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Early Gamma Knife Therapy (Without EBRT) in Operated Patients of Glioblastoma Multiforme

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Abstract

Background: The standard therapy for glioblastoma (GBM) has been external beam radiotherapy (EBRT) with concomitant temozolomide (TMZ) given for six cycles, after maximum possible surgical resection although recurrences after chemoradiation are mostly in-field. **Objective:** To compare the effects of early GKT (without EBRT) along with TMZ to those receiving standard chemoradiotherapy (EBRT + TMZ) after surgery. **Methods:** This was a retro-prospective study on histologically proven GBMs operated at our center between January 2016 and November 2018. The EBRT group consisted of 24 patients who received EBRT + TMZ for six cycles. The GKT arm consisted of 13 consecutive patients who received Gamma Knife within 4 weeks of surgery along with lifelong temozolomide. Patients were followed up every 3 months with CEMRI brain and PET-CT. The primary endpoint was overall survival (OS) with progression-free survival (PFS) being the secondary endpoint. **Results:** At a mean follow-up of 13.7 months, the median overall survivals in GKT and EBRT groups were 11.07 and 13.03 months, respectively (HR = 0.59; *P* value = 0.19; 95% CI: 0.27-1.29). The median PFS for GKT group was 7.03 months (95% CI: 4.17-17.3) as compared to 11.07 months (95% CI: 5.33-14.03) for the EBRT group. There was no statistical difference in the PFS or OS between the GKT and EBRT groups. **Conclusion:** Our study shows that Gamma Knife therapy (without EBRT) to residual tumor/tumor bed after primary surgery with concurrent temozolomide has similar progression-free (PFS) and overall survival (OS) rates when compared to conventional treatment (EBRT).

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Full Text

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor constituting 45.2% of all malignant central nervous system (CNS) tumors and 80% of all primary malignant CNS tumors.[1] It leads to 225,000 deaths per year in the entire world with an incidence of 5 per 100,000 persons.[2] These tumors are generally highly infiltrative and relatively resistant to conventional therapies, such as surgery, radiation therapy, and chemotherapy resulting in rapid progression and fatal outcomes, and typically resulting in death within the first 15 months after diagnosis.[3]

The current standard of care following maximal safe resection is fractionated external beam radiation therapy (EBRT) delivering 60 Gy in 30 fractions with concurrent temozolomide (TMZ) (and subsequently for 6 months).[4],[5] However, long-term efficacy of temozolomide of up to 8 years in GBM has also been reported by some authors.[6–9]

Regardless of initial treatment, recurrences predominately occur in-field, i.e., at the site of the initial tumor[10–15] and more specifically within a 2 cm border of the original tumor following excision and radiation therapy.[12] Despite this, current studies on stereotactic radiosurgery (SRS) in GBMs continue to give EBRT primarily and use SRS only as a boost.[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26] Interestingly, no study compares the effects of early GKT (without EBRT) along with TMZ to those receiving standard chemoradiotherapy (EBRT + TMZ) in the management of GBM.

In this study, we aim to assess the role of SRS with concomitant TMZ and compare it to the standard therapy in the treatment of GBM.

Methods

This was a retro-prospective study on consecutive patients of histologically proven GBMs who were operated on at our center from January 2016 to November 2018. Permission was taken from the institute ethics committee and appropriate consent was taken after informing the patients about the procedure and its deviation from the standard of care before enrollment in the study. The GKT (Test) group consisted of consecutive patients who underwent surgery from May 2016 to May 2017 and received GKT within 4 weeks of surgery with concomitant TMZ which was continued lifelong. The EBRT (Control) arm consisted of patients who underwent surgery from January 2016 onward and who received EBRT at variable periods after surgery. Only patients with Karnofsky performance status of 50 or more were included in the study. Patients with recurrent GBMs or who were operated on outside our institution were excluded. All patients in both groups were followed till 30 November 2018. Data were analyzed using appropriate statistical tests (STATA: Software for Statistics and Data Science.). The control group (EBRT + TMZ) patients were historical controls, and hence, were retrospectively analyzed. The test group patients (GKT + TMZ) were followed prospectively.

