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RECURRENT BRAIN GLIOMA- SURGERY AND CLINICAL OUTCOME

Anaesthesiology

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ABSTRACT

Introduction: Gliomas account for 24% of all primary brain and CNS tumors. Histologically, gliomas were categorized into sub types and grades (I through IV). Low-grade gliomas are grade I and grade II, while high-grade gliomas are grade III and grade IV. The gold standard for treatment of high-grade glioma is the most extensive safe surgical resection followed by radiotherapy combined with chemotherapy. However, recurrence of glioma is inevitable. Management of recurrent cases is still controversy. **Aim & Objective:** The purpose of this research was to examine the efficacy of reoperation for cases of recurrent glioma in improving patients' outcome. **Methods:** This study included 40 patients with recurrent glioma admitted and operated. **Results:** There were 28 male (70%) and 12 female (30%), their age incidence ranged from 20 to 75 years with a mean age of 48.06, gross total resection of recurrent cases could be done in 24 (60%) patients, subtotal resection in 10 (25%) and partial in 6 (15%), all of recurrence were found at the same site almost the same of primary tumor except that two cases were radionecrosis and one patient revealed aggressive transformation from anaplastic astrocytoma to GBM by the end of the study period, and 26 (65%) patients alive and 14 (35%) died. **Conclusion:** Surgical management of recurrent gliomas in selected patients is generally associated with improved functional performance and prolonged survival. Patients' Karnofsky score at recurrence is an important prognostic factor for both low-grade glioma and high-grade glioma.

KEYWORDS

Recurrent glioma, Reoperation & Karnofsky score

INTRODUCTION

Gliomas account for 24% of all primary CNS tumors [1]. The vast majority of gliomas are highly infiltrative tumors that impact many different brain regions. Pilocytic astrocytoma is the least malignant form of glioma, while glioblastoma is the most malignant [2]. Histologically, gliomas were categorized into subtypes and grades (I through IV). Diffuse astrocytomas, oligodendrogliomas, ependymomas, and gliomas/oligoastrocytomas can all be distinguished on a histological basis. Grades of glioma are identified depending on their level of cellular proliferation, degree of mitosis as measured by the mitotic index, the extent of microvascular proliferation, and the presence or absence of necrosis. Low-grade gliomas are grade I and grade II, while high-grade gliomas are grade III and grade IV. It is estimated that over half of all adult malignant primary brain tumors are high-grade gliomas (WHO grade III anaplastic glioma/grade IV glioblastoma).

Glioblastoma may be primary (De Novo) GBM (vast majority, 90%) or secondary GBM which develops from low-grade glioma. Recently, molecular and genetic markers were added to the histopathological classification
of gliomas [3].

The gold standard for treatment of high-grade glioma is the most extensive safe surgical resection followed by a combination of brain irradiation, and adjuvant temozolomide (TMZ) chemotherapy [4]. In low-grade glioma, surgery is the cornerstone in management and adjuvant therapy is reserved for high-risk patients that are above 40 and partially resected lesions [5]. This improves patients' clinical and functional status (Karnofsky score), the progression-free survival (PFS) and overall survival (OS) of the patients. Even though recurrence of glioma is inevitable, the usefulness of reoperation in cases of recurrence is still debatable and more evidence and investigations are needed [6, 7].

The differences in treatment of recurrent gliomas and primary gliomas are because of genetic differences between both types, their diversity in growth patterns, invasiveness and patient clinical presentation [8]. In the literature, other treatment options investigated, as reirradiation alone or more cycles of chemotherapy or combination of both without reoperation, radiosurgery or immunotherapy but the results still dismal [9].

MATERIAL & METHODS

The purpose of this research was to examine the efficacy Of reoperation for cases of recurrent glioma in improving patients' outcome.

An prospective study. The study included 40 patients with recurrent glioma admitted and managed between 01/01/2020 and 1/12/2024.

Inclusion Criteria- Any age, both gender, patients who were operated for glioma then developed clinical, neuroimaging evidence of recurrence who were scheduled for reoperation and different histopathological types of gliomas were enrolled.
Exclusion Criteria- The following conditions were used to eliminate potential study participants: patient who had brain glioma that was de novo, multicentric recurrent glioma (inoperable) and patients who were unfit for any neurosurgical interventions.

All the patients that developed clinical and neuroimaging recurrence after previous glioma surgery were put through: age, sex, comorbidities, initial histopathology in the primary surgery, extent of resection in the primary surgery, KPS (neurological presentation) on recurrence, time interval between the primary surgery and recurrence, extent of resection in the reoperation, histopathology after reoperation and KPS post-reoperation.

