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# Role of Gamma Knife Radiosurgery in the Management of Diffuse Low Grade Astrocytoma

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## ABSTRACT

**Introduction**: Low-grade astrocytoma represent a diverse group of primary brain tumor affecting young people. Gamma knife radiosurgery is a non-invasive therapeutic option for managing diffuse low-grade astrocytoma providing long term tumor control and preventing debilitating treatment-related consequences, particularly for those in deep-seated structures or in critical locations. **Aim: E**valuate the effectiveness, feasibility**,** acute, and subacute side effects of gamma knife radiosurgery in the management of patients with diffuse low-grade astrocytoma. **Patients and Methods:** This a non-randomized clinical trial that was conducted on 68 patients with diffuse low-grade astrocytoma who were treated by Gamma Knife Radiosurgery and followed up at Gamma Knife Center, Nasser Institute, Cairo, Egypt. All patients were followed up till January 2022. The study included 38 males and 30 females with mean age about 31 years (19-65 years). Seventeen patients underwent previous surgery or biopsy. The remaining 51 were diagnosed by MRI combined with MRS. The median tumor volume was 9.2cc (0.2-57.4 cc) and the median prescription dose was 12 Gy (10-16 Gy). Thirty-five patients received single session while 30 patients underwent staged treatments. **Results:** Tumor control after radiosurgery was achieved in 58 cases (15 of these tumors remained radiologically stable and 43 reduced in size) while 7 cases progressed (10.8% of cases). Gender, diagnosis either pathological or radiological, timing of GKRS, number of sessions and total tumor volume were found significantly affecting tumor response (p=0.038, p=0.001, p=0.010, p=0.008 and p=0.003 respectively). Acute toxicities included fatigue, alopecia, and headache and scalp erythema. Toxicities were minimal. No acute toxicities bigger than grade II of Common Terminology Criteria for Adverse Events v4.0 (CTCAE) were reported in treated patients. The progression free survival was 93.8% at 3 years, 90.8 % at 5 years an 89.2% at 8 years. **Conclusions:** Gamma Knife Radiosurgery offers patients with diffuse low-grade astrocytoma long lasting local tumor control with acceptable radiation toxicity, which improves patients' general health, PFS, functional performance and quality of life.

**Keywords**: Diffuse Low Grade Astrocytoma, Gamma Knife, Radiosurgery

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## INTRODUCTION

A diverse group of primary brain tumors known as diffuse low-grade gliomas (DLGG) that develop from supportive glial cells (Lombardi et al., 2020). They exhibit continuous growth and an almost inevitable anaplastic transformation. The median overall survival (OS) was found Between 5 to more than 15 years (Fathallah-Shaykh et al., 2019). According to data from Egypt's national population-based registry program in 2014, there were 7500 instances of brain and nervous tissue cancer, and around 5.29% of all cancer cases. Around 30% of gliomas are low-grade gliomas (LGGs), and their morbidity age is lower than that of high-grade gliomas (Ibrahim et al., 2014). Low Grade Glioma is an infiltrative disease because tumor cells are found outside the radiologically

apparent tumor despite frequently well-defined margins on magnetic resonance imaging (MRI) (Zetterling et al., 2016). The location of LGGs will determine how they will be treated. According to several studies, LGGs are mainly found in "secondary" functional regions that are close to the principal eloquent regions, particularly the SMA (supplementary motor area) and the insular lobe (Parisot et al., 2016).

The European Society of Neuroradiology (ESNR) has approved the use of a standardized conventional MRI (cMRI) acquisition methodology for the diagnosis and clinical management of low-grade gliomas (Thust et al., 2018). Conventional radiotherapy and radiosurgery both employ ionizing radiation, but the physical properties unique to each treatment cause the radiobiologic consequences of these two procedures differ significantly (Régis et al., 2017).In radiosurgery, a predetermined target is destroyed or biologically modified using convergent narrow ionizing beams that are administered in a single or a few sessions with stereotactic accuracy (Faraj et al., 2018).Safety and efficacy of Gamma Knife Radiosurgery in avoiding tumor progression and enhancing patients' overall survival (OS) and progression-free survival (PFS) have been documented in published research (Niranjan et al., 2019). Ideal candidates for radiosurgery include patients with progressing pilocytic or deeply situated grade 2 fibrillary astrocytoma (Niranjan et al., 2019). The major therapy for tumors located in vital areas such as brainstem, thalamus, hypothalamus, and basal ganglia is GKRS. With or without prior surgical intervention, radiosurgery was employed as a subsequent treatment after subtotal surgical resection or to increase the dose previously given by radiotherapy (Niranjan et al., 2019). Patients with low-grade glial tumors respond well to GKRS as it enhanced patients' functional performance and quality of life while maximizing social functioning and reducing disease-related psychological effects (Gagliardi et al., 2017).

