

Carmustine-releasing Wafers for Brain Metastasis: Single Institution Experience and Results of the VIGILANT Prospective Registry

Eleanor C. Smith

Wake Forest University School of Medicine

Bryan T. Mott

Wake Forest University School of Medicine

Jared M. Kaplan

Jared.kaplan@advocatehealth.org

Wake Forest University School of Medicine

Carol Kittel

Wake Forest University

Molly Ehrig

Wake Forest University

Christina K Cramer

Wake Forest University School of Medicine

Jaclyn White

Wake Forest University School of Medicine

Stephen B. Tatter

Wake Forest University School of Medicine

Research Article

Keywords: Carmustine, Brain Metastasis, Radiosurgery, Tumor Recurrence

Posted Date: September 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10780474/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

PURPOSE

Brain metastases affect many patients with solid tumor malignancies. Treatments include surgery, radiation, immunotherapy, and CNS-penetrating chemotherapy. Nonetheless rates of neurologic death remain high. Local recurrence after radiosurgery and tumors too large for radiosurgery present a particular challenge. The VIGILANT (Vigilant Observation of GLIADEL Wafer Implant) registry prospectively examines use and efficacy of carmustine-releasing, wafers including in patients with brain metastases. Here we present results of patients with brain metastasis from the VIGILANT registry.

METHODS

Forty-eight patients were observed after surgical resection of brain metastasis and GLIADEL implantation at Wake Forest Baptist Medical Center. Thirty-three patients underwent treatment for local recurrence following radiosurgery. Fifteen had lesions deemed too large for successful radiosurgery. Patients were evaluated primarily for overall survival (OS) and progression free survival (PFS) from date of surgery, and secondarily for adverse events and local progression.

RESULTS

Median OS was 14.9 months (95% CI 8.3, 26.0). Of 25 deaths, 7 (28%) met criteria for neurological etiology. Twenty-seven (56%) patients had progression during follow up, Six (12.5%) had local progression. Two (4%) had local progression that required additional neurosurgical treatment. Of 15 patients not previously treated with radiosurgery, 8 (53%) had no progression. Forty-three patients had adverse events; two considered possibly GLIADEL related.

CONCLUSIONS

Treatment of brain metastases too large for radiosurgery or that failed initial radiosurgery with carmustine-releasing wafers was associated with favorable OS (14.9 months) and 1-year local progression rate (12%) in this very challenging population and was well tolerated.

Introduction

Brain metastases are the most common Central Nervous System (CNS) malignancy in adults, affecting approximately 30–40% of cancer patients with primary solid tumor malignancies [1, 2]. Lung cancer accounts for the majority of brain metastases, followed by breast cancer and melanoma [3]. Rates of brain metastasis requiring treatment are increasing because of improved control of extracranial disease with systemic treatments leading to improved overall survival as well as increasing detection by

improving imaging [2]. Currently, standard of care treatments for brain metastases includes surgical resection, radiotherapy (both whole brain and stereotactic), as well as cytotoxic chemotherapies and targeted therapies, which often have inadequate efficacy due to limited ability to cross the blood brain barrier (BBB) [1, 2]. Despite this array of therapies, overall survival in patients diagnosed with brain metastasis remains poor, with a meta-analysis of 5325 patients by Li et al. showing an overall survival of 17.9 months in patients with stable extracranial disease, and 8.0 months for patients with progressive disease [4].

Patients with local recurrence after radiosurgery or with very large tumors are particularly problematic because of high rates of radiation toxicity from radiation retreatment or from treating large intracranial volumes.

In order to overcome the BBB, alternative routes of administration of chemotherapeutics have been employed including direct implantation into brain tumor surgical cavities. GLIADEL[®], is a biodegradable carmustine chemotherapy wafer shown to deliver high doses of carmustine to a resection cavity, with limited distant penetration to normal brain tissues [5]. Approved by the US Food and Drug Administration for use in 1996, GLIADEL, an implantable carmustine wafer, has shown efficacy in treatment of recurrent malignant glioma with an acceptable side-effect profile [5, 6].

Retrospective series of GLIADEL for treatment of brain metastases from solid tumors show there may be decreased local recurrence [6–10]. The VIGILANT (Vigilant Observation of Gliadel Wafer Implant) registry, initiated in 2017, aims to prospectively examine the use and efficacy of GLIADEL wafers in the USA, including in patients with brain metastases [11]. Here we present the retrospective, single-institution results of the VIGILANT registry of GLIADEL for treatment of patients with brain metastasis from solid tumors.