All patients enrolled had their demographic data, medical history, and examination findings recorded. Tumor volumes were calculated on CEMRI using the Gamma Plan software (Leksell GammaPlan - Elekta) using the formula (LxBxH)/2.[27] All patients underwent maximal excision of the tumor and had standard postoperative care.

EBRT + Chemotherapy (Control arm)

EBRT was given as a total of 60 Gy in 30 fractions of 2 Gy each along with concurrent temozolomide (75 mg/m2) and adjuvant chemotherapy for 6 months (150 mg/m2; 5 consecutive days per month; six cycles). The tumor volumes were calculated on CEMRI using the formula (LxBxH)/2.

Gamma Knife therapy (Test arm)

GKT was given within 4 weeks (8-32 days) after surgery on the Perfexion® system (Elekta, Stockholm) to the residual tumor + tumor bed. The area targeted for GKT included the contrast-enhancing region (i.e., the tumor) along with the tumor bed (i.e., the tumor seeding area). The tumor bed was defined as a hyperintense area around the resection margin on T2/FLAIR MRI[28] [Figure 1]. The prescription dose (at 50% isodose line) was kept at 18 Gy unless contraindicated. {Figure 1}

Chemotherapy in GKT arm (Test arm)

The dose of temozolomide was 150 mg/m2, 5 consecutive days per month for as long as the patient lives (if no toxicity).

Follow-up

The patients were followed up every 3 months and evaluated clinico-radiologically with contrast enhanced MRI brain and PET-CT wherever required.

Outcome evaluation

The primary endpoint was overall survival (OS) with progression-free survival (PFS) being the secondary endpoint.

Results

A total of 145 patients with high-grade gliomas were enrolled for the study during the study period [Figure 2]. Of these, 106 (73.1%) patients were found to have GBM histopathologically; 13 patients received Gamma Knife + concurrent temozolomide therapy [Table 1] and 93 patients received EBRT + temozolomide therapy. Out of these 93 patients, 69 (74.2%) did not receive/complete the EBRT + TMZ. So, a total of 24 patients comprised the EBRT group.{Table 1}{Figure 2}

The pre-radiation demographic details of the patients were analyzed and found to be matching except for the interval

between the surgery and radiation therapy [Table 2].{Table 2}

The various histopathological and immunohistochemistry (IHC) characteristics were also compared between the two groups and the groups were found to match.

The mean interval between the surgery and the start of radiation therapy in GKT and EBRT groups were 19 and 58 days, respectively (P-value: 0.013).

The median gap between surgery and the start of chemotherapy was 17 days (range 8 – 32 days) in the GKT group. It was continued lifelong [median duration of 11.07 months (range 5.03-20.83 months)]. One patient had nausea and vomiting which was controlled by increasing the dose of antiemetics. No other toxicity was seen in any of the patients in the GKT group.

Follow-up

The mean follow-up in the GKT and EBRT groups was 12.09 +/- 7.74 and 14.5 +/- 8.27 months, respectively. Out of the 13 patients in the GKT group, 11 patients had progression of the disease and died during follow-up and 2 patients were found to be having a stable disease. In the EBRT group, all 24 patients were included in the analysis for OS; 15 of the 24 patients died of disease achieving OS; 7 patients did not have interval MRI scans to calculate PFS, although their overall survival data were available.

The median PFS for patients in GKT group was 7.03 months (95% CI: 4.17-17.3) as compared to a median of 11.07 months (95% CI: 5.33-14.03) in the EBRT group (HR = 0.73; P value = 0.45; 95% CI: 0.32-1.64). The median OS for patients in the GKT group was 11.07 months (95% CI: 5.03-20.83), while that for the EBRT group was 13.03 months (95% CI: 9.9) (HR = 0.59; P value = 0.19; 95% CI: 0.27-1.29).

Nine patients in the EBRT group did not receive EBRT within the recommended 6 weeks of surgery and the remaining 13 patients received EBRT within 6 weeks of surgery. Of these 13 patients, 3 were lost to follow-up and 6 had progression of the disease at the last follow-up.

