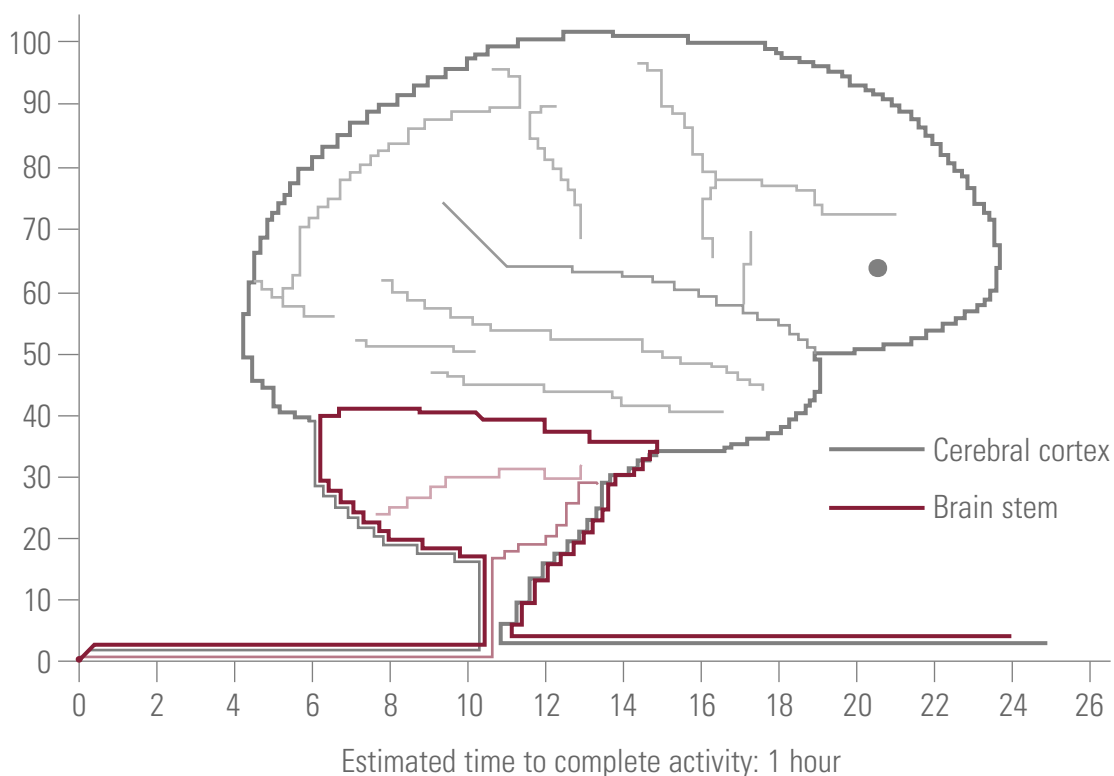


# Current Trends in the Management of Patients with Malignant Gliomas: the Role of Chemotherapeutic Implants

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Sponsored by The School of Medicine  
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Timothy C. Ryken, MD, has consulting agreements with Medtronic, Inc, and Abbot Spine, Inc; is on speakers' bureaus for Schering Plough Inc and Guilford Pharmaceuticals; and receives grants/research support from Northwest Biotherapeutics, Inc. He has no assets or personal financial interest in any of these companies.

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## STATEMENT OF EDUCATIONAL NEED

This activity is designed to meet the educational needs of neuro-oncologists involved in the management of patients with high-grade malignant gliomas.

## EDUCATIONAL OBJECTIVES

*After listening to the CD, reading this monograph, and completing the post-test, participants should be able to:*

- Review the current treatment options for patients with malignant glioma
- Discuss the clinical efficacy of chemotherapeutic implants in malignant glioma
- Describe surgical techniques for patients treated with chemotherapeutic implants, including correct implantation, watertight dural closure, and prevention and treatment of postoperative complications
- Discuss the multidisciplinary care of patients with malignant glioma and new treatment approaches

## STATEMENT OF EDUCATIONAL METHOD

The educational information is presented in a twelve-page monograph and a 25-minute audio CD. This activity is also available at our website: [www.vcu-cme.org](http://www.vcu-cme.org).

## STATEMENT OF EVALUATION INSTRUMENT

A 10-question, multiple-choice post-test is used as the evaluation instrument. An activity evaluation questionnaire will be completed by each participant.

## STATEMENT OF INTENDED, OR TARGET, AUDIENCE

This activity is intended for, but not limited to neuro-oncologists and other physicians who care for patients with malignant gliomas.

## INSTRUCTIONS

To earn 1 hour of category 1 credit, listen to the CD and read the material in this monograph carefully. Complete the activity evaluation and answer the post-test questions on the accompanying questionnaire. Send the questionnaire in the enclosed envelope to Current Trends in the Management of Patients with Malignant Gliomas: the Role of Chemotherapeutic Implants, CPDE REGISTRAR, P.O. Box 980048, Richmond, VA 23298-0048. Your credit certificate will be returned. Participation is confidential.

Estimated program completion time is 1 hour.

