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The Effectiveness of the Prescribed Dose of the Gamma Knife Radiosurgery in Treating Low Grade Glioma

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Abstract

The most prominent form of primary intracerebral tumor is gliomas. Their incidence ranges between 45% and 62% of the population, with a slight prevalence in males (M/F: 1.3). Gliomas are tumors that develop from glial or precursor cells that are neuroectodermal in origin. Gliomas account for 75% of malignant primary brain tumors in adults, with glioblastomas accounting for more than half of glioma. While CNS tumors are rare, they are a significant cause of cancer morbidity and mortality, especially in children and young adults, where they account for roughly 30% and 20% of cancer deaths, respectively. They still have a high death rate compared to other cancers. This benign tumor (WHO Grade I) is mainly found in children and has biological features that differ from diffuse astrocytomas (WHO Grades II-IV). Glioma cells' ability to migrate is a key factor in making glial tumors aggressive. Contrast enhancement cannot distinguish between high- and low-grade gliomas, but low-grade gliomas are considered non-enhancing tumors. Alokaili et al. discovered that 35% of low-grade gliomas improved, while only 16% of high-grade gliomas did not. This study included 75 patients with low-grade glioma; however, due to the spread of Covid-19, some patients were unable to finish the follow-up therefore, they were removed from the total number that became later (31) patients. In the final analysis, (31) people participated in this study, conducted at the Gamma knife center of Neurosciences Hospital, Baghdad/Iraq seven months from June to December, with prescribed doses at 50% from 12Gy to 20Gy. Some patients did the gamma knife radiosurgery before this study begins, but they are included in this study because they are under follow up, and this study needed to do a follow up after one-year post-gamma or more, so will found that there are some of them with a follow up after 2years, 3years post-gamma knife radiosurgery, The follow-up includes MRIs for all patients who were treated at the neuroscience hospital, as well as measurements of tumor size before and after GK for all patients. In all age groups there was a decrease in the average tumor volume after radiosurgery. The highest average tumor volume in the 40-49 age group before radiosurgery. The p-value is significant ≤0.001. The highest rate of improvement in tumor size was in the age group 40-49. The average tumor size in females is greater than the average tumor size in males before radiosurgery. After radiosurgery, the average tumor size in females was lower than in males. The average difference between tumor size before and after GKR and that the rate of decrease in tumor size in females is more than males, p-value was significant (p-value= 0.038)It was found that the tumor volume rates in those who underwent previous surgery were higher than in patients who did not undergo previous surgery. The date of prior surgery is a significant (p-value = 0.046).It is clear that a larger dose was given to patients with a larger tumor size, and that the dose (12 Gy) was the lower effective as the tumor size increased, and the lowest tumor size after radiosurgery was in 2020. That the amount of decrease in tumor size increased relatively with increasing dose, and that the lowest rate of decrease in tumor size was in the lowest dose amount.

Keywords
Gamma Knife, Radiosurgery, GKRS, Low Grade Glioma, Glioma, Radiation Dose.

The most common primary malignant brain tumors are gliomas. All gliomas have an overall age-adjusted incidence rate of 4.67−5.73/100,000 people per year [1]. The World Health Organization (WHO) has divided gliomas into four types of growing malignancy. Essentially, they may be split into two broad groups: low grade gliomas (LGG; WHO 1−2) and high-grade gliomas (HGG; WHO 3−4). GBM (WHO grade 4) is the most lethal glioma in adults with an overall 5 year survival of 0.05−4.7 percent [2]. Generally, gliomas are more prevalent in men than in women [3]. Low-grade gliomas (LGG) represent a category of infrequent, progressive, and slow-growing central nervous system (CNS) tumors that a Hect roughly 3000 and 9000 persons every year in the USA and Europe, respectively, and account for 20 percent of all gliomas[4]When compared to the rapid growth of tumors in those with high-grade glioma, LGG patients often live for five to twenty years. For three typical types of LGG, mean overall survival (OS) ranges from 3 to 6 years, 4 to 7 years, and 9 to 12 years (astrocytoma, mixed oligoastrocytoma, and oligodendroglioma, respectively [5]. A non-enhancing lesion with minimal mass eHect or vasogenic edema, as shown by computerized tomography (CT) or magnetic resonance imaging (MRI), is validated by microscopic inspection of a surgical tissue sample [6].

