

The Surgical Bed After BCNU Polymer Wafer Placement for Recurrent Glioma: Serial Assessment on CT and MR Imaging

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OBJECTIVE. The objective of our study was to describe the CT and MR imaging appearances of the surgical bed in the brains of patients receiving biodegradable polymers impregnated with *N,N'*1, 3-Bis-(2-chloroethyl)-*N*-nitrosourea (BCNU) for recurrent glioma and to determine whether patients receiving placebos could be differentiated from those receiving BCNU based on the pattern and growth kinetics of tumor recurrence.

MATERIALS AND METHODS. The CT and MR images of 20 patients who underwent surgery for resection of recurrent high-grade gliomas and placement of intratumoral wafers (11 received BCNU polymer wafers, nine received control wafers) were analyzed for wafer appearance, volume of gas in the tumor bed, and volume of enhancement on serial scans.

RESULTS. Wafers appeared as linear hyperdense structures on CT and as linear low-signal-intensity structures on MR imaging and caused no significant enhancement. In the BCNU polymer group, gas volume was $4.0 \pm 3.4 \text{ cm}^3$ (mean \pm SD), whereas gas volume was $1.6 \pm 3.0 \text{ cm}^3$ for the placebo group (Mann-Whitney test, $p = 0.03$). A trend toward linear rather than exponential recurrent tumor growth was identified for the BCNU polymer group but not for the placebo group.

CONCLUSION. BCNU polymer wafers have a specific appearance on CT and MR imaging with which radiologists should be familiar: gas in the surgical bed is an expected transient finding, and tumor regrowth in patients receiving BCNU polymer wafers appeared to occur at a slower rate than in those receiving the placebo.

More than one half of the approximately 18,000 primary brain tumors diagnosed annually in the United States are considered high grade—that is, anaplastic astrocytoma or glioblastoma multiforme [1, 2]. Despite being used for over 20 years of systemic chemotherapy does not significantly alter the outcome of patients with glioblastoma multiforme and has only a modest effect on those with anaplastic astrocytoma [3]. Although optimal therapy for patients with high-grade gliomas has not been determined, surgery combined with radiation is considered the best currently available therapy, prolonging median survival to just under a year [4, 5]. Innovative, new approaches are emerging in response to those discouraging results, including more selective cytotoxic agents [6, 7], inhibitors of angiogenesis and signal transduction [8], and regional chemotherapeutic [9] and radiotherapeutic [10] strategies.

Polymer wafers impregnated with *N,N'*1, 3-Bis-(2-chloroethyl)-*N*-nitrosourea (BCNU) were recently approved for use in recurrent glioblastoma multiforme and anaplastic astrocytoma in the United States, Europe, Canada, South America, Israel, and South Korea. Wafers consist of a cytostatic chemotherapeutic agent (BCNU) incorporated into a biodegradable hydrophobic polymer wafer. Those wafers protect the product from hydrolysis and enable slow release of BCNU into the surgical cavity over a 2- to 3-week period after implantation. Reasons for that approach include the fact that roughly 90% of glioblastoma multiforme recur within 2 cm of the primary site and that the probability of extra-central nervous system metastasis is low [3]. Implantation of BCNU polymer wafers in the surgical cavity also bypasses the blood-brain barrier and exposes adjacent tumor to a 113-fold higher concentration of BCNU than does systemic chemotherapy [11].

In the past few years, surgical implantation of BCNU-impregnated biodegradable polymers (Gliadel; Guilford Pharmaceuticals, Baltimore, MD) has been shown to prolong survival in recurrent high-grade gliomas from 23 weeks in

patients receiving placebos to 31 weeks in patients receiving BCNU polymer wafers when implanted in the surgical cavity during resection of tumor for recurrence [12]. As the use of BCNU polymer wafers increases, it is important to have an understanding of the normal radiologic appearance of these wafers and to know the typical response of the brain to their presence. Specifically, clinicians need to know whether the wafers are capable of inciting an inflammatory response that may mimic residual or recurrent tumor and whether the wafers create artifacts, such as gas in the tumor bed, as indicated in one preliminary report (McDaniel T et al., presented at the American Society of Neuroradiology meeting, May 1998).

Our goals are to describe the CT and MR imaging appearances of the wafers in the surgical bed over time in the brains of patients receiving BCNU polymer wafers compared with patients receiving placebos. We also assessed the images for evidence of treatment response and the pattern of recurrence in both groups.

