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Supratentorial Recurrent Glioma, Presentation and Outcome Clinical Study

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ABSTRACT

Gliomas are the most frequent primary brain tumors. Most gliomas require aggressive combination of therapy with radiotherapy and chemotherapy after maximal surgery. Recurrent glioma is a significant deterioration in an existing neurological deficit. The current study aimed to prospectively assess the clinical characteristics of first and second presentations of patients, the optimal treatment among the available modalities for recurrent glioma and to illustrate the highly selected individuals with recurrent glioma and the determinants of treatment modalities and patients recruited for. Hence a prospective study on 24 patients with recurrent cerebral glioma carried out in the Neurosurgical Teaching Hospital in Baghdad/Capital of Iraq during Feb. 2009 to Feb. 2011. Twenty one patients (87.5%) were exposed to second operation directed at their tumor site, and had mean survival of 50 weeks, while 3 patients (12.5%) had been treated by chemotherapy had survived for a mean of 11 weeks. Reoperation was associated with a mortality rate of (4.1%). Best survival and good outcome was found in those who had good neurological performance and they were relatively young age. Malignant transformation and dedifferentiation was found in (75%) of cases. In conclusion, no curable treatment regarding recurrent glioma is definite, but reoperation is feasible and can be carried with less morbidity and mortality when considering a good selection criteria of the patients, preserving chemotherapy for those who are not amenable for surgery.

Keywords: Supratentorial Glioma, Recurrent , pathology, Management, mortality.

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INTRODUCTION

Gliomas are the most frequent primary brain tumors. They include astrocytic glioma oligodendrocystic gliomas, ependymomas and glioma wi mixe ce population. Each glioma type consists of both low grade and malignant atypical varieties. Most gliomas require aggressive combination of therapy with radiotherapy and chemotherapy after maximal surgery**.** Recurrence of growth occurs in the majority of glial tumor, if patient deteriorates clinically, and neuroradiological studies indicate tumor regrowth. The recurrence indicates treatment failure (1,2) .

Recurrent glioma is defined as a significant deterioration in an existing neurological deficit, The appearance of new deficit which could not be explained by intervening illness and/or enlargement of the area of contrast enhancement or perilesional low density (3,4). The incidence and prevalence of primary brain tumors widely vary worldwide, for instance in Japan a study conducted in 1984-1994 reported an incidence rate of primary brain tumor was 8.24 per 100.000 per year, glioma represented (40% - 67%) (5). In Iraq during 1992-1994 among a total of 760 brain tumors (44.6%) -were astrocytoma (4%) ependymoma and (3%) oligodendro glioma (6) . Nonetheless, the previous studies didn't refer to recurrent cases. At the national institute of neurosurgery in Budapest 478 primary , Low grade glioma (LGG) were operated from 1955 to 1986 there were an operative mortality of (7.3%) and (3.9%) were lost to follow up, from other point of view (70%) of the survivors could be followed clinically and radiologically (7). (Angiography radroisotope scan and C.T scan) which might confirm a recurrence of about (18%). Recurrent gliomas generally share the primary untreated gliomas in signs and symptoms which categorized into two categories; First the nonspecific findings which are secondary to elevated intracranial pressure (ICP) and secondly the site specific findings which are secondary to actual location of the neoplasm (8). Signs and symptoms vary in relation to the patients characteristics, however, most patients presented with headache which is usually non localizing but may be lateralized to the side of lesion, it is typically worse in the morning and may be relieved after episode of vomiting usually it is secondary to mild CO2 retention during sleep and concomitant cerebral vasodilation. Patient may presented with drowsiness, neck stiffness, papilledema which i**s a** direct reflection of an elevated ICP. Abducent nerve palsy **u**sually produced by its compression against adjacent structure (8,9). Other signs and symtoms include contralateral spastic weakness. Focal (Jaksonian) motor epilepsy, tremor, impairment of mental faculties such as impairment of memory, lack of concentration rapid and excessive fatigue occurs after destruction of sufficient quantity of Frontal lobe (8,9). Tumors involving upper part of optic radiation as it emerges from the posterior limb of internal capsule gives rise to blindness of

