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Mark Sharobim BSc, MSc, Peter A. Tsivis, MD, MBA

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Mark Sharobim BSc, MSc1*, Peter A. Tsivis, MD, MBA1,2

1Saba University School of Medicine, The Bottom, Saba, The Caribbean Netherlands

2Rocky Vista University College of Osteopathic Medicine, Ivins, Utah, USA

Corresponding author:

Mark Sharobim BSc, MSc

m.sharobim@saba.edu

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List of Abbreviations

2B3-101	(Drug) PEGylated liposomal doxorubicin conjugated to glutathione
AA	Anaplastic Astrocytoma
BBB	Blood-Brain Barrier
BBBD	Blood-Brain Barrier Disruption
BBTB	Blood-Brain Tumor Barrier
CB	Cintredekin besudotox
CED	Convection Enhanced Delivery
CNS	Central nervous system
CR	Complete response
DFI	Disease-free interval
DPG	Diffuse Pontine Glioma
EFS	Event-free survival
GBM	Glioblastoma multiforme
GRN1005	(Drug) Paclitaxel conjugated to the aminoacid sequence angiopep2
IA	Intra-arterial chemotherapy
IDH	Isocitrate dehydrogenase
LRP-1	Lipoprotein receptor-related protein-1
OS	Overall survival
PCV	Procarbazine/CCNU [lomustine]/vincristine
PD	Progressive disease
PEG	Polyethylene glycol
PFS	Progression free survival
PR	Partial Response
RCTs	Randomized Clinical Trials
SD	Stable disease
TMZ	Temozolomide
TP38	Recombinant TGF-α protein fused with Pseudomonas exotoxin
TTP	Time to tumor progression
WHO	World Health Organization
XRT	Radiotherapy

Introduction

Gliomas are cancers of the central nervous system (CNS) that arise from stem and progenitor cells of neuroglial origin. These cancers may generate from any of the following neuroglia: astrocytes, oligodendrocytes, and ependymal cells.[1] Other glial cells include microglia and radial glial cells, and though these cells often do not constitute tissue forming primary CNS tumors, certain lineages such as radial glial cells may be a source of stem cells that give rise to glioma.[2]

Primary brain tumors are grouped according to histologic features and are graded I - IV. Recently expanded criteria include molecular and genetic characteristics. Astrocytomas are the most commonly diagnosed glioma. According to World Health Organization (WHO) guidelines, astrocytomas are separated into four grades (I-IV) based on histologic features and malignant potential. Grade IV tumors include glioblastoma multiforme (GBM; common in adults), or diffuse midline glioma, the latter which affects children.[3] Over 30 different types of glioma are described in the 2016 WHO Classification of Tumors of the CNS report.[3]

Gliomas make up approximately 30% of primary brain tumors, and 80% of malignant cases.[1] In fact, primary CNS tumours account for the highest annual incidence of any neoplasm in children (≤ 19 years old) and are the second leading cause of mortality due to primary cancer in this age group. In adults, they are the most common primary malignant brain tumor. In the United States between 2007 – 2011, the incidence of gliomas was 6.6 per 100,000 people. GBM, the most aggressive subtype, accounted for almost 50% of cases.[4] The incidence of other gliomas can be up to 10 times lower than GBM. Like many other malignancies, incidence increases with age, with rates in the elderly being more than double the population average.[5]

In the most aggressive gliomas, treatment warrants a multi-disciplinary approach from a team of healthcare professionals. Despite major advances in understanding of the pathophysiology of glioma, it is still among the deadliest cancers. Standard treatment is surgical excision of the tumor followed by

concomitant chemotherapy and radiotherapy. The median overall survival (OS) for those diagnosed with GBM is 12 - 18 months and 3-year survival remains below 15%. After disease recurrence, the outcome is almost invariably death, as progression free survival is typically 10 weeks and median OS can be anywhere from 25 - 40 weeks.[6] Another reason for poor patient performance is the fact that current standard of care for gliomas such as GBM is clearly defined, but no consensus is available regarding second line treatment options.[7] Thus, there is a need to develop more efficacious approaches to therapy.

The blood brain barrier (BBB) separates blood perfusing the CNS from the surrounding brain tissue. The BBB is formed by tight junctions between the endothelial cells of vasculature found within the CNS. Furthermore, it is a functional unit composed of neuronal cells, astrocyte foot processes and pericytes which reinforce the barrier.[8] It is also a selective barrier that permits passage of nutrients while excluding entry of neurotoxins or macromolecules that are damaging to nervous tissue.

