

A Comparison of Fluro-Deoxy Glucose-Positron Emission Tomography (FDG-PET) Versus Magnetic Resonance (MR) Based Target Volume Delineation in Post-operative Glioblastoma

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Abstract

Background: Glioblastoma is the commonest brain tumor of adults carrying a very poor prognosis. Targeting the tumor accurately during surgery and radiotherapy holds promise in future. PET with various tracers is being explored worldwide to enhance the accuracy of target delineation. This study was undertaken to evaluate the differences and correlation between the target volumes delineated by using MRI and 18F-FDG PET during RT planning and to evaluate whether inclusion of PET is helpful in better coverage of high risk area for recurrence.

Materials and Methods: Fifteen post-operative patients of glioblastoma were prospectively enrolled. Planning images were acquired with CT, MRI and delayed PET. Image fusion was done to delineate MR-based (GTV-MR, CTV-MR, PTV-MR), PET-based (GTV-PET, CTV-PET) and combined (GTV-X, CTV-X) volumes. Only MR-based volume was used for actual treatment. Mean volumes were calculated for each group for volumetric analysis.

Concordance Index (CI) was calculated for GTV and CTV as $CI = [(M + P)/X] - 1$, to find correlation between volumes, such that full concordance and full non-concordance between MRI and PET volumes would yield a value of 1 and 0 respectively.

On recurrence, the recurrent volumes (rVol) were marked and correlated with initial CTV-MR, CTV-PET and CTV-X to calculate the proportion of rVol covered within these volumes.

Observation and Results: Mean GTV-MR, GTV-PET and GTV-X were 84.4 cc, 11 cc and 89.2 cc, respectively. Median follow-up was 16.6 months for the overall group and 26.1 months for the surviving patients. Overall 1,2 years survival was 80% and 20% respectively.

Conclusion: Inclusion of PET-based abnormality while delineating the target volumes for glioblastoma leads to a non-significant increase in target volumes with better coverage of the high-risk region. Thus, targeting the common volume (CTV-X) for treatment may prove beneficial in avoiding marginal recurrences in glioblastoma.

Keywords: FDG-PET; Glioblastoma; MRI; Radiotherapy; Target delineation

Introduction

Glioblastoma is the commonest primary tumour of adult brain carrying an exceptionally poor prognosis [1]. The mean age at diagnosis is 61 years and males are more frequently affected than females, with a sex ratio of 3:2 [2]. Over the last few decades, radiotherapy (RT) has been shown to prolong survival in glioblastoma patients but unfortunately these patients progress within the treated field [3-5]. Using traditional dose of 6000 centiGray (cGy), approximately 80% of failures occur “centrally,” i.e. within 2 cm of the gross tumor [5,6]. Despite dose escalation trials, local failure in the high-dose region continues to be the primary mode of failure [7].

Addition of concurrent and adjuvant temozolomide (TMZ) resulted in improved 2-year survival of newly diagnosed malignant glioma (mainly glioblastomas) from 11% to 27%, and 5-year survival from 2% to 10% but patients still continue to develop local failures [8]. Thus, there is a huge unmet need for further intensification of local therapy in conjunction with TMZ.

Modern RT techniques like stereotactic radio-surgery (SRS), stereotactic fractionated radiotherapy (SFRT), intensity-modulated radiotherapy (IMRT), and proton therapy have potential to precisely treat the targets to a higher doses but for this to succeed, the first requirement is to define the correct tumor boundaries. Currently, magnetic resonance imaging (MRI) is the gold standard in defining target volumes for brain tumors. The area of enhancement on T1-weighted (T1W) MRI is used to define the gross tumor volume (GTV) although it is not a fool-proof methodology. Several studies have shown

that contrast enhancement on MRI may not represent the exact tumor boundaries as infiltrating glioma cells can be identified beyond the enhancing area [9]. Contrast enhancement is a nonspecific sign of blood-brain barrier disruptions [10] and is influenced by multiple factors like changing steroid dose, antiangiogenic agents, changing radiologic techniques etc. [11]. Moreover, enhancement can be induced by treatment-related inflammation, seizure activity, postsurgical changes, ischemia, subacute radiation effects, and radiation necrosis [12]. Thus, it is imperative to develop imaging methods that view tumor entirely and measure molecular pathologic processes within it [13].