the lower half of the opposite visual field, tumors of posterior inferior part of dominant part of lobe give rise to dysphasia dyslexia, dysgraphia, dyscaculia and also agnosia disorder of awareness apraxia. Tumor in the occipital lobe leads to loss of contralateral homonymous field of vision. (9). Tumors in the temporal lobe remain clinically silent until raised ICP(8,9).. Regarding the diagnosis and follow up of cerebral gliomas, Computed Tomography (C.T) and Magnetic Resonance Images are widely used and are diagnostic in up to 90% of cases (10, 11). Nonetheless, neuroimaging is of value in the follow up of cerebral glioma. Positron emission tomography (PET) provide a measure of metabolism and blood flow in the Tumor and has been proposed as a useful marker to differentiate radiation necrosis from recurrent tumor (12,13). Management depend on the patients characteristics, the treatment of recurrent supratentorial gliomas is palliative, neurosurgeon have many medical and surgical (reoperation) options. Conventional radiotherapy, brachytherapy, stereotactic surgery. The rational for reoperation is the same as that for the original operation its goals are confirmation of a tumor's histological characteristics and reduction of tumor mass without causing new neurological defect. Relatively benign tumors are particularly amenable to repeat resection. Reoperation on malignant glioma is indicated when lengthened survival of high quality will be the probable result (2). A good indication for reoperation was identified by several investigators, although no absolute consensus regarding these indications (9). The current study aimed to show Clinical and pathological variation between first and second presentation and the .optimal treatment among the available modalities for recurrent glioma and to identify the determinants of the selection criteria of subject for re operation.

MATERIALS AND METHOD

A prospective study on 24 patients with recurrent cerebral glioma carried out in the Neurosurgical Teaching Hospital in Baghdad/Capital of Iraq during Feb. 2009 to Feb. 2011. For recruitment of a patient in this study he/she should be at the time of recurrence of his/her tumor or at the time of second reoperation. Had previous surgery with proved histopathological results confirming the primary glial tumors. Received radiotherapy post-operatively (after first surgerv only). The dose was ranging 4500-5500 rad. Patients had a neurological deterioration of pre-existing neurological deficit or a new neurological deficit with or without a neuro-radiological evidence of enlarging tumor mass as confirmed by C.T scan. Patients who did not met these criteria were excluded from the study. A pre constructed data collection sheet was used in data collection included Patient's age, gender, clinical presentation, size, site, type of tumor, treatment option and extent of resection for both first and second operation (if present, intraoperative findings and complications, presence or absence of mass effect, and postoperative follow up and outcome. Karnofsky Performance

Status Scale was used to assess patients pre and post operatively. Complete blood picture, blood urea, serum creatinine, blood sugar and CT scanning were performed routinely in all patients. The size of the tumor was estimated according to the proportion of area the tumor had occupied ; Very Large: More than 75%, large (50-75%), medium (25-50%) and small (Less than 25%) the square area of one side of the section. Moreover , Contrast study was done in some patients. Interoperative interval in those who underwent two operations was assessed Careful follow up for patients was needed depending on regular °ut patient visits, readmission and visiting oncology center. Statistical analysis was performed using the statistical package for social sciences version 17, appropriate descriptive statistics and analysis were performed accordingly at a level of significance of 0.05.

RESULTS AND DISCUSSION

Twenty four patients were enrolled in this study with a mean age of 31.8 (range: 16 – 52) years. Patients were 14 females and 10 males with a female to male ratio of 1.4, the patients were residents of 5 Iraqi provinces and majority of them from Baghdad, and the less frequent residents were from **Kerbala, Anbar Salah-Eddin and Al-Qadisiya.**

The distribution of clinical feature and present finding of the studied group are shown in (**Table 1**).