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## INTRODUCTION

Brain and nervous system tumors are a heterogeneous group of tumors, with variable prognoses.<sup>1,2</sup> An estimated 18,500 new cases of primary brain and nervous system neoplasms are diagnosed each year, and approximately 12,760 deaths due to these tumors occur annually.<sup>3</sup> Approximately 85% to 90% of primary central nervous system (CNS) tumors are brain tumors.<sup>4</sup> Glioblastoma multiforme (GBM), the most common intraparenchymal brain tumor in adults, is highly invasive and has a poor prognosis.<sup>2</sup>

Treatment options include surgery, radiotherapy, localized chemotherapy administered intraoperatively, and systemic chemotherapy.<sup>1,2</sup> With improved treatment, the 5-year relative survival rate for patients with brain and nervous system tumors as a group has significantly increased over the previous 3 decades, from 22% in 1974 to 33% in 2000, suggesting strong reason for optimism.<sup>3</sup> Nonetheless, long-term survival remains poor, particularly among patients with malignant glioma who suffer a median survival time of < 1 year, even with optimal treatment.<sup>5</sup>

In June 2001, a conference was convened in Washington, DC, to develop a consensus on the use of chemotherapeutic implants to treat brain tumors, in particular newly diagnosed and recurrent GBM. The conference also discussed the combined use of localized therapy and radiation, patient selection, perioperative and postoperative issues regarding the use of chemotherapeutic implants, and possible future directions for treating brain tumors. The faculty of this conference concluded their meeting by resolving to follow the progress of a large-scale clinical trial of chemotherapeutic implants then underway, as well as knowledge gained from the use of these implants in clinical practice. They also pledged to update their consensus statement as needed.

Since the publication of the earlier monograph in 2001,<sup>6</sup> the results of the large-scale clinical trial of BCNU (carmustine) wafers in initial surgery of malignant glioma<sup>7</sup>, as well as analyses of the long-term efficacy of implants, have been published.<sup>8-10</sup> In addition, temozolomide, an oral chemotherapy, was approved for the treatment of patients with malignant glioma, alone or in combination with radiotherapy. There was a clear need to update the content of the 2001 monograph; the present document was developed to answer that need.

In June 2005, three thought leaders in the treatment of central nervous system tumors convened to discuss new developments in the treatment of malignant glioma: Henry S. Friedman, MD, of Duke University Medical Center; Lawrence Kleinberg, MD, of The Johns Hopkins University; and Timothy C. Ryken, MD, of University of Iowa Hospitals and Clinics. These physicians represented the three disciplines central to the management of this disease: neurosurgery, radiology, and medical oncology. The faculty members address the educational objectives of this CME program, discussing in depth the current best practices for treatment and management of malignant glioma.

## CURRENT TREATMENT OPTIONS FOR MALIGNANT GLIOMAS

The goals of treatment in malignant glioma are to alleviate symptoms and preserve neurologic function by reducing intracranial pressure and extending survival.<sup>1,2</sup> Obtaining an accurate pathologic diagnosis is central to designing a treatment plan.<sup>2</sup> The World Health Organization (WHO) classification of nervous system tumors incorporates morphology, cytogenetics, molecular genetics, and immunologic markers to determine prognosis (Table 1).<sup>1</sup>

**TABLE 1** WHO Classification and Grading of Tumors of Neuroepithelial Tissue<sup>3,5</sup>

### CLASSIFICATION

#### ASTROCYTIC TUMORS

1. Pilocytic astrocytoma
2. Astrocytoma (fibrillary, protoplasmic, gemistocytic subtypes)
3. Anaplastic astrocytoma
4. Others, including subependymal giant cell astrocytoma and astroblastoma

#### OLIGODENDROGLIAL TUMORS

1. Oligodendroglioma
2. Mixed oligoastrocytoma
3. Anaplastic oligodendroglioma

#### EPENDYMAL AND CHOROID PLEXUS TUMORS

1. Ependymoma (including myxopapillary, papillary, and subependymoma subtypes)
2. Anaplastic ependymoma
3. Choroid plexus papilloma
4. Anaplastic choroid plexus papilloma

#### POORLY DIFFERENTIATED AND EMBRYONAL TUMORS

1. Glioblastoma (including sarcomatous and giant cell variants)
2. Medulloblastoma (including desmoplastic and medullomyoblastoma variants)
3. Gliomatosis cerebri
4. Others (including medulloepithelioma and primitive polar spongioblastoma)

#### PINEAL CELL TUMORS

(Including pineocytoma and pineoblastoma)

#### NEURONAL TUMORS

(Including gangliocytoma and ganglioglioma with anaplastic variants, ganglioneuroblastoma, neuroblastoma)

### GRADING

WHO grade I	Low proliferative potential; frequently discreet nature; possible cure following surgery alone
WHO grade II	Generally infiltrating and low in mitotic activity but recur; some tumor types tend to progress to higher grades of malignancy
WHO grade III	Histologic evidence of malignancy; generally in the form of mitotic activity; clearly expressed infiltrative capabilities; anaplasia
WHO grade IV	Mitotically active; necrosis-prone; generally associated with a rapid preoperative and post operative evolution of disease

