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# Localized Chemotherapy with Carmustine (BCNU) Wafers in High-Grade Gliomas: Clinical Outcomes and Safety Review

**By David Hu**

## AUTHOR BIO

David Hu is a ninth grader at Acton-Boxborough Regional High School in Massachusetts. Outside of school, he enjoys working on research projects, as well as learning more about biology, chemistry, and medicine. He is an active boy scout in his local area, and he loves playing piano and tennis. Besides all of this, he is motivated in volunteer work in his community and is working toward the congressional award. His long-term goal is to pursue a career in medicine or biomedical research, where he can contribute to developing improved treatments and advancing patient care.

## ABSTRACT

Gliadel wafers are biodegradable polymers, impregnated with the chemotherapeutic drug carmustine, also known as 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). These wafers are surgically implanted in order to provide localized chemotherapy to malignant brain tumors. While Gliadel wafers have been used for many years, their positive impacts and adverse effects are still under investigation. This study aims to evaluate the efficacy and safety of these wafers through a review of recent literature. This was conducted using PubMed and Google Scholar, focusing on studies published after 1995. Data were extracted from 14 different sources, including randomized controlled trials (RCTs), cohort studies, and meta-analyses. Each source included study design, sample size, survival outcomes, and reported adverse effects. Studies published prior to 1995, as well as editorials, and case reports, were excluded. Across many included studies, the Gliadel wafer implantation was associated with trends toward improved overall survival (OS). Adverse effects were generally similar to the ones found in localized chemotherapy. Overall, the findings conclude that BCNU wafers may serve as an able adjunct to traditional chemotherapeutic methods.

***Keywords****: Adverse Effects, BCNU, Brain Edema, Carmustine, Chemotherapy, Controlled Release, Gliadel, Glioblastoma Multiforme, Glioma, Implantation, Temozolomide.*

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## INTRODUCTION

Gliomas are the most common type of brain cancer in adults, and are graded on a scale of I to IV, based on severity *(Xing et al., 2015)*. Gliomas between grades of III and IV are "high severity," and the majority of Gliomas that are grade IV are known as Glioblastoma Multiforme (GBM). GBM causes approximately 74,000 cases around the world every year, and accounts for nearly 60% of primary brain tumors *(Xing et al., 2015)*.

Even though traditional treatment methods for Glioblastoma are proven to be very effective, new treatment has emerged on the market. BCNU wafers, also known as Gliadel wafers (Figure 1), are a type of medical treatment designed to reduce systemic distribution, thus reducing side effects and improving local treatment. OS in numerous studies were significantly increased. OS is the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. OS is a much stronger indicator of clinical efficacy than progression free survival (PFS), which is the length of time during and after treatment that a patient lives with a disease, such as cancer, but it does not get worse or progress. Wafers are surgically implanted into the tumor cavity after surgery, and the carmustine (Figure 2) will be slowly released directly into the tumor within the duration of two to three weeks. New data from randomized control trials (RCTs) and meta-analyses show that BCNU wafers can improve OS, but with the consequence of numerous adverse effects, such as Brain Edema (*Salle et al., 2018*).

