Brain metastases are a frequent complication of systemic malignancy. Up to 30% of cancer patients will develop brain metastases, totaling more than 100,000 patients per year in the United States (1, 2). The incidence of brain metastases is likely to increase in the future for several reasons. With the advent of highly effective biological and other targeted therapies in addition to advances in chemotherapy and hormonal therapies, systemic control of metastatic cancer is improving. Because many chemotherapeutic agents do not penetrate into the central nervous system (CNS) well, the brain serves as a sanctuary for metastatic tumor foci. In addition, as a result of prolonged survival, otherwise undetected CNS disease may become more clinically significant. Several recent studies in breast cancer and melanoma have noted an increase in the incidence of CNS involvement with more effective systemic control (3–9). Contrary to the traditional thinking that most patients with brain metastases die of systemic disease, several authors have noted that a substantial proportion of these patients died from CNS progression in the setting of systemic control (8, 9). Thus, as options for systemic control improve, long-term control of CNS disease may be an increasingly important determinant of survival and quality of life.

Currently, treatments for patients with brain metastases are based primarily on the number (and, to a lesser degree, size) of the brain metastases, the extent of systemic disease, and the patient’s performance status. The presence of non-CNS metastases, a poorly controlled primary tumor, a low performance status, and increased age all portend a poor prognosis (10). Of these, poor performance status seems to be the most powerful predictor. Brain metastasis patients with a Karnofsky performance scale (KPS) score <70 have a median survival of only 2.3 months (10). Regardless, even patients with the more favorable prognostic factors (age, <65 years; KPS, ≥70; and CNS as the only site of metastases with a controlled primary tumor) have limited survival at a median of 7 months. Patients who have only a single brain metastasis carry a slightly better prognosis, with median survivals of 40 to 60 weeks in a series of patients treated with some combination of surgery, radiation therapy, or radiosurgery (11–13).
Although single brain metastasis carries a better prognosis, the local failure rate at the surgical bed after craniotomy and postoperative radiation therapy is 10% to 34% at 1 year (11, 14–17), with distant CNS recurrence rates of 14% to 21% (11, 14–16). Recurrence following surgical resection is thought to arise from microscopic, infiltrative tumor left behind at the time of surgery, particularly in eloquent areas of the brain, where attempts at achieving clean surgical margins increase the risk of neurologic dysfunction. This, along with the treatment of microscopic, magnetic resonance imaging (MRI) occult, distant tumor foci, is the rationale for postoperative fractionated whole-brain external beam radiotherapy. Despite local therapy with surgery and postoperative radiation therapy, local recurrences occur and can cause significant morbidity.

One strategy to improve local control of brain tumors is to treat the microscopic residual disease following surgery with additional local therapy. Three potential options exist: (a) placement of chemotherapy wafers in the resection bed following surgery; (b) placement of a local radiation (brachytherapy) device in the resection bed following surgery; and (c) radiosurgical boost to the tumor bed following resection.

The purpose of this study was to test whether adding local chemotherapy delivered from Carmustine polymer wafers to a standard regimen of surgery and external beam radiotherapy for patients with a single brain metastasis is well tolerated and to determine whether that regimen can provide good local control of the tumor.

Materials and Methods

**Participating institutions.** Patients were enrolled at five brain tumor centers: The University of North Carolina at Chapel Hill, H. Lee Moffitt Cancer Center, Emory University, the University of Washington Veterans Administration Puget Sound Health Care System, and the University of Vermont. The protocol was reviewed and approved by the Institutional Review Boards at each institution. Informed consent was obtained from each patient or the patient’s legally authorized representative.

**Study design.** Carmustine polymer wafers had never been administered to patients with brain metastasis in a clinical trial. Therefore, this study was designed to determine the incidence and nature of toxicity associated with addition of locally delivered Carmustine to a standard regimen of surgical resection and external beam radiotherapy for patients with newly diagnosed single brain metastasis. The wafers are available only in a single, fixed dose, so a dose-escalation trial design (classic phase I) was not used. Previous studies have shown the safety of up to eight wafers in patients with high-grade gliomas (18, 19). Because resection cavities with metastases are frequently smaller than those of gliomas and because the wafer placement should not involve significant overlapping of wafers, the protocol limited the dose to a maximum of eight wafers. This is the Food and Drug Administration–approved dose for use in glioma patients. The primary end point was toxicity associated with the addition of the Carmustine polymer wafers to the treatment regimens of these patients. The secondary end points were the incidence of local recurrence, pattern of CNS recurrence, and survival. As a feasibility study, it was not powered to determine efficacy stratified by conventional prognostic factors. However, this study was open to all patients undergoing resection and standard radiation of a single brain lesion at participating study sites, so the patients included in this study may be considered a reasonable representation of the single brain metastasis population at academic brain tumor programs. Surgery was selected over other treatment regimens, such as radiosurgery, by a multidisciplinary team for a number of reasons, including, but not limited to, the patient’s performance status, tumor size and location, and prior treatment history. Enrollment in the trial was offered to all patients for whom the multidisciplinary team recommended surgery as the first option. Patients were accrued over a period of 20 months, from June 1998 to February 2000.