WHO = World Health Organization

### Standard of Care

There is currently insufficient evidence to clearly establish a standard of care for malignant glioma. Surgery remains the cornerstone of the management of malignant glioma, although surgery alone results in a short median survival time of only 4 months. Surgical options include stereotactic biopsy, open biopsy or debulking procedure, and major tumor resection. Optimal debulking surgery with accurate diagnosis using an adequate tissue sample appears to offer the best outcome in eligible patients with good performance status.<sup>2</sup>



Radiotherapy plays an important role in the management of GBM, potentially lengthening survival time.<sup>1,14</sup> Conformal external-beam radiation is the most commonly used approach.<sup>2</sup> Other radiotherapy options include brachytherapy, stereotactic fractionated radiotherapy, and stereotactic radiosurgery. Use of BCNU wafers, placed intraoperatively in the surgical cavity, results in significantly improved survival in some patients with high-grade gliomas.<sup>1,2,7,13,15,16</sup> Systemic chemotherapy provides some benefit in select patients,<sup>2</sup> and has been shown to lengthen disease-free survival in patients with gliomas.<sup>1,17</sup> Table 2 summarizes treatment options recommended by the National Comprehensive Cancer Network (NCCN).

Outcomes Project) suggest many patients with malignant glioma are not receiving full multimodality therapy. Specifically, only 54% of patients received chemotherapy.<sup>18</sup> Involving multiple specialties early in the development of treatment plans may provide more options for patient care.

**BCNU WAFERS IN THE TREATMENT OF MALIGNANT GLIOMA**

Surgery alone confers poor long-term survival in malignant glioma, and local recurrence is the most frequent pattern of failure following resection.<sup>19</sup> Although the mechanisms of regrowth are not fully understood, failure may be related to the increased density of tumor cells remaining at the margins of the cavity following resection.<sup>19-21</sup> Local chemotherapy applied to the resection cavity offers a high concentration of active compound in this key location.<sup>19</sup>

Three randomized trials have evaluated the use of BCNU wafers in patients with recurrent or newly diagnosed malignant glioma (Table 3). Results consistently demonstrate a survival advantage with BCNU wafers compared with placebo.<sup>7,15,16</sup> An early randomized trial showed a 50% increase in 6-month survival with BCNU wafers.<sup>16</sup> A recently completed, large, randomized trial also demonstrated a significant increase in median and 1-year survival independent of prognostic factors, including performance status, age, and histologic diagnosis. Treatment with BCNU wafers resulted in a 28% reduction in the risk of death (Figure 1A). Treatment with BCNU also resulted in longer times to deterioration in performance status and neuroperformance measures compared with placebo, although differences were only marginally significant.<sup>7</sup>

Continued follow-up through 56 months (an average of 3 to 4 years after initial surgery) on patients enrolled in the trial conducted by Westphal et al,<sup>7</sup> showed a 27% reduction in the risk of death for patients treated with BCNU compared with those who received placebo (Figure 1B). A total of 13 long-term survivors were reported, 11 among patients treated with BCNU wafers and 2 among those who received placebo.<sup>22</sup> Similarly, a combined analysis of the trials conducted by Valtonen et al<sup>16</sup> and Westphal et al<sup>7</sup> showed a 25% reduction in the risk of death.<sup>25</sup>

**TABLE 2** Treatment of Gliomas by Presentation: Summary of the NCCN Guidelines<sup>2</sup>

Presentation	Treatment
Adult low-grade astrocytoma/oligodendroglioma	Surgery → RT or CT or observation
Recurrent, progressive low-grade disease	No prior RT: Surgery Surgery (if resectable) → RT ± CT Prior RT: Surgery → CT → RT at progression
Ependymoma	RT (limited field or craniospinal) or observation
Recurrent ependymoma	Surgery (if resectable) → RT (if no prior RT) → consider CT or BSC
High-grade glioma (anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma multiforme)	Maximal excision ± BCNU wafer (Stereotactic or open biopsy if maximal excision not possible) → RT ± CT (concurrent and/or adjuvant)
Recurrent high-grade glioma, diffuse or multiple lesions	BSC (poor PS) or CT or palliative surgery
Recurrent high-grade glioma, localized disease	Surgery (if resectable) ± BCNU wafer → RT (highly conformal) or CT → BSC

NCCN = National Comprehensive Cancer Network; RT = radiotherapy; CT = chemotherapy; BCNU = carmustine; BSC = best supportive care; PS = performance status

**Multidisciplinary Management of Patients**

Multimodality therapy, including surgery, radiotherapy, and local or systemic chemotherapy, offers patients with malignant glioma the best opportunity for lengthened survival. In addition, multiple agents and therapies increase the ability to overcome resistance, which is the primary cause of treatment failure.

The involvement of neurosurgeons, radiation therapists, oncologists, neurologists, and neuroradiologists early in the planning of treatment strategies is essential to optimal management and care. Individual treatment decisions are based on patient age, performance status, histology, and disease characteristics.<sup>2</sup> Results of a recent study (the Glioma

The goals of treatment in malignant glioma are to alleviate symptoms and preserve neurologic function by reducing intracranial pressure and extending survival.