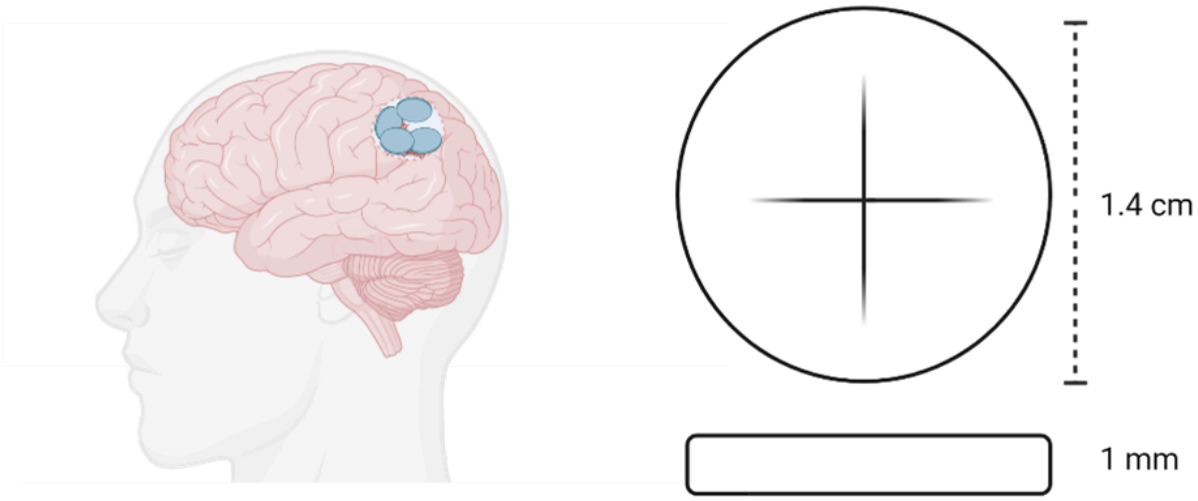


*Figure 1. Implantation of Gliadel wafers in a brain resection cavity and dimensions of a single wafer (Erikspena 2022).*

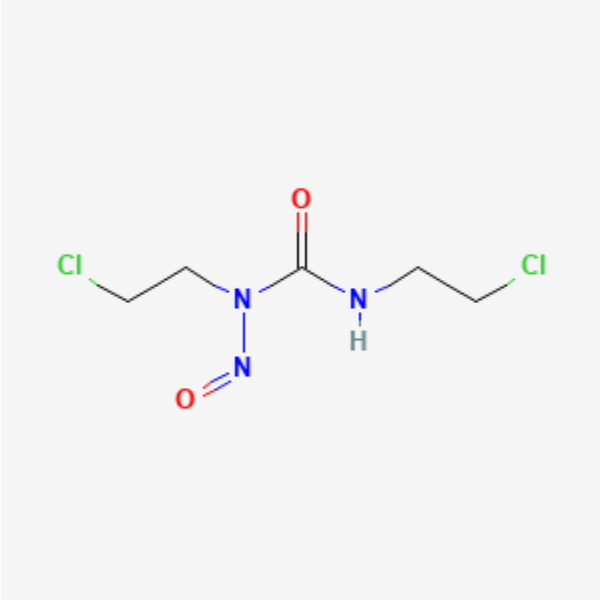


*Figure 2. Chemical structure of carmustine, a chemotherapeutic.*

Usage of these wafers is currently a very controversial topic among neurosurgeons, because of the wafers' potential benefits, as well as their documented adverse effects. The objective of this study is to evaluate the efficacy and safety of these wafers through a review of recent literature. This paper additionally seeks to provide evidence that further investigation into carmustine wafers should be conducted. Further studies might provide proof to help surgeons in deciding whether these wafers should be used to fight GBM.

## METHODS

After searching public medical databases (PubMed and Google Scholar) with the keywords of "Gliadel Wafers", "Gliadel Wafers Side Effects", and "Adverse Effects", the results were analyzed from numerous reviewed and published papers. The selected papers reported relevant OS, and RCTs, cohort studies, and meta-analyses were included.

Papers published after 1995 reporting relevant endpoints were included, while those published earlier, as well as editorials and case reports, were excluded. The relevant data, specifically OS, sample size, study design, and reported adverse effects, were chosen from the included papers, and these data were the basis for evidence. Also, from the included papers, the adverse effects described were compiled and summarized. Finally, trends between Gliadel wafer use and OS were analyzed.

## RESULTS

The results are presented below. First, the improvements resulting from BCNU wafers are summarized. Then, the adverse effects resulting from BCNU wafers are summarized. Finally, the overall findings from the studies are presented.