Methods

Patients undergoing surgical resection of metastatic and primary brain tumors were enrolled at Wake Forest Baptist Medical Center starting in 2017 with a follow up period of 3 years. The protocol was reviewed and approved by the WFU Health Sciences Institutional Review Board and performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. Informed consent to participate was obtained from each patient or the patient's legally appointed representative. Management of the registry was overseen by Azurity Pharmaceuticals, previously Arbor Pharmaceuticals. No sites other than Wake Forest Baptist Medical Center enrolled patients with brain metastases in the VIGILANT registry (NCT02684838, registered February, 2016); so, this report represents prospective results from a single institution.

Inclusion criteria included patients ≥ 18 years of age, eligible to receive GLIADEL for treatment of a CNS malignancy, and no medical comorbidities that increased patient risk in the registry. Patients included in this analysis were limited to those undergoing GLIADEL wafer implantation as part of their care for treatment of CNS metastasis from solid tumor primary malignancy.

Primary objectives include evaluating the overall survival (OS) and progression free survival (PFS) of patients treated with GLIADEL wafers. Secondary objectives include evaluating adverse events related to GLIADEL wafer use in patients with metastasis from solid tumor primary malignancy.

Statistical Analysis

Descriptive statistics were summarized by frequency (percent) or median [IQR]. Two-tailed p-values of less than 0.05 were considered statistically significant for this study. To evaluate associations between overall survival and age, sex, race, dose, residual volume, tumor volume, prior treatment, degree of resection, and pathology (lung, breast, or other), univariate Cox proportional hazards regression models were used. The proportional hazards assumption was assessed for each model, and the assumption did not hold for the race model. Estimates for freedom from overall survival were obtained with the Kaplan-Meier method, and median survival time for patients whose death was considered neurological was calculated by summarizing time to event for this subset of patients.

To investigate associations between age, sex, race, dose, residual volume, tumor volume, prior treatment, degree of resection pathology (lung, breast, or other) and progression, univariate competing risks regression models were used with death considered a competing event. The Fine and Gray method was used for estimating cumulative incidence of progression. Following univariate regression analysis of overall survival and progression, multivariable models were explored via stepwise selection with no predictors ultimately identifying to remain in the models.

Among the subset of patients who underwent prior stereotactic radiosurgery (SRS), cumulative incidence estimation was used to describe local progression where death is treated as a competing event.

Results

A total of 69 patients were consented for the study, and 48 patients were included in the final analysis. 15 patients were not included in analysis due to pathology showing primary CNS lesion, and 6 patients were deemed to not be candidates for GLIADEL wafer placement due to screening failure.

Patient descriptives are presented in Table 1. 30 patients were female, and 18 were male. Median age was 63.6 (IQR 56.8, 68.3) at diagnosis. 25 patients had pathology consistent with lung cancer including 9 non-small cell lung cancer (NSCLC), 10 lung adenocarcinoma, 4 small cell lung cancer (SCLC), 1 neuroendocrine, and 1 carcinoid. Other pathologies included breast (8 patients), colorectal (3 patients), esophageal (2 patients), melanoma (2 patients), squamous cell carcinoma (2 patients), renal cell carcinoma (1 patient), bladder (1 patient), endometrial (1 patient), mediastinal adenocarcinoma (1 patient), adenoid cystic carcinoma (1 patient), unknown origin (1 patient). 33 patients were treated for local recurrence despite SRS while 15 patients had lesions deemed too large for successful primary SRS.

Table 1
Patient Descriptives

Overall (N = 48)	
Age at surgery	
Median [Q1, Q3]	63.6 [56.8, 68.3]
Sex	
Female	30 (62.5%)
Male	18 (37.5%)
Race	
Black	8 (16.7%)
White	40 (83.3%)
Dose	
Median [Q1, Q3]	6.00 [4.75, 8.00]
Residual volume	
Median [Q1, Q3]	0 [0, 0]
Missing	1 (2.1%)
Tumor volume	
Median [Q1, Q3]	6940 [3490, 13600]
Prior treatment	
No	11 (22.9%)
Yes	37 (77.1%)
SRS	
No	15 (31.3%)
Yes	33 (68.8%)
Degree of resection	
Gross Total	39 (81.3%)
Subtotal	8 (16.7%)
Missing	1 (2.1%)
Progression	

Overall (N = 48)	
Age at surgery	
No	23 (47.9%)
Yes	25 (52.1%)
Pathology	
Breast	8 (16.7%)
Lung	25 (52.1%)
Other	14 (29.2%)
Missing	1 (2.1%)
End of study reason	
Investigator Decision	6 (12.5%)
Lost to Follow-Up	4 (8.3%)
Patient Death	25 (52.1%)
Study Completion	12 (25.0%)
Withdrawal of Consent	1 (2.1%)

Median tumor volume was 6940mm³ (IQR 3490, 13600), with residual volume following resection ranging from 0-3.5mm³. The median number of GLIADEL wafers placed was 6 (IQR 4.75, 8.00). Of the 48 patients in the study, 25 died and 23 were censored. 7 of these deaths met criteria for neurological death, 13 due to extra-cranial disease progression, and for 5 patients cause of death was unknown. 25 patients had progression, 13 did not have progression but died, and 10 did not have progression and did not die. 43 total patients had adverse events; two considered possibly GLIADEL related.