Currently, the treatment of gliomas comprises on maximum safe surgical resection, external beam radiation therapy (EBRT), and chemotherapy. However, these tumors do commonly return. Options for salvage treatment include recurrent surgery, re-irradiation with EBRT, chemotherapy, new therapeutics, or a combination of these treatments. Repeated surgery may be a useful choice as salvage therapy, but could be accompanied by postoperative problems. Treatment with EBRT for the second time may be associated with a substantial risk of radiation-related damage and necrosis. In recent years, gamma knife radiosurgery (GKRS) has become considerably more popular as a salvage therapy method for patients diagnosed with recurrent gliomas. The purpose of GKRS for patients with recurrent glioma is to improve survival rates with a minimum burden for these patients [7]. This study presents the results of 31 patients with low-grade glioma who were treated with GKRS. This paper focuses on assessing the different doses of low-grade glioma range (12-20Gy) that give the best and identify the best dose that improves clinical, control tumor size, shrinkage of the tumor.

Methods

Case Selection

This study included 31 patients with low-grade glioma; the follow-up time (range 6- 9 months). Some patients did the gamma knife radiosurgery before this study begins, but they are included in this study because they are under follow up, and this study needed to do a follow up after one-year post-gamma or more, so will found that there are some of them with a follow up after 2years, 3years post-gamma knife radiosurgery. The data collected from the Gamma knife center of Neurosciences Hospital, Baghdad/Iraq.

Patient's Follow-Up

The phone numbers of the patients, as well as the data from their radiosurgery at the Neurosciences Hospital's Gamma knife center in Baghdad/Iraq, have been obtained. The patients were contacted to get their permission to participate in the study. Following approval, the Pre-GK surgery MRI report was gathered from all patients, including those under follow-up. The evaluation was based on knowledge of the effect of radiation on tumor size. The follow-up includes MRIs for all patients as well as measurements of tumor size before and after GK for all patients. All patient pictures and investigations were compared before and after GK.

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-27 (Statistical Packages for Social Sciencesversion 27). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means or Paired-t-test for difference of paired observations (or two dependent means), or ANOVA test for difference among more than two independent means. Statistical significance was considered whenever the P value was equal or less than 0.05.

Results

This study includes a total of 31 patients (males16 (52%), females 15(48%)) with an average age of 31.45. Where the number of those aged <20 (3(10%)), 20-29 (10(32%)), 30-39 (11(35%)), 40-49 6(19%) and ≥50 (1(3%)). The number of those who had undergone prior surgery was (10(32%)), while those who did not undergo (21(68%)). The number of those who underwent surgery ≤ 10 years 8(26%) and the number in 2(6%) years. Number of people who took 12 Gy dose (5(16%)), 14 Gy (8(26%)), 15 Gy (3(10%)), 16 Gy (2(6%)), 18 Gy (8(26%)) and 20 Gy (5(16%)). The number of patients in the years in which the doses were taken was) 11 (35%) (In 2018,) 11 (35%) (In 2019, 4(13%) in 2020 and (5(16%)) in 2021. Table (1) below shows case study.

Relation between Age Groups and GKRS

Table (2) shows the tumor size before and after radiosurgery using the Gamma Knife. Figure (1) shows that in all age groups there was a decrease in the average tumor volume after radiosurgery. The highest average tumor volume in the 40-49 age group before radiosurgery. The p-value is significant <0.001

Table (3) shows the amount of improvement in tumor size, which is the average difference between the size of the tumor before and after radiosurgery. Figure (2) shows that the highest rate of improvement in tumor size was in the age group 40-49, and that the lowest rate of improvement in tumor size was in the age group <20. The p-value was not significant. Also, table (3) shows the number of patients whose tumor size decreases or increases, according to age groups. Where it seems clear that the patients who had an increase in the size of the tumor were present in four different age groups and the decrease was in all age groups

Table 1. Study Population

Subject	Variable	N (%)
Age	<20	3(10%)
	20-29	10(32%)
	30-39	11(35%)
	40-49	6(19%)
	≥50	1(3%)
Gender	Male	16(52%)
	Female	15(48%)
Surgical Removal	Yes	10(32%)
	No	21(68%)
Surgical Date	Never	21(68%)
	≤ 10	8(26%)
	>10	2(6%)
Dose	12	5(16%)
	14	8(26%)
	15	3(10%)
	16	2(6%)
	18	8(26%)
	20	5(16%)
Dose Date	2018	11(35%)
	2019	11(35%)
	2020	4(13%)
	2021	5(16%)