Neuroimaging

Computed tomography (CT) scan was done in the first presentation of the patient but with minimal informative value. Conventional and advanced MRI post-contrast scan analyses were used to quantify tumor, location to be compared with that of initial lesion and relation to ventricular system and crossing to the midline were estimated.

MRI spectroscopy plays an important role in differentiating radionecrosis and true recurrence; however, accurate diagnosis is obtained through histopathological specimen.

RESULTS AND OBSERVATION

A total number of 40 patients were identified following the inclusion criteria. Patients' ages ranged from 20 to 75 years, with a mean age of 48.06. We had 28 (70%) male and 12 (30%) female. As regard co morbidities, 5 (12.25%) and 6 (15%) patients were diabetic and hypertensive, respectively. 4 patients had ischemic heart disease, and 01 patient had chronic renal disease on dialysis. Meanwhile, 24 (60 %) patients had no comorbidities (Table 1).

We identified primary histopathologies of recurrent lesions after initial

surgery. Extent of resection in the primary surgery was identified. Extent of resection was defined as follows: gross total resection when more than 90% of the tumor was removed, subtotal resection when between 80 and 90% was removed and partial resection when less than 80% of the tumor was removed.

08 patients with histopathology of diffuse astrocytoma (low -grade glioma) were partially resected as they were near to eloquent area. Subtotally resected patients 6 GBM, one oligodendroglioma and one anaplastic astrocytoma. All patients received radiotherapy and concurrent chemotherapy after the primary surgery except that patient with cerebellar pilocytic astrocytoma. Primary histopathology and extent of resection are summarized in Table 2.

All the recurrences were found at the same site, almost the same pattern of the primary tumor, no ventricular invasion or crossing to the midline (Table 4). Time interval between the first operation and recurrence time was categorized as the following; within the initial 6 months postoperative, then within 6–12 month time frame, within the period between 12 and 18 months, and final group after more than 24 months after the first surgery (Table 5).

As regards KPS at time of recurrence, we had 8 patients with KPS below 70 distributed as follows: one of them was severely disabled (KPS 30), four were disabled requiring special care and assistance (KPS 40), two require considerable assistance and frequent medical care (KPS 50), and one of them with KPS 60 as he needed occasional assistance. The other 17 patients were with KPS equal or above 70.

During follow-up after reoperation, 40 patients were divided based on their KPS preoperatively into those with KPS above or equal 70 and those with KPS below 70. There were 12 patients with KPS below 70, and their histopathology after reoperation was GBM. Their functional performance in the early period after reoperation remained unchanged in 04 patients, 06 died and 02 patient improved. On follow-up, the t04 patients that remained with the same KPS in the early postreoperation period deteriorated over the period of follow- up and died within 3 months. Gross total resection was achieved in 03 patients: 01 patient with postreoperation improved KPS and the other one remained with stable clinical condition. Subtotal resection was achieved in 06 patients; 03 of them remained with the same KPS, while the other t03 deteriorated (Table 7).

As regards group of patients with KPS 70 or above, 22 patients improved their KPS, 4 had stable disease, and 02 patient deteriorated. Deteriorated patient histopathology was GBM, deterioration was within the first 3 months after reoperation, his preoperative KPS was 70, known chronic renal failure patient on dialysis, and this lesion was partially resected (Table 7).

Our results revealed recurrence within 6 months after first operation for 3 patients, their KPS at recurrence was below 70, and these tumors were subtotally resected in primary surgery; their histopathology was GBM.

As regards histopathology of reoperated lesions, we documented new histopathology in 4 patients that revealed radionecrosis, while their initial histopathology was GBM and 4 patient revealed aggressive transformation from anaplastic astrocytoma to GBM. Patients with diffuse astrocytoma, oligodendroglioma, pilocytic astrocytoma and 2 patients with anaplastic astrocytoma showed clinical and functional improvement. Both patients with radionecrosis remained clinically stable (Table 6).

Summary of clinical characteristics and Karnofsky score (KPS) for patients' at time of recurrence, time interval between the first surgery and recurrence is given in Tables 3, 4, 5, 6 and 7.

As regard postoperative complications, 8 (20%), 6 (15%) and 6 (15%) patients newly developed hemiparesis, deterioration of previous hemiparesis and wound infection (bone flap infection), respectively. Deterioration of conscious level after reoperation occurred with 8 patients (20%). 12 (30 %) patients had no complications.