Table 1:Distribution of signs and symptoms at First and Second presentation

Sign and symptoms	First presentation		Second presentation	
	No.	%	No.	%
Headache	18	75.0	20	83.3
Papilledema	16	66.6	18	75.0
Vomiting	10	41.6	13	54.1
Seizure	10	41.6	10	41.6
Hemianesthesia	8	33.3	9	37.5
Hemiparesis	9	37.5	8	33.3
Cranial Nerve palsy	7	29.1	8	33.3
Impaired	4	16.6	8	33.3
Visual deterioration	5	20.8	5	20.8
Behavioral changes	2	8.3	4	16.6
Dysphasia	1	4.1	2	8.3
Elevated bone flap	0	0.0	2	8.3

It is obvious that headache and Papilledema and Vomiting were the more frequent signs and symptoms in both first and recurrent presentation. According to karnofsky performance scale, our patients scale ranged 40-90. Majority of the patients with a score of 60 or more and the mean score was 72 (median 70) (**Figure 1**)

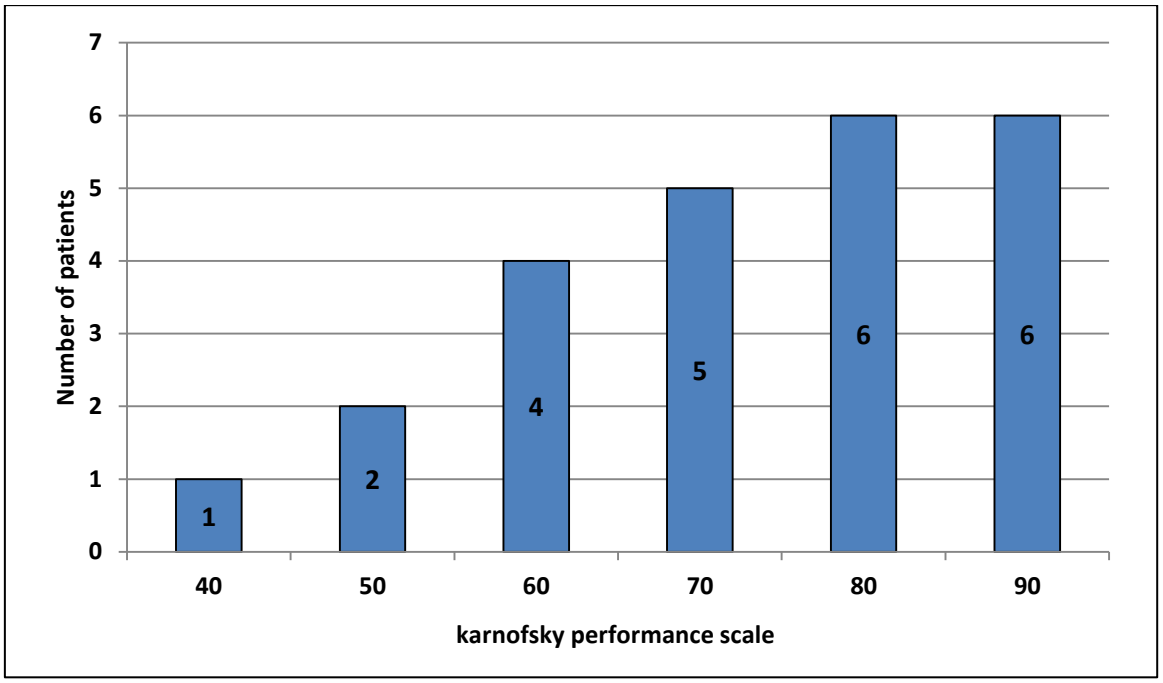

Figure 1:karnofsky performance scale values of the studied group.

Inter-operative interval (period of remission) was 3-36 months. With a mean of 27.7 months

Site of tumor are shown in (**Table 2**), the more frequent site was Frontal in both first and second presentation. However, in the majority of cases, the recurrence occurred in the same area of previous presentation except in one case, a left frontoparietal tumor and total removal was performed, on recurrence showed only left frontal lobe involvement with some extension to the right frontal lobe, and no parietal lobe involvement. Additionally it had been observed that the lesions were more frequent in left than right side.