Median overall survival (OS) was 23 months. Overall survival at 6 and 12 months were 73% and 60%, respectively. Patient descriptives split by overall survival status are presented in Table 2. Of 7 patients with death considered neurological, median OS was 5.3 months. Age, sex, dose, residual volume, tumor volume, prior treatment, degree of resection and pathology were not found to be significantly associated with overall survival. Overall survival probability is shown in Fig. 1.

Table 2
Split by overall survival status

	Censored (N = 23)	Death (N = 25)	Overall (N = 48)
Age at surgery			
Median [Q1, Q3]	61.9 [51.7, 66.9]	67.1 [61.3, 69.0]	63.6 [56.8, 68.3]
Sex			
Female	15 (65.2%)	15 (60.0%)	30 (62.5%)
Male	8 (34.8%)	10 (40.0%)	18 (37.5%)
Race			
Black	5 (21.7%)	3 (12.0%)	8 (16.7%)
White	18 (78.3%)	22 (88.0%)	40 (83.3%)
Dose			
Median [Q1, Q3]	5.00 [4.00, 8.00]	8.00 [5.00, 8.00]	6.00 [4.75, 8.00]
Residual volume			
Median [Q1, Q3]	0 [0, 0]	0 [0, 0]	0 [0, 0]
Missing	1 (4.3%)	0 (0%)	1 (2.1%)
Tumor volume			
Median [Q1, Q3]	4910 [1250, 11700]	8020 [5260, 16400]	6940 [3490, 13600]
Prior treatment			
No	5 (21.7%)	6 (24.0%)	11 (22.9%)
Yes	18 (78.3%)	19 (76.0%)	37 (77.1%)
SRS			
No	6 (26.1%)	9 (36.0%)	15 (31.3%)
Yes	17 (73.9%)	16 (64.0%)	33 (68.8%)
Degree of resection			
Gross Total	18 (78.3%)	21 (84.0%)	39 (81.3%)
Subtotal	4 (17.4%)	4 (16.0%)	8 (16.7%)
Missing	1 (4.3%)	0 (0%)	1 (2.1%)

	Censored (N = 23)	Death (N = 25)	Overall (N = 48)
Age at surgery			
Pathology			
Breast	5 (21.7%)	3 (12.0%)	8 (16.7%)
Lung	9 (39.1%)	16 (64.0%)	25 (52.1%)
Other	8 (34.8%)	6 (24.0%)	14 (29.2%)
Missing	1 (4.3%)	0 (0%)	1 (2.1%)

For the 25 patients that had progression, the median time to progression is 3.5 months (IQR 2.1, 4.9). Considering death as censored, the median progression free survival was 5.5 months. 6 (24%) had local progression, 3 (12%) of which had subtotal resection. 2 (8%) had local progression that required additional neurosurgical treatment. 15 (60%) patients had distant progression, and 4 (16%) had unknown location of progression. Of 33 patients previously treated with SRS 18, (55%) had progression and 5 (15%) had local progression. Of 15 patients not previously treated with radiosurgery, 7 (47%) had progression and 1 (7%) had local progression.

Patient demographics and surgical characteristics are presented in Table 3. Just as with OS, no associations were found between the same variables and progression. Cumulative incidence of progression is shown in Fig. 2.

Table 3
Patient demographics and surgical characteristics

	Censored	Death	Progression	Overall
	(N = 10)	(N = 13)	(N = 25)	(N = 48)
Age at surgery				
Median [Q1, Q3]	57.7 [47.5, 65.8]	62.2 [59.9, 67.1]	66.8 [60.0, 68.9]	63.6 [56.8, 68.3]
Sex				
Female	7 (70.0%)	7 (53.8%)	16 (64.0%)	30 (62.5%)
Male	3 (30.0%)	6 (46.2%)	9 (36.0%)	18 (37.5%)
Race				
Black	3 (30.0%)	2 (15.4%)	3 (12.0%)	8 (16.7%)
White	7 (70.0%)	11 (84.6%)	22 (88.0%)	40 (83.3%)
Dose				
Median [Q1, Q3]	5.00 [4.00, 8.00]	8.00 [5.00, 8.00]	6.00 [5.00, 8.00]	6.00 [4.75, 8.00]
Residual volume				
Median [Q1, Q3]	0 [0, 0.560]	0 [0, 0]	0 [0, 0]	0 [0, 0]
Missing	1 (10.0%)	0 (0%)	0 (0%)	1 (2.1%)
Tumor volume				
Median [Q1, Q3]	8770 [4840, 13800]	9750 [3700, 16600]	6230 [3240, 10200]	6940 [3490, 13600]
Prior treatment				
No	3 (30.0%)	4 (30.8%)	4 (16.0%)	11 (22.9%)
Yes	7 (70.0%)	9 (69.2%)	21 (84.0%)	37 (77.1%)
SRS				
No	3 (30.0%)	5 (38.5%)	7 (28.0%)	15 (31.3%)
Yes	7 (70.0%)	8 (61.5%)	18 (72.0%)	33 (68.8%)
Degree of resection				
Gross Total	6 (60.0%)	12 (92.3%)	21 (84.0%)	39 (81.3%)

