Original Research Paper

Risk of surgical site infection in 401 consecutive patients with glioblastoma with and without carmustine wafer implantation

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Objectives: Patients with glioblastoma (GBM) have an inherently shortened survival because of their disease. It has been recently shown that carmustine wafers in addition to other therapies (surgery, temozolomide, and radiation) can further extend survival. There is concern, however, that these therapies may increase infection risk. The goals of this study were to calculate the incidence of postoperative infection, evaluate if carmustine wafers changes the risk of infection and identify factors independently associated with an infection following GBM surgery.

Methods: All patients who underwent non-biopsy, surgical resection of an intracranial GBM from 2007 to 2011 at a single institution were retrospectively reviewed. Stepwise multivariate proportional hazards regression analysis was used to identify factors associated with infection, including the use of carmustine wafers. Variables with $P < 0.05$ were considered statistically significant.

Results: Four hundred and one patients underwent resection of an intracranial GBM during the reviewed period, and 21 (5%) patients developed an infection at a median time of 40 [28–286] days following surgery. The incidence of infection was *not* higher in patients who had carmustine wafers, and this remained true in multivariate analyses to account for differences in treatment cohorts. The factors that remained significantly associated with an *increased* risk of infection were prior surgery [RR (95% CI); 2.026 (1.473–4.428), $P = 0.01$], diabetes mellitus [RR (95% CI); 6.090 (1.380–9.354)], $P = 0.02$], and increasing duration of hospital stay [RR (95% CI); 1.048 (1.006–1.078); $P = 0.02$], where the greatest risk occurred with hospital stays >5 days [RR (95% CI); 3.904 (1.003–11.620), $P = 0.05$].

Discussion: These findings may help guide treatment regimens aimed at minimizing infection for patients with GBM.

Keywords: Carmustine (Gliadel) wafers, Glioblastoma (GBM), Infection, Risk, Surgery

Introduction

The median survival for patients with glioblastoma (GBM) is 14.6 months after surgical resection, temozolomide chemotherapy and radiation therapy.[1] However, more recently it has been shown that the use of local chemotherapy in the form of carmustine wafers can further extend median survival.[2,3] The median survival for patients who underwent surgery and standard adjuvant therapy (temozolomide and radiation) with carmustine wafer implantation was 21.3 months as compared to 12.4 months for age-matched patients who only underwent surgery and standard adjuvant therapy.[3] Despite this increase in survival with carmustine wafer implantation, there is concern that the use of carmustine wafers may be associated with an increased risk of infection.[4–6] Moreover, the risk of infection among patients with GBM is unclear because prior studies primarily included small patient populations, disparate pathologies, dissimilar surgical approaches and non-multivariate analyses (Table 1).[4–10] An understanding of the factors that may predispose to infection is especially important because infections delay the administration of adjuvant therapy, and this delay results in poorer patient outcomes.[11]

The goals of this study were to therefore: (1) calculate the incidence of postoperative infection, (2) evaluate if the use of carmustine wafers increases

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DOI 10.1179/1743132815Y.0000000042

Table 1 Previous studies designed to evaluate the incidence and risk factors of postoperative infection following intracranial glioblastoma (GBM) study

Study	Year	No. of patients	No. (%) with infection	Included non-GBM patients	Carmustine wafers	Included biopsy patients	Multivariate analyses for infection
Present study	2014	401	21 (5%)	No	Yes	No	Yes
Nuno *et al.*[12]*	2014	437	77 (18%)†	No	No	Yes	No
Samis Zella *et al.*[6]	2014	95	2 (3%)	No	Yes	No	No
Gulati *et al.*[9]	2011	144	4 (3%)	No	No	Yes	No
Rabadan *et al.*[10]	2007	236	11 (5%)	Yes	No	No	No
Chang *et al.*[8]	2003	499	3 (1%)	Yes	No	Yes	No
McGovern *et al.*[4]	2003	32	9 (28%)	Yes	Yes	No	No
Brell *et al.*[7]	2000	200	11 (6%)	Yes	No	Yes	No
Subach *et al.*[5]	1999	62	5 (8%)	No	Yes	No	No

* Population-based database rather than a hospital series.

the risk of infection and (3) identify the clinical factors independently associated with infection following GBM surgery. An understanding of these factors may help guide treatment strategies aimed at minimizing the risk of infection.

Methods

Patient selection and recorded variables

All adult patients (age > 18 years) who underwent surgical resection of a pathologically confirmed intracranial GBM from 2007 to 2011 at a single, tertiary care institution were retrospectively identified and reviewed from an institutional database. This included patients who had prior lower grade gliomas and recurrent tumours. Patients who underwent open biopsies and needle biopsies were excluded. This was done to create a more uniform cohort of patients who underwent surgical debulking of their GBM.