Materials and Methods

This study is a retrospective analysis of CT and MR images obtained at our institution of a subset of the cohort of patients enrolled in the original multicenter BCNU polymer wafer efficacy study [12]. Of the 222 patients enrolled in the efficacy study, 20 patients (15 men, five women; age range, 30–73 years; mean age, 45 years) underwent imaging studies at our institution and had a preoperative and at least two postoperative cross-sectional imaging studies (CT or MR imaging). Written informed consent was obtained for the original study using procedures in accordance with the investigational review board at our institution. Inclusion criteria for the initial study were a unilateral single focus of tumor in the cerebrum with at least 1.0 cm^3 enhancing volume on CT or MR imaging in patients with recurrent malignant glioma, a Karnofsky performance score of at least 60 (i.e., the ability to function independently), completion of external beam radiation therapy, and no nitrosoureas for 6 weeks and no other systemic chemotherapeutic agent for 4 weeks before enrollment. Tumor resection would have been performed in those patients irrespective of study enrollment. Our review of the imaging findings on the selected subset of patients was a retrospective study. As a result, no additional consent was obtained.

Patients underwent craniotomy for maximal resection of tumor. After surgery, up to eight wafers were placed in the surgical cavity. The wafers contained either BCNU ($50 \mu\text{g}/\text{mm}^3$ polymer, for a maximum patient dose of 62 mg) plus polymer matrix or only polymer. The surgeons were unaware of the content (placebo or BCNU) of the polymer wafers they placed. Patients were clinically and radio-

logically reassessed every 2 months. All patients were treated with corticosteroids.

CT and MR images of the selected patients were analyzed for wafer appearance, volume of gas in the tumor bed, and volume of enhancement (contiguous with the tumor bed and remote) on serial scans beginning with the initial postoperative study.

CT consisted of 8-mm thick axial sections from the skull base to the vertex before and after administration of IV iohexol (Omnipaque; Nycomed Amersham, Buckinghamshire, UK) (120 mL). MR imaging was performed with a 1.5-T magnet (Signa; General Electric Medical Systems, Milwaukee, WI) and consisted of an unenhanced T1-weighted localizing sequence (sagittal), axial T1-weighted sequence (TR/TE, 600/15; number of excitations, 0.5–2.0), dual-echo (TR/first-echo TE, second-echo TE, 3000/30, 100; number of excitations, 0.5–2.0), and axial and coronal T1-weighted sequences obtained after IV administration of gadopentetate dimeglumine (0.1 mmol/kg, Magnevist; Berlex Laboratories, Wayne, NJ). Images were acquired with 5-mm thick sections that were either contiguous or contained interposing 1- or 2-mm gaps. Matrix size was either 256×192 or 256×256 . Images were reviewed by two board-certified neuroradiologists who were unaware of the presence or absence of BCNU within the wafers. Enhancing tissue volume was determined by outlining on an independent console using a manual trace software program developed in-house (MedVol 1.7). Statistical analysis and curve fitting were performed using StatView SE + Graphics (version 1.03; Abacus Concepts, Berkeley, CA). Statistical significance was indicated for a *p* value of less than 0.05 using the Mann-Whitney test.

To determine the kinetics of recurrent tumor growth, we attempted linear and exponential curve fits for each patient who had more than two postoperative studies. The fit that provided the lower *p* value was chosen as the best representation of the kinetics of tumor regrowth for that patient. For cases of linear recurrent tumor growth, the data were expressed as rates (cubic centimeters per month), whereas for cases of exponential regrowth, doubling times (days) were used. The numbers of subjects with linear versus exponential kinetics of recurrent tumor growth, for both the BCNU polymer and placebo wafer groups, were compared using the Fisher's exact test.

Results

Patients

BCNU polymer wafers were implanted in 11 patients and placebo polymer wafers, in nine. An average (\pm SD) of 7 ± 1 wafers were implanted per patient. Wafers measured 1.4 cm in diameter and 1.0 mm in thickness. They were placed on the resection surface to cover as much tissue as possible. Sheets of oxidized regenerated cellulose (Surgicel; Johnson and Johnson Medical, Arlington, TX) were used to

secure the wafers in place. All patients were treated with corticosteroids. Four patients in the placebo group and two in the BCNU polymer group underwent repeated surgery within 6 months of wafer implantation. Mean (\pm SEM) survival rates after surgery for wafer placement were 397 ± 91 and 270 ± 89 days for the BCNU polymer and placebo groups, respectively (Mann-Whitney test, *p* = 0.086). Of the four patients who lived more than 400 days, two had anaplastic astrocytoma, and one of those patients underwent additional surgery. The remaining two had glioblastoma multiforme. Three patients were treated with BCNU polymer wafers, whereas one patient received a placebo.

