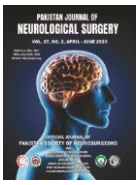

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Original Article

PET-CT Guided Gamma Knife Radiosurgery for Recurrent Glioblastoma Multiforme Recurrent Cases in Pakistan

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ABSTRACT

Objective: The treatment of recurrent Glioblastoma Multiforme (r-GBM) poses a significant confronts to neurosurgeons. This study was conducted to assess the effectiveness of PET-CT-guided Gamma Knife radiosurgery (GKRS) in treating r-GBM. The purpose of the study is to determine the outcome of this treatment approach.

Materials and Methods: Retrospective descriptive research was supervised at the Neurospinal and Cancer Care Institute, Karachi Pakistan between June 2017 to August 2022. The study comprised patients with biopsy-confirmed Grade IV Glioblastoma Multiforme who experienced recurrence during follow-up. PET-CT and MRI brain with contrast were performed to determine the target volume of the tumor, and GKRS was carried out based on the scan findings.

Results: A total of 24 patients, ranging in age from 47 to 77 years with a median age of 50 years, were included in the study. The tumor recurrence occurred within a median interval of 10 months after diagnosis, ranging from 1 to 16 months. The median time for progression-free survival from GKRS was 5 months, ranging from 2 to 6 months. The median overall survival from GKRS was 11 months, ranging from 5 to 12 months.

Conclusion: GKRS is a tool in the multimodal treatment of r-GBM. By co-registering PET-CT-MRI, it becomes possible to plan the treatment more effectively by targeting the active tumor while preserving healthy brain tissue. This approach has the potential to improve overall survival rates and patient outcomes.

Keywords: glioblastoma recurrence • Gamma knife radiosurgery • Positron emission tomography (PET), radiation necrosis.

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INTRODUCTION

Glioblastoma multiforme is a highly aggressive grade IV space-occupying lesion of the brain of the central nervous system, which typically affects individuals at a median age of 64.[1,2] The standard

treatment for recently diagnosed GBM involves safe maximum surgical removal of the tumor, along with chemotherapy and radiotherapy, to optimize the patient's chances of survival. However, despite such aggressive treatment, recurrence of this high-grade tumor is a common phenomenon, which poses a challenge for subsequent treatment due to the radiation impairing the brain tissue and the spread of the tumor to functional areas of the brain. Recent trends indicate a rise in the use of GKRS to treat recurrent glioblastoma multiforme. However, it is important to note that GKRS is not proving to be superior to other treatments such as standardized EBRT for recently recognize GBM.[3] Nowadays, GKRS is commonly used for cases where GBM has returned. During the planning stage, a contrast-enhanced MRI of the brain is typically performed. It is vital to distinguish between disease progression and radiation necrosis to prevent the need for additional surgery or stereotactic radiosurgery. Stereotactic radiosurgery is a treatment method that focuses solely on the affected area, without causing significant side effects. Moreover, patients who are not in good physical condition to undergo another surgical procedure can tolerate stereotactic gamma knife radiosurgery with ease. The use of [18F] FDG is the established radiotracer for cancer imaging in PET,[4,5,] and PET-CT scanning helps distinguish the active tumor area from radiation necrosis. This allows for more accurate target planning for GKRS and ultimately reduces the volume of the area that requires radiation. PET imaging can be used to identify the metabolically active area of a tumor that may not be visible in an MRI scan alone and in addition to MRI, positron emission tomography (PET), computed tomography (CT), single photon emission CT (SPECT), fluorescence imaging (FI), Functional MRI, photoacoustic imaging (PAI) is used to detect residual GBM, in addition MRI, along with CT provides adds to anatomical study. SPECT and PET are used for metabolic or enzymatic processes by use of radiolabelled tracers, expression of EGFR, a receptor tyrosine kinase that can act as a potential therapeutic target, is directly interact by neuroimaging, imaging can give detailed insights into the intratumoral distribution of gene-expression patterns especially in GBM as "infiltrative" imaging phenotype can be used as a predictor for patient outcome.[6,7] Glioblastoma patients typically have a survival rate of 9 – 12 months,[8] which is further reduced after recurrence. Although there is ongoing research to find ways to increase survival rates for recurrent glioblastoma, these efforts have not yet been successful. For patients who cannot tolerate another surgery, GKRS is a salvage option.