Of the patients who met the inclusion criteria, the clinical, operative and postoperative clinical notes from an electronic patient record database were retrospectively reviewed by clinicians. The information collected included patient demographics, co-morbidities, previous surgeries, neurological function, radiographic characteristics, use of carmustine wafers, length of hospital stay, perioperative complications (within 30 days of surgery), adjuvant therapy regimens, wound infections, culture results and antibiotic regimen. A motor deficit was defined as a decrease in motor strength, a language deficit was a decrease in the ability to speak or understand language and a visual deficit was a decline in visual acuity and/or visual field. Moreover, an eloquent tumour location was defined as involvement of language, motor or visual cortices based on preoperative imaging. Severe obesity was defined as BMI > 35. The diagnoses of other co-morbidities including diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disorder, a trial fibrillation, stroke, etc. were based on a pre-existing diagnosis made by their primary care physician immediately before surgery. The use and dosing of steroids were not uniformly available in the patients' charts and so were not included in the data collection. The presence of a wound infection was identified based on postoperative clinical notes with the use of the Centre for Disease Control (CDC) definition of infection (infection involving superficial incisional, deep incisional and/or organ/space surgical site infection).[13] However, time to infection was not limited to 30 days within surgery, but included any infection noted at any time in the follow-up period. This was done, instead of using ICD-9 codes, in order to make sure all infections (both operative and non-operative) were included. Patients who had wound dehiscences without evidence of infection were not considered to have infections. All patients underwent brain MRI with and without gadolinium within 48 hours before and additionally following surgery. Pre- and postoperative tumour volumes were measured as previously described.[14]

General treatment strategy

All patients typically underwent medical evaluation before surgery, which allowed a more comprehensive inclusion of patient co-morbidities. Before incision, the surgical area was typically cleaned with betadine scrub followed by application of a betadine solution. Intravenous antibiotics were administered within 60 minutes of skin incision. Cefazolin (2 g) was typically given and re-dosed every 4 hours while in the operating room. For patients who had a penicillin allergy, clindamycin (600 mg) was administered instead and re-dosed every 8 hours. Antibiotics were continued for 24 hours after surgery.[15]

The general aim of each surgery was to achieve gross total resection of the tumour when possible, where the extent of resection was generally limited by involvement of eloquent regions. Motor and somatosensory evoked potentials were typically used for lesions near the somatosensory cortex, and surgical navigation (MRI wand) was used in all

cases. The use of other surgical adjuncts including awake surgery, motor mapping or electrocorticography largely depended on surgeon preference. The use of carmustine wafers was determined by both the surgeon as well as the patient. These carmustine wafers were not implanted when tumours were multifocal, extended across the corpus callosum or required large openings in the ventricle. The implants were only used when the pathologist was able to identify malignant glioma during the operation on frozen section. The particular use of adjuvant radiation and chemotherapy was determined by a multidisciplinary team including the neurosurgeons, radiation oncologists, neurologists, medical oncologists and the patients themselves.

Patients who developed concern of a postoperative infection underwent MRI of the brain with and without gadolinium, as well as blood analysis that included complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). Wound dehiscences without evidence of infection (i.e. positive cultures, purulence, etc.) were not included in the analyses. An Infectious Disease team was involved in the care of these patients, where they guided the choice and duration of antibiotics based on culture sensitivities. The decision to pursue surgery for the wound infection was based on the surgeon's judgement and the recommendations made by the Infectious Disease consultant.

Statistical analysis

Summary data for parametric values were presented as mean ± standard deviation, while non-parametric values were presented as median [interquartile range (IQR)]. To compare patients with and without carmustine wafer placement, chi-squared analyses were used to compare percentages and the Student's *t*-test or Mann–Whitney *U*-test were used to compare continuous variables where appropriate. Forward, stepwise multivariate proportional hazards regression analyses were used to identify independent factors associated with developing a wound infection. In these analyses, univariate analyses were first performed to identify potential factors associated with infection. Factors with $P < 0.10$ were included into a stepwise multivariate proportional hazard regression analysis. Values with $P < 0.05$ were considered statistically significant. JMP 9 (SAS, Cary, NC) was used unless otherwise specified.

Results

Pre-, peri- and postoperative characteristics

Four hundred and one consecutive patients underwent non-biopsy, surgical resection of an intracranial GBM during the reviewed period (Table 2). The average age of the patients was 56.8 ± 14.0 years, and 246 (61%) were male. Before surgery, 54 (13%) had diabetes, 143 (36%) had hypertension, 26 (6%) had coronary artery disease, 31 (8%) were severely obese, 35 (9%) were smokers, 12 (3%) had chronic obstructive pulmonary disorder, 10 (2%) had a trial fibrillation and 14 (3%) had a history of a stroke. 53 (13%) patients had previous surgery for a lower grade glioma and 146 (36%) had previous GBM surgery. The median [IQR] presenting Karnofsky performance score (KPS) was 80 [70–90], and the major presenting symptoms were headaches in 147 (37%), seizures in 138 (34%), motor deficit in 128 (32%), language deficit in 140 (35%) and cognitive deficit in 115 (29%).

