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Intraoperative and postoperative complications for repeat high-grade glioma resections with concurrent chemotherapy: patient series

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BACKGROUND High-grade gliomas are aggressive primary brain tumors, the most common of which is glioblastoma multiforme. Despite advances in treatment, the prognosis for these patients remains poor. The most common chemotherapeutic agents used in the treatment of this pathology include temozolomide (TMZ), procarbazine, lomustine, and vincristine. It is unclear whether chemotherapy should be held during resection for high-grade gliomas, because the perioperative risk profile is not clearly defined.

OBSERVATIONS The authors report a case series of 18 surgeries to investigate the effects of concurrent TMZ and lomustine chemotherapy on surgical complications in patients undergoing repeat resection for recurrent high-grade gliomas. The authors found no postoperative infections, self-limiting postoperative complications, or excessive intraoperative blood loss and found one intraoperative complication.

LESSONS There may not be a need to pause TMZ and lomustine chemotherapy during recurrent resections for high-grade gliomas, and continuing these medications throughout the perioperative period may be appropriate. This case series suggests that patients receiving TMZ and lomustine chemotherapy who need a repeat resection for recurrent high-grade gliomas should consider remaining on their chemotherapy regimen because it has been shown in the literature to improve recurrence-free survival time.

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KEYWORDS glioma; glioblastoma; concomitant chemotherapy; concurrent chemotherapy; perioperative complications

High-grade gliomas (HGGs) are a heterogeneous and highly aggressive group of central nervous system tumors that arise from supportive glial cells, such as microglia, astrocytes, oligodendrocytes, and ependymal cells.[1] They are the most common type of primary brain tumors and have been reported to have an incidence rate of 6 per 100,000 persons, with glioblastoma multiforme (GBM) being the most common subtype.[2,3] Despite advances in surgery, radiation therapy, and chemotherapy, the prognosis remains poor, with a median survival of only 12–15 months for GBMs and 2–5 years for anaplastic gliomas.[4]

The treatment course depends on the grade and subtype of glioma, with World Health Organization (WHO) grades III and IV tumors considered high grade.[4] Currently, the most common treatment for HGGs involves a multimodal approach with maximally safe surgical resection combined with adjuvant radiotherapy and chemotherapy.[5] Various chemotherapy agents have been indicated in the treatment of HGGs, the most common of which is temozolomide (TMZ), along with the concurrent administration of procarbazine, lomustine, and vincristine.[6] Other agents, such as carmustine biodegradable wafers, have been used as a brachytherapy modality, with survival benefits still under investigation.[6,7]

Unfortunately, treating malignant gliomas is challenging, because recurrence rates are high after initial resection and they can develop chemoresistance and radioresistance, decreasing the effectiveness of adjuvant treatments.[4,8] When it comes to recurrent HGGs, seminal clinical trials such as the RESCUE study have shown that continuous-dose TMZ alongside radiation can improve 6-month progression-free survival for patients with recurrent GBMs compared with other commonly used chemotherapeutic agents.[9] Other large studies have demonstrated a survival benefit for radiation plus concomitant TMZ for

ABBREVIATIONS HGG = high-grade glioma; MTIC = 5-(3-methyltriazen-1-yl)-imidazo-4-carboximide; TMZ = temozolomide; WHO = World Health Organization.

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GBM with minimal added side effects of toxicity.[5] The median time to recurrence for GBMs following treatment with radiotherapy and TMZ is 6.9 months.[5]

In patients with recurrent HGGs, treatment is mainly palliative, because these patients have a 5-year survival rate of less than 10%.[8,10] Although a multimodal approach is typically still employed, the management plan for these recurrent tumors must be considered on an individual basis. Approximately 25% of these patients are candidates for additional resection based on factors such as age, size, tumor location, and Karnofsky performance status.[8,11] One of the challenges with repeat surgery for malignant gliomas is the increased likelihood of perioperative complications, leading to morbidity and mortality.[12]

It is important to understand the factors that predispose people to these complications. In addition to their impact on morbidity and mortality, perioperative complications in patients with gliomas result in a reduced likelihood of receiving effective adjuvant radiochemotherapy, further decreasing survivability.[13] Although neoadjuvant chemotherapy has been identified as a risk factor for all-cause morbidity and mortality in patients undergoing brain tumor resection, more research is needed to determine its effect on perioperative complications and how it impacts repeat surgery.[14] TMZ is generally considered to be safe but can lead to bone marrow suppression and gastrointestinal side effects because of its targeting of rapidly dividing cells.[15] Although mild side effects such as nausea and vomiting can be managed, there is a risk of rare complications such as myelosuppression, lymphopenia, and thrombocytopenia, which can lead to increased infections and bleeding, which are pertinent in the context of surgery.[15,16] Other chemotherapy drugs, such as lomustine and procarbazine, have similar side effect profiles.[17] These side effects have led some clinicians to recommend holding these drugs before surgery, but there is no consensus on whether chemotherapy should be stopped before reresection for HGG.

