete resection of tumor tissue, 44% attained a partial resection, and 16% underwent biopsy sampling only. The survival benefit with TMZ was evident in all cohorts but was more pronounced in patients who underwent complete resection. The median survival duration in patients in whom a complete resection was achieved was 18.3 months (95% CI 15.7–22.5 months) in the radiotherapy plus TMZ group and 14.2 months (95% CI 12.7–16.2 months) in the group undergoing radiotherapy alone. The corresponding results in the groups treated with radiotherapy plus TMZ and radiotherapy alone were 13.5 months (95% CI 11.9–16.3 months) and 11.7 months (95% CI 9.7–13.1 months), respectively, for patients in whom partial resection was performed and 9.4 months (95% CI 7.5–13.2 months) and 7.9 months (95% CI 5.4–10.6 months), respectively, for patients who underwent biopsy sampling only.

The results reported in the Phase III trial are favorable when compared with historical data on systemic chemotherapy for this disease.[112] It should be noted that slides were not available for confirmation of histological diagnosis in 15% of the cases and that 7% of patients had histologically confirmed non-GBM or unconfirmed histological features, pointing out the importance of tissue availability for pathological review of CNS disease. The addition of TMZ resulted in a clinically meaningful and statistically significant survival benefit for patients with newly diagnosed malignant glioma, and led to FDA approval in March 2005 for use as initial therapy in patients with GBM. Toxicity is mainly hematological, with only a minority of patients requiring any kind of replacement transfusion or bone marrow support. Gastrointestinal side effects are also mild to moderate.[77,113,116] To prevent the possibility of developing the lymphocytopenia and opportunistic infection associated with TMZ in earlier trials,[60,110] the patients randomized to receive this agent were prophylactically given inhaled pentamidine or orally administered trimethoprim–sulfamethoxazole against *Pneumocystis carinii pneumonia*.[112]

Advancements in Treatment of Brain Tumors: Multimodal Therapies

The consensus of the data supports the contention that no chemotherapy agent alone can effectively treat high-grade malignant gliomas, nor can surgery or radiation therapy alone. Neither Gliadel nor TMZ represent the "home run" we hope for in the treatment of this deadly disease. Gliadel resulted in a median increase in survival of 2 and 2.3 months for recurrent and newly diagnosed GBM, respectively. When given concurrently with radiation, TMZ resulted in an increased median survival time of only 2.5 months compared with radiation therapy alone. In fact, the mean increase in survival time is only slightly better than that achieved in any of the 12 studies summarized in Stewart's metaanalysis of prior investigations.[109] The future use of these agents will likely be as integrated treatment with target-specific molecules as well as with other antineoplastic drugs. Use of TMZ in combination with other antineoplastic agents, including cisplatin,[4,97] fotemustine,[73] irinotecan,[46] thalidomide,[5,21] retinoic acid,[16] tamoxifen,[105] and O^6-benzylguanine[85] is being tested. Likewise, in several Phase I/II studies, Gliadel has been combined with PCV,[65] TMZ,[48,66] irinotecan,[91] or carboplatin.[72]

The combination of TMZ and Gliadel is especially interesting because of the ability of TMZ to deplete the DNA repair enzyme responsible for BCNU resistance.[32] Preclinical studies support the suggestion that MGMT is part of the resistance mechanism[87] and that synergy or additive effects of the combination of BCNU and TMZ may be due in part to the depletion of this repair enzyme.[76,83] A combination study of TMZ and intravenous BCNU for treatment of advanced solid neoplasms in 63 patients resulted in significant hematological toxicity and limited the TMZ dose to 110 mg/m^2/day.[51] Similar results have been reported in patients with glioma.[21,86] Raizer, et al., found that the maximum tolerated dose for a 28-day cycle of TMZ was 80 mg/m^2/day when used in combination with intravenous BCNU, and they concluded that long-term combined systemic therapies may not be feasible because of exaggerated myelosuppression.

On the other hand, a Phase I dose-ranging study demonstrated the safety of the combination of Gliadel and TMZ in 10 patients with recurrent supratentorial high-grade glioma. Up to eight wafers were positioned in the surgical cavity after resection.[48] The TMZ (100, 150, or 200 mg/m^2/day) was given orally for 5 days beginning 2 weeks postsurgery. Treatment was well tolerated with no new or unexpected toxicities, even at the highest standard dose of 200 mg/m^2/day, demonstrating that TMZ can be administered safely after placement of Gliadel wafers. Two patients were alive without disease progression after 12 months of the combined treatment.