Surgical Bed

Images from a typical case are depicted in Figure 1. The polymer wafers in patients with or without BCNU were linear high-density structures on CT and linear low-signal-intensity structures on MR imaging. Wafers were identified in all patients on the immediate postoperative scan; although approximately seven wafers were placed per patient, only three or four were discretely identified in most cases. Wafers became much less conspicuous on the next scan, which was usually obtained 6 weeks after surgery.

There was no difference in the appearance of the wafers in both groups of patients, suggesting no significant contribution of the chemotherapeutic agent to the signal characteristics of the wafers.

Sixteen patients had gas in the surgical bed where the wafers were placed (Figs. 1B and 2B). In seven of those patients, the volume of gas was less than 1 cm^3 . Gas volume approached 10 cm^3 in four patients. In the BCNU polymer group, gas volume was $4.0 \pm 3.4 \text{ cm}^3$ (mean \pm SD), whereas it was $1.6 \pm 3.0 \text{ cm}^3$ for the placebo group (Mann-Whitney test, *p* = 0.03). In the BCNU polymer group, gas in the surgical bed was detected up to 23 days after implantation of the wafer (range, 1–23 days; median, 11 days). In the placebo group, gas was detected up to 13 days after implantation of the wafer (range, 0–13 days; median, 7 days; Mann-Whitney test, *p* = 0.15).

Concerning the pattern of tumor recurrence, we noted that tumor recurred in the periphery of, rather than within, the surgical bed of two patients receiving BCNU polymer wafers (Fig. 3C). Recurrence in patients who received placebo wafers tended to be less affected by the location of wafer placement, occurring both within and around the