Herein, we describe a retrospective review of patients with recurrent HGGs who underwent resection via open craniotomy at our local site. By analyzing the perioperative complication rates of recurrent HGG surgeries, our objective is to investigate the association between perioperative complication risk and adjuvant chemotherapy.

Study Description

Methods

This study was approved by the institutional review board. The requirement for patient consent was waived because of the retrospective nature of the study and the deidentification of patient data. We performed a retrospective review of the neurosurgical database at our local tertiary hospital to identify 174 patients who had undergone repeat resection of HGGs (WHO grades III and IV) between January 1, 2000, and February 1, 2023.

Patients were included if they had an initial neurosurgical resection of their recurrent tumor with adjuvant or concurrent chemotherapy administered at the time of or within 1 week of their surgery. Demographics including age at treatment and sex were collected. The initial tumor size, tumor imaging, and histological grade/characteristics, laterality, lobe, and presenting symptoms as well as concomitant chemotherapy agents, progression, survival, and complications were collected for analysis. An operation was defined as emergent if the patient presented to the emergency department prior. If a patient had multiple surgeries while undergoing concurrent chemotherapy, data were collected for each surgery and included in the analysis independently.

Results

One hundred seventy-four patients with recurrent HGGs who were treated with reresection were analyzed. Sixteen patients met the inclusion criteria, and 9 (56%) were male. The average age at diagnosis was 48 years (range 22–67 years). At the time of analysis, 12 (75%) of the patients were deceased. Nine (56%) patients initially presented with predominantly right-sided lesions, and the remaining 7 (44%) had left-sided lesions. The average initial size of the tumors based on imaging was 4.4 cm (SD ±1.1 cm, range 2.5–6.4 cm).

Eleven (68.8%) patients were diagnosed with GBMs, 4 (25.0%) had anaplastic oligodendrogliomas, and 1 (6.3%) had an anaplastic astrocytoma. The average number of years from first diagnosis to death was 3.9 ± 2.8 (range 1.1–8.5 years). Patients in our case series had between 1 and 4 recurrences, with a mode of 3. The average number of years from the first tumor resection surgery to recurrence was 2.0 ± 2.1 with a range of 0.3 to 7.5 years. The average number of surgeries for tumor management was 2.8, with a range of 2–5. However, in the majority of these procedures, patients were not receiving concomitant chemotherapy. Of the 16 patients included in this study, 15 had a single procedure while receiving concomitant chemotherapy, and 1 patient had 3 procedures with concomitant chemotherapy, totaling 18 independent procedures included in the analysis. A summary of patient demographics and tumor characteristics can be found in Table 1.

Concurrent chemotherapy drugs included TMZ (14 cases) and lomustine (4 cases). Sixteen surgeries were done with the patient receiving concurrent chemotherapy, and for 2 surgeries, the chemotherapy agents were discontinued within 1 week prior to the operation (at 3 and 6 days prior). Nearly all the initial and recurrent surgeries were done on an emergent basis. The average length of stay after the concurrent surgery was 9.2 ± 10.5 days, with a range of 2–40 days. A summary of concurrent surgeries and intra- and postoperative complications can be found in Table 2.

The estimated blood loss for these surgeries was 180.0 ± 151.9 ml, with a range of 50–500 ml. Only 1 patient had an

TABLE 1. Participant demographics and tumor characteristics in 16 patients with a recurrent high-grade gliomas

Characteristic	Value
Male sex	9 (56%)
Female sex	7 (44%)
Mean age at diagnosis, yrs (range)	48 (22–67)
Mean tumor size, cm (range)	4.4 ± 1.1 (2.5–6.4)
Mode no. of tumor recurrences (range)	3 (1–4)
Time from first surgery to recurrence, yrs (range)	2.0 ± 2.1 (0.3–7.5)
Mean no. surgeries (range)	2.8 (2–5)
Tumor type	
GBM	11 (68.8%)
Anaplastic oligodendroglioma	4 (25.0%)
Anaplastic astrocytoma	1 (6.3%)

GBM = glioblastoma.
Values are presented as the number of patients (%) or mean ± standard deviation, unless noted otherwise.