The permeability of the BBB can be altered in the natural progression of diseases such as infections, brain cancer, multiple sclerosis, and stroke. In the development of a cancer, the changes in tumor microenvironment and neovascularization modify this barrier so that it is considered distinct from a normally functioning BBB, leading some to refer to it as the blood-brain tumor barrier (BBTB).[9] Though the BBTB is more porous than the BBB, it remains unclear whether this permeability difference allows for any meaningful accumulation of chemotherapeutic drugs or substances.[10]

Reports from the 1970s by Rapoport and colleagues demonstrated that injection of hypertonic solutions mixed with Evans blue dye into arteries resulted in staining of surrounding brain tissue. The hypothesis was that the osmotic shift of fluid out of the endothelial cell in a hypertonic environment disrupted the tight junctions and integrity of this barrier.[11,12] Similar experiments subsequently confirmed this hypothesis, and this technique was termed blood brain barrier disruption (BBBD). Amongst the earliest forms of bypassing the BBB, this technique has been used with intra-arterial injection of chemotherapeutic agents to increase uptake of drugs in the CNS. Another method to bypass the BBB is to

couple drugs to ligands that bind receptors on the surface of the endothelial cells lining the barrier. These ligands are transcytosed across the endothelial cell and taken up into the brain parenchyma.[13,14] Another way to bypass the BBB is via direct deposition of drug in the brain cavity. This is routinely done, and the drug can be implanted at the surgical resection site of the tumor. Gliadel® wafers are small circular discs of biodegradable wafer containing a chemotherapeutic agent called carmustine. These wafers disintegrate in the presence of water to allow slow local release of carmustine in a surgical resection cavity.[15] This prevents residual cancer cells from growing. Also, because gliomas such as GBM frequently recur near the primary neoplastic site of origin,[16] they also prevent disease relapse. Many placebo-controlled randomized clinical trials (RCTs) in the past have demonstrated their efficacy in treating different types of primary or recurrent glioma. They have been approved as treatment for newly diagnosed high-grade gliomas by the FDA since 1996.[17]

Candidate treatments not discussed at length in this report still in the early phases of clinical development include bradykinin mediated BBB opening (now discontinued)[18] and drug efflux transporter inhibitors[19], both reviewed elsewhere[9]. In the case of bradykinin mediated BBB disruption, the authors of the most recent clinical trial have suggested the negative results are because the already transient nature of the barrier opening by bradykinin requires concomitant as well as continuous dosing with the desired agent (*e.g.*, chemotherapy) and that these schedules often result in tachyphylaxis to bradykinin, as shown in early animal models. Drug efflux transporters implicated in CNS tumors have not reached clinical trial testing, and while there is more evidence they cause drug resistance in other cancers such as breast and leukemia, no drugs are available in the clinic today.[20]

To date, first line therapy for newly diagnosed GBM is surgical resection followed by concomitant radiotherapy and chemotherapy. This is based off clinical trial data by Stupp *et al.*,

who showed postoperative chemoradiotherapy with the alkylating agent temozolomide (TMZ) improved median survival and 2-year survival as compared to radiotherapy alone. In some cases where a patient carries a favorable genetic mutation, the survival difference can be five-fold.[21,22] Though standard of care, this treatment modality has not been updated recently,[23] and gliomas remain among the most aggressive cancers. Since in this protocol TMZ is given peripherally, it's uptake in the CNS is limited by the BBB. Thus, newer therapies may be designed with the intent of overcoming the limitations of the physiologic barrier to the brain.

The purpose of this report was to review relevant literature to determine if a therapy that bypasses the BBB has resulted in improved treatment outcomes for patients diagnosed with glioma. Though other reports have reviewed the status of treatments that bypass the BBB,[9] none have attempted to make a conclusion as to the efficacy of these treatments relative to standard of care. Our hypothesis is that overall, treatment that actively circumvents this barrier will lead to better outcomes for patients with glioma as compared to treatment that does not actively breach the BBB. To date and to our knowledge, the most clinically developed method of BBB diversion is wafer therapy as they are the only treatment modality that has reached phase III clinical testing. Therefore to test our hypothesis, we analyzed whether wafer implant therapy with or without chemoradiation post surgical resection of brain tumor improved overall survival in patients with high grade gliomas when compared to placebo or no wafer therapy.