Positron Emission Tomography (PET), using diverse radio-labelled compounds is being used for over two decades to characterize the tumour on a metabolic and molecular basis [14]. [F-18]-fluorodeoxyglucose PET (18F-FDG PET) has been postulated to be more accurate for determining target volumes for various tumors. Interestingly, imaging of brain tumors with 18F-FDG PET was the first oncologic application of PET [15]. Goldman et al. determined that areas of increased 18F-FDG PET activity corresponded well to biopsy-proven anaplastic tumor [16]. Likewise, high PET uptake in a previously known low-grade tumor suggests anaplastic transformation [17]. FDG uptake correlates with tumor grade and aggressiveness, and the level of FDG uptake in primary brain tumors can predict survival as well [16-18]. Alavi et al. found that 18F-FDG PET was predictive of survival in high-grade gliomas, with patients having hypermetabolic lesions surviving a mean of 7 months, versus 19 months for patients with hypometabolic lesions [19].

Recently, studies have demonstrated some limitations of 18F-FDG PET while using them for studying brain tumors [20]. Because of the high rate of physiologic glucose metabolism in brain tissue, the delineation of tumors with modest increases in glucose metabolism (low-grade and some recurrent high-grade tumors) is difficult, leading to a decreased specificity [20]. It is not clear which threshold value for the tumor/normal tissue should become the reference value for determining tumors although some reports have suggested a threshold value of 1.3 to 1.7 [21]. Another difficulty with 18F-FDG PET is that postsurgical changes around the resection cavity can exhibit tracer uptake because of inflammation or 18F-FDG leakage caused by disrupted blood brain barrier.

In due course of time, various strategies have been developed to overcome these limitations of 18F-FDG PET. Co-registration of PET images with MR images is one such method which improves the performance of 18F-FDG PET, and it is now a standard practice to have the MR images available while interpreting PET data [22]. Because MRI has high sensitivity but poor specificity, it should be studied first as a screening test [22]. A recent study showed that 18F-FDG imaging 3-8 hours after tracer injection can improve the distinction between tumor and normal gray matter [23]. It is based on the hypothesis that glucose excretion from the normal brain cells is increased when the interval between 18F-FDG administration and data acquisition is extended. This excretion is higher in normal brain than in tumor cells, so tumor cells retain 18F-FDG for a longer duration resulting in improved tumor delineation on delayed images [15]. This phenomenon is attributed to increased rate of dephosphorylation of FDG-6-phosphate in tumor cells relative to the normal brain at delayed time. Multiple studies are available to assess the utility of 18F-FDG PET in target volume delineation but there is paucity of data on the use of delayed PET for this purpose, mainly from the eastern part of the world. As 18F-FDG PET is now available

in India, there is a need to explore its utility in improving outcome of diseases like glioblastoma.

Recently, it has been suggested that amino acid tracers, like 11C-methionine (11C-MET), 18F-fluoroethyltyrosine (18F-FET), and 3,4-dihydroxy-6-(18)F-fluoro-L-phenylalanine (18F-FDOPA) are more useful for imaging brain tumors than 18F-FDG because of their higher uptake in tumor tissues compared to normal brain, giving a better contrast between them [24-28]. Among these tracers, 11C-MET has been most widely studied. However, due to its short half-life, its applicability is limited to facilities with on-site cyclotrons. Thus, it has not achieved a widespread utility in neuro-oncology more-so in developing parts of the world.

The current study is a prospective trial using 18F-FDG PET as a metabolic marker of malignant regions while determining target volumes for RT. A comparison of target volumes between those determined by PET and MRI was done followed by correlation between these volumes and the site of subsequent failure. We hypothesised that PET-based target volumes are different from MRI-based volumes and PET identifies additional foci of active tumor which remains unidentified by MRI alone. These foci remaining obscure on MRI may act as the source for subsequent treatment failure. The idea was to quantitatively assess the advantage of PET in terms of better coverage of high-risk volume and decreased risk of recurrence.

Material and Methods

This study was conducted at a tertiary care hospital from August 2010 through June 2014. Fifteen patients were enrolled in this study after approval from the Institutional Review Board and independent Ethical Committee. The trial was registered with ClinicalTrials.gov, number NCT01083719. Eligibility criteria included histologically confirmed glioblastoma, age above 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0-3. Exclusion criteria included multifocal or recurrent gliomas, and history of diabetes, contrast allergy or prior RT. Informed consent was obtained from each patient before enrolment. Thereafter, each patient underwent clinical work-up and routine blood investigations. Patient underwent thermoplastic cast fabrication for immobilization before simulation scans.