MATERIALS AND METHODS:

Study Design and Setting

This was a descriptive study involving 24 patients, to determine the outcomes of PET-CT-guided GKRS treatment for recurrent glioma. The study was carried out at Pakistan's first gamma knife radiation center, the Neurospinal, and Cancer Care Institute, between June 2017 and August 2022, with approval from the hospital's ethical committee.

Inclusion Criteria

All patients who had previously undergone total gross resection (> 80% resection) for biopsy or those with proven Grade-IV glioblastoma multiforme, followed by radiation, and undergone chemotherapy were included.

Exclusion Criteria

Patients with multi-organ dysfunction, a Karnofsky scale score of less than 70 were excluded, and those with good initial effects of radiation.

Data Collection

Patient demographics, including age, sex, KPS score, history of surgery, conventional radiotherapy, and chemotherapy, were recorded. Tumor recurrence was defined, and tumor progression was assessed according to RANO criteria. Tumor target planning was performed using 18F-FDG PET-CT and MRI brain with contrast. Follow-up assessments, including clinical assessment and MRI brain with contrast, were conducted every two months after treatment. RANO criteria were used to identify the progression or stable disease.

Data Analysis

SPSS version 29.0 is used for data analysis. Descriptive frequencies are noted including the median, range, KFS scale, post-operative radiation, age < 50 and > 50 years confidence interval 95%, and p-value < 0.005.

RESULTS

Gender Distribution

Table 2 presents the results of survival after GKRS for a total of 24 patients, with 16 (66.66%) males and 8 (33, 33%) females.

Age Distribution

The median age of the patients was 50 years, with a range from 47 years to 77 years, while their median KPS score was 70, with a range of 60 – 80.

Progression-Free Survival

As seen in Table 1, the summary of the patient's characteristics and outcomes, including overall survival and progression-free survival. The tumor's median interval between diagnosis and recurrence was 10 months, ranging from 1 – 16 months. GKRS resulted in a progression-free survival (median) interval of 5 months, with a range of 2 – 6 months, and a median local failure rate of 8 months, ranging from 4 – 9 months. The patient's median survival from GKRS was 11 months, with a range of 5 – 12 months. The median survival of GBM from the time of recurrent diagnosis was 19.5 months, ranging from 6-28 months.

Table 3 compares different studies. Furthermore, **Figure 1** illustrates the active area of a 48-year-old women's right temporal recurrent GBM using MRI compared with PET CT. **Figure 2** depicts 52-year-old men with left temporo-occipital recurrent GBM.

Table 1: Background Clinical information.

Data Category	N = 24
Male	16 (66.76%)
Female	8 (33.34%)
Median Age	50 years (47 – 77 years)
< 50 years	12 (50%)
<50 years	12 (50%)
KPS score	Median: 70 (Range: 60 – 80)
> 70	16 (66.7%)
< 70	8 (33.3%)
Previous history of Surgery, radiotherapy, and chemotherapy	All (100%)
Tumor volume cm^3 (median)	23.6 cm^3 (Range: 4.5 – 28.5)
GKRS Max Dose (Gy) Median	13.0 Gy (Range: 8 – 25)
GKRS Isodose Median	50%

Table 2: Survival Duration from the GKRS.

	Time Interval in Months
Progression-free survival after GKRS	5 Mon (range: 2 – 6 months)
Overall survival after GKRS	11 Mon (range: 5 – 12 months)
Overall survival from the time of recognition	19.5 months (range: 6 – 28 months)

Table 3: Comparative Data with Other Similar Studies.