Size of tumor On radiographic bases (C.T scan) the size of tumor was evaluated in both 1st presentation and recurrence, size was divided into 4 groups, very large (5%),large (45%), medium (40%) and small (10%). On second presentation the corresponding proportions were (10%), (10%), (55%), (25%), respectively. Large and very large tumors were represented (50%) at first presentation were represented only (20%) at the second presentation.

Table 2:Sites of tumor in first & second presentation

Site of tumor	First presentation				Second presentation			
	Right	Left	Total	%	Right	Left	Total	%
Frontal	4	4	8	33.3	4	5	9	37.5
Fronto-Parietal	1	3	4	16.6	1	2	3	12.5
Fronto-Temporal	1	1	2	8.3	1	1	2	8.3
Temporal	1	1	2	8.3	1	1	2	8.3
Temporo-parietal	1	2	3	12.5	1	1	2	8.3
Occipito-Temporal	1	0	1	4.1	1	0	1	4.1
Occipito-Parietal	2	2	4	16.6	2	3	5	18.6
Total	**11**	**13**	**24**	**100.0**	**11**	**13**	**24**	**100.0**

Contrast was performed in 22 patients during first course of illness and it was enhancing

tumor in 8 patients who were proved to have high grade glioma, 4 of them had non-enhancing tumor on the second presentation, the the other 14 patients had non-enhancing tumor.

Mass effect: Sixteen patients (66.6%) had mass effect at first presentation, while the other 8 patient (33.4%) had small size tumor with no mass effect. On recurrence 19 patients (79%) had mass effect and 4 patients (116%) had not. Only one patient showed no mass effect on both presentations.

Management: Medical: steroid and anti-epileptics were used, surgical included Subtotal removal in 7 patients (29.2%), Gross total removal in 13 patients (54.1%) and 7 Lobectomy in 4 patients (16.7%), On recurrence, majority of patients, 21 (87.5%) needed re-operation, (**Table 3**).

Table 3:Surgical interventions at first and second presentations

First Presentation	**Operation**	**No.**	**%**
	Subtotal removal	7	29.2
	Gross total removal	13	54.1
	Lobectomy	4	16.7
	Total	**24**	**100.0**
Second Presentation	Subtotal removal	6	25.0
	Gross total removal	14	58.3
	Lobectomy	1	4.2
	No need for reoperation	3	12.5
	Total	**24**	**100.0**

Complications: unfortunately, post-operative complications were developed in some patients; the more frequent complication in first and second presentation was infection (25%) and (20.8%), respectively. Followed by Seizure, Hemiparesis and CSF leak, while only one patient developed dysphasia in the second presentation and one patient (4.2%) unfortunately died (**Table 4**).

Table 4:Post-operative complications

Complication and mortality	**First presentation**		**Second presentation**	
	No.	**%**	**No.**	**%**
Infection	6	25.0	5	20.8
Seizure	3	12.5	4	16.7
Hemiparesis	2	8.3	3	12.5
CSF leak	2	8.3	3	12.5
Dysphasia	-	-	1	4.2
Mortality	-	-	1	4.2

In this study we tried to illustrate the highly selected individuals with recurrent cerebral glioma which are amenable for reoperation.

Females were affected more than males according to this study. It had been noticed that the

tumor is absent in the first decade of life and this might be due to the distribution of primary tumor during the first presentation also appears late in childhood, so at recurrence, logically the tumor should appears later in life. The effect of age on the prognosis and outcome will be discussed later.