PET-CT was performed on a 64 slice lutetium oxyorthosilicate (LSO) based scanner (Siemens Biograph mCT). The patients fasted for at least 4 hours before the study. After blood glucose measurement (glucose between 60-150 mg/dL), 185-190 MBq of 18F-FDG was injected. The dose of F-18 FDG was recorded at the time of injection for estimating standard uptake value (SUV). 18F-FDG was procured from source as unit doses having radiochemical purity in excess of 95%. After injection, patients were instructed to wait quietly for about 30 minutes in an isolated room. Patients' head was immobilized in cast and scanning was performed in supine position after placing the fiducial markers. The PET images were acquired in a 3-dimensional single bed position for 10 minutes using corrected output image (TrueXHD PET). Emission data was corrected for attenuation, scatter, and random coincidence and reconstructed iteratively using gaussian filter with 3 iteration and 24 subsets. Image size was kept at 400 with axial resolution of 2 mm.

Contrast CT was obtained in the same position using field of view (FOV) of 300 mm using non-iodinated contrast (Omnipaque) 350

mg/100 ml as per patient's weight. Simultaneous reconstruction was done at 3 mm using filter H195 low dose for ECT.

Delayed PET scan was acquired at 180-360 minutes [22] after radio tracer injection keeping all the parameters same as in the initial scan. The PET images were fused with attenuation corrected CT.

MRI was performed in supine position using 3-Tesla equipment (Magnetron Verio, Seimens). Images were acquired using standard head coil with rigid immobilization. Axial T1-weighted sequences (matrix size, 256x320; FOV, 250 mm) were obtained using gadolinium based contrast medium. The images were acquired from vertex to foramen magnum at 3-mm slice thickness without gap. The T2 weighted images were acquired with a 256x320 matrix and 250 mm FOV.

The acquired images (CT, MRI and PET) were transferred to FOCAL[®] SIM v.4.64 (Elekta, Kungstengatan, Sweden) contouring platform via DICOM (digital imaging and communications in medicine). Simulation CT scan was fused with T1W MRI and delayed PET using FOCAL SIM. It uses rigid registration using "Auto Fusion" algorithm to optimally register corresponding anatomical details in two and three-dimensional study sets of the same patient's anatomy, using a volume of interest function limited to the region of the tumor. The registration criterion is mutual information, i.e. a measure of the statistical similarity of the overlapping data. The "best registration" is the transformation resulting from an optimization process that gives the maximum value of the mutual information.

Target delineation was performed by the radiation oncologist and verified by another radiation oncologist, a nuclear physician and a radiologist. Three set of volumes were contoured as follows:

MRI-based volumes (for treating patient) by fusing planning CT and T1W MRI

GTV-MR: It included resection cavity with residual tumor (Figure 1).

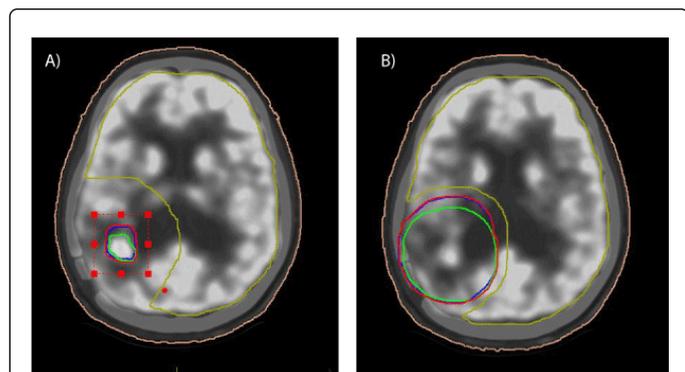


Figure 1: a: Delineation of Gross Tumor Volumes, GTV-MR (Blue), GTV-PET (Green), and GTV-X (Red) on fused image. The GTV-PET is inside GTV-MR yielding CI of 0.05. b: Delineation of respective Clinical Target Volumes, CTV-MR (Blue), CTV-PET (Green), and CTV-X (Red) in the same patient yielding CI of 0.38.

CTV-MR: GTV-MR plus a 2 cm margin all around. The margin was reduced to 5 mm around anatomical barriers such as skull, ventricles, falx etc and to allow for sparing optic nerve/chiasma, if indicated [29] (Figure 2).