	Censored	Death	Progression	Overall
	(N = 10)	(N = 13)	(N = 25)	(N = 48)
Age at surgery				
Subtotal	3 (30.0%)	1 (7.7%)	4 (16.0%)	8 (16.7%)
Missing	1 (10.0%)	0 (0%)	0 (0%)	1 (2.1%)
Pathology				
Breast	2 (20.0%)	1 (7.7%)	5 (20.0%)	8 (16.7%)
Lung	3 (30.0%)	8 (61.5%)	14 (56.0%)	25 (52.1%)
Other	5 (50.0%)	4 (30.8%)	5 (20.0%)	14 (29.2%)
Missing	0 (0%)	0 (0%)	1 (4.0%)	1 (2.1%)

Cumulative incidence of local progression is shown in Fig. 3. Of the 5 patients who underwent SRS and had local progression, the median time to local progression was 3.7 months.

Discussion

The present study focuses exclusively on a population with limited therapeutic alternatives: patients whose brain metastases had recurred after stereotactic radiosurgery or whose presenting tumors were too large for resection followed by radiosurgery. This group faces high rates of local failure, and there is no consensus on optimal salvage therapy. Thus, the outcomes reported here provide valuable insight into a pressing clinical challenge and underscore the potential role of local carmustine delivery as a targeted intervention for improving disease control in patients without other attractive management options

Treatment of brain metastases remains increasingly pertinent as growing numbers of patients with solid tumor malignancy are found to have brain metastases due to prolonged overall survival thanks to improving systemic therapies, and improving imaging modalities allowing earlier and more frequent diagnosis [3]. A series by Benna and colleagues estimated median survival of patients after primary diagnosis of brain metastases to be 4 months [12], with an estimated 23–46% of patients having recurrence after primary treatment within 7 months [13]. Of 11 patients in our cohort who had no prior treatment prior to GLIADEL placement, only 4 (36.4%) had progression of disease, in the same range of estimated risk of progression compared to previously described cohorts.

Carmustine wafers are employed for management of primary brain tumors, with FDA approval for treatment of recurrent high-grade gliomas in 1996, and initial treatment of high-grade gliomas in 2003 [14]. Randomized placebo-controlled trials have been performed evaluating efficacy of carmustine wafers in the treatment of primary and recurrent high-grade gliomas, both showing statistically

significant survival benefit when compared to patients undergoing placebo wafer placement [15. 16]. Carmustine may still not penetrate deeply enough for most effective treatment of infiltrative glioma [17]. On the other hand, histological evaluation of brain metastases shows the maximum infiltration of all evaluated primary pathologies to be less than 2mm into normal brain tissue, within the described volume of highest tissue dose of carmustine, which has been found to be approximately 3mm from the implant in pharmacokinetic studies [5]. Despite these encouraging mechanistic considerations, a paucity of studies evaluate local drug delivery for brain metastasis.

A phase 2 clinical trial performed by Brem and colleagues published in 2013 evaluated the use of surgical resection and placement of carmustine wafers for up front treatment of brain metastasis [18]. 59 patients were included in analysis, which predominantly aimed to evaluate neurocognitive function preservation in comparison to treatment with whole brain radiotherapy (WBRT). Secondary analysis evaluated disease control, which showed 28% of patients developing local recurrence and 48% of patients developing distant recurrence, higher than the rate found in our cohort, though the number of patients undergoing primary treatment in our cohort was smaller.

A retrospective review by Ene et al. in 2016 evaluated 14 patients receiving implantation of carmustine wafers during surgical resection of brain metastasis [19]. All patients had received a prior form of treatment with subsequent recurrence prompting craniotomy and carmustine wafer placement. 50% of patients had tumor recurrence with mean time to progression of 2.5 years, and 5 patients died prior to publication with a mean overall survival of 2.9 years. This cohort found that patients > 53 years old had a longer progression free survival than those < 53 years old, and no variable affected overall survival. Though their PFS and OS reported are higher than our current cohort, this could be secondary to evaluating a significantly smaller retrospective cohort, or shorter median follow up time (18.7 months).