The perioperative characteristics are summarized in Table 2. The median [IQR] preoperative tumour volume was 32.2 (13.7–56.1) cm^3, and the tumours involved eloquent cortex in 190 (46%) patients. The median [IQR] postoperative volume was 2.5 [0.03–9.9] cm^3, where the mean ± standard error of the mean (SEM) per cent resection of 79.1 ± 1.2%. Overall, 103 (26%) had carmustine wafers placed at the time of surgery. Following surgery, 21 (5%) and 17 (4%) developed a new motor and language deficit, respectively. The median [IQR] length of hospital stay was 4 [2–7] days, and 285 (71%) were discharged to home and 116 (29%) were discharged to inpatient rehabilitation following surgery. Perioperatively, 30 (7%) had a urinary tract infection, 8 (2%) pneumonia, 4 (1%) sepsis and 30 (7%) deep vein thromboses (DVT) or pulmonary embolisms (PEs). There were 2 (0.5%) cases of wound dehiscence without evidence of infection.

Postoperatively, 351 (88%) underwent postoperative radiation therapy and 342 (85%) underwent temozolomide chemotherapy. Of the patients who did not undergo radiation therapy, 14 (3%) were considered too medically sick to undergo radiation therapy, 35 (9%) were lost to follow-up and may have received their radiation elsewhere and 1 (0.2%) refused radiation. Of the patients who did not undergo temozolomide chemotherapy, 24 (6%) were considered too medically sick to receive chemotherapy (i.e. thrombocytopenia) and 35 (9%) were lost to follow-up and may have received their chemotherapy elsewhere. At last follow-up, 325 (81%) patients had died at a median time of 11.9 months. The 30-day mortality occurred in 10 (2%). The patients who were not confirmed as dead were followed for a median [IQR] time of 12.2 [3.1–19.5] months. Ten (2%) patients were lost to follow-up, but none of the patients with infections were lost to follow-up.

Postoperative infection

At a median [IQR] follow-up of 10.8 [4.6–16.1] months, 21 (5%) patients developed a surgical site

infection at a median time of 40 [28–286] days following surgery based on the CDC definition of a surgical site infection[13] (Table 3) (the overall infection rate at our institution for all craniotomies ranged from 0.7% to 2.9% during this time interval). The average ± standard deviation age of the patients with infections was 58.6 ± 8.2 years at the time of surgery, and 7 (33%) had carmustine wafers placed at the time of surgery. A total of 20 (95%) infections involved the subgaleal space, 13 (62%) the epidural space and 5 (24%) the intradural space. Of the 20 patients with subgaeal infections, 12 (60%) also involved the epidural space and 5 (25%) involved both the epidural and intradural compartments. Only one (5%) patient

Table 2 Summary of pre-, peri-, and postoperative characteristics of patients who underwent surgical resection of an intracranial glioblastoma (GBM) with and without carmustine wafer placement at a tertiary care institution between 2007 and 2011 ($n = 401$)

