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# Hypofractionated radiation therapy with temozolomide versus standard chemoradiation in patients with glioblastoma multiforme (GBM): A prospective, single institution experience

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ABSTRACT

Background and aim: the study aimed to determine whether hypofractionated radiotherapy (HFRT) with simultaneous and adjuvant temozolomide (TMZ) was feasible and could provide adequate disease control in primary GBM patients with poor prognostic factors including large tumor size, poor performance status, unresectable or multifocal lesions, poor imaging and inflammatory indices. Patients and methods: A total of 93 patients with glioblastoma multiforme were collected and distributed randomly as 1:1.7 of cases to controls; cases or arm (I) received HFRT with 45 Gy in 15 fractions over 3 weeks concurrently with TMZ. Controls or arm (II) received standard conventional fractionation radiotherapy of 60 Gy in 30 fractions over 6 weeks concurrently with TMZ. Results: 35 patients were recruited in arm I while 58 patients in arm II with significant difference in site of GBM, pattern of enhancement, type of surgery, and neutrophil to lymphocyte ratio, while no significant differences in tumor size, focality, responses, progression free survival, and overall survival (OS), only the type of surgery was an independent predictor for OS, no significant difference in the type and degree of toxicity between both arms. Conclusion: Our results showed that HFRT with concurrent TMZ is a feasible therapeutic approach in patients with GBM, especially those with poor prognostic factors, assuring high treatment compliance and low toxicity rates. Dose escalation and reduction in overall treatment time are clear advantages of HFRT, while at least the same survival rates as conventional fractionated RT are maintained.


## 1-. Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor, the median age at diagnosis is 64 years.[1] No current treatment is curative, maximal safe surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide represents the treatment of choice.[2] For elderly and frail patients, less intensified approaches were practiced including hypofractionated radiotherapy (HFRT) with or without temozolomide.[3]

The addition of radiotherapy to GBM increases survival, even though the responsiveness varies greatly, and interstitial brachytherapy is of limited use, except as salvage therapy in recurrent cases.[4]

Temozolomide (TMZ) has the ability to stabilize radiotherapy (RT) induced double-strand breaks, subsequently augmenting the RT effect.[5] While adjuvant chemotherapy can deliver a significant survival benefit, the ideal chemotherapeutic agent that can adequately penetrate the blood-brain barrier and overcome mechanisms of drug resistance is not yet specified. Drugs like TMZ, nitrosoureas, platinum, procarbazine, and topoisomerase I and II inhibitors can be used.[6] Furthermore, this approach brings out a median overall survival (OS) time of 14.6 months (13.2–16.8 months) and a 5-year survival rate of 9.8% (6.4–14.0%).[7]

The impact of HFRT has recently been investigated. Results of initial research intended to reduce the overall treatment time in frail and elderly GBM patients suggested utilizing HFRT concurrently with TMZ as a standard treatment option in this subgroup of patients.[3]

However, there was a paucity of data to support the use of HFRT with TMZ in GBM patients other than elderly and fragile patients, such as those with other conditions conferring a poor progno-

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sis. Our study aimed to confirm that HFRT with simultaneous and adjuvant TMZ was feasible and could achieve adequate disease control in primary GB patients with poor prognostic factors such as large tumor size,[8] unresectable or multifocal lesions,[9] low Karnofsky Performance Status (KPS),[9] presence of unfavorable imaging or inflammatory indices,[10] and ensure comparable survival benefits to the standardized approach.

## 2. Patients and methods

This randomized case controlled study was carried out in the Clinical Oncology and Nuclear Medicine Department at the Assiut University Hospital. The study was conducted between March 2015 and December 2018. G power program was used to calculate the sample size for two independent groups. The minimum required sample size was 84 participants to detect an effect size of 0.8 of difference between means of two independent groups, with P value < 0.05 and a power >90%.

### 2.1. Study subjects

A total of 93 patients with glioblastoma multiforme were collected and distributed randomly as 1:1.7 of cases to controls

- -cases or arm (I): the group who received HFRT with 45 Gy in 15 fractions over 3 weeks concurrently with temozolomide.
- -controls or arm (II): the group who received standard conventional fractionation radiotherapy (CFRT) of 60 Gy in 30 fractions over 6 weeks concurrently with temozolomide.