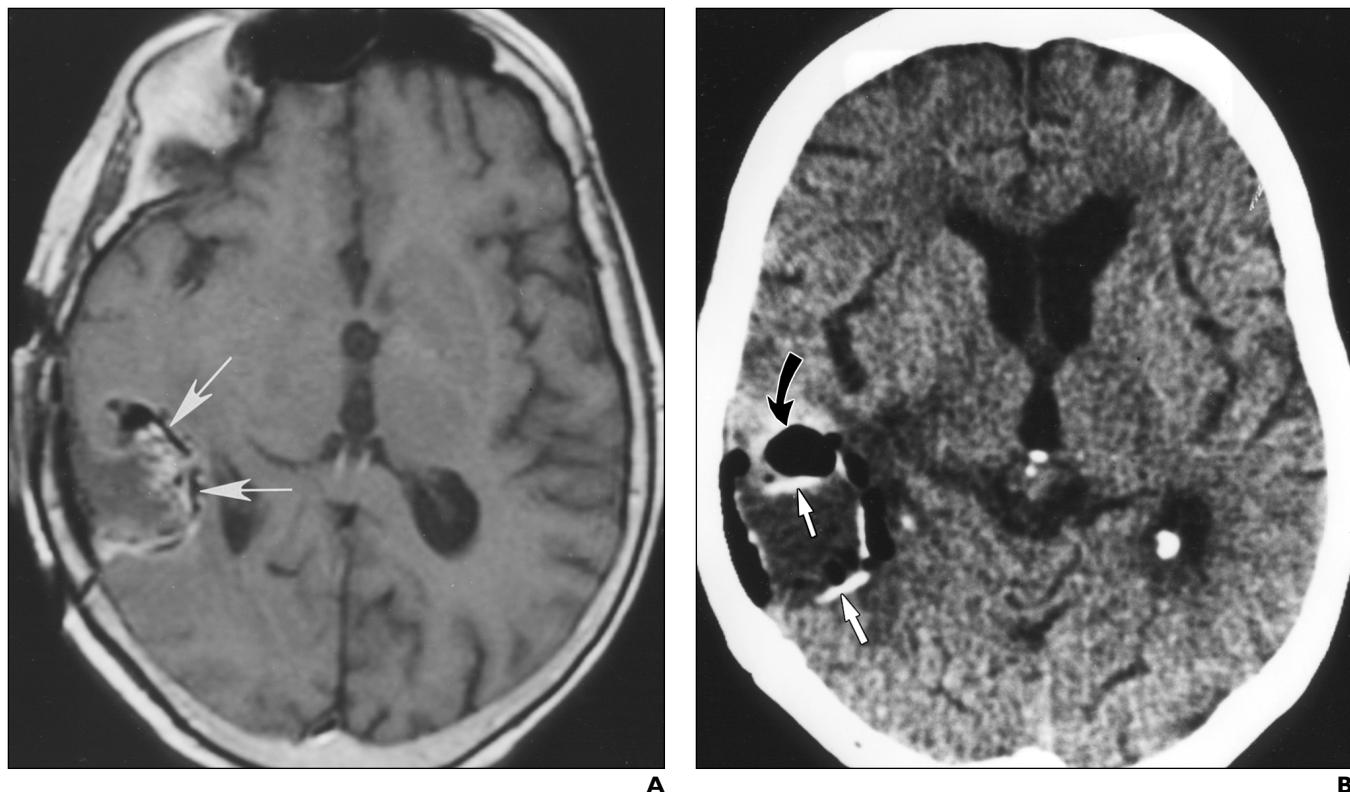


Fig. 1.—Typical wafer appearance in 73-year-old man who underwent resection of anaplastic astrocytoma with placement of *N,N* 1,3-Bis-(2-chloroethyl)-*N*-nitrosourea (BCNU) polymer wafer.

A, Axial T1-weighted MR image obtained 1 day after wafer placement shows that wafers (arrows) are linear and of low signal intensity.

B, Axial unenhanced CT scan obtained 2 weeks after surgery shows radiodense wafers (straight arrows) and gas in surgical bed (curved arrow). Gas in surgical bed was gone by next scan that was obtained 6 weeks later (not shown).

surgical cavity. Tumor recurred remotely in only one patient in this series, and that patient, who was originally diagnosed with anaplastic astrocytoma, received placebo wafers.

There was no significant enhancement adjacent to the BCNU polymer wafers on the immediate postoperative (< 3 days) studies, except in one patient (Fig. 4). In this patient, follow-up images obtained 18 days and 2 months after surgery showed persistence of the originally noted ring enhancement pattern with development of a posteriorly located enhancing mass compatible with tumor recurrence. We speculate that the original enhancement on the immediate postoperative image was due to residual tumor, rather than to the wafers.

Recurrent Tumor Growth Patterns

Using graphical analysis of tumor regrowth kinetics, we attempted to understand the effect that BCNU polymer wafers have on tumor regrowth. Because BCNU is a cytostatic agent, we anticipated that tumors in patients treated with BCNU would display

linear rather than exponential growth kinetics, which would be the pattern in patients treated with placebos.

We determined that 11 patients had a typical postoperative course—that is, with a life span of less than 400 days and recurrent tumor volumes of under 150 cm^3 . Tumor recurrence after BCNU polymer wafer implantation tended to occur within the first 100 days after surgery. The three patients with the longest survival times had been treated with BCNU polymer wafers. Excluding, for the purpose of curve fitting, two patients who had only two postoperative examinations and another patient who was cured surgically, we found a linear curve fit proved better in nine patients, whereas an exponential fit was better in eight.

Among the nine patients with linear recurrent tumor growth kinetics, seven were treated with BCNU polymer wafers, whereas two received placebos. For patients who received placebos and whose tumors revealed linear growth, slopes tended to be higher than those for patients who received BCNU polymer wafers (Mann-Whitney test, $p = 0.088$). Among the eight patients

with exponential recurrent tumor growth kinetics, three were treated with BCNU polymer wafers, whereas five received placebos.

Although there was a trend toward longer postoperative survival in the treatment group, this difference did not reach statistical significance (Mann-Whitney test, $p = 0.086$). Similarly, we could not show a significant difference between the proportions of treated and control subjects with linear versus exponential tumor growth (Fisher's exact test, $p = 0.153$).

Discussion

Localized chemotherapy involving surgical implantation of BCNU polymer wafers has proven effective in increasing the length of survival in patients with malignant gliomas [12]. The benefit of BCNU polymer wafers as the initial treatment of malignant gliomas has also been shown in one prospective randomized study [13]; a second, larger study, similarly designed, is under way. Other applications, such as treatment for metastatic brain tumors and combination therapy with a variety of systemic agents,