The median PFS for patients who received EBRT within 6 weeks was 12.03 months (95% CI: 2.77). (HR = 0.55; P value = 0.25; 95% CI: 0.2-1.5). The median OS for patients who received EBRT within 6 weeks was 18.6 months (95% CI: 7.47) (HR = 0.39; P value = 0.07; 95% CI: 0.14-1.08) [Figure 3].{Figure 3}

The median OS for patients receiving EBRT after 6 weeks of surgery was 11.67 months (95% CI: 4.63- 16.07), which was not statistically significant between the two groups (HR = 2.49; P value = 0.09; 95% CI: 0.87-7.17).

All patients with progression were offered EBRT but some patients refused while others were on the waiting list for EBRT in the radiotherapy department. One patient (Patient 1) agreed to repeat GK after progression and ultimately had an OS of 25.87 months.

[Figure 4] shows a patient from the GKT/TMZ group who showed no residual tumor at 2 years of follow-up as the PET scan showed no FDG uptake.{Figure 4}

Discussion

Until the mid-2000s, radiotherapy was the established standard for the treatment of newly diagnosed GBM. Clinical trials of patients receiving radiotherapy (EBRT) for GBM led to a doubling of overall survival (OS) compared with patients who did not receive EBRT.[29] Results of phase III clinical trial by the European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC) in 2005 led to a new treatment standard for newly diagnosed GBM: the addition of temozolomide given concurrently with EBRT and continued for 6 adjuvant 5-day monthly cycles.[4] The co-administration of TMZ improved survival from 12.1 months (with EBRT alone) to 14.6 months (with the addition of TMZ).[4] Stupp et al.[4],[5] first described the benefits of using temozolomide as adjuvant chemotherapy in the treatment of GBM. Since then, different regimens have been proposed by different authors without standardization of treatment duration. As long as 8 years of chemotherapy with temozolomide have been reported without any serious side effects. [6],[7],[8],[9] In our study, we have given temozolomide therapy to the GKT group for life (median duration of 11.07 months) with no apparent toxicity.

Various studies have also used stereotactic radiosurgery as a booster regimen along with EBRT to treat primary GBM after primary surgery and achieved median OS in the range of 9.5-28 months.[16],[17],[18],[19],[20],[21],[22],[23], [24],[25],[26] This is despite a wide body of knowledge showing that recurrences predominately occur in-field, i.e., at the

site of the initial tumor,[10],[11],[12],[13],[14],[15] and more specifically, within a 2 cm border of the original tumor following surgery and EBRT.[12] Given this finding, single fraction GKT can be a compelling alternative to standard EBRT with all the attendant benefits of single fraction for the patient and families. As there are no trials that compare the effects of early GKT (without EBRT) along with TMZ to those receiving standard chemoradiotherapy (EBRT + TMZ) in the management of GBM, we designed this study using a higher dose of concentrated radiation (with reduced exposure to normal-brain parenchyma) in a single session within 4 weeks of primary surgery along with concurrent chemotherapy and saw its effect on the progression and overall survival. In comparing with patients receiving standard EBRT + TMZ, no statistical difference was found in the OS or the PFS between the two groups. This means that the median survival that is achieved by conventional EBRT + TMZ can also be achieved by giving single-fraction stereotactic radiosurgery (without EBRT). In this study, we further segregated patients who received EBRT + TMZ within 6 weeks of surgery or after 6 weeks of surgery. Interestingly, although the numbers were small, there was no statistical difference in OS and PFS when compared to the GKT group. Case 10 was a unique case with aggressive growth post-surgery resulting in residual volume (87.1) greater than the preoperative volume (62). It could be because of IDH wildtype and p53 positivity that the tumor showed aggressive growth in the immediate postoperative period.