	Time to Recurrence from the First Surgery in Months	KPS Scores	The Volume of Tumor cm^3	GKRS Dose Margin in Gy	Overall Survival after GKRS in Months	Overall Survival from the Time of Diagnosis in Months
Our study at N.C.C. I	10(median)	70	23.6	13.0	11 (95%CI)	19.5 (95%CI)
Skeie et al[9]	11.0 (mean)	70	12.4	12.2	9 (95%CI)	18.0 (95%CI)
Park et al[10]	10.4 (mean)	90	13.6	16	17.9 (95%CI)	33.2 (95%CI)
Koga et al[11]	14.5 (median)	90	NR	20	10.5 (95%CI)	24.0 (95%CI)
Elliott et al[12]	12 (median)	90	1.35	15	13 (95%CI)	26.1 (95%CI)
Pouratian et al[13]	7.9 (median)	80	21.3	6.0	9.4 (95%CI)	17.4 (95%CI)
Kida et al[14]	NR	NR	29.0	14.7	14.0 (95%CI)	27.0 (95%CI)
Kong et al[15]	NR	NR	NR	16	13 (95%CI)	23.0 (95%CI)
Kohshi et al[16]	4.3 (median)	NR	NR	22	11 (95%CI)	21.0 (95%CI)
Hsieh et al[17]	NR	70	21.6	12	10.0 (95%CI)	16.7 (95%CI)

***NR:** Not Reported by Authors.
*Neurospinal and cancer care institute.

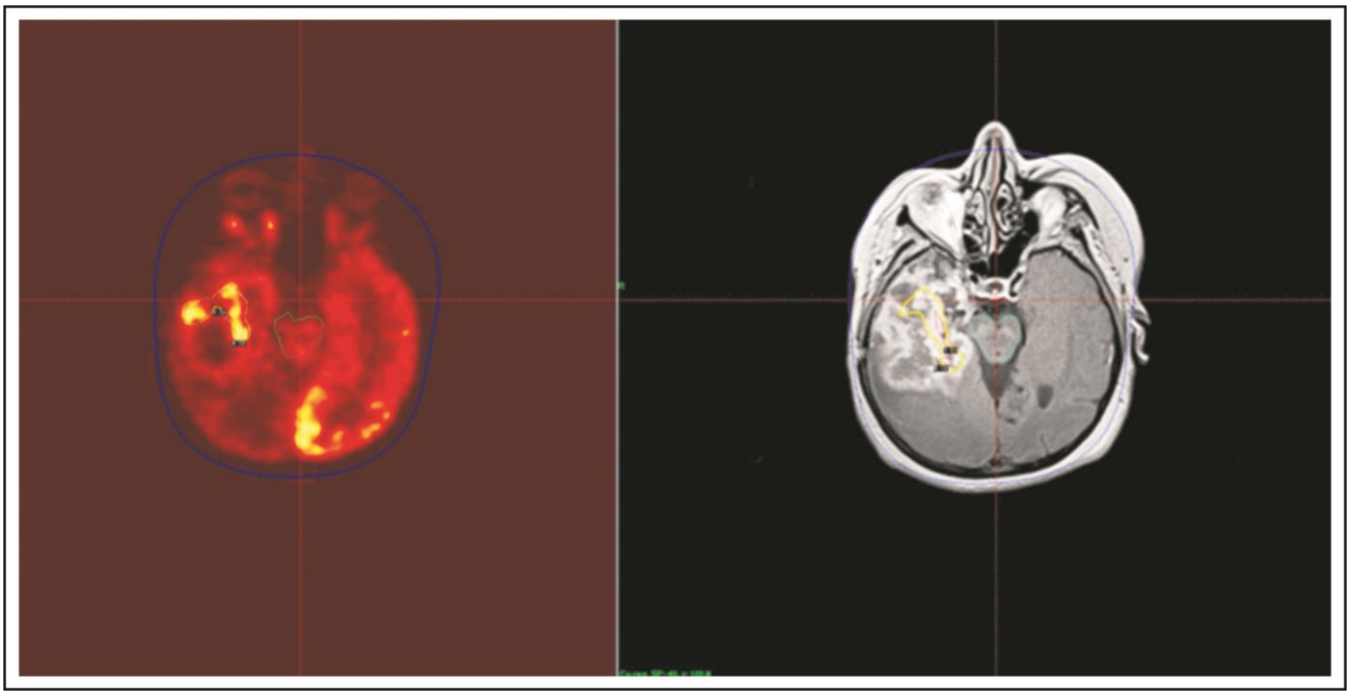

Figure 1: Showing a 48-year-old lady scan, who had right temporal recurrent GBM. PET-CT showed active tumor areas and the left side showed gamma planning covering the active tumor area and leaving the area of radiation necrosis .8Gy margin dose was given to the patient. (Images used with patient's permission).