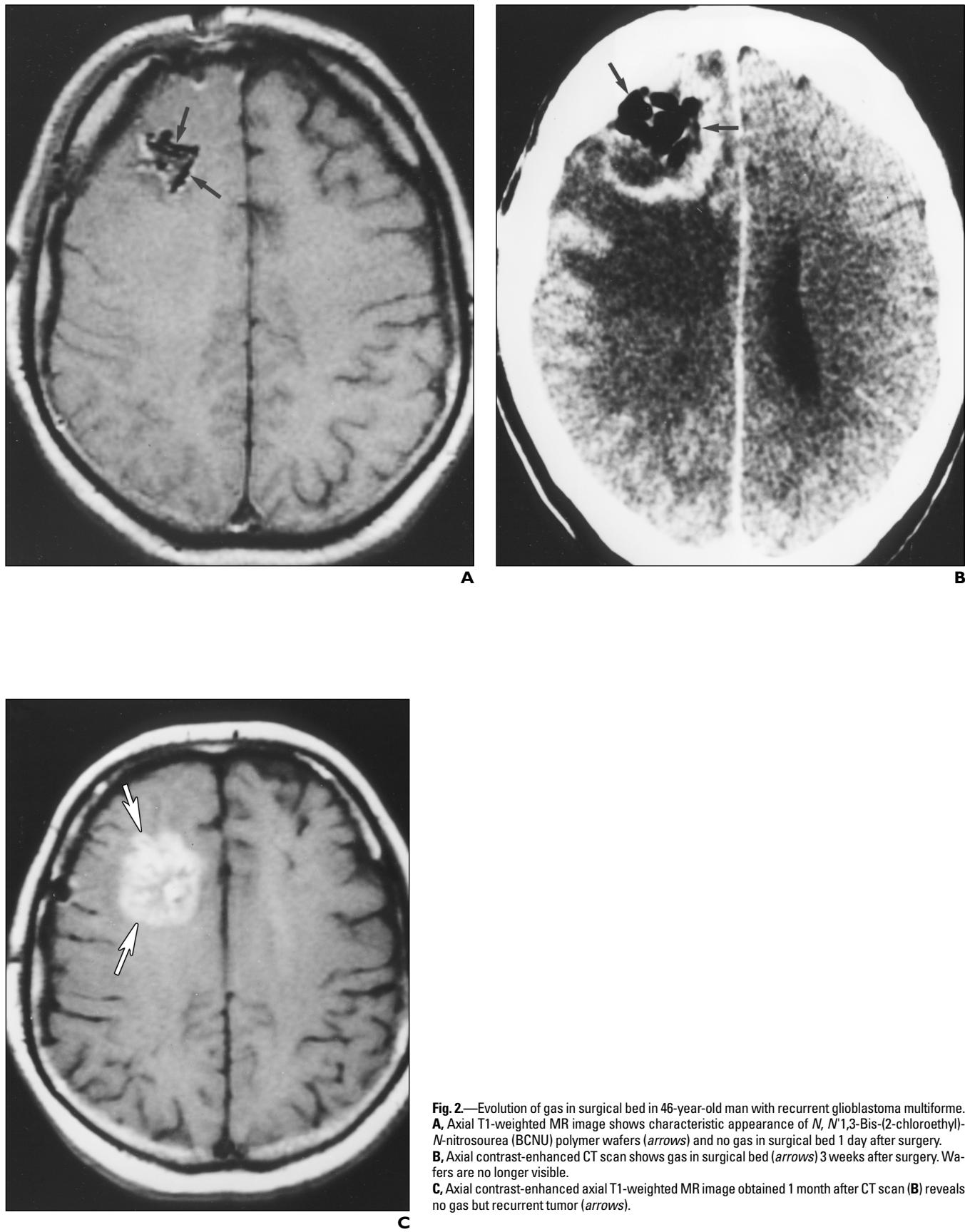
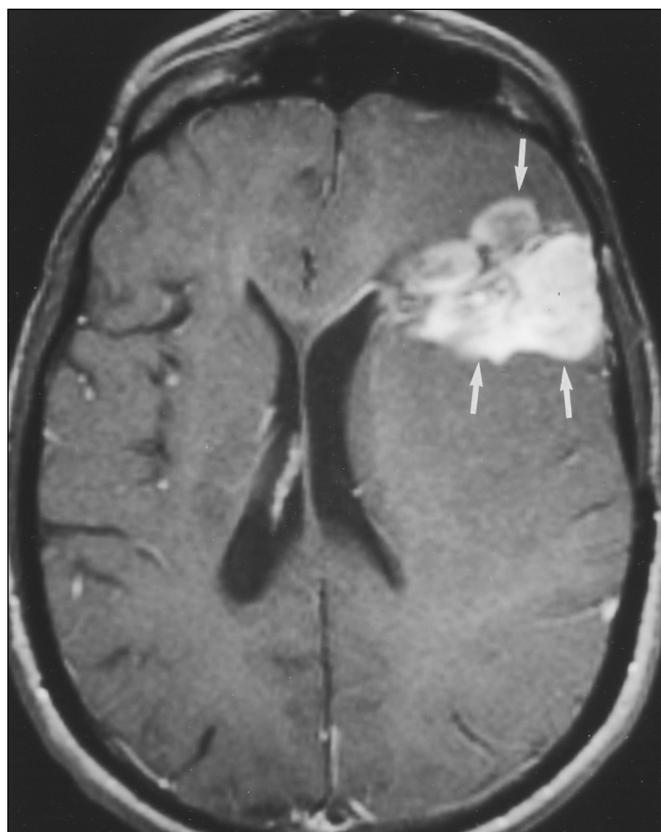