**TABLE 3** Randomized Trials of Intraoperative BCNU Wafers in Recurrent or Newly Diagnosed Glioma<sup>7,15,16</sup>

Trial	Patients	Treatment (n)	Efficacy	P Value
Brem et al, 1995 <sup>15</sup>	Recurrent malignant brain tumors	BCNU wafers (110)	MS: 31 wk 6-mo OS: 44%	.006* .02
		Placebo (112)	MS: 23 wk 6-mo OS: 64%	
Valtonen et al, 1997 <sup>16†</sup>	Newly diagnosed grade III/IV malignant glioma	BCNU wafers (16)	MS: 58.1 wk (Grade IV tumors, 53.3 wk)	.012 .008
		Placebo (16)	MS: 39.9 wk (Grade IV tumors, 39.9 wk)	
Westphal et al, 2003 <sup>7</sup>	Newly diagnosed malignant glioma <sup>‡</sup>	BCNU wafers (120) <sup>§</sup>	MS: 13.9 mo (GBM, 13.5 mo) 1-y OS: 59.2%	.03
		Placebo (120) <sup>§</sup>	MS: 11.6 mo (GBM, 11.4 mo) 1-y OS: 49.6%	

BCNU = carmustine; MS = median survival; OS = overall survival; GBM = glioblastoma multiforme

\* After accounting for the effects of prognostic factors.

† Trial terminated early because study drug became unobtainable.

‡ More than 85% of patients were diagnosed with glioblastoma multiforme.

§ All patients received limited-field radiotherapy.

**FIGURE 1** A

**FIGURE 1** B

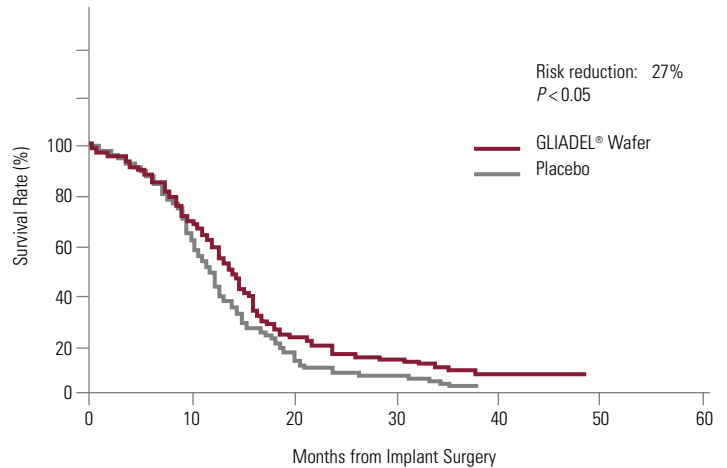
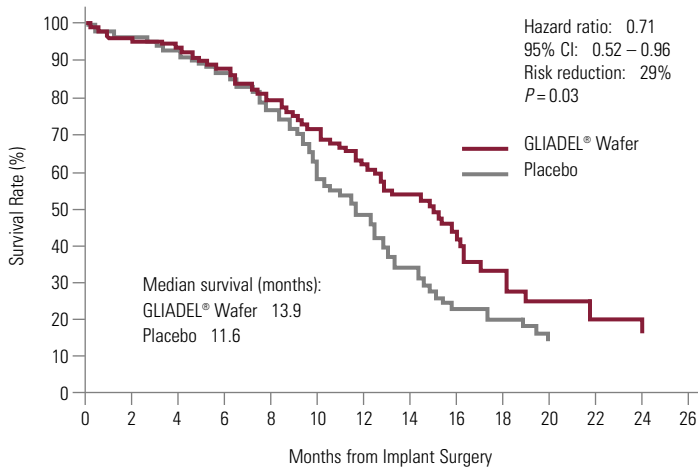


Figure 1: BCNU wafers versus placebo: Kaplan-Meier survival curve in the intent-to-treat population. Results (A) and long-term survival analysis (B) of the trial by Westphal et al.<sup>7,23,24</sup> Prospective, randomized, double-blind, placebo-controlled, multicenter, multinational trial of 240 patients with malignant glioma who underwent surgery and external beam radiation. Patients received up to 8 wafers. Overall survival is the duration between the date of randomization and date of death from any cause or date of last contact. BCNU = carmustine; CI = confidence interval

When results of the trial by Westphal et al<sup>7</sup> were controlled for reoperation, treatment with BCNU wafers conferred an even larger benefit. Patients treated with BCNU wafers survived without second surgery for a median of 14.8 months, versus 11.4 months in the

placebo group (P = .02; risk reduction, 36%). Further, the time to reoperation was delayed in the BCNU wafer-treated group compared with placebo (272 days versus 218 days; Figure 2).