Preliminary data from a Phase II multicenter trial were obtained in 16 patients with surgically accessible, high-grade, newly diagnosed malignant glioma.[66] Following resection and Gliadel wafer placement, patients underwent radiation therapy plus concurrent TMZ (75 mg/m^2, 7 days per week) followed by a monthly standard schedule of adjuvant TMZ (200 mg/m^2 daily for 5 days every 28 days, $\leq$ 18 cycles). After a median follow-up period of 7 months, the median and progression-free survival times had not been reached, and the 1-year survival rate was 63%.

TABLE 2

*Literature review of Phase I/II clinical trials in patients with malignant glioma in whom Gliadel or TMZ was used in novel combination therapies**

Treatment	Authors & Year	No. of Patients & Histological Finding
Gliadel		
carboplatin	Limentani, et al., 2005	16 w/ initial MG
TMZ	Gururangan, et al., 2001	10 w/ rec MG
	LaRocca, et al., 2005[69]	16 w/ initial MG
PCV	LaRocca, et al., 2005[68]	9 w/ initial MG
irinotecan	Sampath, et al., 2005[98]	10 w/ rec GBM
O^6-benzylguanine	Rosenblum, et al., 2002	31 w/ rec MG
iodine-125 seeds	Darakchiev, et al., 2004	34 w/ rec GBM
	Foltz, et al., 2005	10 w/ rec GBM
	Zamorano, et al., 2005	6 w/ initial or rec GBM
	Tozer, et al., 2003	16 w/ rec MG
GliaSite RTS	Sampath, et al., 2005[99]	24 w/ rec GBM
radiosurgery	Smith, et al., 2004	19 w/ initial GBM
TMZ		
cisplatin	Balaña, et al., 2004	40 w/ initial GBM
	Silvani, et al., 2004	33 w/ rec MG
fotemustine	Marzolini, et al., 1998	2 w/ rec MG
carmustine	Raizer, et al., 2004	24 w/ initial MG
thalidomide	Chang, et al., 2004	67 w/ initial GBM
retinoic acid	Butowski, et al., 2005	61 w/ initial GBM
tamoxifen	Spence, et al., 2004	16 w/ rec MG
O^6-benzylguanine	Quinn, et al., 2005	38 w/ rec MG

* MG = malignant glioma; RTS = radiation therapy system.

Gliadel and TMZ are also being investigated as part of other combination chemotherapy regimens or multimodal strategies (Table 2). Gliadel is being evaluated in combination with irinotecan,[25,26,113] carboplatin,[72] and other agents including O^6-benzylguanine (an inhibitor of MGMT).[88] In addition, studies have been conducted to investigate the use of concurrent Gliadel and brachytherapy with the GliaSite system[92,93] or ^{125}I seeds,[28,117,130] and the combination of Gliadel and radiosurgery.[99] Other studies with Gliadel include the evaluation of higher BCNU doses in the polymers, which may penetrate surrounding brain tissue for greater distances.[79] Gliadel is also being tested in the surgical management of brain metastases, and preliminary analysis has shown exceptional local tumor control rates.[14,33,43]

Conclusions

An improved understanding of the pathogenesis of malignant glioma and the rationale for development of therapeutic agents will depend on advances in molecular genetics and the development of therapies targeting critical steps in signal pathways that have yet to be fully elaborated. In the meantime, multidisciplinary, multimodal anticancer treatments will continue to include surgery, radiotherapy, and combination chemotherapy with the addition of immunotherapy and biological response modifiers. Progress continues with novel approaches, including con-

vection-enhanced delivery,[49,81] gene therapy, dendritic vaccination, biological response modifiers,[96] and novel forms of delivery.[70]