DISCUSSION

Ongoing efforts to improve outcomes in recurrent glioblastoma multiforme have been hindered by the lack of established management guidelines. Currently, gamma knife radiosurgery is preferred due to its lower morbidity and its ability to improve local tumor control rates. However, it is important to differentiate between recurrence and areas of radiation necrosis, which can be aided by PET CT imaging and improve planning for active tumor targeting. By combining PET-CT

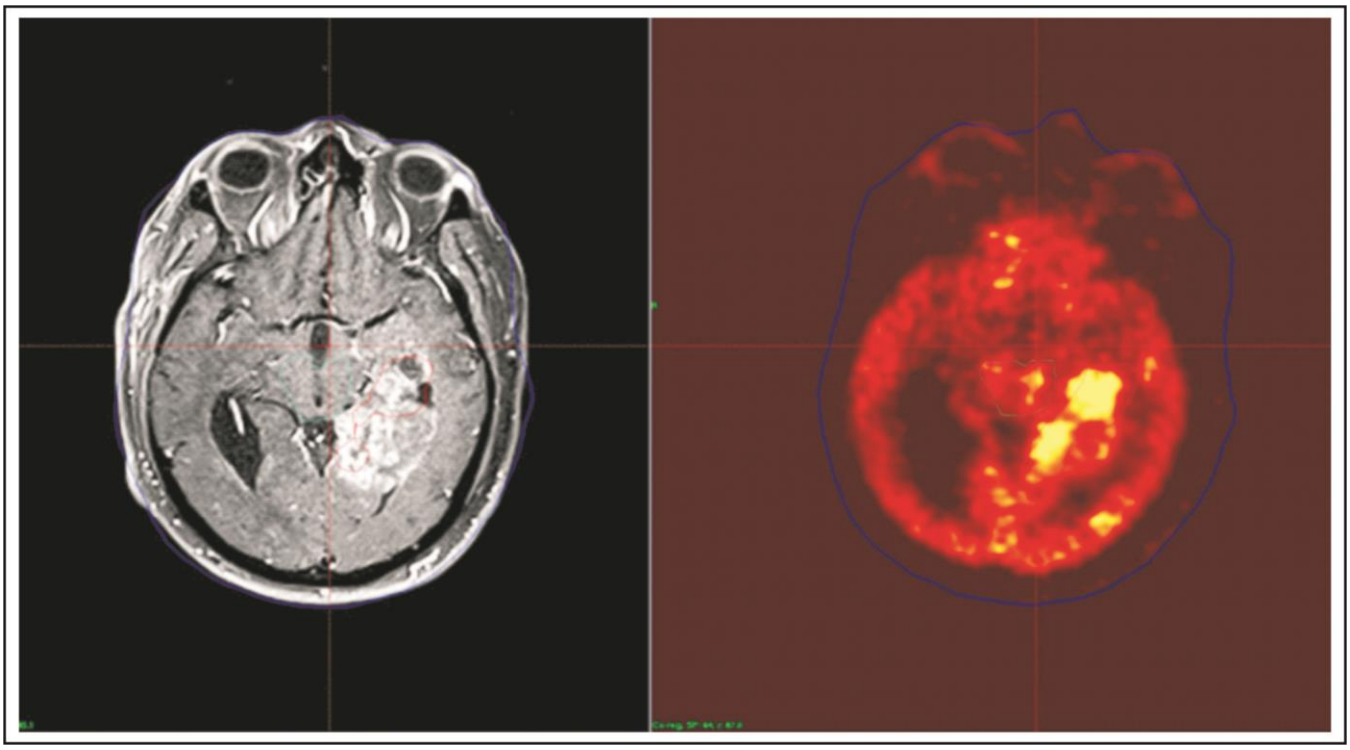

Figure 2: Showing a 52-year-old gentleman scan who had left temporo-occipital GBM, PER-CT guided planning of the lesion was done covering only the active area of the tumor10Gy men margin dose was given. (Images used with patient's permission).