Glioblastomas are aggressive, fast-growing brain tumors. Their rapid growth makes many patients and their families as well as their physicians aspire to immediate adjuvant treatment after surgery. It has been convincingly proven that EBRT should be started within 6 weeks of surgery.[29] However, because of the immense pressure on the radiotherapy department at our institute, the wait time for EBRT for patients with GBM's frequently exceeds the recommended period, so some patients (n = 3) with large residual volumes were offered GKT after getting prior appropriate consent. In our study also there was a trend toward improved survival in patients who received EBRT within 6 weeks (18.6 months) as compared to those who received it later (11.67 months), although it did not reach statistical significance. With the availability of single-fraction radiosurgery, it can be argued that ultra-early GKT (within 1-2 weeks of surgery) may further improve the outcome. Although, we could find no studies in this regard with GKT, Blumenthal et al.[30] have shown that EBRT given within 4 weeks or between 4 and 6 weeks does not matter as there was no statistically significant difference in OS after adjusting for known prognostic factors.

IHC and its effects on survival

IDH wild-type GBM has the poorer prognosis as compared to the mutant type.[31] The p53 mutation in glioblastomas is associated with a poorer prognosis which also decreases the chemosensitivity of GBM to temozolomide by increasing the MGMT expression.[32] The ATRX loss defines a subgroup of astrocytic tumors with a favorable prognosis.[33] Due to the small number of patients in our study, we combined both the GKT and EBRT groups and compared the median survivals in the various subgroups. We did not find any significant difference in the median survivals in the p53 and IDH subgroups. However, the ATRX loss group had better survival than the ATRX retained group (P: 0.023) which agrees with the study done by Holland-Letz et al.[33]

There are some limitations in this study. The sample size in this study is small. EBRT + TMZ (6 cycles) was given by the radiotherapy department whereas GKT + TMZ (lifelong) was given by the neurosurgery department. Both follow different protocols for TMZ. This is an independent confounding factor. As the EBRT group was followed retrospectively, the postop MRIs of patients were not available. So, the residual volumes could not be calculated for the EBRT group. However, because of delay (mean interval from surgery to EBRT being 8.3 weeks), it is possible that the residual tumor sizes may have increased in the EBRT group. Only 24/93 (25.8%) patients undergoing EBRT could complete all the radiotherapy fractions and six TMZ cycles. This is a telling statement on the practical issues faced by patients undergoing EBRT at our institute. We believe that single-fraction GK scores hugely over EBRT with respect to treatment compliance in our setting.

Conclusions

This is the first study of its kind on the role of Gamma Knife therapy (without EBRT) in patients with GBM. Our study shows that Gamma Knife therapy to residual tumor/tumor bed after primary surgery (without EBRT) with concurrent temozolomide has similar progression-free (PFS) and overall survival (OS) rates when compared to conventional treatment (EBRT).

Gamma Knife therapy may have the added advantage of single-session stereotactic radiotherapy and minimal radiation exposure to the normal brain. Gamma Knife therapy (within 4 weeks) is a safe and feasible option in our setting.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but

anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Figure 1: The residual tumor was delineated as enhancing portion on axial sections of CEMRI brain (in the posterior part of resection cavity) (a) and as a hyperintense region around the residual tumor (Tumor bed) on T2W images (b) on the Gamma Plan software