References

1. American Cancer Society: **Cancer Facts & Figures 2004.** Atlanta, Georgia: American Cancer Society Inc, 2004 (http://www.cancer.org/downloads/STT/CAFF_final PWSecured.pdf) [Accessed 16 March 2006]
2. Avgeropoulos NG, Batchelor TT: New treatment strategies for malignant gliomas. **Oncologist 4:**209–224, 1999
3. Baer JC, Freeman AA, Newlands ES, et al: Depletion of O^6-alkylguanine-DNA alkyltransferase correlates with potentiation of temozolomide and CCNU toxicity in human tumor cells. **Br J Cancer 67:**1299–1302, 1993
4. Balaña C, López-pousa A, Berrocal A, Yaya-Tur R, et al: Phase II study of temozolomide and cisplatin as primary treatment prior to radiotherapy in newly diagnosed glioblastoma multiforme patients with measurable disease. A study of the Spanish Medical Neuro-Oncology Group (GENOM). **J Neurooncol 70:** 359–369, 2004
5. Baumann F, Bjeljac M, Kollias SS, et al: Combined thalidomide and temozolomide treatment in patients with glioblastoma multiforme. **J Neurooncol 67:**191–200, 2004
6. Bernstein M, Laperriere N, Leung P, et al: Interstitial brachytherapy for malignant brain tumors: preliminary results. **Neurosurgery 26:**371–380, 1990
7. Bocangel DB, Finkelstein S, Schold SC, et al: Multifaceted resistance of gliomas to temozolomide. **Clin Cancer Res 8:** 2725–2734, 2002
8. Bonadonna G: Karnofsky memorial lecture. Conceptual and practical advances in the management of breast cancer. **J Clin Oncol 7:**1380–1397, 1989
9. Bonadonna G, Brusamolino E, Valagussa P, et al: Combination chemotherapy as an adjuvant treatment in operable breast cancer. **N Engl J Med 294:**405–410, 1976
10. Brandes AA, Tosoni A, Amistà P, et al: How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. **Neurology 63:**1281–1284, 2004
11. Brem H, Ewend MG, Piantadosi S, et al: The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: phase I trial. **J Neurooncol 26:**111–123, 1995
12. Brem H, Mahaley MS Jr, Vick NA, et al: Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. **J Neurosurg 74:**441–446, 1991
13. Brem H, Piantadosi S, Burger PC, et al: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. **Lancet 345:**1008–1012, 1995
14. Brem S, Staller A, Wotoczek-Obadia Mea: Interstitial chemotherapy for local control of CNS metastases. **Neuro-oncol 6:** 370–371 2004 (Abstract)
15. Brock CS, Newlands ES, Wedge SR, et al: Phase I trial of temozolomide using an extended continuous oral schedule. **Cancer Res 58:**4363–4367, 1998
16. Butowski N, Prados MD, Lamborn KR, et al: A phase II study of concurrent temozolomide and cis-retinoic acid with radiation for adult patients with newly diagnosed supratentorial glioblastoma. **Int J Radiat Oncol Biol Phys 61:**1454–1459, 2005
17. Cairncross JG, Ueki K, Zlatescu MC, et al: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. **J Natl Cancer Inst 90:** 1473–1479, 1998
18. CBTRUS: Statistical Report: Primary Brain Tumors in the United States, 1997–2001. Hinsdale, IL: Central Brain Tumor Registry of the United States, 2004 (http: //cbtrus.org/reports//2004–2005/2005report.pdf) [Accessed 10 April 2006]
19. Chamberlain MC, Kormanik PA: Practical guidelines for the treatment of malignant gliomas. **West J Med 168:**114–120, 1998
20. Chan TA, Weingart JD, Parisi M, et al: Treatment of recurrent glioblastoma multiforme with GliaSite brachytherapy. **Int J Radiat Oncol Biol Phys 62:**1133–1139, 2005
21. Chang SM, Lamborn KR, Malec M, et al: Phase II study of temozolomide and thalidomide with radiation therapy for newly diagnosed glioblastoma multiforme. **Int J Radiat Oncol Biol Phys 60:**353–357, 2004
22. Chang SM, Parney IF, Huang W, et al: Patterns of care for adults with newly diagnosed malignant glioma. **JAMA 293:** 557–564, 2005
23. Chinot OL, Honore S, Dufour H, et al: Safety and efficacy of temozolomide in patients with recurrent anaplastic oligodendrogliomas after standard radiotherapy and chemotherapy. **J Clin Oncol 19:**2449–2455, 2001
24. Cho KH, Hall WA, Gerbi BJ, et al: Single dose versus fractionated stereotactic radiotherapy for recurrent high-grade gliomas. **Int J Radiat Oncol Biol Phys 45:**1133–1141, 1999
25. Colvin O, Cokgor I, Edwards S, et al: Phase I trials of Gliadel plus CPT-11 or Temodar. **Proc Am Soc Clin Oncol 19:**172, 2000 (Abstract)
26. Colvin L, Cokgor I, Kerby T, et al: Phase I trials of Gliadel plus CPT-11 or Temodal. Presented at the Annual Meeting of the American Society of Clinical Oncology, 2000 (Abstract) (http://www.asco.org/portal/site/ASCO/menuitem.34d60f5624ba07fd506fe310ee37a01d/?vgnextoid=76f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=abst_detail_view&confID=2&abstractID=202435) [Accessed 16 March 2006]
27. Dang W, Daviau T, Brem H: Morphological characterization of polyanhydride biodegradable implant Gliadel during *in vitro* and *in vivo* erosion using scanning electron microscopy. **Pharm Res 13:**683–691, 1996
28. Darakchiev BJ, Albright RE, Breneman JC, et al: Prolonged survival in patients with recurrent glioblastoma multiforme treated by resection with implantation of permanent I-125 seeds and BCNU-impregnated wafers. **AANS,** October 21, 2004. Article ID: 22629 (Abstract)
29. Dropcho EJ, Rosenfeld SS, Morawetz RB, et al: Preradiation intracarotid cisplatin treatment of newly diagnosed anaplastic gliomas. The CNS Cancer Consortium. **J Clin Oncol 10:** 452–458, 1992
30. Early Breast Cancer Trialists' Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28, 896 women. **N Engl J Med 319:**1681–1692, 1988
31. Engelhard HH: The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. **Surg Neurol 53:**458–464, 2000
32. Esteller M, Garcia-Foncillas J, Andion E, et al: Inactivation of the DNA-repair gene *MGMT* and the clinical response of gliomas to alkylating agents. **N Engl J Med 343:**1350–1354, 2000
33. Ewend MG, Brem S, Gilbert M, et al: Treating single brain metastasis with resection, placement of BCNU-polymer wafers, and radiation therapy. **AANS:**April 21, 2001. Article ID: 13719 (Abstract)
34. Fine HA, Dear KB, Loeffler JS, et al: Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. **Cancer 71:**2585–2597, 1993
35. Fisher B, Fisher ER, Redmond C: Ten-year results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial evaluating the use of L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. **J Clin Oncol 4:**929–941, 1986
36. Fisher B, Ravdin RG, Ausman RK, et al: Surgical adjuvant che-