**Inclusion/exclusion criteria.** All patients had a single, resectable, unilateral cerebral metastasis and were 18 years of age or older. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 preoperatively. However, an ECOG status of 2 was acceptable only if the low performance was directly due to a reversible neurologic deficit resulting from the brain metastasis (such as asymptomatic edema).

Patients had life expectancies of >12 weeks and could not have received investigational therapies in the preceding 3 weeks. Patients could not have had prior cranial irradiation or leptomeningeal involvement of the tumor. Patients were excluded if they had a low neutrophil count (<1,000/mm³) or thrombocytopenia (<75,000/mm³).

If the ventricle was opened during surgery, the communication must have been <7 mm to prevent migration of the Carmustine wafer into the ventricular system.

A prior diagnosis of cancer was not required for enrollment so as not to exclude patients who presented with brain metastasis as the initial or only manifestation of a non-CNS cancer. By necessity, patients were consented preoperatively. Appropriateness for placement of Carmustine polymer wafer was determined intraoperatively on the basis of the frozen section. It was assumed that a small proportion of frozen-section–diagnosed brain metastasis would be termed primary brain tumor (e.g., glioma) on final pathology. Although toxicity data were collected on all consented patients, eligibility for this study and inclusion in the response assessment were based on the final pathologic diagnosis of metastasis because the effectiveness and safety of Carmustine polymer in primary brain tumor has already been established in multiple studies (19–22).

**Preoperative evaluation.** Before craniotomy, all patients underwent the following evaluation: consultations by medical oncology, radiation oncology, and neurosurgery; determination of ECOG performance status; thorough physical examination, including a detailed neurologic examination; and MRI scan of the brain. These studies occurred no more than 3 weeks before surgery.

**Craniotomy for tumor resection.** Craniotomy was done using standard neurosurgical technique under general anesthesia. Stereotaxis was used frequently but was not required. Every effort was made to resect the tumor completely. A diagnosis of metastatic tumor on the basis of intraoperative frozen-section consultation was required for placement of the Carmustine wafers and continuation in the study. Following tumor resection, meticulous hemostasis was obtained. The cavity was then lined with Carmustine polymer wafers. The surgeon evaluated whether the resection was complete or incomplete based on the operative findings.

The Carmustine polymer wafers (Gliadel Wafer, manufactured by MGI Pharma) were provided by Aventis Pharmaceuticals. The wafer composition has been previously described (18, 20, 22). After tumor removal, the wafers were placed in the resection cavity to cover the entire tumor surface, but efforts were made to prevent overlapping of the wafers. A maximum of eight wafers were placed in the resection cavity. Watertight closure of the dura is essential to decrease complications and was attempted in all cases.

Dosage of postoperative steroids and the use of anticonvulsants were determined by the treating physician. Within 72 h of surgery, every patient underwent repeat ECOG performance status determination, physical examination including a full neurologic examination, and a MRI (preferred) or computed tomography (CT) scan. The imaging study determined the extent of resection. The resection was termed complete if all of the enhancing mass was resected. If any residual mass was present, the resection was termed incomplete.

**Postoperative radiation therapy.** Radiotherapy began within 4 weeks of the craniotomy. Whole-brain radiation was administered in 200-cGy fractions for 22 treatments (total 4,400 cGy) using standard techniques.
This fraction schema was selected so that any patient with a brain metastasis who met the eligibility criteria would not be excluded from the study because of radiotherapy considerations. At the time the study was designed, many centers, including the University of North Carolina, had two whole-brain radiation schemas. For patients with a guarded prognosis (systemic metastatic disease, uncontrolled primary disease, or low performance status), the radiation schema was typically 300 cGy/day \times 10 treatments. For patients who might carry a better prognosis (no other systemic metastatic disease; well-controlled primary, high performance status), we frequently employed a longer regimen with small-dose fractions (180-200 cGy/day) to decrease the chance of long-term complications, such as radiation-induced dementia (23). If a shorter radiation schedule with larger dose per fraction were used in this study, we feared that patients with a better prognosis might not be enrolled.