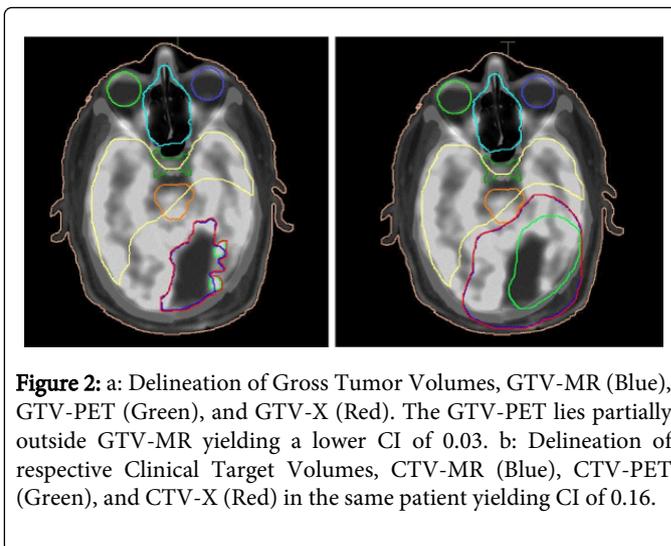


Figure 2: a: Delineation of Gross Tumor Volumes, GTV-MR (Blue), GTV-PET (Green), and GTV-X (Red). The GTV-PET lies partially outside GTV-MR yielding a lower CI of 0.03. b: Delineation of respective Clinical Target Volumes, CTV-MR (Blue), CTV-PET (Green), and CTV-X (Red) in the same patient yielding CI of 0.16.

PTV-MR: CTV-MR plus 5 mm margin all around [29].

PET-based volumes (for experimental purpose) by fusing planning CT and delayed PET:

GTV-PET: Marked as metabolically active tumor volume (MATV) which was contoured using two criteria: a) presence of greater uptake of 18F-FDG than normal white matter (Figure 1). To facilitate this, images were displayed with standard gray-scale windowing with a threshold of 1.5 to normal white matter uptake levels [21] and b) presence of any abnormal 18F-FDG uptake within and adjacent to abnormal region on MRI. Elevated FDG uptake in normal appearing area on MRI away from affected region was considered to be functional rather than tumor.

For lesions with a cold center on PET, contours were drawn to include only the outer rim of increased uptake and to exclude areas with normal uptake. For separate lesions with non-contiguous areas of FDG uptake, non-contiguous contours were drawn, and the tumor volume was taken as sum of these non-contiguous contours.

CTV-PET: GTV-PET plus a 2 cm margin all around respecting anatomical barriers (Figure 2).

PTV-PET: CTV-PET plus 5 mm margin all around.

Combined volumes (for experimental purpose) by combining PET- and MRI-based volumes

GTV-X: It was the volume obtained by combining GTV-MR and GTV-PET and represented the abnormal area using combined modality (Figure 1).

CTV-X: Marked as 2 cm isotropic expansions of GTV-X, cropped to exclude any portion lying outside the brain [8]. It represented the volume that would have been treated by using combined modality (Figure 2).

PTV-X: CTV-X plus 5 mm margin.

PTVs were not considered for volumetric analysis as PTV was just a geometric expansion of CTV and reflected CTV itself with no added information.

Correlation between PET and MRI Volumes

PET based volumes (GTV-PET and CTV-PET) were compared with MRI-based volumes (GTV-MR and CTV-MR) by using a simple ratio between respective volumes.

Volume locations were assessed and the degree of overlap between volumes was determined by calculating Concordance Index (CI) as $CI = [(M + P)/X] - 1$, where M is the MR-based volume, P is PET-based volume, and X is the combined volume encompassing PET and MRI abnormalities.

Complete concordance between P, M, and X, would yield a CI of 1 i.e., $[(1+1)/1] - 1 = 1$. Conversely, complete non-concordance would yield a CI of 0 (i.e., volume P and M would be entirely separate, and thus $[(1+1)/2] - 1 = 0$). For all other possible scenarios, the CI would lie between 0 and 1, with higher values representing greater concordance.

Primary Treatment and Follow-up

Primary treatment included surgery, RT with concurrent and adjuvant TMZ. Patients were treated using IMRT (image guided radiotherapy) to MRI-based target volumes. The dose prescribed to PTV-MR was 5700-6000 cGy in 27-30 fractions with five fractions delivered per week with concurrent TMZ (75 mg/m² daily) from start till last day of RT. Treatment planning was performed using Monaco® v. 3.0 (Elekta, Crawley, UK) planning system.