These results are indicator about the probability of complications with reoperation in recurrent tumors especially in those with KPS below 70 or had bad general condition (Table 8)

Table 1-8

Table 1 Baseline Data Of The Studied Patients

N-40
Age (years)
Range 20–75
Mean 48.06
Sex
Male 28 (70 %)
Female 12 (30%)
Comorbidities
Diabetes mellitus 5 (12.25%)
Hypertension 6 (15%)
Ischemic heart disease 4 (10%)
Chronic renal disease 1 (2.5%)
None 24 (60 %)

Data expressed as frequency (percentage), mean (SD), range. N number

Table 2 Characteristics Of Glioma Among The Studied Patients After Initial Surgery

N-40
Initial WHO histological type
Pilocytic astrocytoma 2 (5%)
Diffuse astrocytoma 8 (20%)
Diffuse oligodendroglioma 1 (2.5%)
Anaplastic astrocytoma 6 (15 %)
Anaplastic ependymoma 2 (5 %)
GBM 21 (52.5%)
Extent of resection
Gross total resection 24 (60%)
Subtotal resection 10 (25%)
Partial 6 (15 %)

Data expressed as frequency (percentage), median, range N number, KPS Karnofsky performance scale

Table 3 Characteristics Of Patients' Among The Studied Patients At The Recurrent Time

N-40
Clinical presentation
Convulsions 9 (36%)
Hemiparesis 11 (44%)
Dysphasia 3 (12%)
Disturbed conscious level 5 (20%)
Visual affection 4 (16%)
Ataxia 2 (8%)
Before second surgery KPS score
Less than 70 (< 70) 12 (30%)
More than or equal (≥ 70) 28 (70%)

Table 4 Location Of The Tumor At Recurrence

Location	
Frontal	12 (30%)
Temporal	10 (25%)
Parietal	10(25%)
Occipital	4 (10%)
Cerebellar	4(10 %)

Table 5 Time Interval Between Surgeries And Its Histopathological Types

Time interval between primary surgery and recurrence		
Within 6 months	GBM	4 (10%)
After 6–12 months	GBM	8 (20%)
After 12–18 months	GBM	10 (25%)
	Anaplastic astrocytoma	4 (10%)
	Anaplastic ependymoma	2 (5%)
After 18–24 months	Diffuse astrocytoma	2 (5%)
After more than 24 months	Pilocytic astrocytoma	2 (5%)
	Diffuse astrocytoma	6 (15%)
	Diffuse oligodendroglioma	2 (5%)

Table 6 Histopathology Of Tumor After Recurrence

Histopathology of lesions excised after recurrence	
Pilocytic astrocytoma	2 (5%)
Diffuse astrocytoma	8 (20%)
Diffuse oligodendroglioma	2(5%)
Anaplastic astrocytoma	4 (10%)
Ependymoma	2 (5%)
GBM	16 (40%)
Radionecrosis	4 (10%)

Table 7 Postoperative Kps And Follow-up

	KPS ≥ 70	KPS < 70
Immediate post-op		
Number of patients	28	12
Clinical condition after reoperation		
Same clinical condition	4 (14.2%)	4 (33.3%)
Improved KPS	22 (78.57%)	2 (16.6%)
Deteriorated KPS	2 (7.1%)	6 (50%)
Radiological condition		
Gross total resection	15 (53.5%)	3 (25%)
Subtotal resection	9 (32.1%)	6 (50%)
Partial resection	4 (14.2%)	3 (25%)
Follow up after 3 months		
Number of patients	26	6
Stable disease	24 (92.3%)	2 (25%)
Progressive disease	2 (7.6%)	4 (75%)
Follow up after 6 months		
Number of patients	28	2
Stable disease	26 (92.85%)	2
Progressive disease	1271.4 (%)	–
Outcome		
Alive	26 (65 %)	
Died	14 (35%)	

Table 8 Postoperative Complications And Outcome In Studied Patients At The Current Time

Postoperative complications	
Newly developed hemiparesis	8 (20%)
Deterioration of previous hemiparesis	6 (15%)
Wound infection	6 (15%)
Deterioration of conscious level	8 (20%)

At the end of period of the study, we had 26 patients' alive and 14 died. Histopathology of the 8 patients who died was GBM.

DISCUSSION

The gold standard for treatment of high-grade glioma is maximal safe surgical resection followed by a combination of brain irradiation, and adjuvant temozolomide (TMZ) chemotherapy [4]. In low-grade glioma, surgery is the cornerstone in management, and adjuvant therapy is not usual practice for all patients; some reserve it for high-risk patients that are above 40 with partially resected lesions, while others reserve it when there is lesion progression [5]. The previous practice improves patients' clinical and functional status (Karnofsky score), the progression-free survival (PFS) and overall survival (OS) of the patients. Even though recurrence of glioma is inevitable, the usefulness of reoperation in cases of recurrence is still debatable and more evidence and investigations are needed [6, 7].