We aimed at this non-randomized clinical trial to examine the effectiveness, feasibility, and acute and subacute side effects of Gamma Knife Radiosurgery in treatment of patients with diffuse low grade astrocytomas.

## PATIENTS AND METHODS

This non-randomized clinical trial involved 68 diffuse low-grade astrocytoma patients who received treatment at Nasser Institute, Gamma Knife Center, Cairo, Egypt. Three patients were lost for follow up. Inclusion criteria were patients with residual low-grade astrocytoma after surgical resection, recurrent low-grade astrocytoma after surgical resection, orthose who were ineligible, inaccessible or rejecting surgery. Included patients aged less than 70 years with Karnofsky performance level≥70.Analysis of data of the patients treated and followed up from April 2009 till January 2022 was done.

Exclusion criteria were patients who received prior radiotherapy, pilocytic astrocytoma or oligodendroglioma, and patients who can’t perform MRI. Analysis of data of the patients treated and followed up until January 2022 was done. Clinical data including age, sex, complain before treatment, type of surgery if done, tumor volume, tumor location and diagnosis was done either histopathologically or radiologically by MRI combined with MRS were recorded. Clinical examination, brain MRI, tissue diagnosis (if surgical excision was feasible), and MRS with perfusion studies if excision was not done were all used to evaluate patients before to therapy. Before beginning therapy, each patient is given a detailed explanation of the treatment procedure, including possible treatment outcome and expected side effects. All patients gave their informed consent before gamma knife treatment and signed by the patient or caregiver before starting treatment.

The Leksell stereotactic head frame was used during the gamma knife procedure while the patient receiving mild intravenous sedation and local anesthetic. A closed high-resolution, 1.5 Tesla MRI machine (SIGNA explorer with XP, General Electric®) is used for brain MRI imaging while a stereotactic frame is in place. 1.6 mm slice-thickness. T2-weighted MR sequences and contrast-enhanced T1-weighted sequences made up the imaging process. Stereotactic images were then imported into the Gamma Plan workstation. Treatment planning using dedicated software (Elekta Industries'

GammaPlan® version 11.0.3 software). Gamma Knife ICON model was used to provide the prescribed doses of GKRS and the stereotactic frame will be removed as soon as the treatment is over.

After GKRS, clinical examinations and contrast-enhanced brain MRIs were performed every 6-month intervals for the first two years of follow-up then every year until the study's end. It was advised that individuals scheduled extra follow-up appointments if they develop any related symptoms. Patients were monitored, interviewed and clinically assessed. Patients who discontinued their prescribed course of treatment or lost follow up as recommended were excluded in the statistical analysis or the survival data.

The tumor control was defined as tumor remission (shrinkage of more than 50% of the volume) or stable (less than 25% increase in volume to less than 50% volume shrinkage) (Park et al., 2011). Tumor progression defined as increase volume of more than 25% (including cyst enlargement) (Park et al., 2011). The tumor's size was measured quantitatively along three dimensions and qualitatively by the degree of surrounding structural distortion. Using the dedicated Leksell Gamma Plan® Version 11.0.3 software, morphological characteristics and tumor volume was defined from pre-treatment MRI images. Using the "volume" function in the "measurements" window of the GammaPlan® version 11.0.3 software, the operating neurosurgeon with the help of a neuroradiologist calculated the tumor volume by contouring the target on each slice by matching T2-weighted, and contrast-enhanced T1-weighted MRI axial scans. For each patient, a qualitative assessment of the tumor volume change at the follow-up MRI (i.e., reduced, no change, or increased) was made. The "volume" function in the "measurements" window of the Gamma Plan® software was also used to quantify the changes in tumor volume during follow-up visits.