motherapy in cancer of the breast: results of a decade of cooperative investigation. **Ann Surg 168:**337–356, 1968 QUERY
37. Fisher B, Redmond C, Brown A, et al: Adjuvant chemotherapy with and without tamoxifen in the treatment of primary breast cancer: 5-year results from the National Surgical Adjuvant Breast and Bowel Project Trial. **J Clin Oncol 4:**459–471, 1986
38. Fleming AB, Saltzman WM: Pharmacokinetics of the carmustine implant. **Clin Pharmacokinet 41:**403–419, 2002
39. Foltz GD, Spence A, Stelzer K, et al: Combined treatment of recurrent glioblastoma with Gliadel Wafers and iodine-125 seeds. Presented at the **Annual Meeting of the Congress of Neurological Surgeons** San Diego, CA, 2001. (http://abstracts.neurosurgeon.org/view.php?id=6949.) [Accessed 6 October 2005]
40. Fung LK, Ewend MG, Sills A, et al: Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. **Cancer Res 58:**672–684, 1998
41. Gaspar LE, Zamorano LJ, Shamsa F, et al: Permanent ^{125}iodine implants for recurrent malignant gliomas. **Int J Radiat Oncol Biol Phys 43:**977–982, 1999
42. Giordano SH, Buzdar AU, Smith TL, et al: Is breast cancer survival improving? Trends in survival for patients with recurrent breast cancer diagnosed from 1974 through 2000. **Cancer 100:** 44–52, 2004
43. Golden GA, Meldorf M, PROLONG Study Group: Patients with metastatic brain cancer, undergoing resection and Gliadel implantation experienced low local recurrence rates in the PROLONG Registry. **Neuro-oncol 6:**375–376, 2004 (Abstract)
44. Greenspan EM: Aggressive chemotherapy for the treatment of breast cancer. **J Clin Oncol 3:**1043, 1985 (Letter)
45. Grossman SA, O'Neill A, Grunnet M, et al: Phase III study comparing three cycles of infusional carmustine and cisplatin followed by radiation therapy with radiation therapy and concurrent carmustine in patients with newly diagnosed supratentorial glioblastoma multiforme: Eastern Cooperative Oncology Group Trial 2394. **J Clin Oncol 21:**1485–1491, 2003
46. Gruber ML, Buster WP: Temozolomide in combination with irinotecan for treatment of recurrent malignant glioma. **Am J Clin Oncol 27:**33–38, 2004
47. Gruber ML, Glass J, Choudhri H, et al: Carboplatin chemotherapy before irradiation in newly diagnosed glioblastoma multiforme. **Am J Clin Oncol 21:**338–340, 1998
48. Gururangan S, Cokgor L, Rich JN, et al: Phase I study of Gliadel wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas. **Neuro-oncol 3:**246–250, 2001
49. Hall WA, Rustamzadeh E, Asher AL: Convection-enhanced delivery in clinical trials. **Neurosurg Focus 14(2):**E2, 2003
50. Halligan JB, Stelzer KJ, Rostomily RC, et al: Operation and permanent low activity 125I brachytherapy for recurrent high-grade astrocytomas. **Int J Radiat Oncol Biol Phys 35:** 541–547, 1996
51. Hammond LA, Eckardt JR, Kuhn JG, et al: A randomized phase I and pharmacological trial of sequences of 1, 3-bis(2-chloroethyl)-1-nitrosourea and temozolomide in patients with advanced solid neoplasms. **Clin Cancer Res 10:**1645–1656, 2004
52. Harris JR, Recht A, Amalric R, et al: Time course and prognosis of local recurrence following primary radiation therapy for early breast cancer. **J Clin Oncol 2:**37–41, 1984
53. Hegi ME, Diserens AC, Godard S, et al: Clinical trial substantiates the predictive value of *O-6-methylguanine-DNA methyltransferase* promoter methylation in glioblastoma patients treated with temozolomide. **Clin Cancer Res 10:**1871–1874, 2004
54. Hegi ME, Diserens AC, Gorlia T, et al: *MGMT* gene silencing and benefit from temozolomide in glioblastoma. **N Engl J Med 352:**997–1003, 2005