### Improvements

#### *Noticeable OS improvement*

When pooling all the six studies found in their meta-analysis, including RCTs and cohort studies, in *The role of Gliadel wafers in the treatment of newly diagnosed GBM: a meta-analysis,* the researchers found the risk of death (OS) of newly diagnosed GBM patients that were treated with BCNU (*Xing et al., 2015)*. Analysis of the pooled RCTs and cohort studies showed a statistically significant 41% reduction in risk for patients treated with carmustine, with minimal heterogeneity ($I^2 = 0.0\%$, $P < 0.0001$), providing strong evidence of a survival benefit from carmustine wafers (*Xing et al., 2015*).

*Lillehei et al. (2017),* who conducted their study as part of the *VIGILANT* registry with 500 patients over a 3 year period, found similar results. The 500 patients were split into recurrent and newly diagnosed patients, with 222 and 272 patients, respectively, in each group. In the recurrent section, patients treated with BCNU had a lengthened 6 month mortality rate (40% vs 53%; $p = 0.06$) and a median overall survival increase (31 vs 23 weeks; $p = 0.06$), which was conducted by *Brem et al. (1995).* Two-thirds of these patients had recurrent GBM, and BCNU wafers were associated with significantly reduced 6 month mortality in this patient group (44 vs 64%; $p = 0.02$). Two Phase III, multicenter, and placebo-controlled trials monitored the newly diagnosed patients as well.

A different international study was a Phase 3 study conducted in 14 different countries including the US, Germany, France, the UK, Scotland, Finland, and Israel (*Iuchi et al., 2022*). It was a study with 506 patients with malignant Glioma, including newly diagnosed and recurrent cases. The majority had glioblastoma (79%). The median OS was 18 months, with survival rates being 39.8% at 2 years and 31.5% at 3 years. These rates suggest survival benefits consistent with or exceeding outcomes reported in previous international studies of Gliadel plus standard therapy.

Lastly, another international study, a 9-year nationwide retrospective study involved 1659 patients, and with 39 institutions being involved. They found, because they did not have a control group, that the Gliadel Wafers may increase OS, especially when combined with Radiotherapy (RT) and Temozolomide (TMZ.) Because of this limited evidence, France has decreased CW usage rate. Even though these are unreliable statistics, the important thing to note is to notice that there may be an improvement, even if it is minor (*Champeaux & Weller., 2020*).

#### *Noticeable improvement with combined treatments*

One paper that demonstrated the efficacy of combined treatments is *Chowdhary et al. (2015),* which was an analysis that included numerous contemporary clinical studies (60 in total); it investigated

the survival outcomes and safety of carmustine wafers when used to treat high-grade Gliomas. The authors of this study pooled survival and safety data from existing literature, and no new patients were enrolled. After comparing OS, median survival time, and adverse effects for periods of 1, 2, and 3 years for grade three and four Gliomas, the results were conclusive. Then, after putting the data into the form of graphs, it was clear that RT/TMZ combined with BCNU were most effective in improving survival rates, and no carmustine wafers, or placebo, were least effective (*Chowdhary et al., 2015.*) For example, the analysis of grade 3 and 4 Gliomas showed that 76 patients that took both treatments survived for 1 year, 34 for two years, and 16 for 3 years. However, with no BCNU, 48 patients would survive for 1 year, 15 for two years, and 7 for three years.

The study with 240 patients (a portion of the total patients tested), *Westphal et al. (2003, 2006)* reported a significant OS benefit of 2.3 months for BCNU wafers followed by RT compared with placebo wafers followed by RT (13.9 vs 11.6 months; $p = 0.03$). Similarly, *Valtonen et al. (1997)* conducted a study of 32 out of the 272 patients, and they demonstrated a significant OS benefit of 18.2 weeks for BCNU wafers followed by RT compared with placebo wafers followed by RT (58.1 vs 39.9 weeks; $p = 0.012$). This shows that BCNU wafer treatment by itself is clinically meaningful, but is also effective when paired with traditional RT/TMZ treatments. This was all summarized as part of *Lillhei et al. (2017)*.