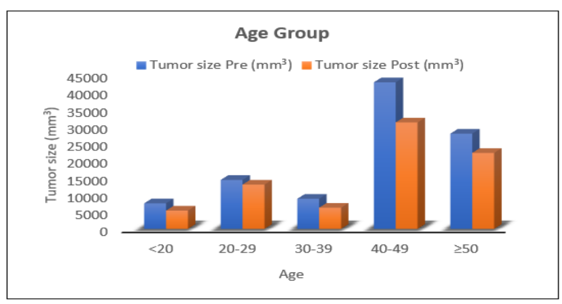

Figure 1. Relation between Age Groups and tumor size before and after GKRS

Table 3. Decrease amount in Tumor Size and number of patients whose tumor size decreases or increases according to Age Groups

	Variable	Improvement(mm^3) Mean ±SD	Increase Tumor N (%)	Decrease Tumor N (%)	P-value
Age Groups	<20	1017±1351	1(3%)	2(6%)	0.830
	20-29	1317±1836	1(3%)	9(29%)	
	30-39	4604±5473	1(3%)	10(32%)	
	40-49	836±756	1(3%)	5(16%)	
	≥50	1875	0(0%)	1(3%)	
Total			4(13%)	27(87%)	

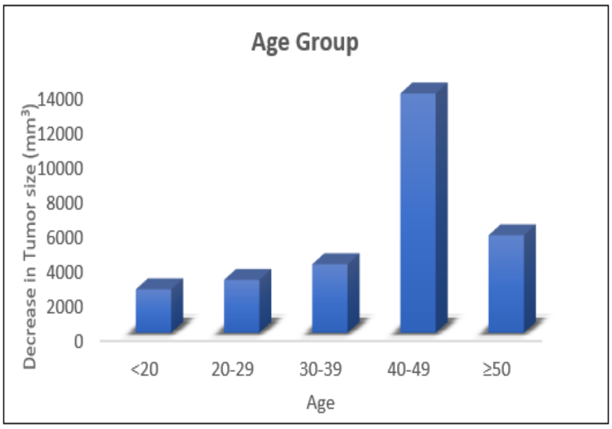

Figure 2. Decrease amount in Tumor Size Related to Age Groups

Table (4) shows that the average tumor size in females is greater than the average tumor size in males before radiosurgery. After radiosurgery, the average tumor size in females was lower than in males, as shown in figure (3). The p-value was not significant

Table (5) showing the average difference between tumor size before and after radiological surgery and that the rate of decrease in tumor size in females is more than males as shown in figure (4) The p-value was significant (p-value= 0.038). Table (5) also, shows that all those who had an increase in the size of the tumor were males.

Relation between Gender and GKRS

Table 4. Relation between Gender and tumor size before and after GKRS

	Variable	Tumor size Pre (mm^3) Mean ±SD	Tumor size Post (mm^3) Mean ±SD	P-Value
Gender	Male	14474±15172	15010±16249	0.093
	Female	20951±27397	12085±17421	

Table 5. Decrease amount in Tumor Size and number of patients whose tumor size decreases or increases according Gender

	Variable	Improvement(mm^3) Mean ±SD	Increase Tumor N (%)	Decrease Tumor N (%)	P-value
Gender	Male	2314±1876	4(13%)	12(39%)	0.038
	Female	8866±11807	0(0%)	15(48%)	
Total			4(13%)	27(87%)	