with an MRI brain with contrast, one can exclude areas of radiation necrosis. The low side effects profile of Gamma radiation makes it a safe option. A study was conducted to assess the improvement in failure rates through PET-guided targeting, but the results did not meet expectations due to the inclusion of a large volume of tumors and low KPS scores in the study participants. Nonetheless, patients tolerated the procedure well as compared to redo surgery, which is less well-tolerated than GKRS The study found that the median age was 50 years, which is similar to the age range found in some Asian studies, where it was around 49-50 years. This similarity may be attributed to the fact that the regional areas studied were similar, although it could vary in different regions worldwide.[18,19]

Studies have demonstrated an association between age and survival rates, indicating that older individuals have a lower chance of survival compared to younger ones. Additionally, the role of KPS (Karnofsky Performance Status) has also been considered.[20] However, our study divided participants into two categories: those aged under 50 and those aged over 50, and found that age did not significantly affect outcomes. It is possible that this lack of effect was due to the relatively small sample size of patients and that with a larger sample size, any differences between the age groups may have become more apparent.

A regional study found that patients with a KPS score of less than 70 had a median survival rate of 6.3 months, while those with a KPS score of 70 had a median survival rate of 8 months.[21] Another study reported a median survival rate of 8.8 months for patients with a KPS score greater than or equal to 70, and 6.7 months for patients with a KPS score of less than 70.[22] Additionally, Tan AC.[23] Another study reported a good median survival rate for patients with a KPS score greater than or with aggressive multimodality management with substantial efforts exploring

immunotherapy, therapeutic options, and precise oncology approaches, compared to these studies, our study revealed a survival rate of 16 months for patients with a KPS score greater than 70 and 8 months for those with a KPS score of less than 70.

Our research found that there was no significant impact on survival outcome based on when the post-operative radiation was given, either within 30 days or after 30 days. Similarly, another study of 161 patients with GBM found no difference in overall survival or PFS between those who received radiation therapy more than 28 days after surgery compared to those who received it less than 28 days after surgery. Another study by Loureiro et al, also reported similar results, with no impact on overall survival as a result of radiation therapy. Overall, these studies suggest that the timing of radiation therapy after surgery may not be a critical factor in determining survival outcomes.[24,25]

The use of amino-acid PET in tumor metabolism assists in identifying high- and low-grade brain lesions without disrupting the blood-brain barrier breakdown. As a result, it is a supplementary tool to brain MRI imaging, which is presently considered the gold standard. Moreover, research has employed amino-acid PET for diagnostic purposes, as well as monitoring treatment and assessing the prognosis of patients with brain metastasis and high-grade gliomas.[26]

LIMITATIONS

The study can be expanded by adding more patients and increasing its scope. To observe the impact on overall survival and tumor-free duration, a multicenter study can be conducted.

CONCLUSION

Our study suggests that Gamma Knife radiosurgery is a commonly used method for treating r-GBM as part of a multimodal approach. PET-CT-MRI co-registration can more accurately plan treatment, focusing solely on the active tumor and avoiding damage to healthy brain tissue. This approach may result in improved outcomes, survival rates, reduced brain swelling, and better Karnofsky Performance Status scores. While age, Karnofsky score, surgical resection, concurrent chemotherapy, and adjuvant chemotherapy play pivotal roles in the outcome.

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Additional Information

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Human Subjects: Consent was obtained from all the patients/participants in this study.
Conflicts of Interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:
Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Zaheen Shibli	1. Study design and methodology, Data collection and calculations.
2.	Aurangzeb Kalhoro	2. Paper writing.
3.	Kashif Ahmed	3. Analysis of data and interpretation of results.
4.	Abdul Sattar M. Hashim	4. Literature review and referencing, Editing and quality insurer.