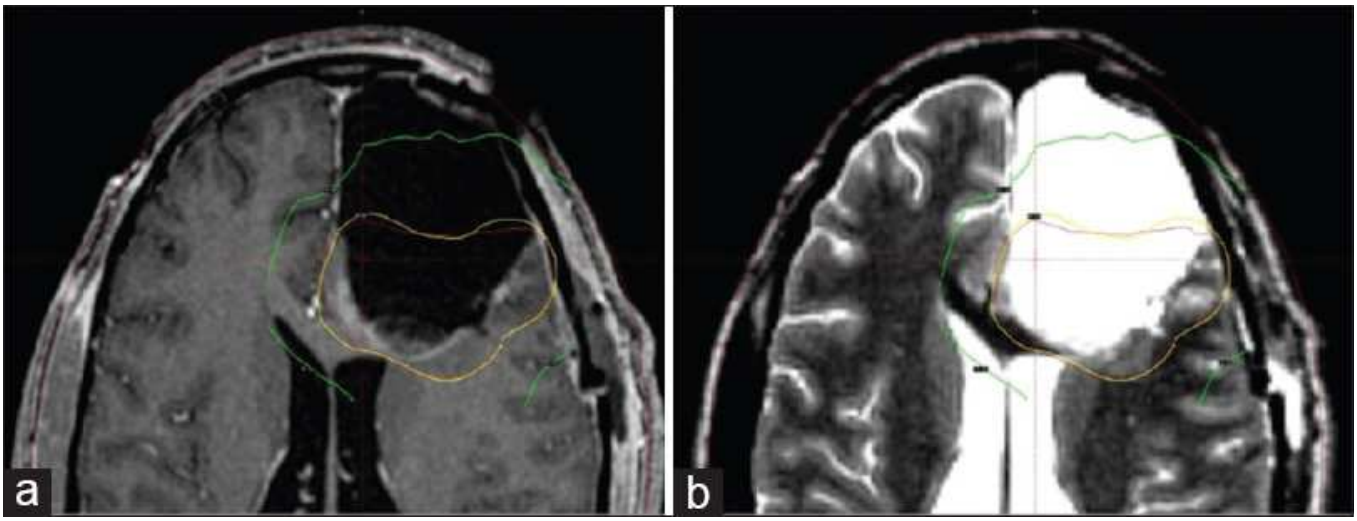

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Figure 2: Details of the patients enrolled in the Gamma Knife + Temozolomide group and EBRT + Temozolomide group