**FIGURE 2**

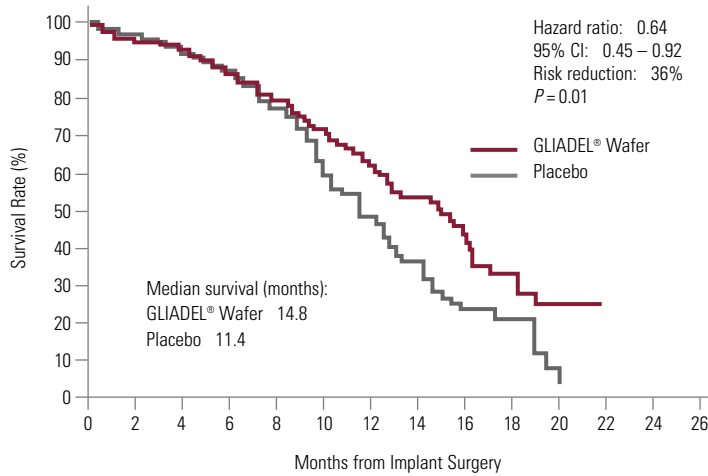


Figure 2. BCNU wafers versus placebo: Kaplan-Meier survival curve censoring patients with reoperation for tumor progression in the intent-to-treat population. Results of the trial by Westphal et al.<sup>7</sup> BCNU = carmustine; CI = confidence interval

Safety profiles were similar between patients implanted with BCNU wafers and those receiving placebo, demonstrating the safety and feasibility of this treatment. Adverse events were as expected in this patient population; the most common events were tumor progression, neurological progression, and general clinical deterioration. Importantly, convulsions, intracranial infections, and healing abnormalities were not more common with BCNU wafers compared with placebo.<sup>7,15,16</sup> Intracranial hypertension, a late event occurring > 6 months after surgery, was more common ( $P = .019$ ) among patients treated with BCNU wafers compared with those receiving placebo in 1 trial; however, investigators considered it unlikely to be treatment related.<sup>7</sup>

A smaller retrospective review demonstrated the safety and feasibility of combining BCNU wafers with subsequent radiotherapy. Post-operative infection, pathology at reoperation, and survival were evaluated in 46 consecutive patients with newly diagnosed malignant glioma implanted with BCNU wafers who went on to receive radiotherapy. Toxicity during radiotherapy was evaluated in 28 patients treated at the study center. Median survival was 12.8 months, suggesting no long-term toxicities impacting overall survival. Radiotherapy was well tolerated, with no need to reduce the dose of radiotherapy. Results did not suggest an increase in toxicity with the use of BCNU wafers. Of interest, a substantial incidence of treatment effect in specimens removed during reoperation for suspected recurrence was noted.<sup>26</sup>

Recently reported phase I results demonstrate the feasibility of administering concurrent chemoradiotherapy in patients implanted with BCNU wafers. Sixteen patients with newly diagnosed high-grade glioma underwent surgical resection with BCNU wafer implantation. Following surgery, patients received carboplatin (dose escalated in cohorts of 3 patients at each dose level) beginning by postoperative day 4 with concurrent external beam radiation beginning on postoperative

**TABLE 4**

Issues in the Management of Patients Treated with BCNU Wafers<sup>28,30</sup>

**Preoperative Issues**

<b>Patient selection</b>	Newly diagnosed patients undergoing near-total resection  Unilateral disease or minimal extension into the opposite hemisphere  Reimplantation of wafers in recurrent disease may be appropriate if the tumor remains localized
<b>Patient consent</b>	Informed patient consent is needed prior to surgery, as treatment decisions are often based on intraoperative findings  Patients should be informed that use of BCNU wafers may limit enrollment in clinical trials

**Perioperative Issues**

<b>Surgical incision</b>	Standard antimicrobial prophylaxis recommended  Linear incisions are preferable to flaps to increase blood supply to the wound; a linear “lazy S” incision can be used to prevent the incision line in the dura from lying directly underneath the incision in the skin (see Figure 3)  Good blood supply and watertight dural closure are central to optimal wound healing
<b>Wafer placement</b>	Full coverage of the resection cavity is essential and may require > 8 wafers (use of > 8 wafers is not approved by the FDA)  Wafers should overlap slightly, but not be stacked  Wafers broken into > 2 pieces should be discarded in a biohazard container  Once full coverage of the surgical cavity is achieved, a single, 1-mm sheet of Surgicel® may be used to secure the wafers in place

day 14 to 36. Treatment was well tolerated, with no grade 3/4 toxicities reported. Median progression-free and overall survival times were 266 days (8.8 months) and 679 days (22.3 months), respectively.<sup>27</sup>

**SURGICAL CONSIDERATIONS IN PATIENTS TREATED WITH BCNU WAFERS**

Surgical techniques in patients implanted with BCNU wafers are similar to those used in patients who do not receive BCNU wafers. Management of patients undergoing treatment with BCNU wafers, however, requires careful attention to several perioperative issues (Table 4, above), including:

- patient selection
- surgical incision, implantation, and closure of the wound
- prevention and management of CSF leaks
- appropriate use of corticosteroids and anticonvulsants.