Patient characteristics	All patients ($n = 401$)	Carmustine wafer ($n = 103$)	No carmustine wafer ($n = 298$)	p-value
Demographics				
Age*	56.8 ± 14.0	57.3 ± 13.2	56.6 ± 14.3	0.63
Male	246 (61%)	74 (72%)	172 (58%)	0.01
Diabetes	54 (13%)	8 (8%)	46 (15%)	0.06
Hypertension	143 (36%)	28 (27%)	115 (39%)	0.04
Coronary artery disease	26 (6%)	5 (5%)	21 (7%)	0.64
Obesity	31 (8%)	8 (8%)	23 (8%)	0.99
Smoker	35 (9%)	11 (11%)	24 (8%)	0.42
COPD	12 (3%)	5 (5%)	7 (2%)	0.20
A trial fibrillation	10 (2%)	4 (4%)	6 (2%)	0.29
Stroke	14 (3%)	3 (3%)	11 (4%)	0.99
Prior lower grade glioma	53 (13%)	14 (14%)	39 (13%)	0.87
Presenting symptoms				
KPS**	80 (70–90)	80 (80–90)	80 (70–90)	0.0003
Headaches	147 (37%)	37 (36%)	110 (37%)	0.91
Seizures	138 (34%)	37 (36%)	101 (34%)	0.72
Motor deficit	128 (32%)	28 (27%)	100 (34%)	0.27
Language deficit	140 (35%)	37 (36%)	103 (35%)	0.81
Vision deficit	62 (15%)	12 (12%)	50 (17%)	0.27
Cognitive deficit	115 (29%)	28 (27%)	87 (29%)	0.80
Radiographics				
Preoperative tumour volume (cm^3)**	32.2 (13.7–56.1)	29.1 (10.9–54.2)	33.7 (14.8–57.3)	0.11
Tumour location	190 (47%)	48 (47%)	142 (48%)	0.91
Eloquent	75 (19%)	7 (7%)	68 (23%)	0.0002
Basal ganglia				
Operative characteristics				
Recurrent GBM	146 (36%)	39 (38%)	107 (36%)	0.72
Awake surgery	16 (4%)	1 (1%)	15 (5%)	0.08
Ventricle entered	93 (23%)	22 (21%)	71 (24%)	0.69
Postop tumour volume (cm^3)**	2.5 (0.03–9.9)	0.8 (0–4.2)	3.5 (0.4–12.8)	0.0001
Percent resection†	79.1 ± 1.2%	87.1 ± 2.0%	76.4 ± 1.4%	0.0001
Perioperative course				
New motor deficit	21 (5%)	4 (4%)	17 (6%)	0.61
New language deficit	17 (4%)	6 (6%)	11 (4%)	0.40
Urinary tract infection	30 (7%)	6 (6%)	24 (8%)	0.52
Pneumonia	8 (2%)	2 (2%)	6 (2%)	0.99
Sepsis	4 (1%)	1 (1%)	3 (1%)	0.99
DVT/PE	30 (7%)	7 (7%)	23 (8%)	0.99
Hospital stay**	4 (2–7)	3 (2–6)	4 (2–8)	0.003
Discharge to rehab	116 (29%)	23 (22%)	93 (31%)	0.10
Discharge to home	285 (71%)	80 (78%)	205 (69%)	0.10
Adjuvant therapy				
Preoperative radiation	122 (30%)	32 (31%)	90 (30%)	0.90
Postoperative radiation	351 (88%)	93 (90%)	258 (87%)	0.39
Preoperative chemotherapy	118 (29%)	30 (29%)	88 (30%)	0.99
Temozolomide chemotherapy	342 (85%)	95 (92%)	247 (83%)	0.02
Carmustine wafer chemotherapy	103 (26%)	103 (100%)	0 (0%)	0.0001
Bevacizumab chemotherapy	71 (18%)	18 (17%)	53 (18%)	0.99
Surgical site infection	21 (5%)	7 (7%)	14 (5%)	0.44
Time to infection (days)**	40 (28–286)	40 (15–295)	38 (28–208)	0.50
Subgaleal	20 (5%)	8 (8%)	12 (4%)	0.19
Epidural	13 (3%)	6 (6%)	7 (2%)	0.11
Intradural	5 (1%)	2 (2%)	3 (1%)	0.61

* mean ± standard deviation; †mean ± SEM; ** median [interquartile range]. *P*-values are comparisons between patients who did and did not have carmustine wafer placement during intracranial surgery.
DVT: deep vein thromboses; KPS: Karnofsky performance score; PE: pulmonary embolism; SEM: standard error of the mean.

Table 3 Summary of pre-, peri-, and postoperative characteristics of patients who did and did not develop a surgical site infection following surgical resection of an intracranial glioblastoma (GBM) ($n = 401$)

Patient characteristics	No. of infections ($n = 380$)	Infections ($n = 21$)	p-value
Demographics			
Age*	56.6 ± 14.3	59.0 ± 8.2	0.44
Male	230 (61%)	16 (76%)	0.17
Diabetes	49 (13%)	5 (24%)	0.18
Hypertension	132 (35%)	11 (52%)	0.11
Coronary artery disease	23 (6%)	3 (14%)	0.15
Obesity	28 (7%)	3 (14%)	0.22
Smoker	33 (9%)	2 (10%)	0.70
COPD	9 (2%)	3 (14%)	0.02
Atrial fibrillation	8 (2%)	2 (10%)	0.09
Stroke	14 (4%)	0 (0%)	0.99
Prior lower grade glioma	53 (14%)	0 (0%)	0.09
Presenting symptoms			
KPS**	80 (70–90)	80 (80–90)	0.49
Headaches	136 (36%)	11 (52%)	0.16
Seizures	132 (35%)	6 (29%)	0.64
Motor deficit	123 (32%)	5 (24%)	0.48
Language deficit	134 (35%)	6 (29%)	0.64
Vision deficit	60 (16%)	2 (10%)	0.76
Cognitive deficit	109 (29%)	6 (29%)	0.99
Radiographics			
Preoperative tumour volume (cm^3)**	32.0 (13.4–56.2)	34.6 (16.9–46.8)	0.75
Tumour location			
Eloquent	188 (49%)	2 (10%)	0.0002
Basal ganglia	72 (19%)	3 (14%)	0.78
Operative characteristics			
Recurrent GBM	140 (37%)	6 (29%)	0.49
Awake surgery	14 (4%)	2 (10%)	0.20
Postop tumour volume (cm^3)**	2.6 (0.1–10.6)	1.4 (0–2.9)	0.21
Percent resection†	78.5 ± 1.3%	90.0 ± 2.9%	0.03
Perioperative course			
New motor deficit	18 (5%)	3 (14%)	0.09
New language deficit	17 (4%)	0 (0%)	0.99
Urinary tract infection	29 (8%)	1 (5%)	0.99
Pneumonia	6 (2%)	2 (10%)	0.06
Sepsis	4 (1%)	0 (0%)	0.99
DVT/PE	29 (8%)	1 (5%)	0.99
Hospital stay**	4 (2–7)	5 (3–8)	0.02
Discharge to rehab	113 (30%)	3 (14%)	0.15
Discharge to home	267 (70%)	18 (86%)	0.15
Adjuvant therapy			
Preoperative radiation	116 (31%)	6 (29%)	0.99
Postoperative radiation	338 (89%)	13 (62%)	0.002
Preoperative chemotherapy	112 (29%)	6 (29%)	0.99
Temozolomide chemotherapy	322 (85%)	20 (95%)	0.34
Carmustine wafer chemotherapy	94 (25%)	9 (43%)	0.07
Bevacizumab chemotherapy	68 (18%)	3 (14%)	0.99