55. Henderson IC: Adjuvant chemotherapy of breast cancer: a promising experiment or standard practice? **J Clin Oncol 3:** 140–143, 1985
56. Huncharek M, Muscat J: Treatment of recurrent high grade astrocytoma; results of a systematic review of 1, 415 patients. **Anticancer Res 18:**1303–1311, 1998
57. Ino Y, Betensky RA, Zlatescu MC, et al: Molecular subtypes of anaplastic oligodendroglioma. Implications for patient management at diagnosis. **Clin Cancer Res 7:**839–845, 2001
58. Jeremic B, Milicic B, Grujicic D, et al: Multivariate analysis of clinical prognostic factors in patients with glioblastoma multiforme treated with a combined modality approach. **J Cancer Res Clin Oncol 129:**477–484, 2003
59. Kelly KA, Kirkwood JM, Kapp DS: Glioblastoma multiforme: pathology, natural history and treatment. **Cancer Treat Rev 11:**1–26, 1984
60. Khan RB, Raizer JJ, Malkin MG, et al: A phase II study of extended low-dose temozolomide in recurrent malignant gliomas. **Neuro-oncol 4:**39–43, 2002
61. Kleinberg LR, Weingart J, Burger P, et al: Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. **Cancer Invest 22:**1–9, 2004
62. Kortmann RD, Jeremic B, Weller M, et al: Radiochemotherapy of malignant glioma in adults. Clinical experiences. **Strahlenther Onkol 179:**219–232, 2003
63. Laperriere N, Zuraw L, Cairncross G, et al: Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. **Radiother Oncol 64:**259–273, 2002
64. Laperriere NJ, Leung PMK, McKenzie S, et al: Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. **Int J Radiat Oncol Biol Phys 41:** 1005–1011, 1998
65. LaRocca R, Glisson S, Hargis J, et al: High-grade glioma treated with surgery; carmustine wafer; postoperative radiation; and procarbazine, lomustine, and vincristine chemotherapy. **Neurosurgery Quarterly 15:**167–171, 2005
66. LaRocca RV, Vitaz TW, Morassutti DJ, et al: A phase II study of radiation with concomitant and then sequential temozolomide in patients with newly diagnosed supratentorial high grade malignant glioma who have undergone surgery with carmustine (BCNU) wafer insertion. **J Clin Oncol 23 (June 1 Suppl):**1547, 2005
67. Larson DA, Suplica JM, Chang SM, et al: Permanent iodine 125 brachytherapy in patients with progressive or recurrent glioblastoma multiforme. **Neuro-oncol 6:**119–126, 2004
68. Laws ER, Parney IF, Huang W, et al: Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Glioma Outcomes Project. **J Neurosurg 99:**467–473, 2003
69. Leong KW, Brott BC, Langer R: Bioerodible polyanhydrides as drug-carrier matrices. I: Characterization, degradation, and release characteristics. **J Biomed Mater Res 19:** 941–955, 1985
70. Lesniak MS, Brem H: Targeted therapy for brain tumors. **Nat Rev Drug Discov 3:**499–508, 2004
71. Levin VA: Relationship of octanol/water partition coefficient and molecular weight to rat brain capillary permeability. **J Med Chem 23:**682–684, 1980
72. Limentani SA, Asher A, Heafner M, et al: A phase I trial of surgery, Gliadel wafer implantation, and immediate postoperative carboplatin in combination with radiation therapy for primary anaplastic astrocytoma or glioblastoma multiforme. **J Neurooncol 72:**241–244, 2005
73. Marzolini C, Decosterd LA, Shen F, et al: Pharmacokinetics of temozolomide in association with fotemustine in malignant melanoma and malignant glioma patients: comparison of oral, intravenous, and hepatic intra-arterial administration. **Cancer Chemother Pharmacol 42:**433–440, 1998
74. Medical Research Council Brain Tumour Working Party: Randomized trial of procarbazine, lomustine, and vincristine in the