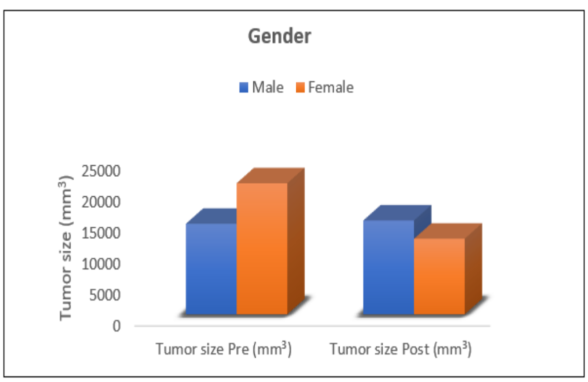

Figure 3. Relation between Gender and tumor size before and after GKRS

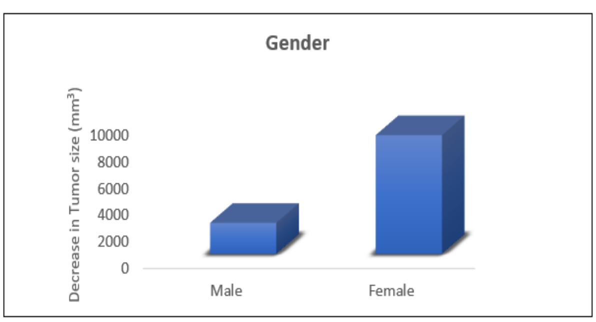

Figure 4. Decrease amount in Tumor Size Related to Gender

Relation between Prior surgical and GNRS

Looking at a table (6), the results show the difference in tumor size before and after radiological surgery between patients who had previous surgery, whether (<10 or ≥ 10 year) and patients who did not have any previous surgery. It was found that the tumor volume rates in those who underwent previous surgery were higher than in patients who did not undergo previous surgery. As shown in the figure (5), (6). The date of prior surgery is a significant (p-value = 0.046).

The percentage of decrease in the size of the tumor was higher in those who underwent previous surgery, and the more recent the surgery, the greater the percentage of decrease in the size of the tumor as in the table (7) and figures (7), (8). Most patients who had previous surgery did not have an increase in the size of the tumor, whether the surgery was in (<10 or ≥ 10 year), as shown in table (7).

Table 6. Relation between Prior surgical and tumor size before and after GKRS

	Variable	Tumor size Pre (mm^3) Mean ±SD	Tumor size Post (mm^3) Mean ±SD	P-Value
Prior Surgical	Yes	30092±30211	20704±19973	0.171
	No	11664±13732	10209±14034	
Prior Surgical Date	Never	11664±13732	10209±14034	0.046
	<10	33404±32812	22764±21491	
	≥10	16841±15456	12464±13689	

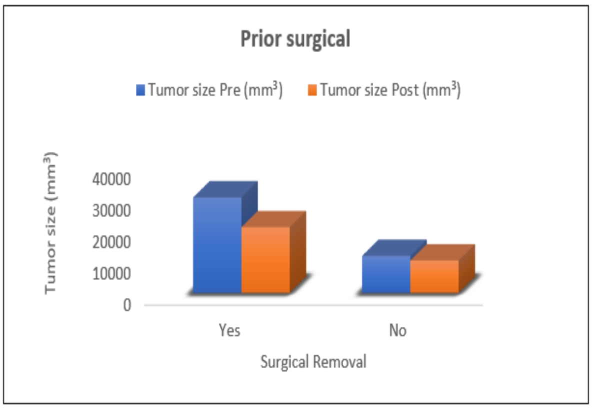

Figure 5. Relation between Prior surgical and tumor size before and after GKRS

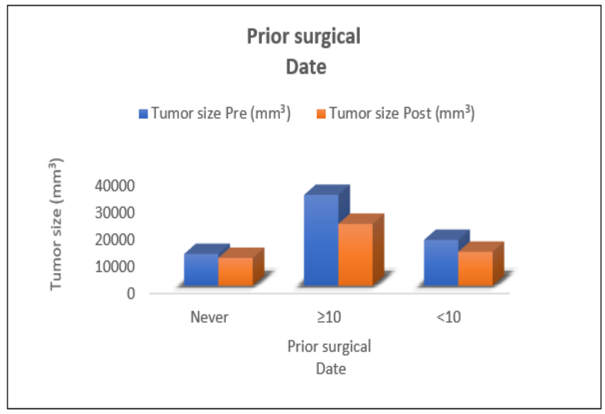

Figure 6. Relation between Prior surgical date and tumor size before and after GKRS

Table 7. Decrease amount in Tumor Size and number of patients whose tumor size decreases or increases according to Prior surgical