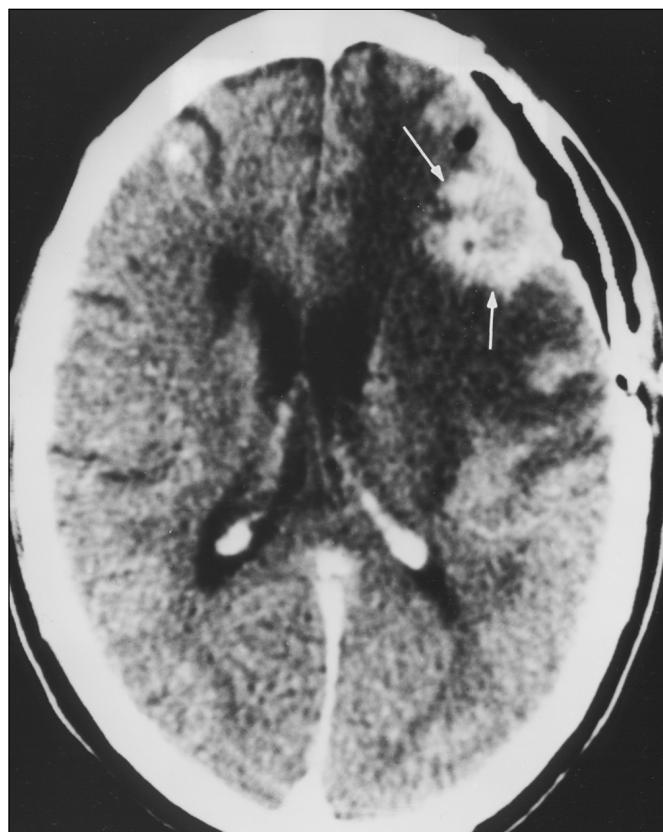
Fig. 2.—Evolution of gas in surgical bed in 46-year-old man with recurrent glioblastoma multiforme. **A**, Axial T1-weighted MR image shows characteristic appearance of *N,N'*-Bis-(2-chloroethyl)-*N*-nitrosourea (BCNU) polymer wafers (arrows) and no gas in surgical bed 1 day after surgery. **B**, Axial contrast-enhanced CT scan shows gas in surgical bed (arrows) 3 weeks after surgery. Wafers are no longer visible.

C, Axial contrast-enhanced axial T1-weighted MR image obtained 1 month after CT scan (**B**) reveals no gas but recurrent tumor (arrows).

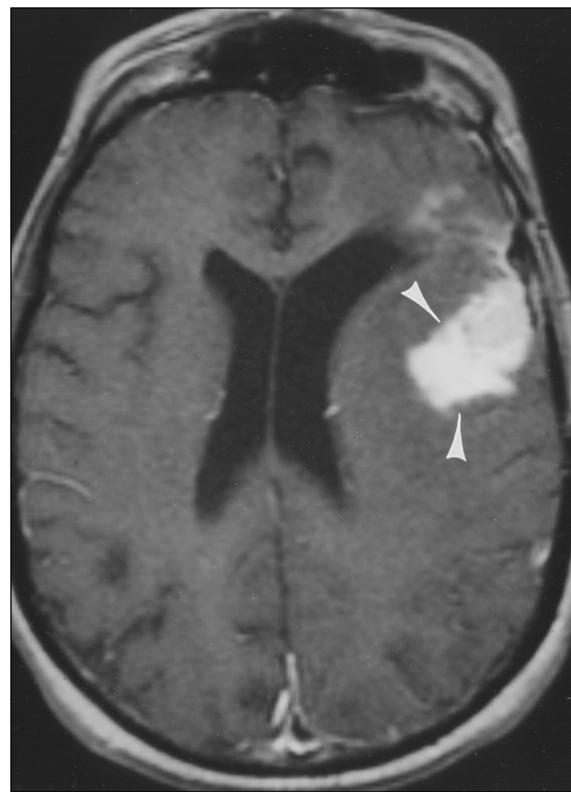
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A



B



C

Fig. 3.—Tumor recurrence near surgical bed in 31-year-old man with recurrent glioblastoma multiforme.