Radiosurgery is a commonly used adjuvant modality for brain metastasis treatment following maximum safe total resection to combat microscopic tumor cells outside of the resection cavity. Unfortunately, the brain has limited tolerance to radiation therapy, and over treatment with radiation can lead to complications such as tumor necrosis. A retrospective review of 31 patients undergoing placement of carmustine wafers for treatment of brain metastasis following radiosurgical failure was performed by Mu et al. in 2015 to evaluate alternatives to re-irradiation [17]. Median overall survival for these patients was 10 months, with 45% dying of neurological cause. Local control for these patients at 1 year was 70%, with 16% undergoing further salvage therapy, as compared to our cohort with a 1 year survival of approximately 60% and 12.5% of patients with local progression undergoing subsequent therapies. Additionally, median overall survival in our cohort was comparatively prolonged at 23 months, which may be secondary to the homogeneity of patients undergoing primary or secondary treatment for brain metastasis in our cohort. When accounting only for patients who had previously undergone radiotherapy, 5 (15%) had local recurrence in our cohort, similar to the rates described in the Mu et al. cohort, and 4 of 33 previously treated with SRS had local recurrence in 1 year, giving a 1-year local progression rate of 12%. Comparatively, local progression rates for patients undergoing reirradiation following radiosurgical failure are reported up to 39%, with OS ranging from 7.9–24 months in some series [20].

Limitations

While we describe one of the largest prospectively evaluated cohorts of patients undergoing implantation of GLIADEL wafers during resection of brain metastasis with the goal of describing progression free and overall survival, our population size is limited. Additionally, we have no prospective control group to compare, and thus can only provide descriptive evaluation of our results. Further large prospective or randomized controlled trials are needed to draw significant conclusions regarding benefit on overall and progression free survival.

Conclusion

Patients described in this series represent a particularly challenging population—those with brain metastases that had either recurred after stereotactic radiosurgery or were initially too large for resection followed by radiosurgery to the resection cavity to have a high probability of success. For these individuals, effective salvage or alternative local therapies are extremely limited. By focusing on this high-risk group, our results provide evidence supporting a feasible and well-tolerated strategy for improving local control in patients for whom few other options exist.

Placement of GLIADEL wafers for treatment of brain metastases was associated with encouraging rates of overall survival and of local progression free survival compared to historical rates described in the literature, particularly in those who have failed radiosurgery as initial management. GLIADEL was well tolerated, with few adverse events attributable to GLIADEL placement.

Declarations

Disclosures:

None

Funding:

N/A

Author Contribution

E.S. and B.M. were involved in data collection/generation and wrote the main manuscript text. C.K and M.E. prepared figures and formal analysis. C.C was involved in investigation and study design. J.W and S.T contributed project conceptualization, supervision, administration, and data collection. J.K was involved in revision, manuscript/figure editing. All authors reviewed the manuscript.

Acknowledgement

The authors wish to thank Azurity Pharmaceuticals, Inc. for their help with providing comprehensive data and trial management.

Data Availability

<https://clinicaltrials.gov/study/NCT02684838>

References

1. Kotecha R, Gondi V, Ahluwalia MS, Brastianos PK, Mehta MP (2018) Recent advances in managing brain metastasis. *F1000Res* ;7
2. Singh K, Saxena S, Khosla AA, McDermott MW, Kotecha RR, Ahluwalia MS (2022) Update on the Management of Brain Metastasis. *Neurotherapeutics* 19(6):1772–1781
3. Sacks P, Rahman M (2020) Epidemiology of Brain Metastases. *Neurosurg Clin N Am* 31(4):481–488
4. Li AY, Gaebe K, Zulfiqar A et al (2023) Association of Brain Metastases With Survival in Patients With Limited or Stable Extracranial Disease: A Systematic Review and Meta-analysis. *JAMA Netw Open* 6(2):e230475–e230475
5. Fleming AB, Saltzman WM (2002) Pharmacokinetics of the carmustine implant. *Clin Pharmacokinet* 41(6):403–419
6. Abel TJ, Ryken T, Lesniak MS, Gabikian P (2013) Gliadel for brain metastasis. *Surg Neurol Int* 4(Suppl 4):S289–293
7. Ewend MG, Brem S, Gilbert M et al (2007) Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer Res* 13(12):3637–3641
8. Newton HB, Volpi C, Burkart J et al (2006) Phase III randomized multicenter trial of surgical resection, BCNU-impregnated wafers, and irradiation versus surgical resection and irradiation alone for treatment of operable, solitary brain metastasis from systemic cancer. *J Clin Oncol* 24(18suppl):11513–11513
9. Ryken T, Evans L, MLTI-11. IMPLANTABLE POLYMERIC BCNU AS AN ADJUNCT TO SURGERY FOR METASTATIC INTRACRANIAL DISEASE (2019) *Neuro-Oncology Adv* 1:i16–i16
10. Golden GA, Meldorf M, Grp PS (2004) Patients with metastatic brain cancer undergoing resection and Gliadel implantation experienced low local recurrence rates in the prolong registry. *Neurooncology* 6(4):375–376
11. Lillehei KO, Kalkanis SN, Liao LM et al (2017) Rationale and design of the 500-patient, 3-year, and prospective Vigilant Observation of Gliadel WAfer ImplANT registry. *CNS Oncol* 7(2):CNS08