**Follow-up evaluations.** Within 3 weeks of completing radiation therapy, all patients underwent repeat physical examination, including detailed neurologic examination, determination of ECOG performance status, and enhanced MRI scan (preferred) or CT scan.

Patients were followed every 2 months for the first year and every 4 months thereafter. These visits consisted of an enhanced MRI or CT scan, physical examination including neurologic evaluation, and determination of ECOG performance status.

**Outcomes and data analysis.** Postsurgical imaging studies were reviewed for evidence of CNS recurrence. Local recurrences were defined as those within 2 cm of the initial tumor resection bed. Distant CNS recurrences were defined as any of the following: >2 cm from the initial surgical site, on the contralateral side, in the posterior fossa, in the spinal cord, or in the cerebrospinal fluid. For patients who died, cause of death and date of death were recorded. The minimum follow-up was 12 months after the last patient was enrolled or until death. Adverse events, defined as undesirable events occurring over the course of the trial, were recorded. All adverse events were graded for severity (mild, moderate, severe, or fatal). They were also graded as to whether the investigator felt the event was related to the use of the chemotherapy wafer (unlikely, possibly, probably, or definitely related to the Carmustine polymer wafers). Toxicities were graded using the National Cancer Institute’s Common Toxicity Criteria Version 2.0.

**Statistical analysis.** Cox regression was used to examine the impact of covariates on time to death. The Kaplan-Meier (or product limit) method was used to estimate the survivorship function. The log-rank and the Wilcoxon tests were used to test for possible differences between estimated survival curves. For continuous variables, such as age, the Wilcoxon rank-sum test (using normal scores) was used for comparisons. For data categorized into 2 \times 2 contingency tables, Fisher’s exact test was used for comparisons. Statistical analyses were done using JMP Version 5 and SAS/STAT statistical software, version 8.2, both products of the SAS Institute Inc.

### Results

**Patient population.** A total of 35 patients were consented to the study, 25 of whom completed the protocol. Ten patients were considered ineligible for the following reasons: six were found at surgery to have a primary brain tumor (five glioblastoma multiforme, one ependymoma), one patient was treated elsewhere after consent, two patients could not have chemotherapy wafers placed for intraoperative technical reasons, and one patient could not receive radiation therapy due to rapidly progressive non-CNS disease.

Patient demographics and tumor characteristics are presented in Table 1. The median age was 52 years. Fifteen patients were male, and the majority (52%, 13/25) had metastatic lung cancer. Eleven (44%) had ECOG performance status scores of 0 (normal activity), and 13 (52%) had ECOG performance status scores of 1 (symptoms of disease, but ambulatory and able to carry out activities of daily living). One patient had ECOG performance status of 2 that was attributable to the brain tumor. Seventeen (68%) patients had non-CNS metastases at the time of enrollment into the study.

**Treatment.** Surgery was done successfully in all patients. An average of 5.8 Carmustine wafers were placed in the surgical cavity (median, 6; range, 3-8). Mean resection cavity size was 2.5 \times 1.7 \times 1.6 cm. The largest measured diameter was 6 cm; the smallest measured diameter was 1 cm. In 14 of the 25 patients, the resection cavity exceeded 3 cm in at least one dimension. Gross total resection, as determined both by the surgeon’s intraoperative evaluation following craniotomy and by the postoperative MRI, was obtained in all cases. Radiation therapy was delivered according to the protocol in 24 of 25 cases. A single patient, thought to have a rapidly declining systemic status, received an accelerated course of 400 cGy \times 5 fractions (2,000 cGy total dose). This patient did well and survived more than 2 years after resection.

**Toxicity.** There were no deaths in the perioperative period (first 30 days after surgery). Ten adverse events were felt to be probably related to the Carmustine polymer wafer therapy; three events were described as severe. One patient had a seizure on day 15. A second patient had two concurrent adverse events. The first was a seizure on day 20 with immediate respiratory compromise following the seizure. The respiratory failure was defined as a separate adverse event related to the seizure and, thus, to wafer placement. Both patients recovered with medical therapy. Seven other adverse events that were mild or moderate in severity and were thought to be related to the wafer were reported. They included nausea (2), constipation (3), right eye pain (1), and fever (1). There were no postoperative wound infections in the study population; however, one patient was noted to have a mild subgaleal fluid collection on postoperative day 9 that did not require treatment. One of the patients excluded on the basis of final pathologic diagnosis of glioblastoma multiforme (GBM) rather than metastasis developed a postoperative wound infection requiring removal of the bone flap. Statistical analysis showed no correlation between the occurrence of adverse events and any of the following variables: age, tumor cavity size, number of wafers used, preoperative ECOG performance status, or tumor histology.