*mean ± standard deviation; †mean ± SEM; ** median [interquartile range]. *P*-values are comparisons between patients who did and did not have a surgical site infection.
DVT: deep vein thrombosis; KPS: Karnofsky performance score; SEM: standard error of the mean; PE: pulmonary embolism.

had infection limited to only the epidural compartment, and none (0%) had infection limited to the intradural compartment. Of the patients with infections, all (100%) were taken back to the operating room, five (24%) required more than one wound washout and nine (43%) had their bone removed at the time of surgery. Of the five patients who had more than one washout, all five patients required two washouts because of persistent infection noted because of wound purulence in four and epidural collection on imaging in one. Seven (33%) had negative cultures, six (29%) *Staphylococcus* infection, five (24%) *Propionibacterium* acnes infection and two (10%) Serratia infections (Table 3). Twenty-one (100%) patients received intravenous antibiotics for a median [IQR] duration of 28 [14–42] days, while 10 (48%) received oral antibiotics for a median [IQR] duration of 28 [28–35] days. Of these patients who received antibiotic therapy, four (19%) underwent oral and intravenous concomitant therapy and six (29%) received oral antibiotics after intravenous antibiotics. Two (10%) patients required long term (>3 months) suppressive antibiotics. At a median [IQR] follow-up time of 6.4 [2.2–12.7] months, no (0%) patients had signs of recurrent infection based on CBC, ESR and CRP.

Comparison between patients with and without infections

The 21 patients who developed infections were compared with the 380 patients who did not develop intracranial infections following intracranial GBM surgery. Among preoperative characteristics, patients with infections more commonly had COPD (14% vs 2%, $P = 0.02$) and less commonly had eloquent tumours (10% vs 49%, $P = 0.002$). Patients who had infections underwent a greater per cent resection (90.0% vs 78.5%, $P = 0.03$), had longer hospital stay (5 vs 4 days, $P = 0.02$) and less commonly had postoperative radiation (62% vs 89%, $P = 0.002$).

In survival analyses, there was no difference in 30-day mortality between patients with and without infections (0% vs 3%, $P = 0.99$). In addition, there was no difference in survival between patients with and without infections (median survival: 14.4 vs 11.8 months, $P = 0.11$). In subgroup analysis, for patients who received carmustine wafers, there was also no difference in survival between patients with and without infections (median survival: 18.9 vs 12.9 months, $P = 0.61$). However, among patients without carmustine wafers, patients who had infections lived significantly longer than patients without infections (14.4 vs 4.5 months, $P = 0.01$). In order to control for potential confounding variables, multivariate proportional hazards analysis was conducted. In multivariate analysis after controlling for factors known to be associated with survival (age, KPS, per cent resection, temozolomide, radiation), postoperative infection was not associated with prolonged survival [RR (95% CI): 0.612 (0.274–1.175); $P = 0.15$].

Infections in patients with and without carmustine wafers

A surgical site infection occurred in 7 (7%) patients who had carmustine wafers and 14 (5%) patients who did not have carmustine wafers ($P = 0.44$). The median [IQR] time to infection was 40 [15–294] and 38 [28–208] days for patients with and without carmustine wafers, respectively (Table 2). In stepwise multivariate analysis, the use of carmustine wafers was not independently associated with a postoperative infection [RR (95% CI): 1.598 (0.824–4.135); $P = 0.22$]. Even after controlling for differences among patients with and without carmustine wafers (male, diabetes, hypertension, KPS, basal ganglia involvement, postoperative tumour volume, hospital stay and temozolomide), the use of carmustine wafers was still not associated with postoperative infection [RR (95% CI): 1.298 (0.623–1.823); $P = 0.21$].