Methods

Inclusion and Exclusion Criteria

Initially, all studies gathered were RCTs or studies with a treatment arm and control arm, with treatment arms including intervention consisting of post surgical tumor resection wafer therapy with or without chemoradiation; control arms used no wafer or placebo wafer (for specific keywords used, see below). Studies with adult patients of all ages that had a histologically confirmed diagnosis of recurrent or de novo glioma were considered. Studies with patients that had prior unrelated malignancy that was present in the patient's medical history were excluded. Therefore, patients with brain metastases were not included as this represents a different primary disease.

For efficacy analysis comparing wafer therapy to published data from trials using current standard of care protocols only, patients with primary gliomas were not compared to those with recurrent glioma (see Results section), since a recurrent tumor is frequently a different disease to manage.[24] Also for efficacy analysis, gliomas in children were not included since pediatric and adult tumors are frequently unrelated.[25] The primary outcome for analysis was the percent change in median survival or OS and all studies compared included this measure.

Search Methods

Two databases, PubMed and Web of Science were used to gather data. The keywords ("glioma(s)" OR "glial cell tumor(s)" OR "malignant glioma(s)") were used with the terms (carmustine wafers OR BCNU wafers OR chemotherapy wafers OR Gliadel wafers) as described previously[15]. Of note, the keywords carmustine, BCNU, and Gliadel wafer refer to the same drug and were thus linked using the "OR" Boolean operator.

Study Tabulations and Outcomes Measured

The definitions of clinical outcomes from various studies are summarized in Table 1. Percent increase in survival rates among treatment versus control cohorts using wafer therapy was graphed for studies meeting inclusion and exclusion criteria are shown in Figure 1. Statistical significance was determined by $p<0.05$ and survival rates were depicted in each study using Kaplan-Meier survival analysis, differences were determined using the log-rank method unless otherwise stated in the Results section. The evidence table (Table 3) generated in Appendix A describing the types of study was determined using previously published criteria.[26]

Results

Using the search criteria outlined previously in the methods section, a total of 10 papers were gathered. These encompassed over 500 patients across all studies. The studies gathered included 2 RCTs, 3 prospective cohort studies, and 6 retrospective case control studies, as summarized in Appendix A. The following includes a summary of major outcomes from each study. In each study, median survival or OS was depicted using Kaplan-Meier survival analysis and differences were determined using the log-rank method unless otherwise stated.

Summary of Drug Wafer Therapy Studies

The earliest study published on this treatment modality is by Brem and colleagues.[27] The trial enrolled 222 patients with recurrent malignant glioma confirmed by CT or MRI imaging. All patients had not taken systemic chemotherapeutic drugs at least one month prior to treatment. Patients were randomized into two treatment groups: surgical resection followed by carmustine wafer implant versus resection followed by placebo wafer implant. Most patients (~ 65%) had glioblastoma multiforme. The primary outcome reported by the authors was mortality rate after treatment at 6 months. The authors demonstrated that implantation of wafers significantly decreased mortality in patients when stratified according to specific pathology (*i.e.*, GBM or anaplastic astrocytoma) but no difference when combined. In glioblastoma, treatment with wafer implants resulted in a mortality rate at 6 months of 44% as opposed to 64% in the control group (OS of 56% and 37%, respectively; p=0.02). This resulted in a hazard ratio of 0.67 (95% CI: 0.48 – 0.95, p=0.02). Across all patients, mortality at 6 months was 40% in the treatment group, and 53% in the control group (OS of 60% and 47%, respectively; p=0.061), with a hazard ratio of 0.67 (95% CI: 0.51 – 0.90, p=0.061).

In a prospective cohort study, Valtonen and colleagues[28] enrolled 32 patients with a histopathological diagnosis of grade III or IV glioma. Other inclusion criteria included unilateral tumor based on CT or MRI imaging, age between 18 and 65 years, and a minimum score of 60/100 on Karnofsky performance scale (KPS). Exclusion criteria were evidence of systemic disease, thrombocytopenia, pregnancy or hypersensitivity reaction to contrast material. Patients in the treatment group received Gliadel wafers or placebo wafer post surgical resection of brain tumor. In patients with grade IV tumors (n=27), median survival post surgical resection in the control group was 39.9 weeks (95% CI: 37.6 – 45.0) as compared to 53.3 (95% CI: 40.1 – 77.7) in the wafer group (p=0.008). Treatment was associated with a hazard ratio of 0.28 (95% CI: 0.10-0.71, p=0.008) using the Cox proportional hazards model. No difference was seen with variables such as KPS or age using the same model.