TABLE 2. Characteristics and complications of repeat surgeries completed with chemotherapy

Characteristic	Value
Chemotherapy agent	
TMZ	14 (77.8%)
Lomustine	4 (22.2%)
Estimated blood loss, ml (range)	180 ± 151.9 (50–500)
Intraop complication	1 (5.6%)
Postoperative infection	0 (0.0%)
New postoperative neurological complication	7 (38.9%)
Mean postoperative stay, days (range)	9.2 ± 10.5 (2–40)

Note that a single patient had 3 separate surgeries that met the chemotherapy criterion (n = 18). Values are presented as the number of patients (%) or mean ± standard deviation, unless noted otherwise.

interoperative complication, which was described as severe bradycardia with a period of asystole. The patient stabilized, and the operation proceeded smoothly. No patient had any reported postoperative infection or postoperative infectious disease consultations. Seven (43.8%) patients had newly reported postoperative complications, which were all transient, lasting fewer than 7 days. These complications included general confusion, seizures, aphasia, hemiplegia, hemiparesis, blurry vision, spatial neglect, and proprioception deficits. Table 3 has a summary of all eligible patients and surgeries in this case series.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

The purpose of this case series was to investigate the effects of concurrent chemotherapy on surgical complications for patients undergoing repeat resection for recurrent HGGs. Of the 18 surgeries included, there was only 1 significant intraoperative complication. All patients were receiving either TMZ or lomustine. Estimated blood loss did not exceed 500 ml for any surgery, and no postoperative infections were documented.

Blood loss was of particular interest for this case series, because alkylating chemotherapy agents have the potential to increase surgical blood loss through their mechanism of action. TMZ, a common chemotherapeutic drug for HGG, is widely considered to have an acceptable toxicity profile. At physiological pH, TMZ undergoes spontaneous hydrolysis to produce the active compound 5-(3-methyltriazen-1-yl)-imidazo-4-carboximide (MTIC). MTIC exerts its cytotoxic effects primarily through the process of DNA alkylation, with the O6 and N7 positions of guanine being the primary targets of this reaction. This leads to the formation of a highly cytotoxic adduct that triggers a cascade of events leading to DNA damage and cell death. TMZ is highly selective for rapidly dividing cells, making it an effective treatment for cancer.[15] However, its mechanism of action can also lead to adverse effects on healthy cells, such as bone marrow suppression and gastrointestinal toxicity. Although the most common side effects of gastrointestinal upset, such as nausea and vomiting, are easily controlled by antiemetics, other more serious side effects need to be considered, especially in the context of surgery. Notably, TMZ has been found to occasionally cause myelosuppression, lymphopenia, and thrombocytopenia. As a result, the risk of increased opportunistic infections and increased bleeding has been documented, but these effects are considered rare.[15,16] Other chemotherapy drugs, including lomustine and procarbazine, are also alkylating agents with similar mechanisms of action and side effect profiles.[17]

In our case series, the estimated blood loss did not exceed 500 ml for any surgery, and no blood transfusions were required. In the literature, blood loss over 500 ml has been reported to increase the rate of postoperative hemorrhage due to a reduction of platelets and coagulation factors.[18] The average blood loss was lower than this threshold at 199 ± 153.9 ml. Furthermore, no postoperative infections were reported, which are a potential concern, given the myelosuppressive effects of certain alkylating chemotherapeutic agents.

The number and characteristics of postoperative complications were also consistent with the current literature on potential complications for brain tumor resections.[19] Additionally, all these postoperative complications were transient and left no long-term deficits, demonstrating that these patients did not experience more complications despite receiving concurrent chemotherapy. Currently, there is little documented in the literature regarding the complications associated with the resection of HGGs in patients who are receiving concurrent chemotherapy. This case series contributes to the existing literature and provides insights into the complication profile for patients who undergo repeat resection while receiving concurrent chemotherapy. The findings of this study can help clinicians to better understand the potential risks associated with this treatment approach and make more informed decisions regarding the management of patients with recurrent HGGs.

Lessons

The results of our case series did not demonstrate an increase in intraoperative or postoperative complications for patients undergoing reresection for HGGs while receiving concurrent chemotherapy with TMZ or lomustine. These findings suggest that there may not be a need to discontinue or hold these chemotherapy drugs during the perioperative period in tumor reresection, and a continuation of alkylating chemotherapeutic agents such as TMZ and lomustine may be appropriate. Because the literature has demonstrated that continuous-dose chemotherapy, especially TMZ, improves recurrence-free survival time, surgeons who are performing a repeat resection for recurrent HGG should consider continuing their patient's chemotherapeutic regimen during the perioperative period.[5,20] Understanding the risk factors for perioperative complications and the influence of adjuvant chemotherapy treatment will be useful in guiding the perioperative management of these agents. This knowledge could be used to optimize treatment regimens for recurrent HGGs.