During RT patients were reviewed weekly with clinical examination and complete haemogram for assessing treatment toxicity as per Radiation Therapy Oncology Group (RTOG) criteria. After RT completion, patients were followed-up after one month with blood investigations and contrast MRI Brain. They were started on adjuvant TMZ (150-200 mg/m²/day) for five days every 28 days for six cycles. An MRI was repeated after third and sixth cycle for response assessment. After six cycles, complete responders were followed up six monthly with contrast MRI brain. In other cases, treatment beyond six cycles was individualized as per the tumor board decision and institutional protocol. In addition, follow-up over phone was continued in case the patient missed his due visits for any reason and this telephonic contact was documented as follow-up. Time to recurrence, last follow-up or overall survival was measured from the date of surgery.

Definition of Response and Analysis of Recurrent/Progressive Cases

Treatment response was defined as per McDonald criteria [30]. Response to primary treatment was assessed on MRI after one month of completing adjuvant TMZ.

Complete response (CR) was defined as disappearance of all enhancing disease with stable or improving neurologic examination, no new lesion and no increase in steroid dose.

Partial response (PR) required all of following: $\geq 50\%$ reduction in sum of products of perpendicular diameters of enhancing lesions, no new lesion, stable/reduced steroid requirement, stable or improved clinically

Stable disease (SD) included presence of condition not qualifying for CR, PR or PD, and stable clinically.

Progressive disease (PD) was defined as greater than 25% increase in the sum of the product of the perpendicular diameters of enhancing lesions, appearance of any new lesion or clinical worsening.

MRI changes occurring 1–3 months following RT in the absence of clinical symptoms or increased need for steroids were followed closely to rule-out pseudo-progression [31]. If subsequent imaging proved progression, the date of progression was the date of scan which first raised this issue [30].

Recurrence was defined as appearance of new lesion in cases showing CR or a separate lesion in those showing PR or SD. Recurrence free survival (RFS) was calculated from the date of diagnosis to the date of MRI suggesting recurrence. At recurrence, salvage treatment was offered in an individualised manner according to the clinical situation and physician's discretion.

In recurrent cases, the MRI demonstrating recurrence was co-registered with the initial planning CT containing the previously delineated target volumes. A recurrent volume (rVol) was marked by a neuro-radiologist and a radiation oncologist as the current contrast-enhancing region on T1W MRI. The overlapping volume between rVol and CTV-MR, CTV-PET and CTV-X was calculated as a proportion of rVol lying within the respective CTV. This area of overlap signified the proportion of recurrent volume that would have been covered in the respective CTV.

Statistics

The primary objective was to assess the volumes delineated using MRI, PET and combined modality and to quantify their mutual agreement with each other. The secondary objectives were to assess overall survival, overall follow-up and recurrence free survival. SPSS® v. 12.0 (SPSS Inc., Chicago, IL) software for Windows (Microsoft, Redmond, CA) was used for statistical analysis. Differences in the volume of the consensus MRI, PET, and MRI-PET based contours were quantified using Concordance Index and were statistically tested using 2-sided paired t-tests ($\alpha=0.05$). A p-value of 0.05 was considered as significant.

Observation and Results

Patient characteristics and outcomes

All 15 enrolled patients completed the study with no refusals or drop outs. The mean age at diagnosis was 52 years with male: female ratio of 2:1 (Table 1).

All patients underwent maximal resection with one-third achieving gross total resection and others achieving near total resection of tumor. O(6)-methylguanine-DNA methyltransferase (MGMT) methylation study was done in only six patients, out of whom half were found to carry methylated promoter region.

These were the patients who were enrolled once MGMT testing became a standard departmental protocol.

Radiotherapy was started after an average interval of 22 days from surgery. Median RT dose was 6000 cGy over six weeks and there were no unplanned gap of more than a week in any patient.

All patients could continue their TMZ during RT without any unplanned gap except one patient whose TMZ was withheld for a week during RT due to skin rash which was later attributed to

phenytoin and subsided once phenytoin was replaced with levetiracetam. A median of six cycles of adjuvant TMZ were received by patients with no skin or haematologic toxicity beyond grade II in any of them.