**FIGURE 3** Flap and Linear Incisions

**Handling of wafers** Safe handling procedures for chemotherapy, including use of surgical gloves and dedicated sterile surgical instruments during the procedure and appropriate disposal of waste, should be observed

**Wound closure** Watertight dural closure is critical to prevent extravasation of CSF containing BCNU  
Dural graft is recommended if it is not possible to close the dura without creating significant surface tension, but synthetic materials are not recommended

Tissue sealant or fibrin glue may be used to ensure a watertight seal

**Postoperative Issues**

**CSF leakage** Early and aggressive management with antibiotics and skin suturing; lumbar drain; and wrapping the head in an ACE bandage, if needed<sup>28</sup>

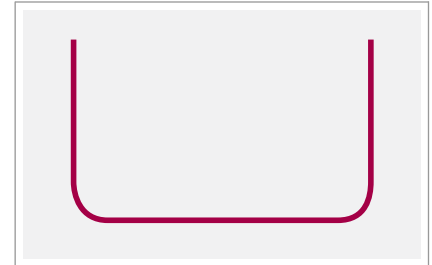
**Cerebral edema** Aggressive management with corticosteroids<sup>29,30</sup>  
— Dexamethasone up to 95 mg/d *or*  
— Methylprednisone 200-2,000 mg/d  
  
Steroids may be tapered off approximately 3 days after control of edema is achieved

**Prophylactic anticonvulsant therapy** Follow common practice for patients undergoing craniotomy  
— Phenytoin 1,000 mg IV (50 mg/h) loading dose immediately before or during surgery, followed by 300 mg/d IV or PO  
— Phenobarbital and valproate are also appropriate

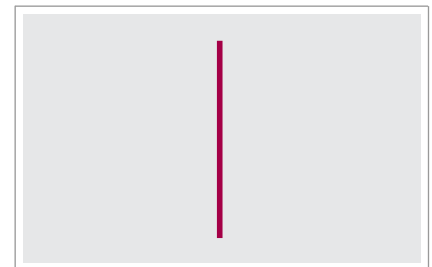
**Postoperative MRI** Resorption of air is significantly delayed in patients implanted with BCNU wafers  
— Residual air may mimic an abscess on MRI, and treatment decisions should not be based on radiological findings alone

BCNU = carmustine; FDA = Food and Drug Administration; CSF = cerebrospinal fluid; IV = intravenously; PO = orally; MRI = magnetic resonance imaging

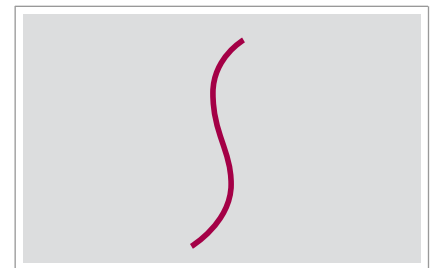
Flap Incision



Linear Incision



Linear "Lazy S" Incision



**COMBINATION THERAPY WITH BCNU WAFERS AND TEMOZOLOMIDE**

Temozolomide, an oral imidazotetrazine derivative that undergoes spontaneous conversion to the alkylating agent MTIC and readily crosses the blood-brain barrier, has shown promise in treating malignant gliomas.<sup>21-33</sup> Randomized trials demonstrate the activity and tolerability of temozolomide in newly diagnosed and recurrent malignant glioma. A randomized phase II trial showed significantly improved progression-free and overall survival for patients treated with temozolomide compared with those treated with procarbazine at first relapse. Treatment was generally well tolerated.<sup>34</sup> A separate analysis demonstrated significantly improved health-related quality of life with temozolomide versus procarbazine. The investigators concluded the improvement likely resulted from both a tolerable safety profile and a delay in disease progression with temozolomide.<sup>35</sup> A large, randomized trial compared temozolomide in combination with radiotherapy in patients with newly diagnosed malignant glioma. Combination therapy significantly improved overall survival compared with radiotherapy alone, resulting in a clinically meaningful survival benefit with minimal additional toxicity.<sup>36</sup>

With careful patient management, implantation of BCNU wafers does not significantly increase surgical complications compared with craniotomy alone. Specifically, the incidence and severity of edema and the frequency of new or worsened seizures were not significantly different between patients treated with BCNU wafers and those implanted with placebo wafers. Three randomized trials demonstrated no significant increase in treatment-emergent edema in patients with recurrent or newly diagnosed disease (Table 5).<sup>7,15,16</sup> These trials also demonstrated no significant difference in seizure activity between the BCNU wafer and placebo wafer groups. In the large, randomized trial,<sup>7</sup> there was no significant difference in seizure frequency or time to seizure. Results from the other 2 trials showed no significant increase in the frequency of seizures, but did show shortened time to onset of seizures among patients treated with BCNU wafers.<sup>15,16</sup> Taken together, the results of these 3 trials demonstrate the safety and feasibility of BCNU wafers in this treatment setting.<sup>7,15,16</sup>



**TABLE 5** Treatment-Emergent Cerebral Edema from Recurrent and Initial Surgery Trials<sup>7,15,16</sup>

Treatment Setting	Incidence of Cerebral Edema	
	BCNU Wafer Group	Placebo Wafer Group
Recurrent surgery <sup>15</sup>	2.0%	0
Initial surgery <sup>16</sup>	5.8%	6.7%
Initial surgery <sup>7</sup>	22.5%	19.2%