A, Axial contrast-enhanced T1-weighted MR image before repeated surgery and placement of *N,N'*-Bis-(2-chloroethyl)-*N*-nitrosourea (BCNU) polymer wafer shows tumor (arrows) in left frontal lobe.

B, Axial contrast-enhanced CT scan obtained 1 day after surgery shows blood in surgical bed (arrows).

C, Axial contrast-enhanced T1-weighted MR image obtained 16 months after **B** shows tumor recurrence in posterior periphery of original tumor margin (arrowheads).

are being studied in ongoing clinical trials [14, 15]. The growing use of BCNU polymer wafers to treat recurrent brain malignancies underscores the importance of knowing their appearance on routine cross-sectional imaging studies.

The questions we addressed in this study included the appearance of the wafers on CT and MR imaging, whether gas in the surgical bed is an expected finding or an indicator of infection, and whether the wafers are capable

of inciting an inflammatory reaction with enhancement that may mimic tumor on a contrast-enhanced study. We have determined that because they are invariably imaged in cross-section, the wafers appear linear and are of the

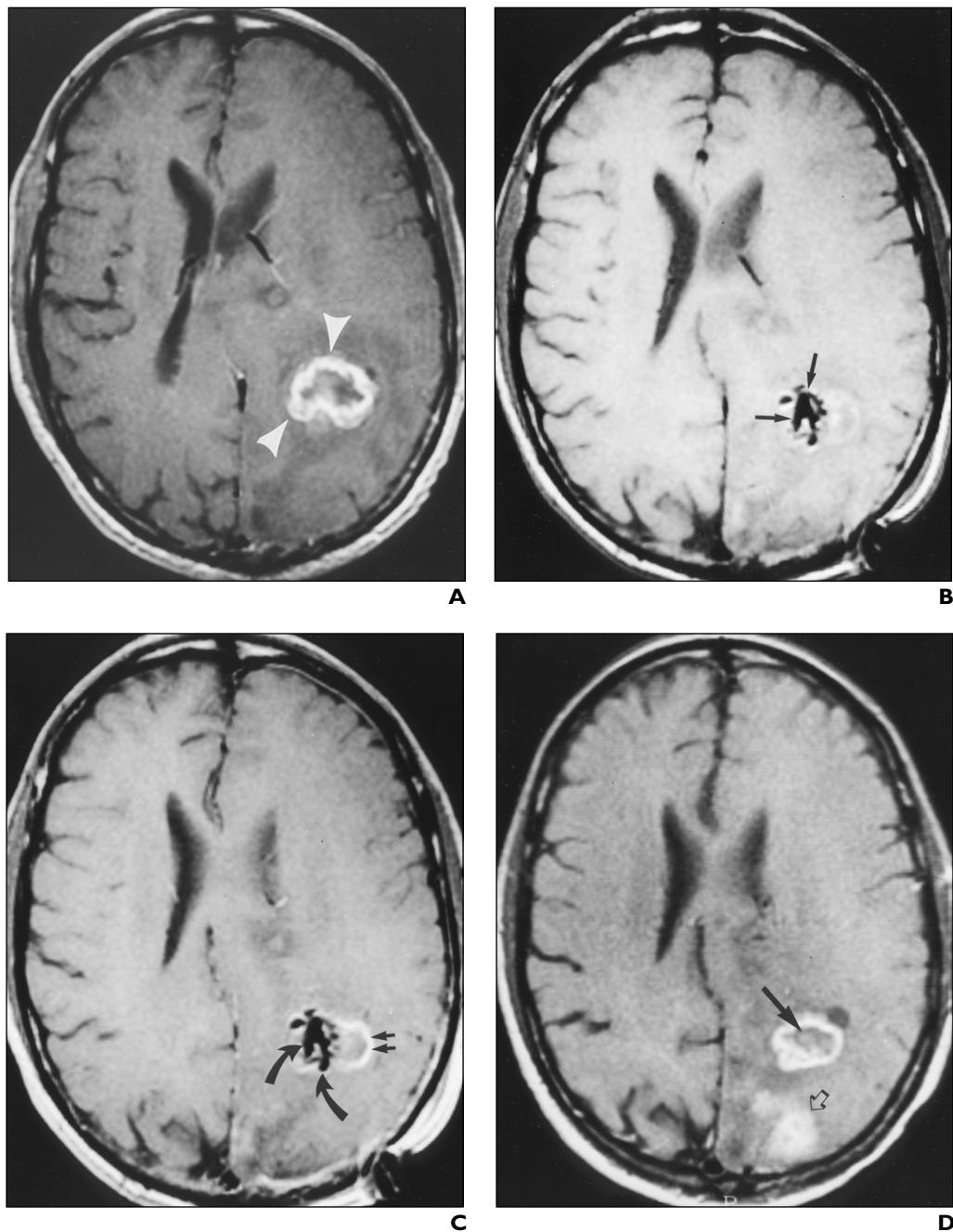


Fig. 4.—42-year-old man with recurrent left parietal anaplastic astrocytoma.
A, Axial contrast-enhanced T1-weighted MR image shows minimal enhancement surrounding surgical cavity (arrowheads).
B and **C**, Axial T1-weighted MR images obtained 18 days after surgery show polymer wafers (arrows, **B**) composed of *N,N'*1,3-Bis-(2-chloroethyl)-*N*-nitrosourea (BCNU) before (**B**) and after (**C**) contrast enhancement. Enhancing rim around surgical cavity (straight arrows, **C**) near wafers (curved arrows, **C**) conforms to original tumor shape.
D, On axial contrast-enhanced T1-weighted MR image, wafers are not seen, and surgical bed, where wafers were placed (solid arrow), is stable 2 months after placement, suggesting that original enhancement pattern was due to residual tumor rather than wafers. New enhancing mass is identified along posterior aspect of surgical bed (open arrow), compatible with tumor recurrence.

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expected increased density and decreased signal intensity characteristic of polymer materials on CT and MR imaging, respectively (Fig. 1). The gas in the surgical bed (Figs. 1B and 2B) is an expected finding that dissipates with time and does not indicate infection (although superimposed infection cannot be excluded), supporting a previous study (McDaniel T et al., the American Society of Neuroradiology meeting, May 1998). The origin of this gas remains unclear, but it may be due to expansion of the air trapped between the wafers and overlying Surgicel at a higher—that is, body—temperature, or it may be related to the chemical breakdown of the wafer. That BCNU polymer wafers produced more gas than placebo polymer wafers suggests that BCNU engenders gas production, perhaps by inciting an intense, local inflammatory reaction and necrosis. Nevertheless, an inflammatory reaction sufficient to produce contrast enhancement on MR imaging more than 3 days after surgery [16] was not seen in our patient cohort (Fig. 4). Prager et al. [17] obtained similar results.