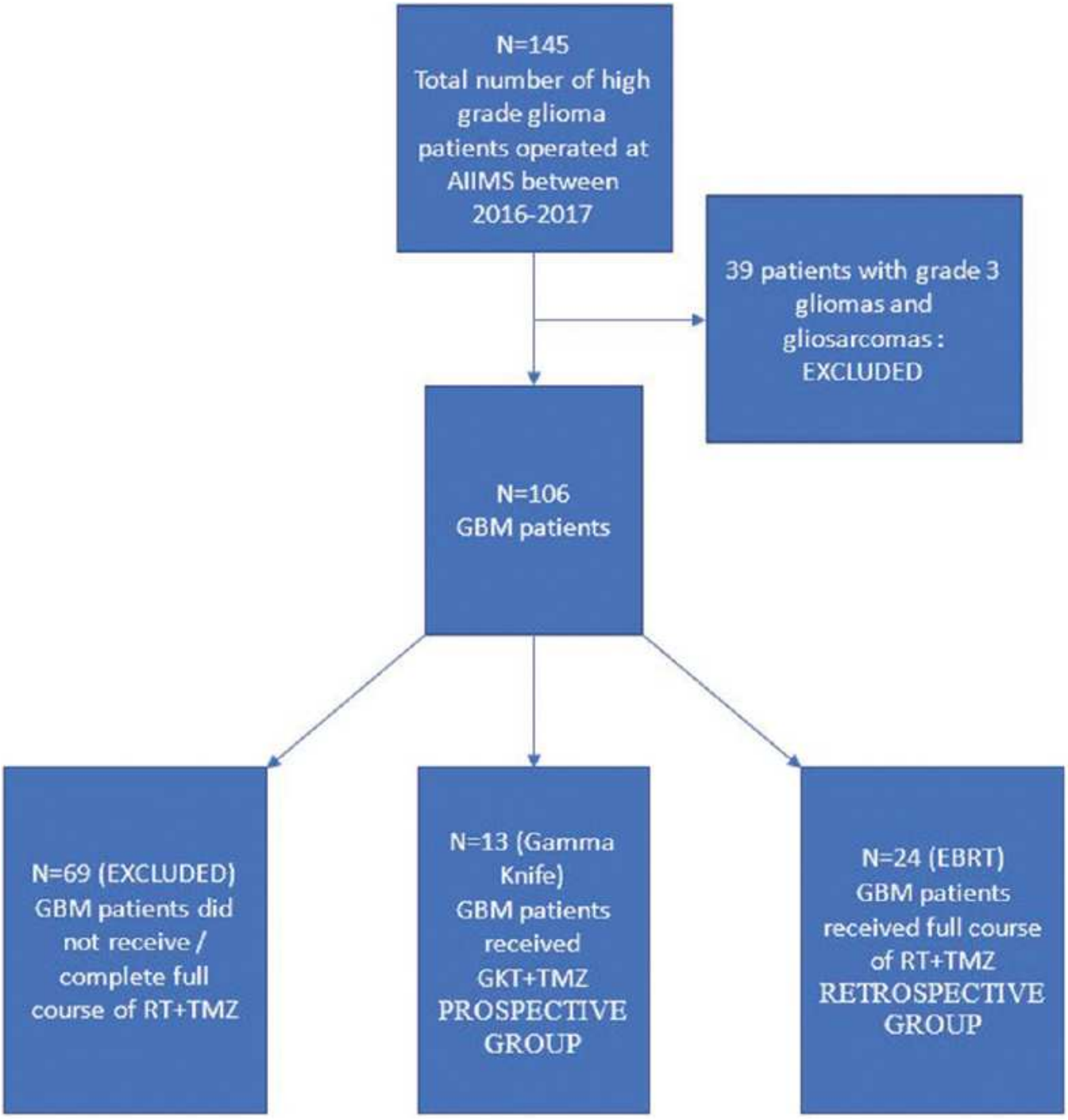

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Figure 3: The Kaplan–Meier curve comparing the progression-free survival (a) and overall survival (b) between the GKT and EBRT groups. Kaplan–Meier curve comparing the progression-free survival (c) and overall survival (d) between the GKT + TMZ and RT + TMZ groups when radiation was started within 6 weeks of primary surgery