Characteristics	
Age in years (n=15)	
Mean	52.8
Median	54
Range	18-70
Sex (n=15)	
Male	10
Female	5
Dose (in cGy)	
Mean	6000
Median	6000
Median number of adjuvant TMZ cycles	6
MGMT status (n=6)	
Methylated	3
Unmethylated	3
Type of surgery (n=15)	
Gross total resection	05
Near total resection	10
Gap between surgery and starting RT (in days)	
Mean	22
Median	19
Range	14-32
Skin toxicity (n=15)	
Grade 0	00
Grade 1	14
Grade 2	01
Haematologic toxicity (n=15)	
Grade 0	07
Grade 1	05
Grade 2	03

Table 1: Demographic and treatment characteristics.

Volumetric analysis

Volumetric analysis was carried out in all 15 patients as per protocol (Table 2). Mean GTV-MR was 84.4 cc while GTV-PET was 11 cc, which was only 13 % of GTV- MR and was significantly smaller than GTV-MR (p=0.001). At the same time, mean GTV-X was 89.2 cc and was 6% larger than GTV-MR, the difference between the two was non-significant (p=0.86).

Thus, PET-based GTV produced a minimal change when combined with MRI volume. In majority of cases, increased PET activity appeared within the region of contrast-enhancement on MRI. However, there were cases where GTV-PET extended beyond GTV-MR. In two cases, there was no PET uptake at all and thus GTV-PET was zero. The mean CI for GTVs was 0.10 which signifies that only 10% volume of GTV-X was overlapping between two modalities. It is expected because of the minimal contribution of GTV-PET to GTV-X.

Mean CTV-MR was 334.2 cc while CTV-PET was 130.2 cc (39 % of CTV-MR). Again, the PET-based volume was significantly smaller than the MRI-based volume (p=0.00). Mean CTV-X was 363 cc and was just 8.6% larger than CTV-MR and the difference between them was non-significant (p=0.60). Thus, CTV-PET produced a minimal overall change when combined with CTV-MR to generate CTV-X.

The mean CI for CTVs was 0.35 which is modest and signifies that 35% of the combined volume (CTV-X) was overlapping between the two modalities. It is expected because, a) CTV-PET contributed more to CTV-X as compared to respective GTVs and, b) the 2 cm expansion of the overlapping GTVs resulted in higher overlapping of CTVs.

	GTV MR	GTV PET	GTV X	CI (GTV)	CTV MR	CTV PET	CTV X	CI (CTV)
Number of patients	15	15	15	15	15	15	15	15
Mean	84.41	11.04	89.22	0.10	334.26	130.24	363.06	0.35
Median	64.33	4.72	64.33	0.04	283.64	117.88	330.19	0.35
Range	26.55-318.43	0-30.35	31.78-318.43	0-0.24	123.3-714.85	0-295.28	128.1-735.32	0-0.75

Table 2: Volumetric analysis of different target volumes (in cc).

Treatment response and recurrence pattern

Disease response could be assessed in 14 patients. In one patient, no follow-up scans were done hence response remained unknown. Overall, one-third patients achieved CR with primary treatment while one-third developed progressive disease (Table 3).

All patients were analyzed for patterns of failure. During follow up, 10 patients developed recurrence by clinical and radiological criteria.

Recurrence was histologically confirmed in only two cases where re-surgery was done. All other cases were labelled as 'recurrent' on the basis of clinical and MRI findings. The mean RFS for overall group was 11 months while it was 8.6 months for patients who experienced a recurrence. The recurrence pattern correlated with the initial response to primary treatment as only three out of five complete responders, while four out of five patients with PD developed recurrence.

Characteristic	Numbers (%)
Response to primary treatment (n=15)	
Complete response	05 (33)
Partial response	04 (27)
Stable disease	00 (00)
Progressive disease	05 (33)
Unknown	01 (07)
Total no. of recurrences	10
Recurrent volume in cc (n=10)	
Mean	18.57
Median	13.12
Range	2.17-68.37
Time to recurrence in months (n=10)	
Mean	8.6
Median	7.5
Range	2.8-15.0
Recurrence w.r.t. primary response	
Recurrence in complete responders	60%
Recurrence in partial responders	75%
Recurrence on progressive cases	80%
Recurrence free survival (in months) For whole group (n=15)	

Mean	11.1
Median	9.5
Patients with recurrence (n=10)	
Mean	8.6
Median	7.5
Patients without recurrence (n=5)	
Mean	16
Median	13.2

Table 3: Response to primary treatment and recurrence pattern.

Volume and location of recurrent disease

The mean recurrent volume (rVol) was 18.5 cc (Table 4) which was significantly smaller than GTV-MR. In one patient, two recurrent lesions were seen, which were counted as two separate lesions. One of these lesions was completely away from all three initial CTVs.