12. Benna M, Mejri N, Mabrouk M et al (2018) Brain metastases epidemiology in a Tunisian population: trends and outcome. *CNS Oncol* 7(1):35–39
13. Tewarie IA, Hulsbergen AFC, Jessurun CAC et al (2022) Risk Factors of Second Local Recurrence in Surgically Treated Recurrent Brain Metastases: An Exploratory Analysis. *World Neurosurg* 167:e639–e647
14. Fisher JP, Adamson DC (2021) Current FDA-Approved Therapies for High-Grade Malignant Gliomas. *Biomedicines* 9(3):324
15. Brem H, Piantadosi S, Burger PC et al (1995) Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 345(8956):1008–1012
16. Westphal M, Hilt DC, Bortey E et al (2003) A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 5(2):79–88
17. Mu F, Lucas JT Jr., Watts JM et al (2015) Tumor resection with carmustine wafer placement as salvage therapy after local failure of radiosurgery for brain metastasis. *J Clin Neurosci* 22(3):561–565
18. Brem S, Meyers CA, Palmer G, Booth-Jones M, Jain S, Ewend MG (2013) Preservation of neurocognitive function and local control of 1 to 3 brain metastases treated with surgery and carmustine wafers. *Cancer* 119(21):3830–3838
19. Ene CI, Nerva JD, Morton RP et al (2016) Safety and efficacy of carmustine (BCNU) wafers for metastatic brain tumors. *Surg Neurol Int* 7(Suppl 11):S295–299
20. Kotecha R, La Rosa A, Brown PD et al (2025) Multidisciplinary management strategies for recurrent brain metastasis after prior radiotherapy: An overview. *Neuro Oncol* 27(3):597–615
21. Clinicaltrials.gov (2026) <https://clinicaltrials.gov/study/NCT02684838>. Registered February 2, 2016