On MRI images, computerized assessment of volume of the residual or recurrent tumor was done and the preoperative MRI images were compared. To achieve proper precision while using the computerized volumetry approach, thin cuts less than 3mm must be taken through the region of target. The sum of the regions delineated on each cut multiplied by the cut thickness was used to determine the total tumor volume as they shown in MRI examinations.

The period from treatment until the lesion started to enlarge was used to determine radiological progression free survival. The exception to this rule was if the tumor grew just after GKRS and then shrank, which was regarded as transient tumor swelling.

Clinical assessment after GKRS included: clinical response if the patient's symptoms and signs are stable or better and no response if the patient's symptoms and signs worsen or if new symptoms or signs related to the disease occurred (Heppner et al., 2005). The period of time between the GKRS and the time of clinical condition worsening was known as clinical progression free survival. A team of highly qualified neuroradiologists carried out the neuroradiological assessment. Toxicities were evaluated using version 4.0 of CNS toxicity of the National Institutes of Health National Cancer Institute Common Terminology Criteria for Adverse Events (NIH NCI CTCAE) (Basch et al., 2017).

**Statistical analysis**

Version 22 of the IBM SPSS statistical analysis application was used (IBM Inc., Chicago, IL, USA). Mean and standard deviation were used to depict quantitative parametric data (SD). The median and interquartile range were used to show quantitative non-parametric data (IQR). Frequency and percentages (%) were used to illustrate qualitative characteristics. The Chi-square test was used to analyze data from three or more groups. The time from the GKRS treatment to progression or death at the study time interval was referred to as the progression free survival rate. Kaplan Meier curves were used to calculate progression free survival, and the log-rank test was used to determine its statistical significance.

The Kaplan-Meier technique was used to determine overall survival from the time of diagnosis to the last known follow-up visit or death from any cause. The Kaplan-Meier curves

were subjected to both multivariate analyses using the Cox proportional hazard ratio and univariate analysis using the long-rank statistic. Statistical significance was defined as a two-tailed P value 0.05.

## RESULTS

Table 1 shows patients characteristics. Moreover, it demonstrates that lobar tumors were present in 41 patients (frontal lobe in 20 patients, parietal lobe in 4 patients, temporal lobe in 14 patients, and occipital lobe in 3 patients) and deeply seated tumors in 27 patients (brainstem in 5 patients, thalamus in 10 patients, sylvian in 3 patients, tectal in 6 patients, optic in one patient, and ventricles in 2 patients). The age of patients ranged from 19-65 years old (mean age 31 years).

**Table 1.** Patients' characteristics in the 68 patients with diffuse low-grade astrocytoma

| Patients' characteristics | N=68 | (%) |
|---|---|---|
| **Sex** | | |
| Male | 38 | 55.9 |
| Female | 30 | 44.1 |
| **Age** | | |
| <30 y | 45 | 66.2 |
| ≥30 y | 23 | 33.8 |
| **Tumor location** | | |
| Lobar | 41 | 60.3 |
| Deep | 27 | 39.7 |
| **Timing of GKRS** | | |
| Primary treatment | 51 | 75 |
| Secondary treatment | 17 | 25 |
| **Type of clinical onset** | | |
| Symptomatic | 29 | 42.6 |
| Accidental | 39 | 57.4 |
| **Diagnosis** | | |
| Pathological diagnosis | 17 | 25 |
| Radiological diagnosis | 51 | 75 |

GKRS: Gamma Knife stereotactic radiosurgery

Table 2 demonstrates radiosurgical treatment parameters in which tumor volumes varied from 0.2 to 57.4 cc (median tumor volume was 9.2 cc and mean tumor volume was 11.3cc). The prescribed dose ranged from 10 to 16Gy (median dose was 12 Gy) with isodoses ranged from 50- 70% (median 50%), and a percentage tumor cover of 90 to 100% (median tumor coverage was 99%). Thirty-five patients received a single session, whereas 30 patients received staged treatment (up to 4 sessions). When a tumor is close to critical structures, the dosage falloff is carefully evaluated. If the given dose is more than tolerance of these critical structures, treatment planning is adjusted to a more suitable dose. Several isocenters were needed for the optimization of conformal dose planning.