Many studies failed to demonstrate the efficacy of reoperation for clinical outcome and survival in cases of recurrence, while others demonstrate that benefit in special occasions [10]. In the literature, many factors affect the efficacy of surgery in cases of recurrence as patient clinical performance at recurrence, aggressiveness of recurrent tumor, infiltration into eloquent areas of the brain beyond the primary site especially with high-grade gliomas (extent of resection) and possibility of reirradiation after reoperation especially in cases of rapid recurrence as it may lead to toxicity of neural tissue. In low-grade glioma, many reports considered reoperation as an effective treatment option [11]. Effect, frequency, and consequences of repeated surgical resection, as well as the availability of further adjuvant therapy, were analyzed by McGirt et al., and the authors noted that the median overall survival (OS) for patients who received chemotherapy (CHT) or radiosurgery (SRS) was 8.5 months, much longer than the 3 months OS for patients who underwent surgery alone. Surgical treatment should be considered if further adjuvant therapeutic alternatives can be used [12]. Azoulay et al. lead a cohort study in which he compared between reoperated recurrent GBM and those non-surgically treated patients; they concluded that reoperation combined with adjuvant chemoradiotherapy associated with improved survival in recurrent GBM [13].

It is important before decision of reoperation to determine radiological pattern of recurrence as the previous location of primary lesion, new invasion to eloquent area, subventricular zone or ventricles itself and midline crossing. In a study by Brandes et al., almost 80% of recurrences were in the resection cavity of excised primary lesion or at the margin of radiotherapy field [14]. Another study by Rapp et al. concluded the same results as previous one [15]. In our study, we had recurrence within almost the same location and pattern of primary lesion, these criteria which helped the decision of reoperation. Many studies documented the importance of KPS at time of recurrence as tool for patient selection for reoperation and associated with better outcome [10,16]. Our finding is that patients with both low-grade and high-grade gliomas and their KPS 70 or more at time of recurrence experienced improvements in their clinical and functional performance after reoperation. Even those with KPS below 70, you may experience improvement in clinical and functional performance and this may be associated with those that have good general condition and gross total excision achievement. Another study supports the improvement in KPS after reoperation, and Gabrovsky et al. found that patients with tumors of grade III had a preoperative KPS of 77.65, whereas those of grade IV had a score of 71.35. There is a statistically significant increase in mean KPS to 82.24 and 78.41 after the first procedure. All relevant age groups, including those in their sixth, seventh, and eighth decades, had a considerable improvement in performance status after the initial procedure. There was no statistically significant decline in the mean KPS scores from before to after the second surgery, and while there was no evidence of improvement, there was also no clear evidence of worsening in this group of patients (n = 100) [17].

The importance of extent of resection for glioblastoma has been debated for decades. Some studies showed the relevance of extent of resection at recurrence is increasing as patients with glioblastoma are surviving longer. Current literature revealed an overall survival between 52 and 86 weeks when microsurgical excision exceeds 98% of the lesion, while it declines to 35–64 weeks if microsurgical excision is less [18–20]. We discovered that extent of resection may be correlated more with survival as more resection is associated with longer free survival, while improvement of clinical and functional status depends mainly on the initial KPS at presentation. Also our results concluded the fact that as the risk of surgical complications was high in cases of reoperation, it was not linked to an intolerable risk of functional deterioration and this is consistent with many publications [21].

This study highlights the importance of documenting the frequencies of complications and the impact they have on functional status in individuals who have undergone numerous cranial glioma operations. The most important potential application of these data is in patient counseling for second-time glioma operations. The interval between primary surgery and tumor recurrence could be considered as a predictor for tumor aggressiveness. We documented that patients who had their recurrence and reoperation after 6 month of their first operation are presented in good KPS and have better clinical outcome. In Baker study, forty-six of 301 patients underwent reoperation within 2 years of their initial diagnosis, and the median survival following resection was 9 months. Higher preoperative KPS scores and reoperation predicted longer overall survival [7]. By the end of the study, a total of 8 (36%) patients deteriorated and died and 17 (68%) patients were still alive. Overall survival among the studied group was 13.05 months (9.65–17.55). As regards overall survival, Barbagallo and colleagues reported median survival following reoperation for recurrent GBM at 3–13 months [18].

CONCLUSION

Surgical management of recurrent gliomas in selected patients is generally associated with improved functional performance and prolonged survival. Patients' Karnofsky score at recurrence is an important prognostic factor for both low-grade glioma and high-grade glioma. The authors recommend Karnofsky score of 70 or more in patient selection for reoperation in cases of recurrent low-grade and high-grade glioma surgery. Larger and more studies may be needed to release statistically significant data. Evaluation of the role of extent of resection and its role in clinical improvement and survival needs more studies with a larger number of patients. Each operation comes with a greater risk of complications.These results may help clinicians better advise patients who are contemplating re-operating on a glioma. Further large-scale research including larger patients numbers is required.

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