![Table 1](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAgAAAAAQCAYAAABk0c5A+4AAAABGdBTUEAALGPC/xhBQgBAS8ALRS4CGxXeFecAAAAASUVORK5CYII=)

**Table 1.** Patient demographics and tumor characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>52 (29-73)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Primary tumor site, n (%)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Breast</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Renal cell</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Germ cell</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Adenoid cystic</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (44)</td>
</tr>
<tr>
<td>1</td>
<td>13 (52)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Metastases outside CNS at time of CNS diagnosis</td>
<td>17 (68)</td>
</tr>
</tbody>
</table>
Recurrence. At a median follow-up of 36.1 weeks (or until death), there were no recurrences at the site of tumor resection in the 25 patients (Table 2). The 95% confidence interval for recurrence at the tumor resection cavity is 0% to 12%. There were new metastases in the brain at sites distant from the surgical bed in four patients (16%), and two patients (8%) had new metastases in the spinal canal. One developed a cauda equina mass (more than 8 months after craniotomy), and the other had multiple spinal lesions likely representing carcinomatous meningitis (3 months after craniotomy). The overall CNS recurrence rate was 24%, all remote from the craniotomy bed. Distant CNS recurrence occurred in 2 of 13 patients with non–small cell lung cancer, 2 of 3 breast cancer patients, 1 of 4 melanoma patients, and the single patient with a malignant yolk sac tumor. None of three renal cell carcinoma patients suffered CNS recurrence. In no case did recurrence appear along the surgical corridor between the resection cavity and the surface of the cortex.

Survival. Median survival was 33 weeks (range 5-127 weeks) for the patients with brain metastases. Approximately 33% of patients survived 1 year, and 25% survived 2 years. Sixteen patients died during the study, and nine were alive at last follow-up. Five of the sixteen died from CNS disease (31%). These five patients included all four patients with CNS recurrence within the brain at sites other than the surgical bed and the patient with multiple spinal lesions. Six of the sixteen patients (38%) died from progression of their systemic cancer. Five patients died of other or unknown causes (myocardial infarction, pontine hemorrhage, respiratory arrest, two unknown).

Multivariate/univariate analysis showed that preoperative ECOG performance status was a significant predictor of survival. Patients with an ECOG performance status of 0 had a median survival of 347 days. Patients with an ECOG status of 1 or 2 had a median survival of 184 days (P < 0.001). In univariate and multivariate analysis, age, tumor type, gender, size of lesion, number of wafers used, cause of death, recurrence in the CNS, and recurrence within the brain versus elsewhere in the CNS [spinal cord, cerebral spinal fluid (CSF)] were not significant predictors of survival.

Six of the patients taken to surgery with a presumed diagnosis of metastasis were found to have primary brain tumors on final pathology. Five patients had GBM, and one had ependymoma. Five of the six had wafers implanted (four with GBM, one with ependymoma). Median survival for the group of six patients was 59.4 weeks. The GBM subgroup had a median survival of 56 weeks. The five patients who received wafers had a median survival of 62.4 weeks. The patient with supratentorial ependymoma has survived more than 5.5 years.

Table 2. CNS recurrence following craniotomy for placement of carmustine polymer wafers

<table>
<thead>
<tr>
<th>Site</th>
<th>Number (%)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical bed</td>
<td>0/25 (0)</td>
<td>None</td>
</tr>
<tr>
<td>Distant sites in CNS</td>
<td>11/25 (44)</td>
<td>Lung (2), Breast (2)</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>1/25 (4)</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Multiple spinal canal lesions</td>
<td>0/25 (0)</td>
<td>Yolk sac tumor</td>
</tr>
</tbody>
</table>

Discussion

The addition of carmustine polymer wafers to a regimen of surgery and postoperative fractionated external beam radiotherapy for single brain metastasis resulted in the absence of local recurrences (0%). This is the first trial studying this treatment paradigm, and the rate of local recurrence compares favorably with traditional single brain metastasis treatment regimens (11, 14–17). Serious adverse events were rare and controllable with medical therapy. We believe this approach is clinically feasible and may provide additional local control in brain metastasis patients, as evidenced by the absence of local recurrence in the study population.

The postoperative seizure and infection rates in this study seem to be lower than those seen in patients treated with carmustine polymer wafer for newly diagnosed glioma (19). Several possible reasons for this observation exist. A number of the implantation techniques that were learned during the glioma studies were applied for this protocol. For example, careful dural opening and watertight dural closure are essential to prevent the collection of CSF (containing carmustine) under the skin incision. In addition, it has been our observation that patients can be more quickly tapered off steroid following resection of a brain metastasis compared with patients undergoing glioma resection. If true, the more rapid steroid taper may promote wound healing and help avoid complications.