**Table 2.** Radiosurgical treatment parameters among the 65 patients with diffuse low-grade astrocytoma

| Radiosurgical treatment parameters | |
|---|---|
| Treatment volume range<br>Median tumor volume<br>Mean tumor volume | 0.2-57.4cc<br>9.2cc<br>11.3cc |
| Prescription dose<br>Median dose | 10-16 Gy<br>12 Gy |
| coverage | 90-100% |
| isodose | 50-70% |
| Single session<br>Staged treatment | 35<br>30 |

Tumor control after GKRS was seen in 58 cases (89.3%) (15 of these tumors remained radiologically stable and 43 reduced in size from them tumor disappeared (complete remission) in 7cases, shrunk (partial remission) in 36 cases) while 7 were progressed (10.8% of cases). Gender, diagnosis either pathological or radiological, timing of GKRS, number of sessions and total tumor volume were found significantly affecting tumor response (p=0.038, p=0.001, p=0.010, p=0.008 and p=0.003 respectively) (Table3).

Acute toxicities were defined that toxicities developed within first three months from treatment completion. Treatment was well tolerated (patients experienced slight transient headache which disappeared spontaneously) & all patients returned home on the same treatment day. (All treated patients with low grade astrocytoma). The increased T2-weighted signals surrounding the tumor suggesting break in the blood-brain barrier developing after GKRS (adverse radiation effects shown on MR imaging). Radiation-related edema, symptomatic edema, decreased appetite, sleep problems, temporary localised hair loss, escalating or new headaches, and radiation dermatitis were among the acute toxicities. minimal toxicities were observed.

**Table 3.** Correlation between patients' characteristics and tumor response among the 65 patients with diffuse low-grade astrocytoma

| | | | Tumor response | | | $X^2$ | P-value |
|---|---|---|---|---|---|---|---|
| | | | Stable | Progression | Tumor reduction | | |
| Gender | Male | N | 13 | 4 | 21 | 6.559 | 0.038* |
| | | % | 86.7% | 57.1% | 48.8% | | |
| | Female | N | 2 | 3 | 22 | | |
| | | % | 13.3% | 42.9% | 51.2% | | |
| Age | < 30 years | N | 10 | 4 | 30 | 0.448 | 0.799 |
| | | % | 66.7% | 57.1% | 69.8% | | |
| | ≥ 30 years | N | 5 | 3 | 13 | | |
| | | % | 33.3% | 42.9% | 30.2% | | |
| Type of clinical onset | Symptomatic | N | 8 | 0 | 21 | 7.837 | 0.098 |
| | | % | 53.3% | 0% | 48.8% | | |
| | Accidental | N | 7 | 7 | 22 | | |
| | | % | 46.7% | 100 % | 51.2% | | |
| Diagnosis | radiological | N | 5 | 7 | 36 | 17.401 | 0.001* |
| | | % | 33.3% | 100% | 83.7% | | |
| | Pathological | N | 10 | 0 | 7 | | |
| | | % | 66.7% | 0% | 16.3% | | |
| Timing of GKRS | Primary treatment | N | 15 | 7 | 29 | 9.132 | 0.010* |
| | | % | 100% | 100% | 67.4% | | |
| | Secondary treatment | N | 0 | 0 | 14 | | |
| | | % | .0% | 0% | 32.6% | | |
| Number of sessions | staged | N | 7 | 7 | 16 | 9.552 | 0.008* |
| | | % | 46.7% | 100% | 37.2% | | |
| | Single session | N | 8 | 0 | 27 | | |
| | | % | 53.3% | 0% | 62.8% | | |
| Total tumor volume | < 9 cc | N | 4 | 1 | 37 | 15.842 | 0.003* |
| | | % | 26.7% | 14.3% | 86% | | |
| | ≥ 9cc | N | 11 | 6 | 6 | | |
| | | % | 73.3% | 85.7% | 14% | | |
| Tumor location | Lobar | N | 11 | 4 | 23 | 1.809 | 0.405 |
| | | % | 73.3% | 57.1% | 53.5% | | |
| | Deep | N | 4 | 3 | 20 | | |
| | | % | 26.7% | 42.9% | 46.5% | | |
| Dose | <13Gy | N | 9 | 4 | 23 | 0.204 | 0.905 |
| | | % | 60% | 57.1% | 53.3% | | |
| | ≥13 Gy | N | 6 | 3 | 20 | | |
| | | % | 40% | 42.9% | 46.5% | | |