Subach *et al.*[29] reviewed the outcomes of 94 patients with recurrent GBM treated with craniotomy and surgical resection of tumor followed by wafer implant. All participants were included if there was histological confirmation of GBM, completion of prior radiotherapy, radiographic evidence of tumor growth, and a KPS score of ≥ 70. Patients were excluded if they received systemic chemotherapy less than 1 month prior to surgery. The treatment arm consisted of surgical resection with carmustine wafer implantation. A mean of 6 wafers were implanted in each surgical resection cavity. The control group was made up of patients receiving surgical resection of tumor only. Median survival from surgery was 14 weeks for the wafer treatment group and 54 weeks in the control group (p<0.001).

Westphal *et al.*[30] conducted a clinical trial with 240 patients who had malignant glioma. All patients had a supratentorial, unilateral, cerebral tumor as evidenced by MRI and KPS score

of ≥ 60. After tumor resection, patients either received implanted carmustine wafer or placebo wafer. Post-operative radiotherapy was administered to both groups. Most patients (~83%) had GBM. Differences in prognostic factors of survival in multiple-regression analysis was calculated using Cox proportional hazards model. Median survival time was 13.9 months for the wafer group and 11.6 months in the placebo group (p=0.03). This was associated with a hazard ratio of 0.71 (95% CI: 0.52 – 0.96, p=0.03). Stratifying patients by GBM diagnosis only did not reveal a difference in survival.

In the investigation by Affronti *et al.,*[31] retrospective chart reviews from 176 patients with primary GBM were used to determine if wafer implants improved clinical outcome. All patients must have had a primary GBM diagnosis based on histology, a lack of chemotherapy treatment prior to resection, gross or total resection, and post-surgical adjuvant radiotherapy and temozolomide treatment. No significant differences in overall, 1-year, 2-year, and median survival was observed across both treatment groups. Despite this, median survival was higher in the carmustine wafer group as compared to control (89.4 [95% CI: 65.9-136.4] vs. 72.7 [95% CI: 62.7-84.3] weeks, respectively; no p value reported).

McGirt and colleagues[32] combined the use of wafer implants with adjuvant temozolomide therapy and radiation. All patients had received a primary resection of malignant GBM. All patients received adjuvant radiotherapy (XRT) and temozolomide (TMZ) therapy as described in the Stupp protocol.[22] 33 patients received XRT + TMZ + Gliadel wafer, 45 received XRT + TMZ alone post resection. Patients receiving the treatment regimen lacking Gliadel wafers had a median survival of 14.7 months as compared to a similar cohort with Gliadel wafers who had a median survival or 20.7 months ($p < 0.01$). A difficulty arose in which some patients

did not receive Gliadel because total resection was not achieved in all patients. Thus, more patients (60% vs. 30% in control vs. treatment groups, respectively, $p < 0.05$) in the control group had subtotal resection. In cases where gross total resection was achieved, median survival increased in both cohorts but was disproportionately increased in the control group, and therefore the difference in survival was not significant.

The report by Chaichana and others[33] limited the scope of their study to patients over 65 with primary supratentorial GBM. All patients received either wafer or none post-resection and post-surgical radiotherapy. The median survival for the treatment arm was 8.7 months while it was 5.5 months for control (p=0.007). Survival rates were also significantly higher (p=0.04) for the treatment group at 3, 6, 9, and 12 months. The same trend was found in patients older than 70 and 75 years.

165 patients with newly diagnosed or recurrent GBM were treated in the study by De Bonis *et al.*[34] Histological diagnosis of grade IV GBM was performed after craniotomy and resection. Patients received either Gliadel wafers or nothing post surgical resection. All were treated with TMZ and XRT post surgery. If TMZ was too toxic, other drugs such as cisplatin and irinotecan were used. 47 patients were in the treatment group and 13 in the control arm. Median survival did not significantly change between treatment or control groups (14 months [95% CI: 8 – 18] versus 11 months [95 % CI: 8 – 14], respectively; p=0.77). The same was true when patients were stratified for recurrent or de novo GBM.

In the study by Noël *et al.*,[35] 28 patients received Gliadel wafers post surgical resection of histologically confirmed grade III or IV glioma (treatment group) versus 37 patients with similar

glioma who did not receive wafer treatment. There was no difference in median OS in either treatment group (20.6 vs 20.8 months, p=0.81).

In the most recently published study on wafer implant therapy, Samis-Zella *et al.*[36] compared the use of implantable wafers for recurrent grade IV GBM with patients with similar glioma who did not get wafer treatment. All patients were given TMZ as well as prophylactic cefazolin and dexamethasone post-surgically. 63 patients received wafer therapy and 32 did not post resection. Patients were matched for age, KPS performance and treatment for initial primary tumor. The primary outcome reported was PFS. The median PFS from disease recurrence was 6.0 months (95 % CI: 4.2 – 7.7) in the treatment group and 5.0 months (95% CI: 2.3 – 7.6) in the control group, and this difference was not significant (p=0.8).