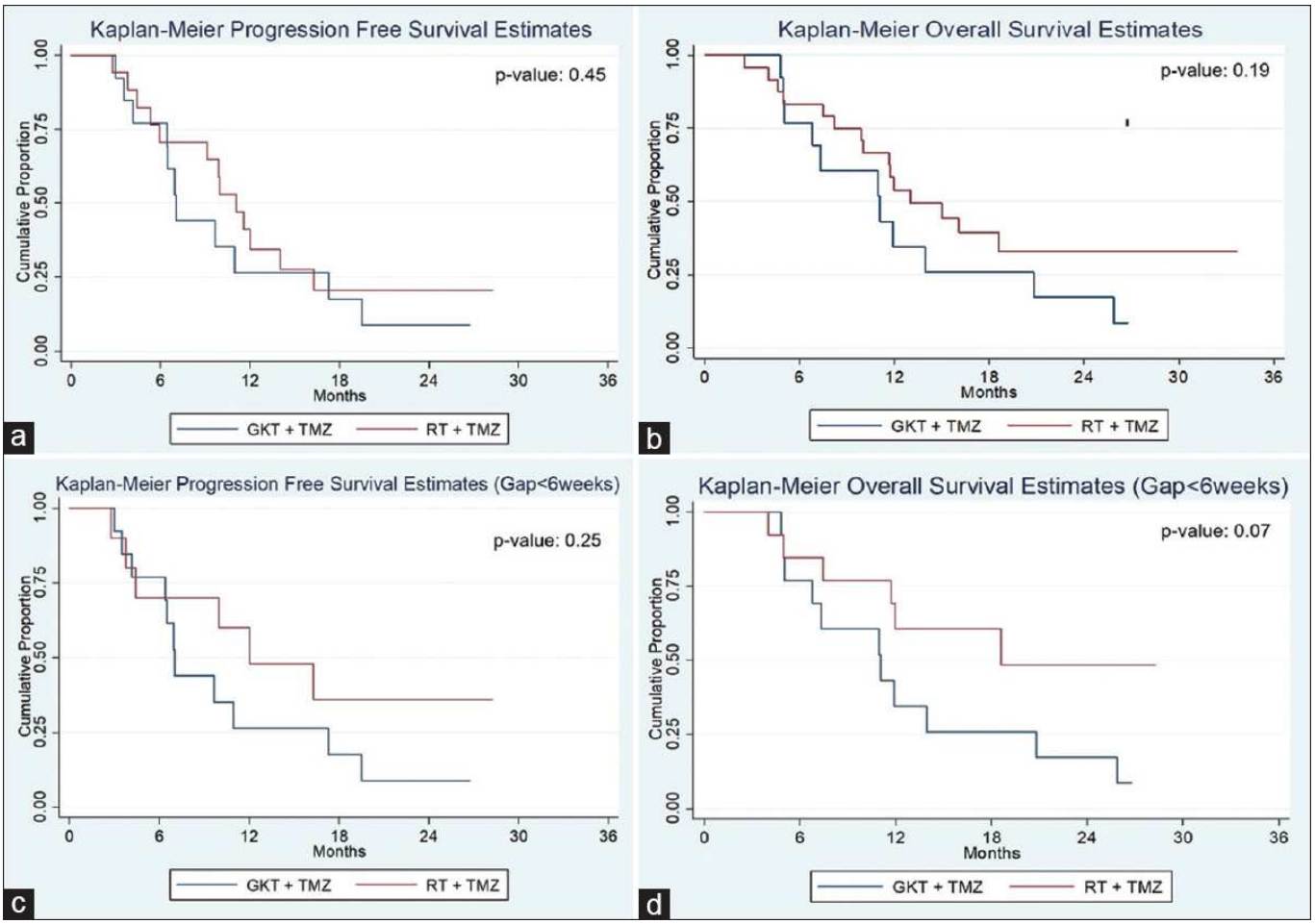

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Figure 4: (Patient 5 from Table 2) (a) Preop CEMRI brain axial section showing a large left frontal GBM. (b) Pre-GKT CEMRI showing left frontal resection cavity with residual tumor. (c and d) CEMRI at 6 months and 1 year showing complete resolution of the tumor, respectively. (e) CEMRI at 2 years showing radiation necrosis as confirmed by PET-CT (f) which is showing no FDG uptake