Figures

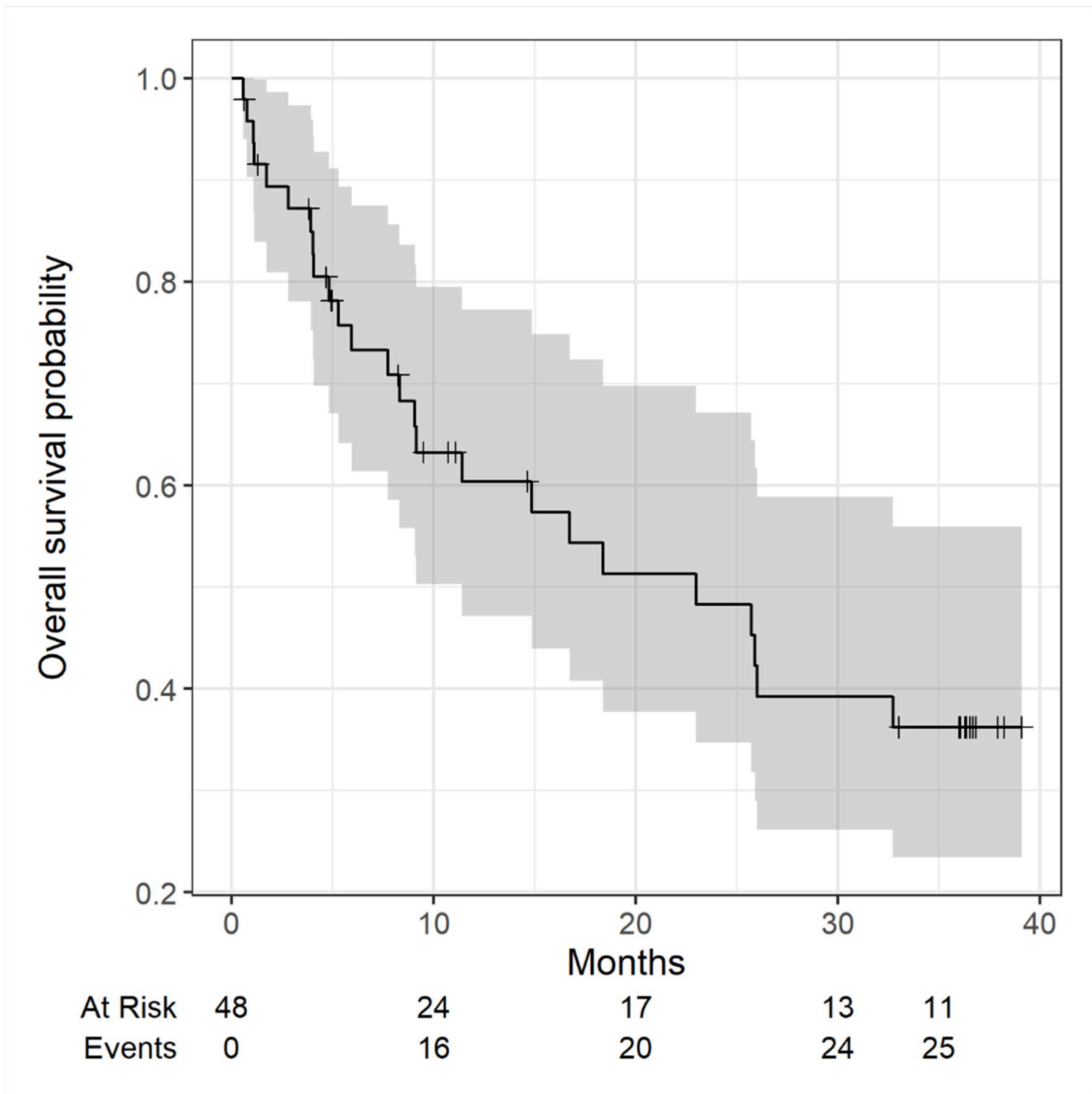


Figure 1

Survival plot

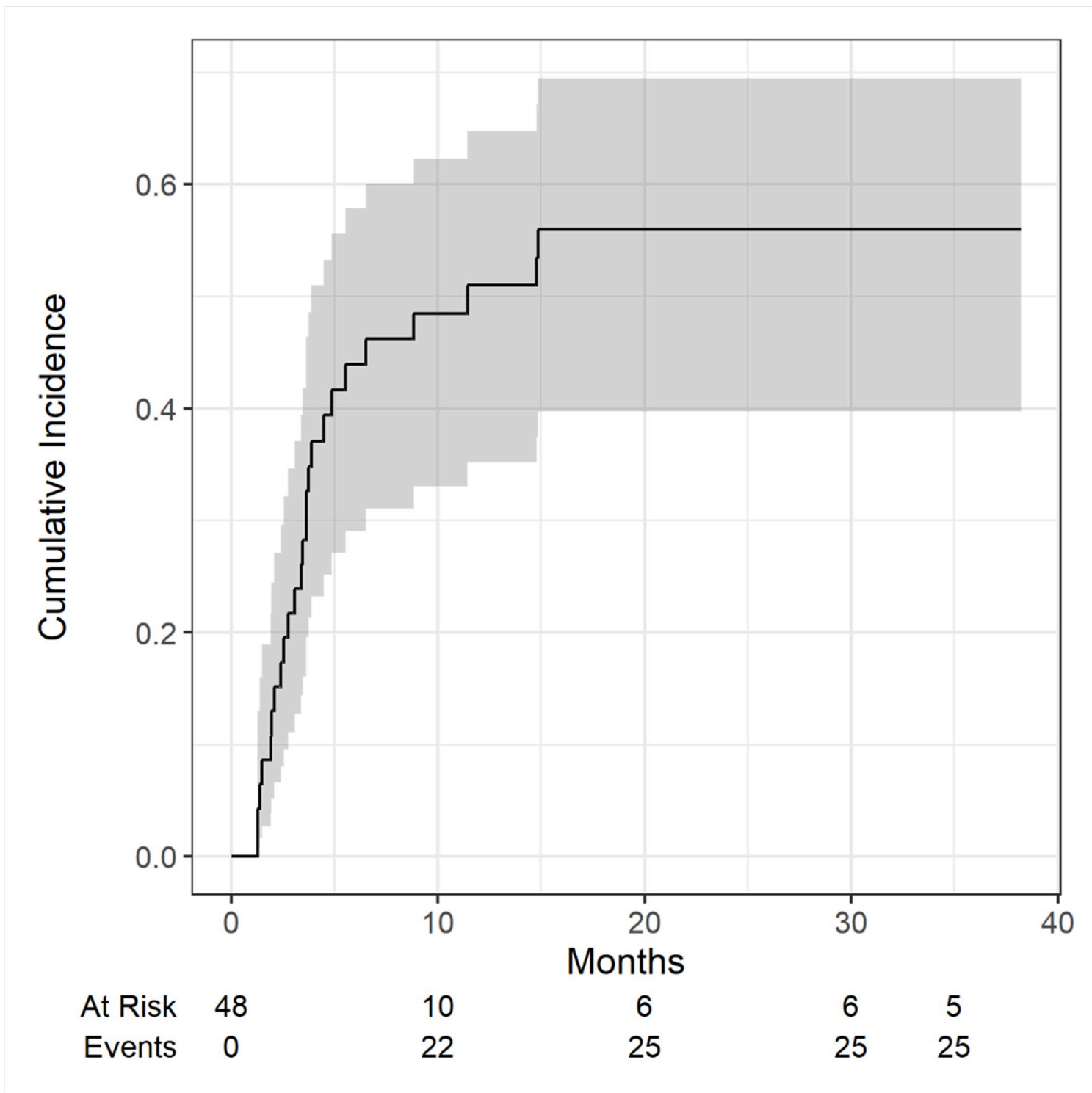


Figure 2

Cumulative incidence of progression