5 of the 10 studies determined statistically significant differences in median survival or OS as determined by Kaplan-Meier survival analysis (indicated by a *, where $p<0.05$ in Table 2). Their efficacy as compared to standard of care is further analyzed in the proceeding section. A summary of the results of these studies are found in Table 2. A similar table comparing only study designs and evidence level is found in Appendix A (Table 3).

Overall Efficacy

To determine whether carmustine wafer treatment resulted in improved clinical performance for glioma patients, the percent change in survival seen in wafer studies was compared to previously established guidelines of first line treatment. In all 10 studies gathered, 6 trials using therapeutics that bypassed the BBB met criteria for analysis as determined in the methods section *(e.g.*, exclusion of patients with disease recurrence). One study did not report OS or median survival and was also excluded.[36] All patients had high-grade III or IV glioma. Of

the 6 trials, 4 (75%) demonstrated a significant ($p \leq 0.05$) percent increase in median survival as compared to control, or non-disruptive treatment (Figure 1). Two studies did not find a significant increase in survival.[31,35] Thus, 75% of eligible trials using wafer treatments showed a significant survival advantage over no wafer treatment.

To determine the usefulness of carmustine wafer therapy compared to current first line treatment for GBM, the percent change in survival seen amongst each study using wafer therapy was plotted against the survival benefit seen in the Stupp study, which was the first trial which described current treatment protocols.[22] This is depicted in Figure 1. In the 4 trials that demonstrated a significantly increased survival benefit with wafer therapy, 3 (75%) showed equal or greater percent increase in survival than the Stupp study.

Discussion

Glioblastoma multiforme (GBM) is the most common malignant brain tumor and is associated with poor clinical outcomes. First line treatment for gliomas such as GBM consists of surgical resection followed by concomitant radiotherapy and temozolomide chemotherapy, referred to as the Stupp protocol[22]. Phase III studies have shown significant survival improvements using this protocol. Since no other treatment regimen is currently comparable, and nothing is effective at treating recurrent GBM, more research is needed to further improve patient outcomes.

An area of interest is in the circumvention of the BBB, since most therapeutics that would otherwise effectively treat cancer cannot accumulate in sufficient concentration in brain parenchyma. One of the most clinically developed modalities that physically bypasses the BBB is via direct access through the cranium. With drug wafer treatments, surgically resected cancers can be treated by inserting a polyanhydride drug wafer (made up of the alkylating agent, carmustine) into the resection cavity, allowing for its slow release over time.

Compared to current first line treatment for GBM (Stupp protocol), 3 out of 4 (75%) selected studies in this report determined a greater overall percent increase in survival when using wafer implants. This indicates that using wafers may improve existing established treatment guidelines. In general, 9 out of 10 studies showed some benefit to receiving wafer post surgical resection. Some studies were underpowered (Valtonen *et al.*[28], n=27) and yet still were able to distinguish a statistically significant difference in survival. It is possible more patients would further separate changes in clinical outcomes. The only study to demonstrate risk, and not benefit, to using wafers was by Subach *et al.*[29] This may be partially because both treatment and

control groups were not the same size (n=17 and 45, respectively), and nearly half the patients in the wafer group (47%) had perioperative complications as opposed to only 13% of those who did not receive wafers post resection. Furthermore, some have suggested tumor location can be a prognostic factor, and thus easily accessible tumors (cerebrum vs. brainstem) have better prognosis.[37] Indeed, a greater proportion of tumors were in the frontal and temporal lobes of control group cases (72%) as compared to treatment cases (67%).

A major limiting factor in the results is the heterogeneity of controls between all the studies. There was not one variable that was consistently controlled for across all studies, though age and functional impairment score (KPS) were the most common. This is in line with others that show age and Karnofsky performance are both independent factors predicting outcome of GBM.[38] Only one study (Brem and colleagues[27]) matched patients according to race. Others have shown similar survival outcomes across Caucasian and Afro-Caribbean patients with GBM, but significantly decreased survival in those of Hispanic descent.[39] Therefore. in addition to age and performance, race is a factor that was not properly controlled that could change patient outcomes. Furthermore, the number of patients was not congruent in all 10 reports, with treatment arm sizes ranging from 17 – 120.