	Variable	Improvement(mm^3) Mean ±SD	Increase Tumor N (%)	Decrease Tumor N (%)	P-value
Prior Surgical	yes	11072±13672	1(3%)	9(29%)	0.642
	no	2823±3111	3(10%)	18(58%)	
Prior Surgical Date	never	2823±3111	3(10%)	18(58%)	0.710
	<10	4377±1767	0(0%)	2(6%)	
	≥10	12746±14963	1(3%)	7(23%)	
Total			4(13%)	27(87%)	

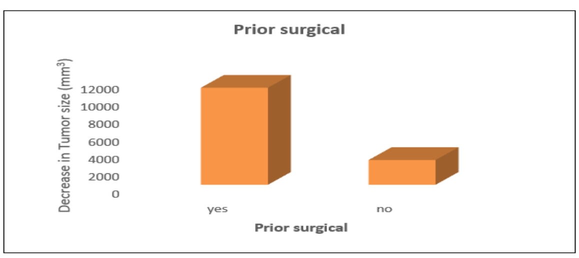

Figure 7. Decrease amount in Tumor Size Related to Prior surgical

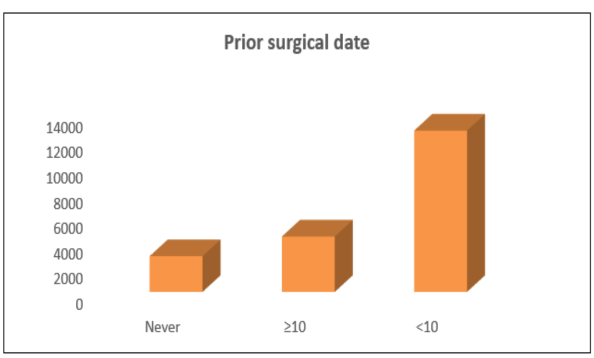

Figure 8. Decrease amount in Tumor Size Related to Prior surgical date

Relation between Dose and GKRS

Table (8) presents the tumor size in patients before and after gamma knife radiosurgery according to the amount and date of the radiation dose. It is clear that a larger dose was given to patients with a larger tumor size, and that the dose (12 Gy) was the lower effective as the tumor size increased, and the lower tumor size after radiosurgery was in 2020 as shown in the figures (9) and (10)

Table (9) shows that the amount of decrease in tumor size increased relatively with increasing dose, and that the lowest rate of decrease in tumor size was in the lowest dose amount. It is also clear that the older the dose the greater the improvement in the size of the tumor as in the figures (11), (12). Also, table (9) shows that all patients who took doses (15, 16 and 20Gy) had no increase in tumors.

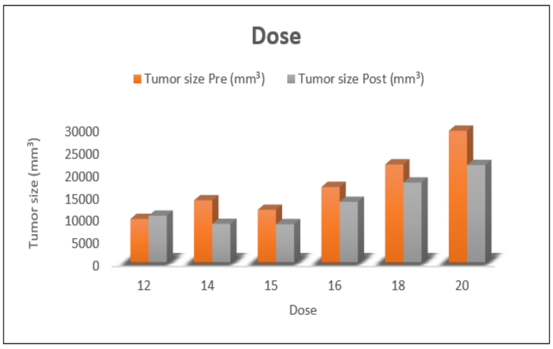

Figure 9. Relation between Dose and tumor size before and after GKRS

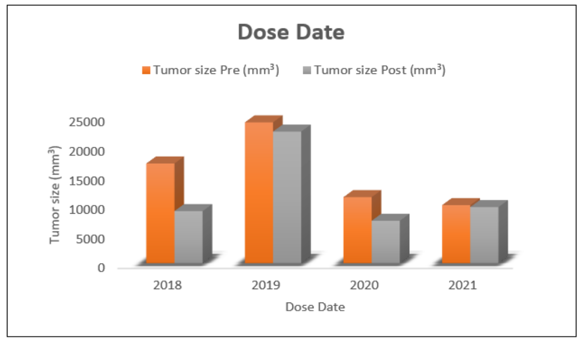

Figure 10. Relation between Dose Date and tumor size before and after GKRS

Table 8. Relation between Dose and tumor size before and after GKRS

		Tumor size Pre (mm^3) Mea ±SD	Tumor size Post (mm^3) Mean ±SD	P-Value
Dose (Gy)	12	9630±3165	10326±8375	0.425
	14	13749±19348	8534±18136	
	15	11652±14150	8464±11904	
	16	16704±4600	13417±5996	
	18	21701±27554	17692±17124	
	20	29148±33706	21554±25161	
Dose Date (year)	2018	17001±24899	8878±13634	0.670
	2019	24025±25723	22453±20705	
	2020	11264±6204	7232±4278	
	2021	9902±10479	9570±13456	