adjuvant treatment of high-grade astrocytoma: a Medical Research Council Trial. **J Clin Oncol 19:**509–518, 2001
75. Middleton MR, Lee SM, Arance A, et al: *O*^{6}-methylguanine formation, repair protein depletion and clinical outcome with a 4 hr schedule of temozolomide in the treatment of advanced melanoma: results of a phase II study. **Int J Cancer 88:**469–473, 2000
76. Mitchell RB, Dolan ME: Effect of temozolomide and dacarbazine on O6-alkylguanine-DNA alkyltransferase activity and sensitivity of human tumor cells and xenografts to 1, 3-bis (2-chloroethyl)-1-nitrosourea. **Cancer Chemother Pharmacol 32:** 59–63, 1993
77. Newlands ES, Stevens MF, Wedge SR, et al: Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials. **Cancer Treat Rev 23:**35–61, 1997
78. Nieder C, Andratschke N, Wiedenmann N, et al: Radiotherapy for high-grade gliomas. Does altered fractionation improve the outcome? **Strahlenther Onkol 180:**401–407, 2004
79. Olivi A, Grossman SA, Tatter S, et al: Dose escalation of carmustine in surgically implanted polymers in patients with recurrent malignant glioma: a New Approaches to Brain Tumor Therapy CNS Consortium trial. **J Clin Oncol 21:**1845–1849, 2003
80. Paoletti P: Therapeutic strategy for central nervous system tumors: present status, criticism and potential. **J Neurosurg Sci 28:**51–60, 1984
81. Parney IF, Kunwar S, McDermott M, et al: Neuroradiographic changes following convection-enhanced delivery of the recombinant cytotoxin interleukin 13-pE38QQR for recurrent malignant glioma. **J Neurosurg 102:**267–275, 2005
82. Patel S, Breneman JC, Warnick RE, et al: Permanent iodine-125 interstitial implants for the treatment of recurrent glioblastoma multiforme. **Neurosurgery 46:**1123–1130, 2000
83. Plowman J, Waud WR, Koutsoukos AD, et al: Preclinical antitumor activity of temozolomide in mice: efficacy against human brain tumor xenografts and synergism with 1, 3-bis(2-chloroethyl)-1-nitrosourea. **Cancer Res 54:**3793–3799, 1994
84. Prados M: Temozolomide in combination with other cytotoxic agents. **Semin Oncol 28 (4 Suppl 13):**24–33, 2001
85. Quinn JA, Desjardins A, Weingart J, et al: Phase I trial of temozolomide plus *O6*-benzylguanine for patients with recurrent or progressive malignant glioma. **J Clin Oncol 23:** 7178–7187, 2005
86. Raizer JJ, Malkin MG, Kleber M, et al: Phase 1 study of 28-day, low-dose temozolomide and BCNU in the treatment of malignant gliomas after radiation therapy. **Neuro-oncol 6:** 247–252, 2004
87. Rhines LD, Sampath P, Dolan ME, et al: *O*^{6}-benzylguanine potentiates the antitumor effect of locally delivered carmustine against an intracranial rat glioma. **Cancer Res 60:**6307–6310, 2000
88. Rosenblum M, Weingart J, Dolan E, et al: Phase I study of Gliadel combined with a continuous intravenous infusion of O6-benzylguanine in patients with recurrent malignant glioma. **2002 ASCO Annual Meeting:** Abstract No. 314 (http: //www.asco.org/ac/1,1003,_12–002636–00_18–0016–00_19–00314,00. asp) [Accessed 2 May 2005]
89. Rosenblum ML, Wheeler KT, Wilson CB, et al: *In vitro* evaluation of *in vivo* brain tumor chemotherapy with 1, 3-bis(2-chloroethyl)-1-nitrosourea. **Cancer Res 35:**1387–1391, 1975
90. Salcman M, Scholtz H, Kaplan RS, et al: Long-term survival in patients with malignant astrocytoma. **Neurosurgery 34:** 213–220, 1994