In this study, the combination of surgical resection, carmustine polymer wafer placement, and external beam radiation therapy resulted in the absence of local tumor recurrence at the site of the initial brain metastasis. The recurrence rate at distant sites in the brain was 16%, similar to other studies of brain metastasis (11, 14–16). These findings are consistent with animal studies, suggesting that the carmustine is concentrated around the tumor bed (24–26) and thus would not offer any additional protection from tumor growth at sites remote from the tumor resection.

Although metastatic cancer is a systemic illness, there are several reasons why the addition of a local therapy such as the carmustine polymer wafer may be of benefit for treatment of metastases in the brain. First, local recurrences occur despite the best standard therapies. In studies of surgery and external beam radiotherapy, the recurrence rate at the site of surgery was 10% to 34% (11, 14–17). Second, metastases in the CNS often require treatment that is distinct from the treatment of the non-CNS metastases. The use of targeted treatments such as monoclonal antibodies to treat primarily extracranial disease may be a futile if CNS disease cannot be controlled (5). As systemic therapies have improved, the CNS has become a more prominent and therapeutically challenging metastatic issue (3–9). For example, breast cancer patients treated with an aggressive regimen of neoadjuvant chemotherapy at the University of North Carolina showed a higher-than-anticipated incidence of CNS involvement among those who relapsed, often in the setting of absent or well-controlled systemic disease (9). These patients almost uniformly died of CNS progression, despite having primary tumors that were sensitive to systemic therapy. Clearly, CNS may require unique and separate treatments to keep patients free of metastatic progression.

The patients treated in this study are similar to those treated in other surgical trials for brain metastasis resection with regard...
to age, preoperative histology, and preoperative performance status (11, 15, 27). However, it is unlikely that they are comparable with patients treated in most published radiosurgery series. All of the patients enrolled in this study were evaluated at centers that routinely use both radiosurgery and open surgery. All patients had a preoperative radiation oncology evaluation. As such, each was evaluated as a candidate for both radiosurgery and open surgery, with craniotomy being selected as the better option. The most likely reasons for this decision were (a) tumor size, (b) degree of mass effect or edema, and (c) need for tissue diagnosis. The data from the study confirm this observation. A total of 14 of the 25 patients had a measured tumor cavity resection diameter exceeding 3 cm, the typical upper size boundary for radiosurgery. As such, comparisons of this study group with radiosurgery groups should be done with care.

Carmustine is not commonly used in the systemic treatment of tumors prone to CNS metastases. However, in animal models of CNS metastasis, locally delivered carmustine slows growth and prolongs survival in multiple tumor types, including breast, melanoma, and renal cell carcinoma (28). The explanation may lie in the significant difference in local concentration achievable by polymer-based therapy. Treatment with a carmustine polymer achieves CNS concentrations up to 1,000-fold greater than those achieved by systemic administration (25). Thus, it may not be possible to extrapolate the efficacy of carmustine polymer therapy from the response of a particular tumor type to systemic carmustine administration. For example, although camptothecin and its analogues would be a better choice for systemic therapy of colon cancer, locally delivered carmustine with concurrent radiation therapy prolonged survival in a rodent model of colon carcinoma brain metastasis, whereas locally delivered camptothecin with concurrent radiation did not (28).

Despite the excellent local control rate achieved in this study and the fact that distant CNS relapse rate was 24%, similar to other studies (11, 15), median survival was only 33 weeks. As expected, patients with a higher performance status at presentation had a longer survival (50 weeks). Patients who had distant CNS recurrences died from the CNS disease, but the other patients died from systemic progression of their cancer or from treatment-related morbidity. This study shows that excellent local control of CNS tumor, although necessary for prolonged survival, is not sufficient alone to ensure long-term survival. Long-term survival will be achieved only when concurrent advances are made in treatment of local and distant CNS disease and the systemic cancer.

In conclusion, the use of carmustine polymer wafers, in addition to surgery and whole-brain radiotherapy, is safe and seems to improve local tumor control. Further study is required to validate the effectiveness of improving local tumor control and to determine any survival benefit. With progress in treating the systemic manifestation of cancer, improvements in the control of CNS disease will be increasingly important.

Acknowledgments

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References

Treatment of Single Brain Metastasis with Resection, Intracavity Carmustine Polymer Wafers, and Radiation Therapy Is Safe and Provides Excellent Local Control

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