In the future, the development of treatment modalities that actively disrupt the BBB is desired. Not only does survival statistics for high-grade gliomas remain poor, standard first line temozolomide therapy may not benefit patients with genetic variations in certain DNA repair mechanisms.[40] Thus, temozolomide resistance is a problem for patients with GBM as there is no widely accepted second-line treatment for this patient population. Further work in developing treatments that open the BBB may therefore alleviate this problem.

Conclusion

The blood-brain barrier (BBB) provides a significant hurdle to developing chemotherapeutics that could successfully treat brain tumors such as glioma. One notable hindrance to reducing the dismal clinical outcomes in glioma is that no method to breach the BBB has proved to be successful enough to be used as a primary treatment. The challenge is that the understanding of the pathophysiology of gliomas may develop at a quicker pace than our knowledge of how to circumvent the BBB. Future work must address this disparity to adequately improve patient outcomes.

This report reviewed all the relevant studies regarding wafer therapy, a method of actively bypassing the BBB via the direct implantation of drug-eluting wafers in an intracranial resection cavity to treat brain cancer. Other, newer therapies such as receptor mediated transport drug conjugates are promising due to their potential for low side effect profile, however they are less clinically developed. For example, since only two studies[41,42] to date that describe drugs using receptor mediated transport have failed to reach phase II level of development, more research is needed to develop more clinically suitable targets. At this time, of the candidate therapies that can bypass the BBB, carmustine wafers for patients with glioma have the most utility. In some cases, we have showed they offer a clear advantage to current treatment regimens, but further investigation may be necessary to determine who may benefit from this therapy the most. This may be inherent to the mechanism of action of carmustine wafer therapy, an alkylating agent, as certain genetic factors may play a role in treatment response[21]. This is in line with our current hypothesis that truly effective opening of the BBB will improve clinical performance of patients with glioma.

These minor, yet significant successes have also demonstrated there is clinical value in pursuing the goal of overcoming the BBB. The future will determine if the goal of translating research on the bench to outcomes at the patient bedside is feasible. Past trials have already provided valuable lessons that can be applied to current research paradigms. Development of clinical trials addressing the lessons and questions outlined in this report may lead to the discovery of novel therapies that change the lives of those with malignant brain tumors.

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Outcome Parameter	Definition	Source
Partial Response (PR)	≥50% reduction of the initial enhancing tumor, stable or reduced use of steroids, and stable or improved neurological function. Must be sustained for 4 weeks.	1
Complete Response (CR)	Resolution of the enhancing tumor as shown on computed tomograms or magnetic resonance (MR) images, no need for steroids, stable or improved neurological function, and negative results on CSF tests.	1
Stable Disease (SD)	No CR, PR, or progression. Stability of tumor on imaging (T2 or FLAIR)	1
Progression	≥25% increase in perpendicular diameter of tumor Significant increase in tumor size on imaging with stable or increasing doses of steroids	1
Overall Survival (OS)	Length of time from diagnosis that patient remains alive.	2
Event Free Survival (EFS)	The time it takes from the end of primary treatment for cancer until there arises a complication the treatment is trying to prevent.	3,4
Time to tumor progression (TTP)	Essentially the same definition as EFS, except the "event" is progression of the tumor.	3,4

Table 1. Definitions of patient outcomes measured in cancer clinical trials.