91. Sampath P, Sungarian A, Alderson L, et al: BCNU-impregnated wafers (Gliadel) plus irinotecan (Camptosar) in combination treatment for patients with recurrent glioblastoma multiforme. Presented at the annual meeting of the CNS, Boston, October 8–13, 2005. (Abstract) (http://abstracts.neurosurgeon.org/view.php?id=19824.) [Accessed 11 January 2006]
92. Sampath P, Weaver CEJ, Alderson L, et al: Consecutive use of brachytherapy (Gliasite) and intratumoral chemotherapy (Gliadel) for recurrent glioblastoma. A phase I / II study with independent clinical review. Presented at the annual meeting of the CNS, Boston, October 8–13, 2005. (Abstract) (http: //abstracts.neurosurgeon.org/view.php?id=19741.) [Accessed 11 January 2006]
93. Sanan A, Stea BD: Initial experience with brachytherapy of recurrent malignant gliomas using the Proxima Therapeutics GliaSite RTS System. **AANS** April 26, 2003 Article ID: 17640, (Abstract)
94. Scott JN, Rewcastle NB, Brasher PM, et al: Which glioblastoma multiforme patient will become a long-term survivor? A population-based study. **Ann Neurol 46:**183–188, 1999
95. Selker RG, Shapiro WR, Burger P, et al: The Brain Tumor Cooperative Group NIH Trial 87–01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. **Neurosurgery 51:**343–355, 2002
96. Sikorski CW, Lesniak MS: Immunotherapy for malignant glioma: current approaches and future directions. **Neurol Res 27:** 703–716, 2005
97. Silvani A, Eoli M, Salmaggi A, et al: Phase II trial of cisplatin plus temozolomide, in recurrent and progressive malignant glioma patients. **J Neurooncol 66:**203–208, 2004
98. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. **N Engl J Med 344:** 783–792, 2001
99. Sledge GW Jr, Loehrer PJ Sr, Roth BJ, et al: Cisplatin as first-line therapy for metastatic breast cancer. **J Clin Oncol 6:** 1811–1814, 1988
100. Smith K, Brachman D, Ashby L, et al: Prospective phase I-II trial of up-front Gamma Knife boost following Gliadel implant in newly diagnosed glioblastoma multiforme. Presented at the 39th annual meeting of the Rocky Mountain Neurological Society, 2004. (Abstract) (http: //www.rmns.org/library/past_meetings/2004/2004_abstracts/24.asp.) [Accessed 11 January 2006]
101. Sneed PK, Gutin PH, Larson DA, et al: Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. **Int J Radiat Oncol Biol Phys 29:**719–727, 1994
102. Sneed PK, Lamborn KR, Larson DA, et al: Demonstration of brachytherapy boost dose-response relationships in glioblastoma multiforme. **Int J Radiat Oncol Biol Phys 35:** 37–44, 1996
103. Sneed PK, Stauffer PR, McDermott MW, et al: Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost ± hyperthermia for glioblastoma multiforme. **Int J Radiat Oncol Biol Phys 40:**287–295, 1998
104. Souhami L, Seiferheld W, Brachman D, et al: Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93–05 protocol. **Int J Radiat Oncol Biol Phys 60:**853–860, 2004
105. Spence AM, Peterson RA, Scharnhorst JD, et al: Phase II study of concurrent continuous temozolomide (TMZ) and tamoxifen (TMX) for recurrent malignant astrocytic gliomas. **J Neurooncol 70:**91–95, 2004
106. Spiro TP, Liu L, Majka S, et al: Temozolomide: the effect of once-and twice-a-day dosing on tumor tissue levels of the DNA repair protein *O*^{6}-alkylguanine-DNA-alkyltransferase. **Clin Cancer Res 7:**2309–2317, 2001
107. Stea B, Rossman K, Kittelson J, et al: Interstitial irradiation versus interstitial thermoradiotherapy for supratentorial malignant