Factors associated with intracranial infection

In univariate proportional hazards regression analysis, the factors associated with postoperative infection were diabetes, hypertension, eloquent tumour location, prior resection and duration of hospital stay. No other clinical factors were associated with postoperative infection including older age, smoking status, distal infections, obesity, preoperative neurological function, preoperative adjuvant therapy, preoperative tumour volume, ventricle entry and postoperative adjuvant therapy.

In stepwise multivariate proportional hazards regression analysis (Table 4), the factors that remained significantly associated with an *increased* risk of infection were prior surgery [RR (95% CI): 2.026 (1.473–4.428); $P = 0.01$], diabetes mellitus [RR (95% CI): 6.090 (1.380–9.354); $P = 0.02$] and increasing duration of hospital stay [RR (95% CI): 1.048 (1.006–1.078); $P = 0.02$]. In a separate analysis, the duration of hospital stay was dichotomized by days to find the greatest risk of infection. The greatest risk of an infection occurred with hospital stays >5 days [RR (95% CI): 3.904 (1.003–11.620); $P = 0.05$].

Discussion

In this study of 401 consecutive patients who underwent surgical resection of an intracranial GBM, 21 (5%) patients developed postoperative infections. The use of carmustine wafers was not independently associated with an increased risk of infection among patients undergoing GBM surgery. In multivariate analysis, the factors independently associated with an increased risk of infection were repeat resection, diabetes mellitus and prolonged hospital stay. Patients who underwent repeat resection, had

Table 4 Multivariate associations between pre-, peri-, and postoperative characteristics with infection following non-biopsy, surgical resection of an intracranial GBM

Variable	Risk ratio (95% CI)	*p*-value
Factors positively associated with infections		
Prior resection	2.026 (1.473–4.428)	0.01
Diabetes	6.090 (1.380–9.354)	0.02
Hospital stay	1.048 (1.006–1.078)	0.02
Hospital stay >5 days*	3.904 (1.003–11.620)	0.05
Factors notably not associated with infections		
Older age	1.020 (0.990–1.054)	0.20
Smoker	1.143 (0.183–3.918)	0.86
Obesity	2.533 (0.591–7.549)	0.18
Karn of sky performance score	1.002 (0.971–1.040)	0.93
Preoperative tumour volume	1.004 (0.992–1.014)	0.49
Ventricle entered	0.614 (0.144–1.800)	0.41
Postoperative motor deficit	1.537 (0.361–4.520)	0.51
Preoperative radiation	0.986 (0.352–2.409)	0.98
Preoperative chemotherapy	1.047 (0.374–2.565)	0.92
Carmustine wafers	1.598 (0.824–4.135)	0.22

* A separate multivariate analysis was performed with hospital stay dichotomized by daily increments to find the hospital stay with the greatest risk ratio of developing a postoperative infection.
CI: confidence interval; GBM: glioblastoma. Bolded terms refer to items that were statistically significant.

diabetes mellitus and/or had hospital stays >5 days had a two-, six- and four-fold increased risk of infection, respectively.

Patients with GBM represent a subset of patients with arguably the highest risk of infection following craniotomy. According to the National Nosocomial Infections Surveillance (NISS) report, the rates of craniotomy infections for all patients undergoing a craniotomy regardless of pathology were 0.9, 1.7, and 2.4% for patients categorized into low-, moderate- and high-risk groups, respectively.[16] Patients with GBM are arguably among the highest risk in the high-risk group because of prolonged steroid administration, radiotherapy, high rates of reoperations and administration of adjuvant therapies including radiation and chemotherapy and possible immunosuppression.

Incidence of postoperative infection

An understanding of the incidence of postoperative infections as well as the factors that predispose patients to developing infections is critically important for patients with GBM. Patients with GBM are known to have relatively shortened survival times,[14,17] where the median survival is 14.6 months for patients who undergo surgical resection, temozolomide chemotherapy and radiation therapy.[1] Patients who develop perioperative complications including neurological deficits, intracranial haemorrhages and perioperative infections will have delays in the administration to adjuvant therapy.[11] Subsequently, a delay in adjuvant therapy results in further shortened survival times.[11]

The incidences of postoperative infections for patients undergoing GBM surgery are heterogeneous, where the percentages range from 3% to 27% in several studies.[4–6,8,9,18] In this study, the incidence of infection for GBM patients was 5%. Gulati *et al.* retrospectively reviewed 144 patients who underwent surgery (including biopsies) for a primary GBM from 2004 to 2009, and 3% of patients developed surgical site infections.[9] In this study, they found that patients who developed perioperative complications were significantly less likely to receive radiation and chemotherapy.[9] Bock *et al.* evaluated 44 patients with GBM who underwent surgical resection with carmustine wafer implantation, radiation therapy and temozolomide chemotherapy and reported seven patients with wound healing abnormalities, three with meningitis and two with an intracranial abscess (total 27%).[19] Rabadan *et al.* studied 236 consecutive patients who underwent open surgery for a malignant tumour including malignant astrocytomas and metastatic brain tumours.[10] Eleven (5%) patients had surgical site complications and found that the factors associated with any type of complication included preoperative neurological function, American Society of Anesthesiologist (ASA) physical health status and histology.[10] Despite these previous studies, the true incidence of postoperative infection for patients undergoing surgical resection of a GBM is unclear because prior studies included needle biopsies, small patient populations and disparate tumour pathologies including non-GBM gliomas and metastatic tumours.[4–10] Their findings may not be entirely applicable for patients undergoing surgical resection of a GBM.