BCNU = carmustine

Based on the activity of temozolomide and BCNU wafers in patients with malignant glioma and preclinical evidence of synergy or additive effects of BCNU and temozolomide,<sup>37</sup> investigators are evaluating the combination of these 2 therapies. A phase I trial demonstrated the safety and feasibility of temozolomide following resection with implantation of BCNU wafers in patients with recurrent high-grade gliomas. Temozolomide was administered daily for 5 days each month for up to 12 months. Treatment was generally well tolerated, with manageable toxicity even at the highest planned study dose.<sup>38</sup>

An ongoing phase II trial is assessing the efficacy and safety of temozolomide following surgical resection with implantation of BCNU wafers in newly diagnosed patients with high-grade malignant glioma. Following resection and implantation with BCNU wafers, patients received radiotherapy plus continuous daily temozolomide followed by maintenance monthly temozolomide for up to 18 cycles. Interim analysis reported results in 20 patients. At a median follow-up of 9 months, median survival has not yet been reached. Recurrence has been documented in 13 patients, and 5 patients are alive without disease progression (on study). Two patients have achieved progression-free survival > 1 year. Eleven patients remain alive and on study, and 7 patients have died. Four patients experienced grade 3/4 adverse events, including pulmonary embolism (resulting in death in 1 patient), bacterial pneumonia, and sterile brain abscess.<sup>39</sup> The adverse event profile in this trial is similar to those reported with either agent alone in this patient population.<sup>7,15,16,36</sup> These results demonstrate the feasibility of adjuvant temozolomide chemotherapy in patients treated with BCNU wafers and suggest that further study of this combination is warranted.<sup>39</sup>

Ongoing investigations continue to evaluate new approaches to therapy in this disease. Strategies to improve efficacy of therapy include reversal of drug resistance and use of targeted therapies, such as antiangiogenics, antimigration agents, and differentiation agents.

## Summary and Future Directions

Multimodality therapy and multidisciplinary care offer new hope to patients with malignant glioma. Combined therapy, including surgery, radiotherapy, and local and systemic chemotherapy, is lengthening survival for some patients. Current treatment guidelines recommended a combined approach in all eligible patients to maximize treatment benefit.

BCNU wafers continue to play a substantial role in the management of patients with glioma. Phase III trials show a consistent benefit to BCNU wafers over placebo, with no significant increase in surgical complications.<sup>7,15,16</sup> Careful attention to patient management — specifically appropriate patient selection; surgical incision, implantation of wafers, and closure of the wound; prevention and management of CSF leaks; and appropriate use of corticosteroids and anticonvulsants — minimizes adverse events. Results of a retrospective analysis demonstrate the safety and feasibility of combining BCNU wafers and radiotherapy.<sup>26</sup> In addition, phase I/II results demonstrate the feasibility and activity of combined BCNU wafers and temozolomide chemotherapy.<sup>38,39</sup>

## Future Directions in the Management of Malignant Glioma

Patients with malignant glioma should be considered for clinical trials whenever available. Ongoing investigations continue to evaluate new approaches to therapy in this disease. Strategies to improve efficacy of therapy include reversal of drug resistance and use of targeted therapies, such as antiangiogenics, antimigration agents, and differentiation agents. Targeted therapies under investigation include dendritic cell vaccination, tyrosine kinase inhibitors, farnesyl transferase inhibitors, viral-based gene therapy, and oncolytic viruses.<sup>1</sup> A phase II trial showed modest activity of an oral farnesyl transferase inhibitor in patients with GBM.<sup>40</sup> In addition, clinical trials are evaluating the use of radiosensitizers, hyperthermia, and interstitial brachytherapy in conjunction with external-beam radiotherapy.<sup>1</sup>

Research continues to identify mechanisms of treatment resistance and disease proliferation in malignant glioma. Increased O<sup>6</sup>-alkylguanine-DNA-alkyltransferase (AGT) confers resistance by preventing BCNU from binding to and cross-linking DNA. High levels of AGT correlate with reduced survival. Investigations are evaluating the use of O<sup>6</sup>-benzylguanine in combination with BCNU wafers as a means to overcome this resistance.<sup>41</sup> A recent study of tissue samples from patients with high-grade gliomas identified several pathways related to immune and inflammatory response, including the AKT and RAS pathways, that are enriched in GBM compared with anaplastic astrocytoma. Deregulation of these growth and survival pathways correlates with adverse clinical outcome, and some pathways may play a vital role in radiation resistance.<sup>42</sup>

Recently completed trials have investigated the use of BCNU wafers in a variety of treatment settings:

- Recurrent supratentorial low-grade glioma (National Cancer Institute [NCI]-G98-1470)
- Supratentorial brain metastases (New Approaches to Brain Tumor Therapy [NABTT]-9802)
- In combination with weekly irinotecan in recurrent supratentorial high-grade gliomas (NCI-G98-1464)
- In combination with iodine I<sup>125</sup> interstitial seed implants in recurrent or refractory malignant glioma (NCI-V99-1543)