**Adverse Effects**

***Cerebral Edema and Neurologic Effects***

*Azurity Pharmaceuticals (2025)*, the current manufacturer of Gliadel wafers, published an article about the Gliadel wafer, as well as its potential side effects from previous papers that were combined into one list. The most common adverse effects for newly diagnosed high-grade Glioma patients are Cerebral Edema, asthenia, nausea, vomiting, constipation, wound healing abnormalities, and depression. The most common adverse reactions in recurrent high-grade Glioma patients include urinary tract infection, wound healing abnormalities, and fever.

Another study specifically examined the adverse effects associated with the use of carmustine (BCNU) wafers in conjunction with chemotherapy. The authors reported serious postoperative complications, including the development of severe Cerebral Edema and the formation of a cystic lesion within the surgical resection cavity. These findings suggest that, while carmustine wafers may offer localized chemotherapeutic benefits, their use can also be associated with inflammatory and structural complications that may negatively impact postoperative recovery and neurological outcomes (*Salle et al., 2018*).

With 31 total surgical cases involving 28 adult patients who underwent BCNU wafer implantation, this study conducted by *Fujii et al. (2022)* also concluded that adverse effects such as Cerebral Edema can occur. Other intermediate grade Gliomas were also linked to a high risk of Cerebral Edema after surgery. An increased Cerebral Edema rate was also linked with a higher likelihood of postoperative seizures.

**Combination Therapy Toxicity**

*Salle et al. (2018)* reports that some series of small, retrospective studies have shown a very high rate of adverse events when multiple treatments are layered together. It proposed that a combination of local chemotherapy with BCNU and concomitant radiochemotherapy with temozolomide (TMZ) appears to be attractive to enhance the overall survival, even though these treatments may potentially accumulate in their toxicity.

*Lillehei et al. (2017)* found that nine of the 11 trials reported serious grade 3 and 4 adverse events. For 372 patients in these nine trials, a total of 147 grade 3 and 4 adverse events were reported. Myelosuppression, neurologic deficit, healing abnormalities, and seizures were the most commonly reported grade 3 and 4 adverse events. These adverse events were the separate adverse event profiles of BCNU wafers and RT/TMZ combined into one, but not with worse symptoms.

**Postoperative and Surgical Complications**

*Lillehei et al. (2017)* reported the incidence of postoperative cerebral spinal fluid leaks (16.0 vs 12.0%) and intracranial hypertension (9.0 vs 2.0%) was higher in patients receiving BCNU wafers than in patients receiving placebo wafers during surgery. These findings suggest that BCNU wafer implantation may modestly increase the risk of certain postoperative complications, likely related to local tissue irritation and altered wound healing at the resection site.

Finally, *Double-edged Sword in the Placement of Carmustine (BCNU) Wafers along the Eloquent Area: A Case Report* showed that very serious adverse effects such as brain edema, healing delay, cerebral spinal fluid leak, intracranial infections, and cyst formation could occur. This was a report examining serious adverse effects of BCNU wafers, and was conducted in Nagoya Medical Center Clinical Research Journal in 2014. *Kuramitsu et al. (2015)* says, even though there are clear benefits of BCNU, adverse effects should still be noticed, especially how the implantation of BCNU might negatively affect a patient's quality of life.

**Study Results**

These studies indicate that Gliadel provides a benefit with OS. The largest increase in OS were found in studies that used Gliadel in combination with traditional chemotherapeutics. Adverse effects were predictable and included cerebral edema, neurologic deficits, wound healing abnormalities, and postoperative complications, with increased toxicity when combined with additional therapies. Overall, the available evidence suggests that Gliadel wafers offer a meaningful therapeutic benefit, particularly in combination treatments. However, adverse effects should be carefully monitored to balance therapeutic benefit and patient safety.

## DISCUSSION

These relevant RCTs and cohort studies show how effective BCNU wafers can be, especially after being paired with more traditional methods. In all of these published works, there were clear benefits, with increased OS, for recurrent, and newly diagnosed patients as well.