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[3]Definition of event-free survival - NCI Dictionary of Cancer Terms - National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/event-free-survival. Accessed May 5, 2018.
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	Authors	Method of BBB Disruption	Study Methods, Population, Exposure	Notes/Outcomes
1)	(Brem *et al.*, 1995)[27,*]	Carmustine Wafers	Patients undergoing surgical excision of glioma received carmustine or placebo wafer.	• Most patients had GBM, but other types of glioma (e.g., anaplastic astrocytoma, oligodendroglioma) were also compared. • 222 patients with recurrent brain tumors were randomized to wafer or no wafer therapy. • A significant overall survival difference at 6 months was seen for patients with GBM or anaplastic astrocytoma.
2)	(Valtonen *et al.*, 1997)[28,*]	Carmustine Wafers	Patients received carmustine or placebo wafers after surgical excision and then radiotherapy	• Patients had either grade III or IV glioma as determined by histopathology • 32 patients, 16 in each treatment group. • OS increased in the wafer treatment group significantly by about 20 weeks as compared to control.
3)	(Subach *et al.*, 1999)[29]	Carmustine Wafers	Patients undergoing secondary excision of recurrent GBM received wafers (study group) or simply a craniotomy (cohort group)	• Patients all had recurrent GBM and all received similar primary treatment with radiotherapy while most had received prior systemic chemotherapy (carmustine/cisplatin). • 62 patients underwent operation, 17 were implanted with wafers, 45 did not. • A survival benefit was seen in the control group as opposed to the wafer group, but this was not significant.
4)	(Westphal *et al.*, 2003)[30,*]	Carmustine Wafers	Carmustine wafers + radiotherapy as compared to placebo wafers + radiotherapy	• 120 patients were in the placebo group and 120 were in the Carmustine wafer group. • Most patients had a diagnosis of glioma, 1 and 2 patients in either group with brain metastases were not included in the outcome calculations. • Overall survival of GBM patients (majority of the patients) was significantly higher in the carmustine wafer group at 13.6 months and 11.4 months for the placebo wafer group.
5)	(Affronti *et al.*, 2009)[31]	Carmustine Wafers	Surgical resection, temozolomide, radiotherapy with or without wafer implantation	• All patients treated had GBM, majority of patients were Caucasian and above 50 years old • 97 patients did not receive wafers, 85 did. • No significant differences in OS were observed
6)	(McGirt *et al.*, 2009)[32,*]	Carmustine Wafers	Patients received resection, radiotherapy, and temozolomide with or without carmustine wafers.	• All patients had GBM • Median survival significantly increased in patients having implanted wafers by 9 months. • 38 patients were treated with wafers, 78 patients were treated without. • Survival at 2 years was also doubled for those receiving wafers (statistically significant). • 6-month PFS was also significantly higher, more than double in wafer treatment group (90% vs. 40%).
7)	(Chaichana *et al.*, 2011)[33,*]	Carmustine Wafers	Standard treatment (including surgical excision) with wafers as compared to standard treatment without wafers.	• Patients > 65 years of age with a supratentorial GBM were selected. • 45 patients with carmustine wafer implantation were matched with 45 who did not. • Patients receiving resection with wafer implant as opposed to those without were matched for other variables such as age, extent of resection, and post-operative radiation or chemotherapy.

				• A significant OS difference (p=0.007) was seen in the wafer treatment group as compared to control (8.7 and 5.5 months respectively).
8)	(De Bonis *et al.*, 2012)[34]	Carmustine Wafers	Standard treatment (including surgical excision) with wafers as compared to standard treatment without wafers.	• Both patients with newly diagnosed (n=77) and recurrent (n=88) GBM were treated. • Use of wafers did not significantly affect overall survival in either group of patients as compared to without wafers.
9)	(Noël *et al.*, 2012)[35]	Carmustine Wafers	Standard treatment (including surgical excision) with wafers as compared to standard treatment without wafers.	• Patients were treated for either grade III or IV glioma. • 65 patients underwent surgery, 28 had wafer implants, 37 did not. • Use of Gliadel wafers did not change PFS or OS significantly.
10)	(Samis Zella *et al.*, 2014)[36]	Carmustine Wafers	Patients had surgical resection, radiotherapy, and concomitant temozolomide. Patients then either received wafers or no wafer treatment post excision.	• All patients had supratentorial grade IV glioma (GBM) • 63 patients were given wafers post resection and 32 without implantation. • No significant difference in disease-free interval (DFI) or PFS in both treatment groups.

Table 2. Summary of studies demonstrating clinical outcomes after use of carmustine (Gliadel) wafer therapy in patients with glioma.
A * indicates that the study determined a significant difference in overall survival in treatment vs. control groups.