gliomas: a comparative survival analysis. **Int J Radiat Oncol Biol Phys 30:**591–600, 1994
108. Stenning SP, Freedman LS, Bleehen NM: An overview of published results from randomized studies of nitrosoureas in primary high grade malignant glioma. **Br J Cancer 56:**89–90, 1987 (Letter)
109. Stewart LA: Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. **Lancet 359:**1011–1018, 2002
110. Stupp R, Dietrich PY, Ostermann KS, et al: Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. **J Clin Oncol 20:** 1375–1382, 2002
111. Stupp R, Gander M, Leyvraz S, et al: Current and future developments in the use of temozolomide for the treatment of brain tumors. **Lancet Oncol 2:**552–560, 2001
112. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. **N Engl J Med 352:**987–996, 2005
113. Sungarian AS, Sampath P, Maestri X, et al: CPT-11 used in combination with BCNU-impregnated polymer (Gliadel) in the treatment of recurrent glioblastoma multiforme: a preliminary clinical study. Presented at the annual meeting of the CNS, San Diego, CA, 2001. (Abstract) (http://abstracts.neurosurgeon.org/view.php?id=6913.) [Accessed 12 June 2005]
114. Tatter SB, Shaw EG, Rosenblum ML, et al: An inflatable balloon catheter and liquid ^{125}I radiation source (GliaSite Radiation Therapy System) for treatment of recurrent malignant glioma: multicenter safety and feasibility trial. **J Neurosurg 99:**297–303, 2003
115. Todd M, Shoag M, Cadman E: Survival of women with metastatic breast cancer at Yale from 1920 to 1980. **J Clin Oncol 1:**406–408, 1983
116. Tolcher AW, Gerson SL, Denis L, et al: Marked inactivation of *O*^{6}-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules. **Br J Cancer 88:**1004–1011, 2003
117. Tozer K, Silbergeld DL, Rostomily RC, et al: Concomitant use of Gliadel and permanent low-activity I-125 seed implants for recurrent malignant glioma. Presented at the annual meeting of the CNS, Denver, CO, 2003. (Abstract) (http://abstracts.neurosurgeon.org/view.php?id=10536.) [Accessed 6 October 2005]
118. Tsao MN, Mehta MP, Whelan TJ, et al: The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for malignant glioma. **Int J Radiat Oncol Biol Phys 63:**47–55, 2005
119. Valtonen S, Timonen U, Toivanen P, et al: Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. **Neurosurgery 41:** 44–49, 1997
120. van den Bent MJ, Chinot O, Boogerd W, et al: Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972. **Ann Oncol 14:**599–602, 2003
121. van den Bent MJ, Stupp R, Mason W, et al: Impact of extent of resection on overall survival in newly-diagnosed glioblastoma after chemo-irradiation with temozolomide: further analysis of EORTC study 26981. **Eur J Cancer Suppl 3:**134, 2005 (Abstract)
122. van den Bent MJ, Taphoorn MJ, Brandes AA, et al: Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971. **J Clin Oncol 21:**2525–2528, 2003
123. Vogel CL, Nabholtz JM: Monotherapy of metastatic breast cancer: a review of newer agents. **Oncologist 4:**17–33, 1999
124. Walker MD, Alexander E Jr, Hunt WE, et al: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. **J Neurosurg 49:**333–343, 1978
125. Walker MD, Green SB, Byar DP, et al: Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. **N Engl J Med 303:**1323–1329, 1980
126. Wen PY, Alexander E III, Black PM, et al: Long term results of stereotactic brachytherapy used in the initial treatment of patients with glioblastomas. **Cancer 73:**3029–3036, 1994
127. Westphal M, Hilt DC, Bortey E, et al: A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. **Neuro-oncol 5:**79–88, 2003
128. Yung WK, Albright RE, Olson J, et al: A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. **Br J Cancer 83:**588–593, 2000
129. Yung WKA, Prados MD, Yaya-Tur R, et al: Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. **J Clin Oncol 17:**2762–2771, 1999
130. Zamorano L, Li Q, Levin K, et al: Brachytherapy with I-125 permanent implant combined with sequential gliadel in the treatment of GBM: a novel approach. **AANS** April 17 2005. Article ID: 24746 (Abstract)

Manuscript received January 17, 2006.
Accepted in final form February 27, 2006.
Editorial assistance was provided on this manuscript by Nexus Communications, Inc. (North Wales, PA), through an unrestricted grant from MGI Pharma (Bloomington, MN).

Address reprint requests to: Timothy C. Ryken, M.D., University of Iowa Hospitals and Clinics, Iowa City, Iowa. email: timothy-ryken@uiowa.edu.