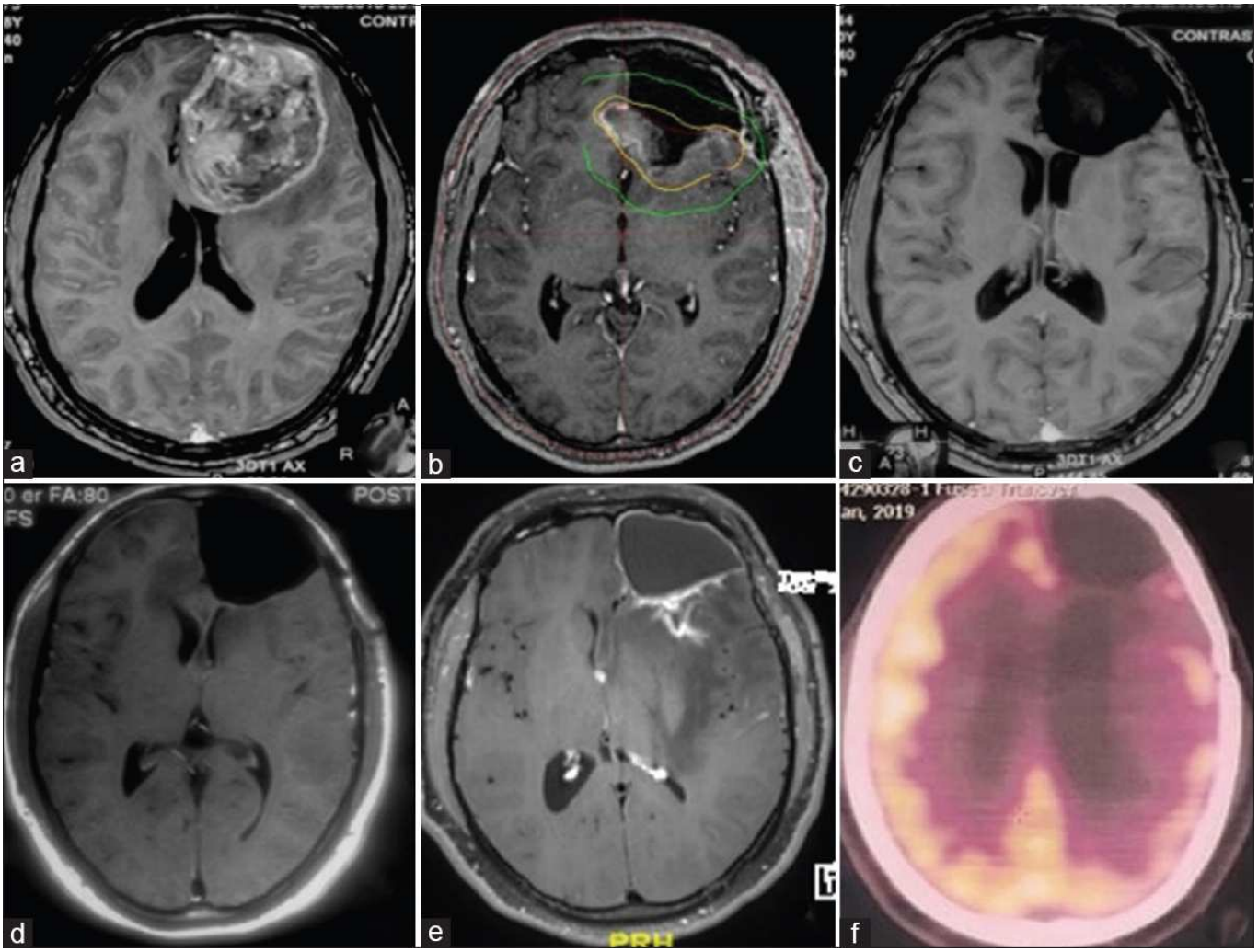

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Table 1: Details of all patients with GBM in the Gamma Knife therapy + temozolomide group

Patient	Age (yrs)	Sex	Pre-GKT KPS	Preop Volume (cc)	Residual Volume (cc)	IDH	ATRX	MIB%	P53	Gap b/w Surgery and GKT (days)	Radiation dose (50% isodose) (Gy)	Progression Free Survival (Months)	Overall Survival (Months)	Additional comments
1	57	M	90	80.8	22	Wild	Retained	30	Positive	13	18	19.5	25.87	Redo GKT after recurrence
2	58	F	70	163.5	69.74	Wild	Retained	10	Negative	15	20	4.17	5.03	
3	28	F	80	72.93	34.4	Wild	Retained	18	Negative	22	20	3.53	4.8	
4	53	M	70	43	Rim only	Wild	Retained	15	Negative	17	20	7.03	10.97	
5	19	M	90	114.6	3	Wild	Retained	12	Negative	15	20	None	Alive	
6	25	M	50	82.6	8.7	Wild	Lost	4	Negative	30	20	17.3	20.83	
7	34	F	90	24	Rim only	Wild	Retained	60	Negative	15	25	6.43	7.33	
8	33	M	70	65	20.58	Mutant	Retained	65	Positive	30	20	6.97	11.9	
9	60	M	70	40.7	21.09	Wild	Retained	45	Positive	24	20	10.97	13.93	
10	45	F	70	62	87.1	Wild	Retained	35	Positive	8	20	3	5	2 Fractions of GKT
11	50	M	70	134	Rim only	Wild	Retained	20	Positive	18	25	9.67	11.07	
12	47	F	90	14.9	6.04	Wild	Retained	14	Positive	32	25	6.5	6.8	
13	61	F	80	36.4	Rim only	Wild	Retained	20	Positive	9	25	None	Alive	

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Table 2: Characteristics of both the groups

Variable	GKT/TMZ	EBRT/CT	P
Age (years) Mean	43.8 +/- 14.4	44.4 +/- 14.2	0.91
Sex	7 Males 6 Females	Males 18 Females 6	0.19
Preop KPS Median	70 (50-90)	70 (30-90)	0.89
Pre-radiation KPS Median	70 (50-90)	70 (40-90)	0.17
Preop Volume (cc) Median	65 (14.9-163.5)	40 (5-107.7)	0.058
MIB (%) Median	20 (4-65)	15 (1-70)	0.70
Gap b/w surgery and start of radiation (Days) Median	17 (8-32)	47 (17-259)	0.0002
Gap b/w surgery and start of radiation (Days) Mean	19.08 +/- 7.93	58.05 +/- 52.73	0.013