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**CME Post-Test**

*seven correct answers are required for credit*

1. World Health Organization (WHO) classification and grading of tumors of neuroepithelial tissue is based on
  - A. Proliferative potential and prognosis.
  - B. Mitotic activity.
  - C. Anaplasia.
  - D. All of the above.
2. Current treatment options for patients with malignant glioma include all of the following *except*
  - A. Surgery alone.
  - B. Surgery plus radiotherapy.
  - C. Surgery plus BCNU wafer, followed by radiotherapy plus chemotherapy.
  - D. Surgery plus BCNU wafer, followed by radiotherapy.
3. The primary goals of treatment in patients with malignant glioma include
  - A. Alleviating symptoms and preserving neurologic function by reducing intracranial pressure.
  - B. Extending survival.
  - C. Early treatment of metastases to other tissues.
  - D. A and B.
4. Advantages of multidisciplinary care in malignant glioma include
  - A. Coordination of care and early planning of treatment strategies.
  - B. Use of multiple modalities, including surgery, radiotherapy, and chemotherapy, to treat the disease.
  - C. The best opportunity for lengthened survival.
  - D. All of the above.
5. What is the rationale for use of BCNU wafers in malignant glioma?
  - A. Surgery alone confers poor long-term survival.
  - B. Local recurrence is the most frequent pattern of failure.
  - C. BCNU wafers target the highest concentration of tumor cells in the cavity.
  - D. All of the above.
6. Phase III trials of BCNU wafers in malignant glioma demonstrated
  - A. Decreased disease symptoms, but no survival benefit.
  - B. Treatment benefit only in patients with recurrent disease.
  - C. Consistent survival advantage, with tolerability comparable to placebo.
  - D. Increased adverse events and surgical complications with BCNU wafers.
7. Careful management of patients treated with BCNU wafers includes all of the following, *except*
  - A. Early and aggressive treatment of CSF leakage.
  - B. Use of only 8 or fewer wafers, regardless of coverage of surgical cavity.
  - C. Appropriate use of steroids to minimize edema.
  - D. Appropriate use of anticonvulsant therapy.
8. Appropriate patient counseling prior to the use of BCNU polymeric therapy should include discussion of possible
  - A. Episodes of increased cerebral edema.
  - B. Increased need for steroid medication.
  - C. Alterations in wound healing.
  - D. All of the above.
9. Phase I/II results demonstrate that temozolomide following surgical resection with BCNU wafer implantation
  - A. Significantly increases toxicity over either treatment alone.
  - B. Shows no activity.
  - C. Is safe and feasible, with adverse events similar to either treatment alone.
  - D. Significantly improves survival over either treatment alone.
10. Investigational treatment approaches in malignant glioma include
  - A. Reversal of drug resistance.
  - B. Use of targeted therapies, including antiangiogenics, antimigration agents, and differentiation agents.
  - C. High-dose single-modality therapy.
  - D. A and B.

# Activity Evaluation and Personal Information

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## Activity Evaluation

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1. As a result of the information contained in this activity, will you make any changes in your practice? Yes \_\_\_\_\_ No \_\_\_\_\_  
If yes, what changes? \_\_\_\_\_  
\_\_\_\_\_
2. In your opinion, how could this activity be improved? (e.g., change format, more details, fewer details, discuss other topics, change length) \_\_\_\_\_  
\_\_\_\_\_
3. Please rate the educational value/clinical relevance of this activity.  
\_\_\_\_ Excellent/outstanding \_\_\_\_ Very good \_\_\_\_ Good/above average  
\_\_\_\_ Fair/acceptable \_\_\_\_ Poor/unacceptable
4. Please rate the extent to which the learning objectives were met.  
\_\_\_\_ Excellent/outstanding \_\_\_\_ Very good \_\_\_\_ Good/above average  
\_\_\_\_ Fair/acceptable \_\_\_\_ Poor/unacceptable
5. Was the material presented objectively and did it avoid commercial bias?  
Yes \_\_\_\_\_ No \_\_\_\_\_ Comments: \_\_\_\_\_  
\_\_\_\_\_
6. Suggestions for future topics: \_\_\_\_\_  
\_\_\_\_\_
7. Other comments: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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I have listened to the CD, read the monograph, and completed the post-test and activity evaluation.

Signature \_\_\_\_\_ Date \_\_\_\_\_

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# Current Trends in the Management of Patients with Malignant Gliomas: the Role of Chemotherapeutic Implants

Activity Number: IND 00 101 01 05

Expiration date: 09-30-07

To earn one (1) hour of category 1 CME credit after reading this monograph and listening to the accompanying audio CD, please mail the completed post-test answers, activity evaluation, and personal information questionnaire in the enclosed envelope.

## **CME Post-Test Answers**

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(Circle the appropriate letter for each question.)

- |            |             |
|------------|-------------|
| 1. A B C D | 6. A B C D  |
| 2. A B C D | 7. A B C D  |
| 3. A B C D | 8. A B C D  |
| 4. A B C D | 9. A B C D  |
| 5. A B C D | 10. A B C D |



CURRENT TRENDS IN THE MANAGEMENT OF PATIENTS WITH MALIGNANT GLIOMAS: THE ROLE OF CHEMOTHERAPEUTIC IMPLANTS