Table 9. Decrease amount in Tumor Size and number of patients whose tumor size decreases or increases according to Dose

		Improvement(mm^3) Mean ±SD	Increase Tumor N (%)	Decrease Tumor N (%)	P-value
Dose (Gy)	12	2277±1382	1(3%)	4(13%)	0.586
	14	5357±7425	1(3%)	7(23%)	
	15	3188±2408	0(0%)	3(10%)	
	16	3288±1396	0(0%)	2(6%)	
	18	7707±14360	2(6%)	6(19%)	
	20	7594±9319	0(0%)	5(16%)	
GK Date (year)	2018	8123±12628	0(0%)	11(35%)	0.661
	2019	4455±6746	2(6%)	9(29%)	
	2020	4032±2362	0(0%)	4(13%)	
	2021	3106±6029	2(6%)	3(10%)	
Total			4(13%)	27(87%)	

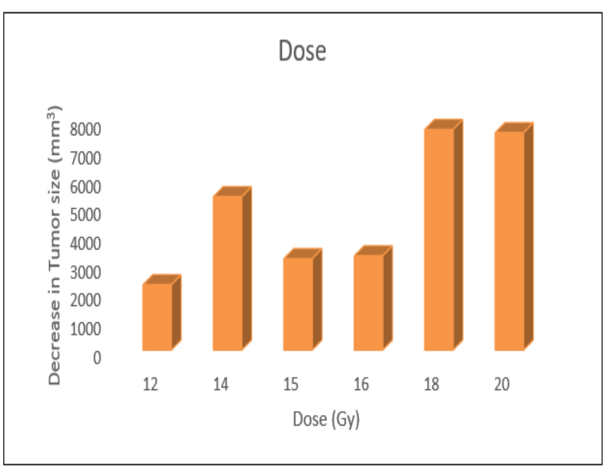

Figure 11. Decrease amount in Tumor Size Related to Dose

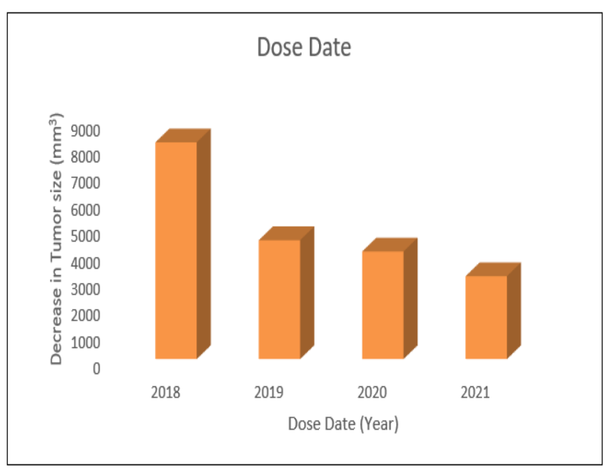

Figure 12. Decrease amount in Tumor Size Related to Dose Date

Follow-Up patients

Table (10) and figure (13) showing duration of follow-up of patients after a gamma knife dose. Patients were followed up during the study period, which is 9 months, by telephone and inquiring about the side effects that appeared after radiosurgery.
There are also patients who were followed up before the start of this study, and this study continued their follow-up. Results indicated that all patients were survived after radiosurgery.