Use of carmustine wafers is not associated with an increased risk of infection

The typical current care for patients with GBM is extensive surgical resection, followed by radiation and temozolomide chemotherapy.[1] Before temozolomide chemotherapy, the Food and Drug Administration (FDA) approved carmustine wafers for use in patients with both primary and recurrent malignant gliomas.[20,21] In a phase III clinical trial for patients with recurrent malignant gliomas, the median survival for patients with carmustine wafers was 2 months longer than patients without carmustine wafers (31 vs 23 weeks).[20] Similarly, in another phase III clinical trial for patients with newly diagnosed malignant gliomas, the median survival for patients with carmustine wafers was 2.3 months longer than patients without carmustine wafers (13.9 vs 11.6 months).[21] This survival advantage is similar to the 2.5-month increase in survival associated with temozolomide use (14.6 vs 12.1 months).[1] More recently, it has been shown that the use of carmustine wafers in addition to temozolomide chemotherapy can have a further increase in survival in some,[3] but not all studies.[22] Patients who underwent carmustine wafer implantation and temozolomide chemotherapy had an 8.9-month increased survival advantage when compared with age-matched patients who only underwent temozolomide chemotherapy (21.3 vs 12.4 months).[3]

Despite this apparent survival advantage of multimodal therapy (carmustine wafers with temozolomide), there is a concern that the use of carmustine wafers can be associated with an increased surgery-related complications.[4–6,19] In three randomized control trials designed to evaluate the efficacy of carmustine wafers on survival for patients with malignant gliomas, there was no association between the use of carmustine wafers and infections.[20,21] In addition, prior studies have evaluated if the use of carmustine wafers were associated with an increased risk of wound healing and cerebral oedema.[2,20,21,23] While the rate of poor wound healing and cerebral oedema were higher in the carmustine wafer cohort,

the difference was not statistically significant.[2,20,21,23] In addition, there is a concern that carmustine wafers are associated with a higher rate of infections.[4,5] McGovern *et al.* identified 32 patients who underwent carmustine wafer implantation from 1996 to 1999 and found that nine (28%) patients developed infections.[4] Subach *et al.* evaluated 62 patients who underwent GBM surgery and found that the incidence of infection was higher in the 17 patients who underwent wafer placement (four infections) than the 45 patients who did not receive wafers (1 infection), but this difference was not statistically significant.[5] Similar findings have been reported in other studies.[6,19]

In order to critically evaluate the risk of infection with carmustine wafer implantation, 401 consecutive patients were evaluated who underwent surgical debulking of an intracranial GBM, whereas 103 patients underwent carmustine wafer implantation. This is the largest study-to-date that was designed to critically evaluate the risk of infection with the use of carmustine wafers. The use of carmustine wafers in this study was not significantly associated with an increased risk of infection. This remained true in multivariate analyses after controlling for clinical differences between patients with and without wafer implantation. Therefore, the use of carmustine wafers does not significantly change the risk of infection for patients undergoing craniotomy of a GBM.

Factors independently associated with an increased risk of infection

The development of a postoperative infection for patients with GBM will ultimately delay the implementation of adjuvant therapies, and this delay can result in worsened survival.[9,11] It is interesting to note that some patients with GBM and infection have noted longer survival times,[9,11] and in this study, there was some trends that patients with infections may have improved survival when compared with patients without infections. Therefore, there is an impetus to understanding the factors that may predispose patients to developing postoperative infections. However, the risk of infection among patients with GBM remains unclear because prior studies primarily included small patient populations that prevented statistically powered analyses, disparate pathologies that have different recurrent and survival outcomes, dissimilar surgical approaches including needle biopsies and non-multivariate analyses to control for confounding factors (Table 1).[4–10]

This study found that patients who underwent recurrent GBM resection had a two-fold increased risk of a postoperative infection. Patients who undergo repeat resections are known to have higher rates of infection than patients undergoing first time resection.[24] In a multi-institutional French study for all patients undergoing a craniotomy regardless of pathology, surgical site infections occurred in 4% of the 2922 patients who underwent craniotomy over a 15-month period at 10 institutions.[25] Reoperation and cerebrospinal fluid leak were independently associated with an increased risk of infection.[25] Moreover, Tenney *et al.* found that infections were more common in craniotomies than spinal surgery, and, among craniotomies, infections were more common in recurrent glioma surgeries than other types of craniotomies.[26] For patients undergoing repeat operations, it is therefore imperative to attempt measures to minimize infections, which may include preoperative hair washes, water-tight dural closures, meticulous wound closures, rapid evaluation and repair of any wound dehiscence and surgical drainage, among others.