	CTV MR (%) [n=11]	CTV PET (%) [n=10]	CTV X (%) [n=11]
Mean	73.7	57.7	81.7
Median	100	69	100
Range	0-100	0-100	0-100

Table 4: Overlap of recurrent volume with different CTVs.

On an average, 73.7% of rVol was overlapping with CTV-MR (n=11, as two lesions in a patient) while 81.7% of rVol was overlapping with CTV-X. Thus, coverage of recurrent volume was higher with CTV-X as compared to CTV-MR, although the difference was statistically non-significant (p=0.49). It indicates that if CTV-X would have been used for initial treatment, higher proportion of 'at risk' volume would have been treated.

Characteristic	Numbers
Salvage treatment (n=10)	
Chemotherapy only	03
RT only	01
Surgery + Chemotherapy	01
RT + Chemotherapy	03
Surgery+RT+Chemotherapy	01
None	01
Follow-up after salvage treatment (n=9) in months	
Mean	11.9
Median	9.7
Range	1-28

Table 5: Salvage treatment and follow-up.

Salvage Treatment

Out of the 10 recurrent cases, nine underwent salvage treatment (Table 5). Four patients received re-irradiation as a part of salvage treatment where treatment was given to the recurrent lesion with strict margins using stereotactic techniques. Stereotactic RT was delivered using linear accelerator as well as Cyberknife.

In seven cases, chemotherapy was given as a part of salvage treatment, where five patients received metronomic schedule of TMZ and other two received bevacizumab based chemotherapy. One young patient underwent multiple salvage treatments during his follow-up of 23.4 month including re-irradiation twice (one SFRT and one SRS), two salvage surgeries and bevacizumab based chemotherapy. He survived 17 months following recurrence. Out of two patients who underwent re-surgery, one patient also underwent intra-operative Carmustine wafer placement. Response to salvage treatment was not recorded. Average follow-up after starting salvage treatment was 11.9 months.

Survival and follow up

Last data analysis was done in June 2014, with a follow-up of 22 months for the last recruited patient (Table 6). Median follow-up was 16.6 months for the overall group and 26.1 months for the patients surviving at last follow-up.

Overall, four patients were alive at more than two years of follow-up, with two of them having disease-free status. These two patients had RFS of 29.6 and 22.7 months, both them had CR to primary treatment. Overall 1- and 2-year survival was 80% and 20% respectively. If last follow-up is taken as an event, the median survival of the whole group was 16.6 months.

Characteristic	
Median survival (n=15)	16.6 months
Overall survival (n=15)	
12-month	80%
18-month	46.6%
24-month	20%
Follow up of overall group (n=15) in months	
Mean	19.0
Median	16.6
Range	4.8-42.8
Follow-up of surviving patients (n=4) in months	
Mean	29.3
Median	26.1
Range	22-42.8
Status at last follow-up (n=15)	
Alive with disease	02 (13.3%)
Alive without disease	02 (13.3%)
Died	11 (73.3%)

Table 6: Overall survival and follow-up.

Discussion

This study is first of its kind to be conducted in India involving patients of GBM. The overall idea of this study was to assess the potential utility of 18F-FDG PET in identifying regions which are at high risk for recurrence while delineating target volumes for RT. We hypothesized that if PET is used in addition to MRI for delineating such regions, there would be lesser marginal failures.

Although, statistically non-significant, we found a better coverage of recurrent lesions when PET and MRI were used together to delineate CTV-X. Moreover, this better coverage of 'at risk' region was achieved by adding a non-significant volume of normal brain to CTV-MR, as CTV-X was just 8.6% larger than CTV-MR.

The mean PET-based volumes were consistently smaller than MR-based volumes with low CI. The low CI verified the qualitative observation that regions of FDG uptake overlapped some but not all regions of enhancement on MRI and extended outside GTV-MR in some cases. Such discordance has also been described by other investigators and may be of prognostic significance [19]. In one such study, 87% of patients were found to have discrepancies between the gadolinium-enhancing volume and areas of increased PET activity [32]. However, that study did not include data on subsequent failures,

so it remained unclear whether PET activity would be important in identifying regions at high risk for progression [32]. Our study has tried to answer these queries. While studies document the level of 18F-FDG uptake in tumor to be predictive of survival, there is limited literature to exactly show that the 18F-FDG-avid volume and its spatial distribution may also predict outcome.