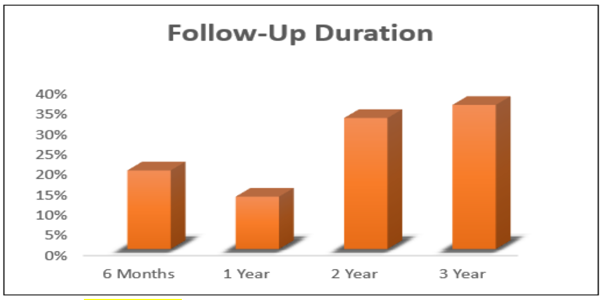

Figure 10. Duration of Follow-Up of Patients

Table 10. Duration of Follow-Up of Patients

Duration	No. (%)	Survival	Dead
6 Months	6(19%)	6(19%)	0(0%)
1 Year	4(13%)	4(13%)	0(0%)
2 Year	10(32%)	10(32%)	0(0%)
3 Year	11(35%)	11(35%)	0(0%)

Discussion

Relation between Age and GKRS

For the elderly who want to avoid the hazards of open surgery or who may refuse it, radiosurgery is a good option[7]. Furthermore, older individuals are more likely to have medically linked comorbidities, which may prevent them from undergoing open brain surgery[8]. The findings of Kaul et al [9] suggest that FSRT for the treatment of meningiomas may help elderly patients (aged ≤ 65). Radiosurgery, on the other hand, is a viable choice for youngsters. Despite the fact that a child's growing brain is more sensitive to radiation-induced harm than an adult's [10]. Despite advancements in neurosurgical technique, a considerable percentage of children with brain tumors are either not curable or have a high risk of morbidity and death if surgery is performed alone [11]. More recently, stereotactic radiosurgery has seen increasing application among the pediatric population[12].
The results of the current study were on an average age of 31.45 ±10.51, where it was found that 87% of patients had a decrease in tumor size after radiosurgery. Perhaps young age rate had an effect on the improvement in the size of the tumor, as it has been verified Larson et al. [13] found that youthful age was related with considerably superior outcomes in a multi-institutional research. GKRS produced more promising results in individuals with high-grade gliomas and metastatic brain illness than traditional therapy techniques [12]. Age was also a significant multivariable predictor, supporting prior findings that increasing age is a moderating factor related with decreased survival [14]. While Fokas et al. came to the conclusion that age had no effect[15]

Relation between Gender and GKRS

Gamma Knife surgery, which was initially intended to treat deep cerebral lesions, has surfaced as a therapy option for localized brainstem gliomas. According to the findings of Yen et al [16] there was a reduction in size or total elimination of the tumor in 16 of 20 patients. In the current study, 26 of 31 patients had a decrease in tumor size or complete removal of the tumor; all of the patients who did not have a drop or disappearance of the tumor were male. Several earlier research [17] shown that females, regardless of age, had a stronger reaction to the gamma knife than males, and this was confirmed by the findings of this study, which demonstrated that gender is a major determinant and that females are more receptive than males.
Other studies [18] [19] [20] found no link between gender and responsiveness to the gamma knife, and no correlation between gender and problems that arise after radiosurgery. According to Seneviratne et al.[21] Increased intracranial displacement during frameless gamma knife radio-surgery is related with male gender.

Relation between Prior surgical and GKRS

Despite advances in microsurgery, such as intraoperative brainstem evoked responses and neuron avigation, surgical treatment of tumors within the brainstem is still associated with significant morbidity and mortality[22]. The location and histology of brainstem lesions are important factors in postoperative morbidity and mortality [23]. If total resection is not achievable for low-grade gliomas, at least tumor mass reduction should be sought for[24][25]

Previous research has found that past surgical intervention is a poor prognostic factor. According to Young et al[26] although 14 of 22 patients (63.5 percent) had an excellent or good performance at the last follow-up, only 11 (50 percent) were judged excellent. There were seven treatment failures (31.8 percent), which is over three times the failure rate (10.3 percent) among individuals who had never had surgery. This is congruent with the current study's findings, since the tumor growth rate prior to radiosurgery is substantially greater than that of individuals who did not have surgery. Although the rate of tumor size decrease following radiosurgery was greater. Sheehan et al [27] verified that individuals who had not had previous surgery did not suffer nervous system problems, and tumor control was better than in those who had those operations following radiosurgery.. While Fokas et al [15] found that past surgery was an unimportant influence.