Because little contrast enhancement occurs in the surgical bed adjacent to the BCNU polymer placement site, enhancement in this location should be considered recurrent tumor or treatment necrosis until proven otherwise pathologically.

We found that tumors would still generally recur in the surgical bed despite the BCNU polymer wafers. However, two patients in the treatment group and none in the placebo group experienced recurrence adjacent to, rather than within, the surgical bed. That finding may reflect the local nature of this therapy.

We found that tumor recurrence generally occurred within the first 100 days after repeated surgery for implantation of BCNU polymer wafers. Although the patients with longer survival and slower tumor regrowth curves tended to be those who received BCNU polymer rather than placebo polymer wafers, no statistically significant difference between the two groups regarding regrowth kinetics emerged. Similarly, no significantly prolonged survival was established in the treatment group versus the placebo group.

Because our goal was to perform a blinded, controlled, and longitudinal study

of the CT and MR imaging appearances of the effects of BCNU polymer wafers on the brain, we had a limited group of patients from which to choose. Nevertheless, the trends that we showed—linear rather than exponential growth kinetics of recurrent tumors ($p = 0.153$), lower growth rates of recurrent tumors in patients with linear kinetics ($p = 0.088$), and higher survival ($p = 0.086$) in patients treated with BCNU polymer wafers rather than with placebos—suggest that the treatment effects of BCNU polymer wafers can be followed accurately on CT and MR imaging, with recurrent tumor growth kinetics predicting survival. Those imaging end points, rather than survival, may consequently be used as surrogate markers in evaluating local therapies for brain tumors. Analogous to the trend that we showed herein regarding survival in the subgroup of patients we studied from the original clinical study [12], in which definite efficacy was found, the trends that we see in our imaging findings probably reflect selection bias and would also likely reach statistical significance given a larger sample size.

In summary, BCNU polymer wafers have a consistent appearance on postoperative CT and MR imaging with which radiologists should be familiar. Gas in the surgical bed is an expected transient finding that may last up to 3 weeks and does not necessarily represent infection, particularly because gas-forming organisms in the brain are rare. We also conclude that tumor regrowth in patients receiving BCNU polymer wafers appeared to occur at a relatively slower rate than in those receiving placebos, reflecting the prolonged survival of those patients, which has been shown previously in larger clinical trials [12].

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