In addition to repeated resections, the presence of diabetes and prolonged hospital stay were each independently associated with an increased risk of infection. Patients who had diabetes had a six-fold increased risk of infection when compared with patients without diabetes. Diabetic patients have an increased propensity for developing intracranial infections, but several clinical studies have also shown that hyperglycaemia increases morbidity and mortality, length of hospital stay, and long-term functional deficits in critically ill patients. Moreover, hyperglycaemia has also been associated with decreased overall survival, decreased progression free survival and increased risk of neurological deficits among glioma patients.[27]

In addition to diabetes, duration of hospital stay was also associated with an increased risk of post-GBM resection infection. The longer the hospital stay, the higher the risk of infection, where patients who stayed >5 days had an approximate four-fold increased infection when compared with patients who stayed a lesser number of days. This is important because previous studies have shown that increased hospital stays are associated with an increased risk of nosocomial infections, including urinary tract infections, pneumonia and blood stream infections. These infections also more commonly occur with more virulent and antibiotic-resistant organisms. Therefore, these results stress the need for strict glucose control as well as a need to minimize hospital stays in order to minimize nosocomial infections including surgical site infections. However, it should be noted that it remains unclear whether increased hospital length of stay is the cause of increased infection risk or if it merely reflects patients who are more at risk of adverse outcomes.

Strengths and limitations

The authors believe this study provides several useful insights. First, the incidence of infection following surgical resection of an intracranial GBM is unclear because most studies on infection include disparate pathologies, small patient populations and dissimilar surgical strategies. This study shows that the incidence of infection is ~5% following surgical resection of a GBM. Patients with GBM arguably have the direct consequences if they develop infections since their survival is already shortened from their disease process and a delay in adjuvant therapy can possibly shorten this survival.

This study also shows that the use of carmustine wafers is not associated with an increased risk of infection. This remained true in multivariate analyses controlling for difference in pre-, peri-, and postoperative clinical variables between patients with and without carmustine wafers. Finally, repeat operations, diabetic co-morbidity and prolonged hospital stay were each independently associated with an increased risk of infection. These findings may help guide pre- and perioperative care to minimize the chance of infections.

This study, however, has some limitations. One limitation is that this study was not designed to evaluate the efficacy of perioperative sterilization techniques (shampoo regimen, prep application, etc.), as well as peri- and postoperative antibiotic regimens. The perioperative sterilization techniques and antibiotic regimen were not consistently recorded, and therefore their effects on outcome could not be assessed. Moreover, it was not designed to evaluate other surgeon-specific parameters such as amount of hair shaved before incision, use of bipolar cautery and/or use of drains. An additional limitation is that a significant number of patients in this study did not receive triple combinatorial adjuvant therapy (carmustine wafer, temozolomide and radiation). Some of these patients received non-temozolomide adjuvant therapy, were poor candidates for adjuvant therapy or were lost-to-follow-up and had their adjuvant care at another hospital. The relevance of this study's findings may therefore be altered if all patients received the most aggressive treatment regimens. In addition, it was aimed to control for differences between patients with and without carmustine wafers by using multivariate analyses to attempt to control for differences in characteristics between patients with and without carmustine; however, the best statistical tools cannot completely eliminate measured and non-measured confounders between groups. As a result, the use of carmustine wafers cannot be completely eliminated as a source of increased risk of infection. Finally, this study is inherently limited by its retrospective design, which may introduce an inherent bias associated with patient selection and treatment. An ideal study would be randomized in design; however, this may not be practical or feasible. The authors attempted to create as uniform a patient population as possible by utilizing strict inclusion criteria and using multivariate analyses to control for potential confounding variables in order to provide the most relevant information for patients who underwent intracranial resection of a GBM at our institution. Given these criteria and relatively precise outcome measures, the authors believe our findings are useful for the care of patients with GBM. However, prospective studies are needed to provide better data to guide clinical decision-making.

Conclusions

Patients with GBM have an inherently shortened survival because of their disease. Patients with GBM who develop infections further jeopardize their length of survival because an infection can lead to delays in the administration of adjuvant therapies and diminishes their quality of life. This study showed that the incidence of infection is 5% for patients who underwent GBM resection. Carmustine wafers were not associated with an increased rate of infection. Patients who underwent reoperations, had a diabetic co-morbidity and/or had prolonged hospital stay, however, had an independently increased risk of infection. These findings may lead to treatment strategies aimed at decreasing the risk of infection for patients who are undergoing a resection of an intracranial GBM.

Disclaimer Statements

Contributors All the authors played a critical role in the manuscript.

Funding None.

Conflicts of interest The authors declare no conflicts of interest.

Ethics approval The work of this study has been approved by the Johns Hopkins IRB 36785.

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