Although, 18F-FDG PET volumes were an indicator of area at risk for geographic miss, the rate of false-negative PET studies is worrisome as PET is not an absolute indicator of absent disease. Moreover, it is unclear whether the additional volume delineated with PET should be used for overall treatment or as a boost. Gross et al. incorporated FDG-PET results with MRI for delineation of the 3-dimensional 60 Gy treatment volumes for 18 cases of high-grade glioma. Their reported median survival of 44 weeks showed no improvement compared with other studies. They concluded that FDG-PET did not add useful information for conventional treatment planning but suggested that it might prove useful to define a boost volume [10]. Although, few centers are exploring the incorporation of FDG-PET volumes for a simultaneous integrated boost in IMRT and for planning SRS target volumes [33], these approaches need to demonstrate efficacy before they are applied in clinical practice.

Our study shows that RT protocols based on 18F-FDGPET imaging are feasible and suitable for patients in developing countries like India where other amino acid based PET are currently unavailable for routine clinical use. Although, 18FDG-PET has its limitations in delineating brain lesions, it can be overcome upto an extent by using delayed scans as delineation of gliomas from both gray matter and white matter improves both visually and by SUV analysis on delayed PET [23] at the cost of extra waiting time for the delayed scan. In future, similar strategies could be applied to identify regions of hypoxia, proliferation, protein synthesis, or membrane biosynthesis.

Although combined volume (CTV-X) showed potential for covering increased proportion of 'at risk' volume, treatment using PET-based volumes may not be fool-proof method as one patient in this study developed a recurrent lesion even outside CTV-X. Thus, there is a need to balance the margins used for delineating CTVs and the acceptable toxicity to normal brain.

The age and sex distribution is comparable to literature, although the median age at diagnosis seems lesser (52 years) than reported in literature [2]. One specific feature of our study was no denial, drop outs or loss of follow-up which may be contributed to the stringent and streamlined enrolment, treatment and follow-up process where mutual communication with patients using telephone and e-mails was encouraged to keep them informed and updated regarding their status. Our median OS (16.6 months) is a shade superior compared to 14.6 months reported by Stupp et al. [8]. However, the 2-year OS of 20% in our study is mildly inferior to other similar study [34] but it may improve in future as last two recruited patients complete their 2-year follow-up.

This study shows that Indian patients tolerates concurrent RT with TMZ well, as there were no severe skin or haematological toxicity reported in any of our patients. Moreover, all patients completed their primary treatment without any unplanned gap in treatment.

Metronomic dose of TMZ requires special mention as it was the commonest salvage treatment in inoperable patients at recurrence. It seems to be a feasible, acceptable and well tolerated salvage treatment showing satisfactory results. The patient having longest follow-up (42.8 months) has been continuing his metronomic TMZ for 28 months following recurrence. Similarly, re-irradiation using stereotactic radiotherapy was also well tolerated without any untoward toxicity. Thus, in properly selected patients, re-irradiation followed by metronomic TMZ may be an ideal approach as patient can continue this treatment while at home and without compromising their quality of life. This strategy needs further exploration in future studies.

Although, MGMT methylation status was analyzed in six patients, no formal analysis could be done due to limited numbers for deriving any meaningful conclusion. This widely studied prognostic and predictive aspect in Western literature needs to be studied in Indian patients in future studies.

One limitation of this study is the small number of participants. It was a pilot study where the purpose was to evaluate whether delayed PET might be feasible and useful for treatment volume delineation in glioblastoma patients and we could get an appropriate answer. The correlation we found between the location of increased PET activity and the subsequent failure provides justification for same and warrants additional work in this direction. Another potential limitation is limited follow-up for the patients enrolled at the end, although that factor may be addressed by continuing the data collection and reporting in future.

Further research is warranted to determine whether treatment planning using novel biological imaging can improve outcome for high-grade glioma. In future, it seems likely that the complementary information obtained with multiple imaging modalities will lead to more efficient delineation of target volumes but till then F18FDG-PET may serve this purpose.

Conclusion

- Delayed 18-FDG PET is a feasible method to provide additional information for delineating target volumes for RT planning in glioblastoma patients.
- Inclusion of delayed FDG-PET based abnormality while delineating the target volumes for GBM leads to a marginal and insignificant increase in target volume.
- There is better coverage of 'high risk' volume using combined volume for radiation.
- Treating this common volume (CTV X) instead of CTV MR may be beneficial in avoiding marginal recurrences in future.
- Future trials with more number of patients and a longer follow-up may further augment our findings

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