estimates with 95% confidence intervals

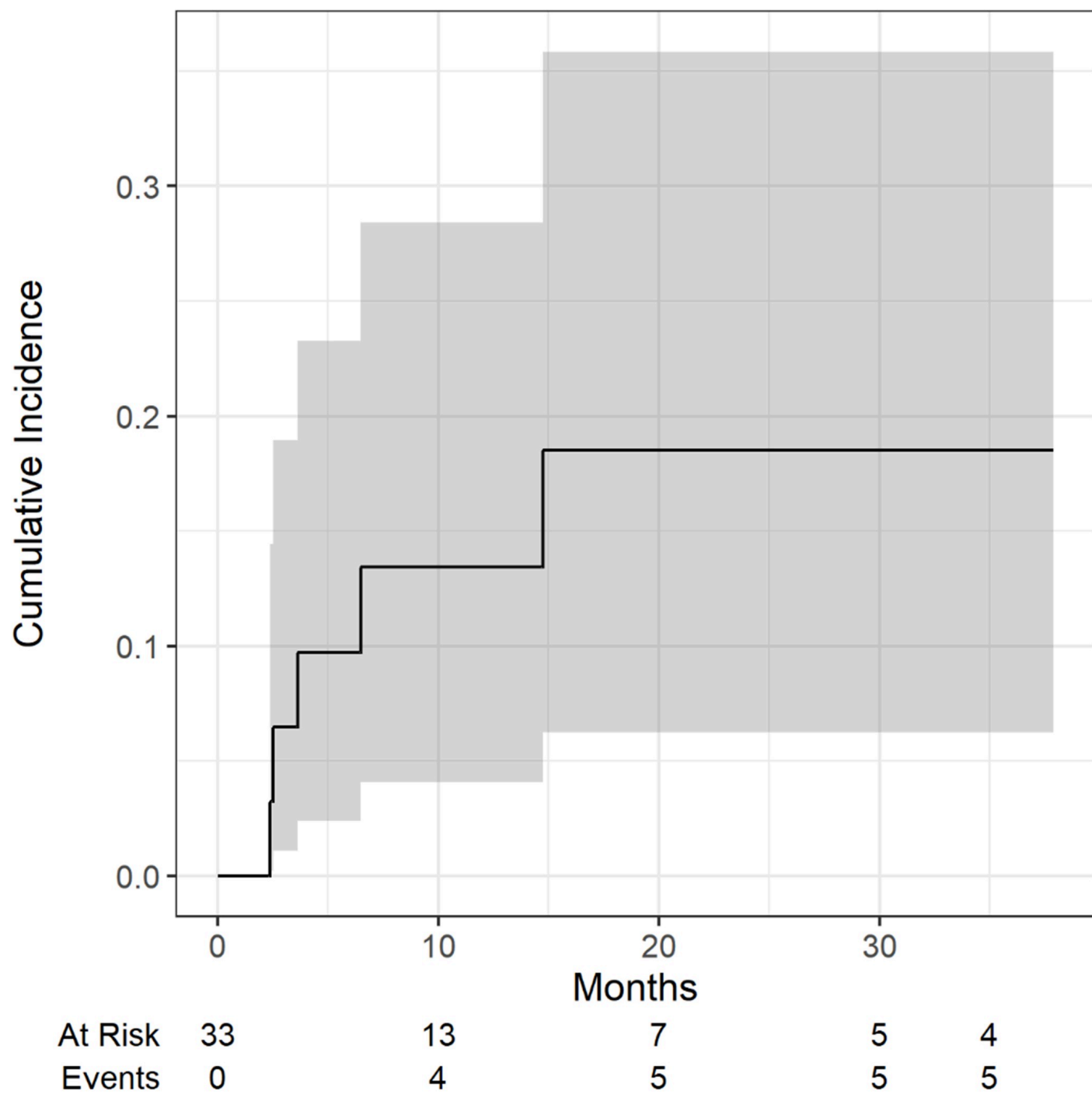


Figure 3

Cumulative incidence of local progression estimates with 95% confidence intervals