BCNU wafers demonstrate advantages due to the fact that they primarily target local areas with controlled delivery, instead of spreading to the rest of the body. By doing this, these wafers reduce adverse effects that may occur in chemotherapy, such as intestinal damage. Wafers are implanted directly into the brain cavity after tumor removal, and release chemotherapeutic drugs to prevent the tumor from coming back. They bypass the blood brain barrier during surgery, and do a controlled release over 2-3 weeks. Also, these wafers demonstrate "synergy with surgery," meaning effects are strengthened when treatments are combined (specifically with more radiation and temozolomide). Numerous papers demonstrated this, where patients treated with both wafers and RT/TMZ had the highest overall survival rate.

Despite being proven effective, the chemotherapeutic wafers can come at a cost. Serious adverse effects have been found in nearly all studies that have taken place which investigated the usefulness of these wafers. As a result, the clinical use of BCNU wafers requires careful consideration of both survival benefit and potential complications, rather than assuming the treatment is suitable for all Glioblastoma patients. One adverse effect that appeared commonly was Brain Edema, which is the swelling of the brain due to inflammatory responses due to the wafers. The effects of BCNU wafers, after being implanted in the cavity, do not necessarily stop at the cavity; they may spread to beyond the tumor, injuring nearby tissue. Besides damaging healthy tissue, implantation of the wafers also disrupts the structure of the blood–brain barrier, increasing its permeability and causing swelling.

A few studies also found that an increased cerebral edema rate was linked with a higher likelihood of postoperative seizures. These seizures happen primarily when chemicals enter the brain from surgery, which causes neurons to trigger abnormal neuronal activity. Also, nearby inflamed tissue puts pressure on neurons, causing them to behave strangely as well.

Lastly, a very common side effect is infection. This itself does not come from the wafer, but comes from the process of implanting it. Bacteria from the scalp can enter the wound, and with the blood brain barrier being temporarily disabled, infections can occur very fast in the warm, humid brain. It might lead to the need for another surgery, to fight the infection.

There are many reasons why data were not consistent across studies. Results may vary among studies because of patient count. Reliable studies have numerous patients with many RCTs, which produce reliable data. Patient characteristics, such as age, tumor stage, and prior treatments, can influence survival and side effect profiles. Finally, differences in study design and treatment protocols including whether BCNU wafers were combined with temozolomide, radiation, or specific surgical techniques may lead to variation in outcomes. These are also limitations of evidence.

BCNU wafers appear to convey more benefits when implanted in patients that are newly diagnosed, not recurrent. Patients that have had impaired wound healing ability after surgery and an inclination toward infection should not undergo treatment with BCNU wafers. Careful patient selection is essential to maximize benefits while minimizing the potential for serious adverse effects. Future studies should focus on large scale trials with standardized treatment, so that data can be as consistent as possible. Research comparing BCNU wafers in combination with standard therapies, versus standard therapy alone, could isolate their true benefit, and consistently documenting adverse effects and post-surgery outcomes could guide clinical decision making and improve patient care.

Overall, BCNU wafers are an alternative in certain patients to their traditional treatment methods. The ability of wafers to deliver chemotherapeutics directly to local areas offers meaningful survival benefits, particularly when combined with radiation and temozolomide. However, the associated risks that come with this treatment underscore the need for careful patient selection and continued research to ensure beneficial treatments.

## LIMITATIONS

This paper has limitations, some of which are also described in the “discussion” section. First of all, the conclusions that were drawn in this paper were based on secondary data from previous studies rather than conducting original clinical trials. Sample sizes also varied widely from study to study, which may reduce statistical accuracy and conclusiveness. Studies also had different methods of approach, with differences in design, follow up duration, and documentation of adverse effects. Variability in patient background and treatment also contributes to uncertainty, leading to a need for standardized studies with the same protocols in future studies.

## CONCLUSION

Although carmustine wafers have demonstrated a survival benefit in selected patient populations, their clinical use requires careful consideration of the balance between therapeutic benefit and treatment-related morbidity. Reported adverse effects, including cerebral edema and local inflammatory complications, may negatively impact postoperative recovery and overall quality of life. Nevertheless, the survival advantages observed in multiple studies underscore the continued relevance of this therapy.

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