GKRS: Gamma Knife stereotactic radiosurgery

Patients receiving treatment did not show any acute toxicities more than grade II of the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (Table 4) (Basch et al., 2017). Subacute toxicities are those developed after 90 days from treatment completion. No one experienced permanent side effects. No severe or life-threatening toxicities being reported. Five patients developed cysts, with one developed multicystic changes and needed cyst aspiration; the others were asymptomatic and subsequently shrank. Five patients developed hydrocephalus which needed ventriculo-peritoneal shunt. Progression to more aggressive histologic type confirmed by MRS occurred in seven patients (Table 4).

In this series, OS rate was 96.9% at 3 years and 95.4% at 5 years. At the last FU in January 2022, 95.4% of patients were alive& the remaining 3 patients (4.6%) were died due to local progression of disease at 14, 18, 37 months (Figures. 1, 2). Case: Female patient aged 23 years with pathologically diagnosed LGG located in right parietal region. Tumor was treated with 14 Gy and 50% isodose shell with 100% coverage of target. Follow up after 12months of GKRS treatment showed the same delineation but hyperintense T2 signal within target delineation of treatment was much reduced (partial remission) (Figures 3,4).

**Table 4.** Acute and subacute toxicities among the 65 patients with diffuse low-grade Astrocytoma

| Toxicities | Number of Patients | (%) |
|---|---|---|
| **Acute toxicities** | | |
| Radiation-related edema | 31 | 47.7 |
| Symptomatic edema | 23 | 36 |
| Reduced appetite | 23 | 36 |
| Sleep disturbances | 14 | 21.5 |
| Transient focal hair loss | 11 | 16.9 |
| Increasing or new headache | 20 | 30.8 |
| Radiation dermatitis | 2 | 3 |
| **Subacute toxicities** | | |
| Cysts | 5 | 7.7 |
| Hydrocephalus | 5 | 7.7 |
| Progression to aggressive type | 7 | 10.8 |