### 2.2. Compliance with ethical standards

Informed consent in a written form was taken from all participants. The study objectives were explained to all subjects. Approval for this study was obtained from the Institutional Review Board of Ethical Committee of Faculty of Medicine, Assiut University, prior to study execution (approval number 17200486/ 2015), and all experiments were performed in accordance with relevant guidelines and regulations.

## 3. Patients

### 3.1. Inclusion criteria

- Patients who were diagnosed as high grade glioma by MRI (spectroscopy ± diffusion MRI), biopsy or postoperatively.
- Ages eligible for study: 18–60 years with Karnofsky Performance Status >50 - ≤70, or patients more than 60 years old with Karnofsky Performance Status ≥70.
- Patients reliable for follow up.

### 3.2. Exclusion criteria

- Prior chemotherapy or radiation for high grade glioma or radiotherapy to the brain.
- Serious concomitant diseases preventing the safe administration of radiotherapy or likely to interfere with the study assessments.
- Concomitant administration of any other experimental drug under investigation.
- Previous history of low grade glioma treatment.

### 3.3. Data assessed were

- Age of the patient
- Sex of the patient
- Performance status (KPS)
- Site of the lesion
- Enhancement pattern in MRI.
- Diagnostic procedure whether by surgery, biopsy, or magnetic resonance imaging
- Size of the lesion
- Lateralization and symptoms
- Neutrophil to lymphocyte ratio (NLR).
- Type of surgery
- Response to the treatment
- Progression free survival (PFS)
- Overall survival (OS)
- Toxicity from the treatment

## 4. Method

**Diagnosis:** diffusion MRI and MRS were the prime diagnostic modalities in many subjects; however, pathologic examination of biopsy, debulking specimens or surgically resected tumor were accomplished in some subjects; and all patients with glioblastoma multiforme only were included in our study.

The extent of surgical resection was determined on MRI done 48 h after surgery where complete resection (CR) was defined as residual tumor volume lower than 1 $cm^3$, subtotal resection (SR) as residual tumor volume between 1 $cm^3$ and 10 $cm^3$ and partial resection (PR) or debulking as residual tumor volume greater than 10 $cm^3$.[11]

## 5. Concurrent chemoradiation protocols

Recruited patients 3-4 weeks after surgery underwent MSCT brain required for target definition in radiotherapy, and our patients received either

- CFRT treatment technique which included phase I; 40 Gy/20 fractions/4 weeks to the mass and surrounding edema and 2-3 cm as PTV by the 3DCRT technique, or whole brain radiotherapy (WBRT) by 2D planning in phase I, both were followed by phase II with 20 Gy/10 fractions/2 weeks to the mass plus 2 cm by the 3DCRT technique.

Or

- HFRT: 45 Gy over 15 fractions, 5 fractions per week to the mass and edema and 2−3 cm margin as PTV or, in some cases where edema was massive, we started with WBRT 40 Gy by the 2D technique then HFRT in phase 2 with 21 Gy over 7 fractions by 3DCRT.

TMZ: concomitant administration of oral TMZ (75 $mg/m^2$), followed by adjuvant TMZ (200–250 $mg/m^2$ for 5/28 days) for about 6–8 cycles for both arms were given.

### 5.1. Assessment of response

Clinical outcome was evaluated by neurological examination and brain contrasted MRI performed 1 month after radiation therapy and then every 3 months later.

MRI images acquired during the follow up period were co-registered with pre-radiation therapy MRI to precisely define the site of relapse. Response was recorded using the Response Assessment in Neuro-Oncology (RANO) criteria.[12] Because of the difficulties of Mac-Donald and RECIST criteria to quantify non-enhancing disease progression, the RANO-HGG criteria suggest that any qualitative increase in non-enhancing disease represented disease progression.

Hematologic and non-hematologic toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0. Follow up was done monthly during the adjuvant TMZ, then every 3 months for 2 years, and every 4-6 months thereafter. Patients were assessed by gadolinium-enhanced MRI 4 weeks after RT and then every 3 months, or at time of clinical evidence of neurologic progression also follow up of treatment toxicities was done as cognitive impairment, headache.