However, it is important to note that this was a single-center case series; therefore, further studies are needed to confirm our findings. Given the nature of retrospective case reviews, this study is unable to draw causal inferences on the effect of concurrent chemotherapy on surgical complications. Because the number of patients was limited, this case series may have lacked the power to detect small increases in complication rates that would only be made evident with a larger sample size. Additionally, there was no control condition in this study, limiting our ability to draw casual

TABLE 3. Demographics, clinical findings, and complications of patients who underwent repeat resection for HGG while receiving concurrent chemotherapy

Case No.	Op No.	Age at Diagnosis (yrs)/Sex	Age at Op (yrs)	Diagnosis	Lobe/Laterality	Symptoms	Chemo	Estimated Blood Loss (ml)	Surgical Complications	Immediate Postoperative Complications
1	1	36.3/M	41.6	OG	Temporal/lt	Language deficits, coordination deficits	TMZ	90	—	Aphasia
2	2	45.2/M	48.4	OG	Parietal/lt	Progressive numbness, arm/hand paresthesia, decreased hand sensation	TMZ	NA	—	Rt hemiplegia of extremities, petit mal seizures
3	3	67.2/F	68.5	GBM	Frontal/rt	Optic neuropathy	TMZ	100	—	General confusion
4	4	47.8/M	49.4	GBM	NA	—	TMZ	NA	—	—
5	5	31.4/F	32.6	GBM	Parietal/lt	—	TMZ	NA	—	—
6	6	22.7/F	30.2	Astrocytoma	Frontal/lt	—	Lomustine	500	—	Aphasia, hemiparesis
7	7	41.9/M	42.9	GBM	Occipital/rt	—	TMZ	NA	Severe bradycardia, short asystole	—
8	8	55.3/F	60.2	GBM	Temporal/rt	—	Lomustine	NA	—	—
9	9	30/M	31	GBM	Frontoparietal/lt	Numbness, arm/leg paresthesia, incoordination	TMZ	NA	—	—
10	10	50.7/M	52.7	OG	Occipital/rt	Generalized confusion	TMZ	50	—	Intermittent blurry vision
11	11	67.1/M	70	GBM	Parieto-occipital/lt	Generalized confusion, optic neuropathy	Lomustine	NA	—	—
12	12	41.2/M	49.3	OG	Temporal/rt	Tinnitus, arm/leg paresthesia, facial paresthesia	TMZ	300	—	Weakness, lt spatial neglect
13	13	60.8/F	61.4	GBM	Frontal/rt	Face drop, slurred speech, hand paresthesia	TMZ	200	—	—
14	14	53.2/F	54.5	GBM	Temporal/rt	Recurrent headaches	TMZ	NA	—	—
15	15	59.9/M	60.1	GBM	Parietal/rt	Cognitive changes, hand clumsiness & decreased sensation, dysarthria	TMZ	NA	—	—
15	16	59.9/M	60.4	GBM	Parietal/rt	Cognitive changes, hand clumsiness & decreased sensation, dysarthria	TMZ	100	—	—
15	17	59.9/M	60.7	GBM	Parietal/rt	Cognitive changes, hand clumsiness & decreased sensation, dysarthria	Lomustine	NA	—	Proprioception deficits, weakness
16	18	58.4/F	59.3	GBM	Parietal/rt	Recurrent headaches, incoordination, generalized weakness	TMZ	100	—	—

NA = data not available; OG = oligodendroglioma.

inferences. A potential future direction for research could involve case matching this group of patients with patients with recurrent gliomas undergoing resection without concurrent chemotherapy to further explore the impact of concurrent chemotherapy on surgical outcomes. This approach would allow a more robust comparison of the impact of concurrent chemotherapy on surgical outcomes and minimize the confounding effects of other factors such as age, sex, tumor location, and diagnosis. However, it is important to consider that because these postoperative complications may be relatively rare, it may still be unlikely to detect a difference in complication rates in a smaller cohort.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Analysis and interpretation of data: Makarenko, Ong. Drafting the article: Ong. Critically revising the article: all authors. Reviewed submitted version of manuscript: Makarenko, Ong. Approved the final version of the manuscript on behalf of all authors: Makarenko. Statistical analysis: Ong. Administrative/technical/material support: Makarenko. Study supervision: Makarenko, Hounjet.

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