Regarding clinical presentation, headache was the most common presenting symptom in our patients, in first and second presentation, (75%) and (83.3%), respectively. Berger found headache in (20%) of his patients (3). Because the brain itself is not pain sensitive, the headache could be due increased intracranial, invasion or compression of pain sensitive structures in the dura, blood vessels or periosteum, secondary to difficulties with vision (14). Vomiting and Seizure were the second frequent symptom, in both presentations, Seizure was a sign of recurrence of glial tumor in (15%) of patient in a study conducted by Berger et al (3). The seizure were of generalized type except in four patients and not correlated with the age of the patients. Behavioral changes were also noticed in (16.6%) of our patient with recurrent tumor, all were malignant. In previous study (3) behavioral changes reported in 10% of the patients. Our findings regarding the symptoms of the were comparable to that of Berger et al (3). The tumor site was distributed on cerebral hemisphere and was more frequent in frontal lobe. We can noticed a higher proportion of frontal lobe involvement if we compare with Berger study (3). The size of tumor during recurrence was smaller than itself during first presentation. In majority of cases tumors were of medium size while they were of large size during first presentation, this might be due to early detection of recurrence because of awareness of tumor or coincidental finding during follow up C.T scan. Tumor enhancement was noticed in all cases of high grade glioma during 1st presentation and second presentation, (not all patient underwent contrast study, see the result). This might explain the increased vascularity of high grade tumors. This agrees with P.C. Berger et al, all recurrent high grade gliomas are contrast enhancing expensile lesion (3). C.T scan is indicated immediately postoperatively, to detect post-operative complications and also it used in Subsequent follow up 3 month post operatively as it is recommended (15).

Regarding management medical methods are essential in reducing intracrainial pressure. With or without mannitol steroid is effective for reduction of perifocal edema and improvement of neuronal action (14,16). Prophylactic or therapeutic agent for seizures Carbamazipine was ideal in controlling seizures. On the other hand, management of recurrent primary brain tumor it varies from repeated efforts at aggressive surgical resection or chemotherapy to no therapeutic intervention. The general indication for reoperation was recurrent increased intracranial pressure and or focal neurological sign caused by mass lesion . The criterion for performing the second operation depend on the surgeon's opinion also this

general indication was followed by Harsh et al and Young et al (4, 17). In this study gross total removal was the more frequently performed surgical intervention (68.3%) of cases, subtotal removal in (27.1%) and one case (4.1 %) in which Omyah was done. In Piepmeier J.M study (14%) had total removal and (78%) subtotal (18). The type of surgery was decided according to the patient's condition, accessibility of the tumor and the nature of the tumor (cystic or solid). Reoperation Gross total or subtotal is more effective as a modality of treatment than radiation and or chemotherapy especially in patients who have mass lesion this agreed with Kelly P.J.(19).

Also it was found that patients with gross total removal of the tumor respond better to adjunctive therapy than do those who have a more limited resection. The extent of resection in our study was found to influence the outcome, patient with gross total did better than those with subtotal resection (2,20).

The post-operative complications, (36%) of cases, wound infection and seizure were more frequent both were treated successfully by conservative measures. Harsh et al and Ammirati et al, showed a morbidity rate of (5.7%), (16%) in their studies, respectively (4,21). Moreover, morbidity was higher in reoperation patient than those who had one operation, this because of devitalized tissues especially those who received radiotherapy (8). Surgical mortality for such procedure is high (10-20%)but one operative mortality was recorded in this study (5.5%). Harsh et al. study showed mortality rate (3.4%) (4). In the current study some limitations were faced including difficulties in following up patients in oncology centers. Shortage of some chemotherapies during the course of therapy might affect the final outcome and survival.

CONCLUSION

Glial tumor can recur at any site of cerebral hemisphere affecting both male and female in equal distribution, it can affect all ages with some middle age group preponderance. Malignant transformation should be suspected in majority of recurrent cases. The optimal treatment of recurrent cerebral gliomas remains to be defined but reoperation is feasible and can be accomplished with acceptable morbidity and mortality. Patient’s Age, preoperative neurological performance, tumor grade, extent of resection and mass effect where among the determinant of survival after reoperation, while gender and site of tumor were not related to the duration of survival. Reoperation or chemotherapy will not cure the patient's malignant brain tumor but surgery almost certainly relieves his disabling symptoms and there is small but definite chance of providing satisfactory period of higher quality survival.

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