Tumor response according to RANO criteria:

- **Complete response (CR)**: included all of the following: complete disappearance of all enhancing measurable and non-measurable diseases sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; patients were off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically.
- **Partial response (PR):** included all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with the baseline scan; the corticosteroid dose at the time of scan evaluation should be no greater than the dose at time of the baseline scan; and stable or improved clinically.
- **Stable disease (SD):** required all of the following: did not qualify for CR, PR or progression; stable non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with the baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging showed that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD was the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- **Progressive disease (PD) :** defined by any of the following: a) ≥25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids; b) significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with the baseline scan or best response after initiation of therapy not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes or other treatment effects); c) any new lesion; d) clear clinical deterioration could not be attributable to causes other than the tumor (e.g. seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose; e) failure to return for evaluation as a result of death or deteriorating condition; f) or clear progression of non-measurable disease.

### 5.2. Statistical analysis

G-power 3.1 program was used for calculation of the sample size. Descriptive data in the form of mean, median, standard deviation, standard error, and percentages were used, the Shapiro-Wilk test was used for detection of normal distribution of data, and the z-test for homogeneity of data. Inferential statistics in the form of an independent sample *t*-test, the Man Whitney U-test, and the Kruskal-Wallis test were used for the relations between scale and categorical variables, and the $Chi^2$ test and Cramer's V test were used for the relations between categorical variables. Kaplan-Meier test was performed for drawing of survival curves and the Log rank test for comparison according to different prognostic factors. Multiple linear regression test was done for determination of independent prognostic factors and the percentage of change in the variance of survival caused by different prognostic factors. Cox-regression test was used for determination of different hazard ratios of prognostic factors of survival. PFS was calculated from time of diagnosis to time of true disease progression (not pseudo-progression) or death. OS was calculated from time of diagnosis to time of death of any cause or last follow up.

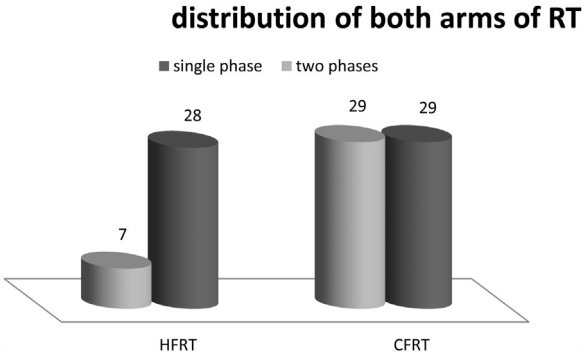


**Fig. 1.** Distribution of both arms, CFRT; conventional fractionated radiotherapy, HFRT; hypofractionated radiotherapy.

## 6. Results

Descriptive analysis of study patients' characteristics and demographic data of both arms; the experimental arm; arm I (HFRT concurrently with temozolomide) and control arm; arm II (CFRT with temozolomide) and their significance were set forth in Tables 1 and 2, Figs. 1, both study arms had comparable age, sex, and performance status

More patients (58.6%) in arm II had eloquent sites of GBM when compared to arm I with significant difference (P = 0.001), unintentionally, patients in arm II had worse other tumor characteristics regarding the pattern of enhancement with significant impact (P = 0.045), although the size of GBM was larger in arm I than arm II, it failed to reach a significant level (P = 0.076), Table 2.

The most common surgical intervention in arm I was biopsy, while debulking was done in 29.3% of patients in arm II compared with 5.7% of arm I, surgery in the form of debulking and subtotal resection was done in a significantly lower percentage of patients in arm I compared with arm II (P = 0.05), Table 3, in addition, most patients in arm I received their RT protocol as a single phase compared to only 50% of patients in arm II (P = 0.005). NLR was found to be significantly higher among patients of arm II compared with arm I. In spite of these differences in tumor characteristics and treatments received in both study arms, no significant differences in the patterns of response with SD was the predominant pattern of response as illustrated in Table 3 (Fig. 2 and 3).

### 6.1. Survival analysis in both arms

PFS was a little bit higher for patients treated with the standard arm compared to our experimental arm but with no significant difference (log rank = 2.936, P = 0.087), Table 4, Figs. 4.