Relation between Dose and GKRS

Despite recent breakthroughs in the treatment of glioma patients with radiation, chemotherapy, and surgery, neurosurgeons and oncologists still have a difficult task in treating these tumors. Furthermore, the patient's Karnofsky performance status (KPS), age, tumor histology, and radiation dosage have all been demonstrated to influence patient outcomes [28]. This was obtained in previous research 10 to 15 years ago with a projected marginal tumor dosage of 20 Gy and higher [29][30]. Over the previous nine years, the dosage has been lowered to 12 to 14 Gy because of the substantial morbidity[8] [7] The tumor size was decreased in 87 percent of patients in this study, with doses ranging from 12 to 20 Gy depending on the size of the tumor. Many earlier studies[13] [16] found that the dosage amount had a substantial impact on tumor growth and problems following radiosurgery, as well as the length of life after radiosurgery. Gerszten et al. [31] treated seven patients with low-grade gliomas in the tectal region. They pointed out the importance of dose-volume effects in relation to tumor histology.

Researcher [32] report of Gamma-Knife radiosurgery of 11 patients with benign and 12 patients with malignant midline gliomas. Peripheral dosages of 10- 22 Gy were given to benign gliomas and 9-30 Gy to malignant gliomas. Local control of benign tumors has been accomplished in 78 percent of patients. Glioblastoma patients had an average survival duration of 6 months. While Shuto et al [33] have confirmed the impact of radiosurgery is determined by the prescribed marginal tumor dosage, which should be 15 Gy or fewer to minimize brain stem radiation harm. According to a previous research [18] concluded there was no difference in survival between individuals who received higher, intermediate, or lower doses of radiation, specifically 50−70 Gy, 45 Gy, or 35 Gy.

Follow-Up patients

Survival rates have improved as a result of the utilization of sophisticated microsurgery and chemotherapy. Patients with glioblastoma formerly had a 9-12 months survival rate; but, with contemporary treatment, survival rates of up to 19 months may be attained, and recurrences can be greatly postponed. However, as exciting as these advancements are, overall survival remains a challenge. Gamma Knife radiosurgery (GKRS) may represent a promising additional treatment option when used in a logical time frame and integrated into established therapy concepts[34]. However, whole brain radiation is associated with hair loss, somnolence, hearing loss, skin reactions, and neurological deficits such as cognitive and memory loss, and requires 2 or more weeks of daily hospital visits for treatments [35].

As previously stated, various factors have been linked to improved tumor size and survival following Gamma Knife radiosurgery. All participants in this study were followed up on and showed no side effects after radiosurgery. There were no deaths during the follow-up period. Furthermore, the tumor was under control in 27 of the 31 individuals. This is in line with the findings of a previous study[36] which found that none of the patients experienced serious adverse effects that necessitated an unplanned office visit or admission. Lim et al. [37] found similar results in patients with chiasm gliomas. In England, a prospective study [38]of 65 patients was conducted to look into the long-term effects of the Gamma Knife. Only 47 (72%) of the 65 patients could be reached by phone. Following Gamma Knife, 64% of people had adverse effects. The majority of them (91%) were mild to moderate. Headache, pin-point pain/numbness, new/worsening neurological impairments, weariness, nausea/vomiting, and balance disruption were also common symptoms. Samuel et al[39] demonstrated that tiredness after radiosurgery was less prevalent than before radiosurgery in the majority of patients. At the start of the study, 40% of the participants reported tiredness symptoms, which declined to around 20% in subsequent surveys.

Baracia et al [40] describe how they used a conventional gamma source to treat 16 patients with deep-seated low-grade gliomas. Although they achieved good clinical results for 13 of their patients, with the tumor disappearing in 50% of cases, shrinking in size in 13%, and ceasing to grow in 31%, three patients with brainstem tumors and poor health prior to treatment deteriorated, which is similar to the findings of this study. While Baumann et al [41]observed local tumor control in two out of five patients with malignant gliomas within a follow-up period of 10 months.

Conclusions

The results of the current study were on an average age of 31.45 ±10.51, where it was found that 87% of patients had a decrease in tumor size after radiosurgery. Perhaps young age rate had an effect on the improvement in the size of the tumor. Females have a greater response to the gamma knife than males, regardless of age. The tumor size rate before radiosurgery is much higher than that of those who did not undergo surgery, although the rate of reduction in tumor size after radiosurgery was higher. That the dose amount had a significant effect on reducing tumor size and complications after radiosurgery and on the duration of survival after radiosurgery. All participants in this study were followed up on and showed no side effects after radiosurgery. There were no deaths during the follow-up period. Furthermore, the tumor was under control in 27 of the 31 individuals.

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