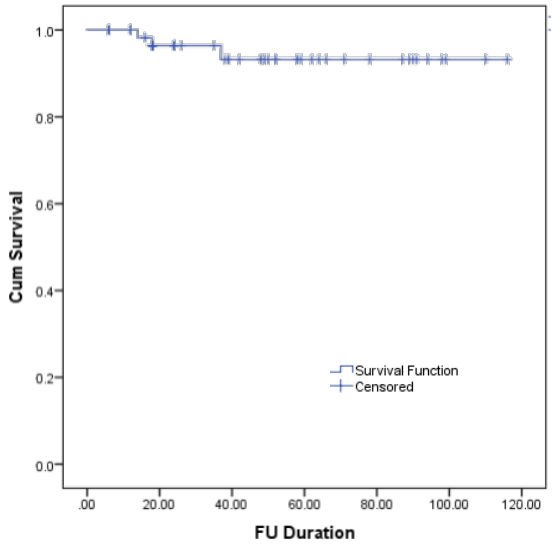


**Figure 1.** Kaplan-meier curve of overall survival for all patients

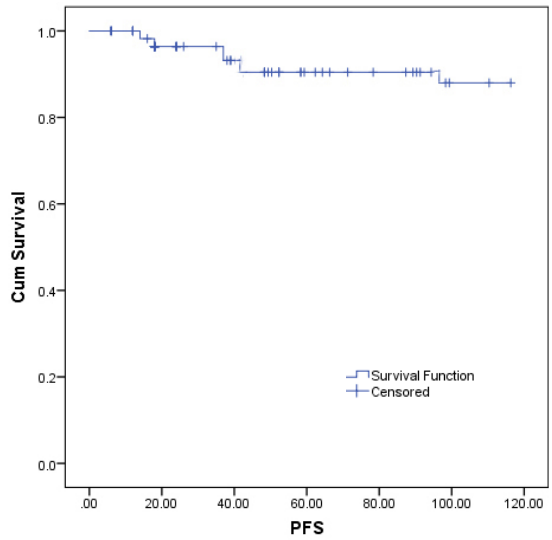


**Figure 2.** Kaplan-meier curve of progression free survival for all patients

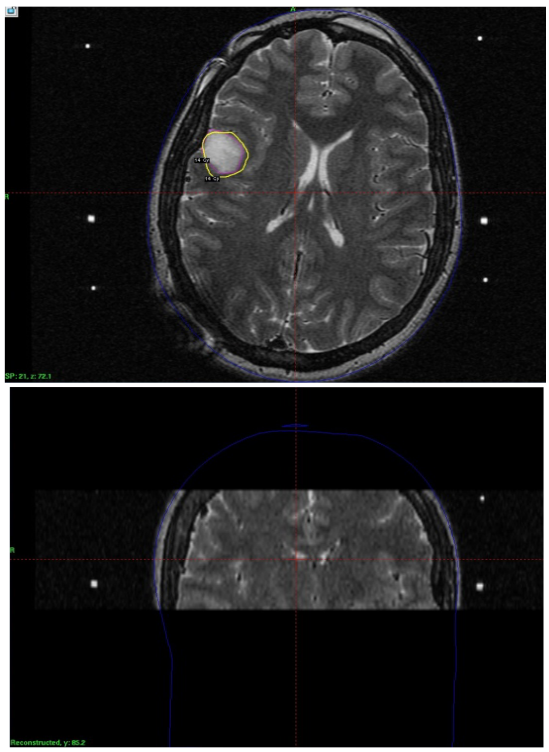

**Figure 3.** Target delineation of tumor located in right parietal region then sharp fall off the dose and all the tumor is covered (100% coverage) with 14 Gy and isodose shell to 50%

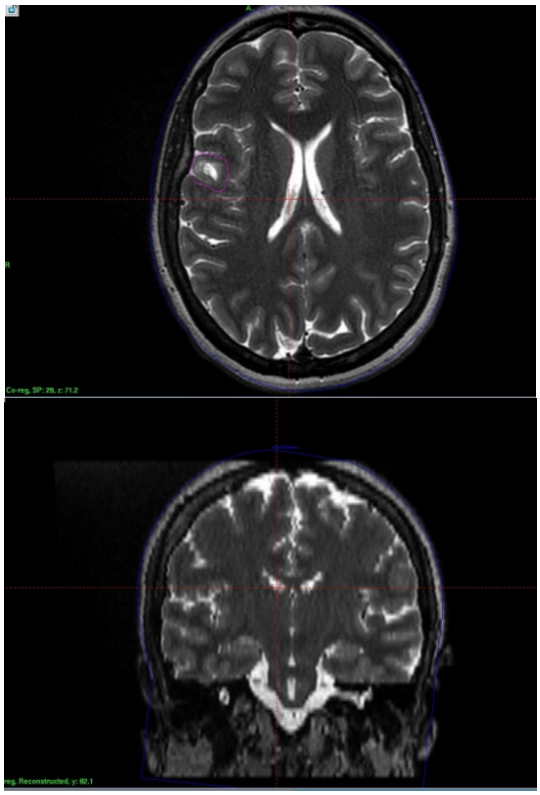

**Figure 4.** Follow up T2 -weighted MRI images obtained after 12 months of GKRS shows the same delineation but hyperintense T2 signal within target delineation of treatment is much reduced (partial remission).

## DISCUSSION

Patients with diffuse low-grade astrocytoma have high rate of tumor control using gamma knife radiosurgery, with tolerable radiation-related adverse events. Nonetheless, several studies have demonstrated the effectiveness of GKRS in the treatment of low-grade astrocytoma (Kano et al., 2009, El-Shehaby et al., 2015, Niranjan et al., 2019, Deora et al., 2020).

The main clinical series of GKRS in low-grade glial tumors belonged to Kida et al., 2000, Hadjipanayis et al., 2002, Heppner et al. et al., 2005, and Szeifert et al. 2007, who concluded the same experience over a shorter duration of follow up.