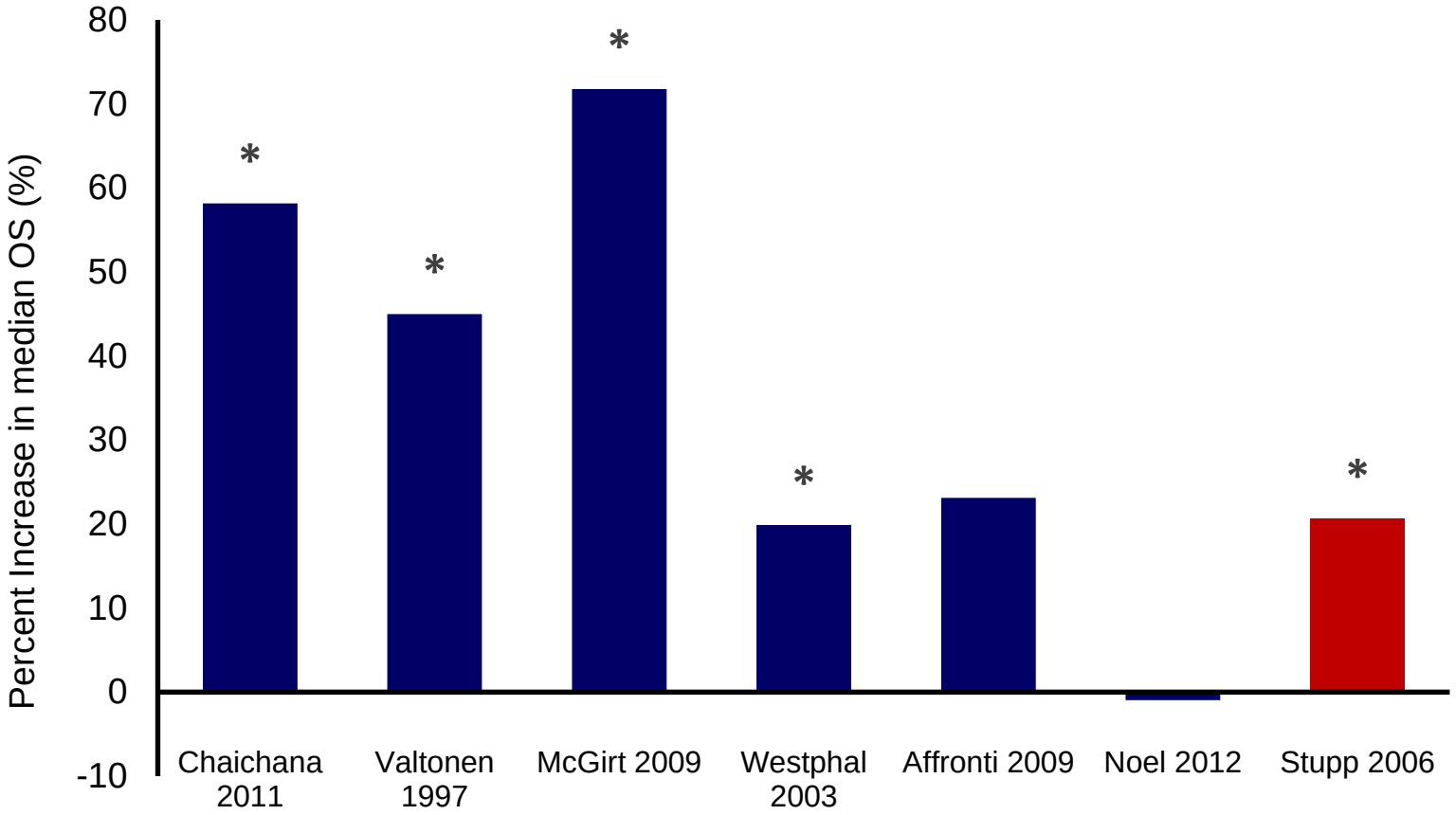

Figure 1. Percent (%) increase in overall survival (OS) in treatment vs. control groups from carmustine wafer studies and the Stupp protocol. Percent increase in OS from all studies in carmustine wafer trials (blue bars). These were compared to the percent increase in OS demonstrated previously in standard of care for GBM (temozolomide AND radiotherapy vs. radiotherapy alone – red bars) according to the Stupp protocol[22].

* indicates a study that demonstrated a significant difference in OS as compared to control ($p < 0.05$).

Appendix A

	Authors	Method of BBB Disruption	Study Type	Evidence Level
1)	(Westphal *et al.*, 2003)	Carmustine Wafers	Randomized Clinical Trial (RCT)	1
2)	(De Bonis *et al.*, 2012)	Carmustine Wafers	Prospective Cohort study	2
3)	(Noël *et al.*, 2012)	Carmustine Wafers	Retrospective Case Control Study	3
4)	(Chaichana *et al.*, 2011)	Carmustine Wafers	Retrospective Case Control Study	3
5)	(Affronti *et al.*, 2009)	Carmustine Wafers	Retrospective Case Control Study	3
6)	(Valtonen *et al.*, 1997)	Carmustine Wafers	Prospective Cohort Study	2
7)	(Subach *et al.*, 1999)	Carmustine Wafers	Prospective Cohort Study	2
8)	(Brem *et al.*, 1995)	Carmustine Wafers	Randomized Clinical Trial (RCT)	1
9)	(McGirt *et al.*, 2009)	Carmustine Wafers	Retrospective Case Control Study	3
10)	(Samis Zella *et al.*, 2014)	Carmustine Wafers	Retrospective Case Control Study	3

Table 3. Summary of study types and evidence level

The criteria used to determine the evidence level for each study design were determined using previously published guidelines[26].