Most patients with low-grade glioma (LGG) manifested by seizures, according to Gogos et al., and only a small percentage does so after imaging done for a sign or symptom unrelated to the tumor (Gogos et al. 2020). These results are consistent with our findings and are explained by the gradual, ongoing growth of LGG (4 mm/year), which enables functional rearrangement & their indolent behavior and is typically not accompanied by any obvious or only mild functional impairment in patients at the time of onset of disease.

In our series, the proportion of treated patients who were still alive and had no evidence of tumor progression at the time of final follow-up in January 2022 was 89.3% (58 patients), whereas local tumor progression occurred in 7 patients (10.7%). Our patients had a tumor control rate that was close to that of other series that used the same inclusion criteria (El-Shehaby et al., 2015, Kida et al., 2000, Hadjipanayis et al., 2002). Lower tumor control ratio compared to other studies previously reported may be explained by our extended follow-up period (6-116 months), which revealed later tumor progression.

Heppner et al. came to the conclusion that in symptomatic patients with suspected low-grade astrocytoma, maximal safe surgical resection should be taken into account as a standard treatment, with use of GKRS for residual or recurrent disease. Yet, GKRS may be a significant alternative option for individuals with deeply-seated lesions in brain (Heppner et al., 2005). According to Park et al., a substantial difference in tumor control rates between patients receiving GKRS as their first treatment and those receiving GKRS as a second treatment for residual after surgery was confirmed (Park et al., 2005) These finding supports our findings.

In our series, progression free survival at 3 years, 5 years, and 8 years was 89.2%, 90.8%, and 93.8%, respectively & OS rate was 95.4% after five years and 96.9% at three years. This improvement is likely the result of early diagnosis using MRI scanning technology and more modern gamma knife machines (ICON model). In our series, multivariate analysis using the Cox regression approach found type of clinical onset, total tumor volume, timing of GKRS, and number of sessions were statistically significant for longer PFS (p=0.024, p=0.043, p=0.032 and p=0.042). Other variables including gender, age, tumor location, and dosage had no appreciable impact on PFS.

The five-year PFS in the current series was 96% for tumors with a volume less than 9 cc and 85% for tumors with a volume equal to or more than 9 cc. The total tumor volume influenced PFS significantly. (Multivariate, P=0.043; univariate, P = 0.024). According to Niranjan et al., marginal dosage of 15 Gy or higher and tumor volume smaller than 6$cm^3$ were substantially correlated with a longer PFS (Niranjan et al., 2019).

According to research by Park et al., progression-free survival rates at 2 and 5 years for tumors larger than 6 $cm^3$ were 66.7% and 29.6%, respectively. Patients exhibited a PFS rate of 90.9% and 71.6% at 2 and 5 years, respectively, when the tumor volume was 6$cm^3$ or smaller (Park et al., 2011). These results supported our findings that total tumor volume impacts tumor progression survival rates and also revealed that patients treated with 15 Gy or more had 5-year PFS rates of 77.8%, compared to 29.6% for patients treated with lesser dose (P = 0.035). Tumor volume between the two groups did not differ significantly (mean, 6.7 cm3 vs. 4.7 cm3, P = 0.087), The larger dosage administered was most likely responsible for the better PFS. (Park et al., 2011). This is in contrast to our findings, which

showed that PFS was not significantly affected by marginal dosage (P = 0.643).

Park et al., 2011 & Antico and Almedia, 2014 discharged patients on the same treatment day unless treated patients developed any clinical or neurological symptoms, these results matching those of our study. We found that radiation - related edema was noted in 47.7% (31 cases) and in 36% were symptomatic and demonstrated clinical increase of neurological symptoms that correlated with an occurrence of perifocal edema and treated with steroid administration. Adverse radiation related effects experienced in most patients were transient perhaps because use of GKRS ICON model used in the management of well demarcated DLGG that agree with what Wang and his collogues found (Wang et al., 2006), While disagree with Hadjipanayis et al. who had no patients with WHO grade II Fibrillary Astrocytoma experienced radiation related edema (Hadjipanayis et al., 2002).

## CONCLUSION

GKRS is an effective and safe treatment for diffuse low-grade astrocytoma. In patients with diffuse low-grade astrocytomas, gamma knife radiosurgery improves functional outcomes and quality of life while providing long-lasting local tumor control with tolerable treatment-related radiation toxicity.

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## CONFLICT OF INTEREST

No conflict of interest

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