Likewise, OS showed no significant difference between both arms with the mean OS in the experimental arm found to be $10.03 \pm 0.971$ months compared with $11.48 \pm 1.01$ months, (log rank = 0.790, P = 0.374), Table 5, Figs. 5.

Prognostic factors of survival for patients who received HFRT:

Upon analyzing the prognostic factors affecting PFS and OS for those patients who received hypofractionated arm, we found a negative correlation of OS with age with a significant effect; however,

**Table 1**
Demographic data of study arms.

| Data | Arm I(experimental) | Arm II (control) | P value |
|---|---|---|---|
| Age (mean ± SD) | 54.1 ± 16.55 | 49.79 ± 14.1 | 0.205 |
| Median | 55 years | 50 years | |
| Min-max | 21–80 | 21–80 | |
| Gender | | | 0.985 |
| Male | 23 (63.9%) | 38 (65.5%) | |
| Female | 12 (33.3%) | 20 (34.5%) | |
| Male/female ratio | 1.92/1 | 1.9/1 | |
| KPS | | | 0.889 |
| <70 | 15 (41.7%) | 24 (41.4%) | |
| ≥70 | 20 (55.6%) | 34 (56.6%) | |

Data expressed as mean ±SD, percentages, median, independent t test for significance.

**Table 2**
Tumor characteristics in both arms.

| Data | Arm I | Arm II | P value |
|---|---|---|---|
| **Site** | | | 0.001 |
| Eloquent | 8 (22.9%) | 34 (58.6%) | |
| Near eloquent | 18 (51.4%) | 20 (34.5%) | |
| Non eloquent | 9 (25.7%) | 4 (6.9%) | |
| **Size** (mean ± SD) $cm^2$ | 30.81 ± 20.26 | 23.41 ± 17.13 | 0.076 |
| Min-max | 8.1–90 $cm^2$ | 2.4–62.48 $cm^2$ | |
| **Focality** | | | 0.880 |
| Unifocal lesion | 23 (63.9%) | 39 (67.2%) | |
| Multifocal lesion | 12 (33.3%) | 19 (32.8%) | |
| **Pattern of enhancement** | | | 0.045 |
| Diffuse | 3 (8.6%) | 17 (29.3%) | |
| Heterogonous | 15 (42.9%) | 23 (39.7%) | |
| Peripheral | 17 (48.6%) | 18 (31%) | |

Data expressed as mean ±SD, number, percentage, independent sample t test, Chi square test for significance.

**Table 3**
Treatment and response criteria.

| criterion | Arm I | Arm II | P value |
|---|---|---|---|
| Surgical treatments | | | 0.05 |
| No surgery | 10 (28.6%) | 14 (24.1%) | |
| Biopsy | 13 (37.1%) | 14 (24.1%) | |
| Debulking | 2 (5.7%) | 17 (29.3%) | |
| Subtotal resection | 10 (28.6%) | 13 (22.4%) | |
| RT protocol | | | 0.005 |
| • Single phase | 28 (80%) | NA | |
| • involved field 45 Gy/15 F (3D) | | | |
| • involved field 60 Gy/30 F (3D) | NA | 29 (50%) | |
| • two phases | | | |
| • 1st phase wholen brain 40 Gy/20 F (2D) followed by 2nd phase involved field 20 Gy/10 F (3D) | NA | | |
| • 1st phase whole brain 40 Gy/20 F (2D) followed by 2nd phase involved field 21 Gy/7 F (3D) | | 29 (50%) | |
| | 7 (20%) | NA | |
| NLR (mean ± SD) | 4.86 ± 3.89 | 6.92 ± 5.01 | 0.04 |
| Min-max | 0.89-18 | 1.04-19.97 | |
| Response | | | 0.104 |
| CR | 3 (8.6%) | 12 (20.7%) | |
| PR | 9 (25.7%) | 15 (25.9%) | |
| SD | 20 (57.1%) | 20 (34.5%) | |
| PD | 3 (8.6%) | 11 (19%) | |

Data expressed as mean ±SD, number, percentage, Mann-Whitney U test, Chi square test for significance, Gy; grey, NLR; neutrophil to lymphocyte ratio, CR; complete response, PR; partial response, SD; stable disease, PD; progressive disease, NA; not applicable.

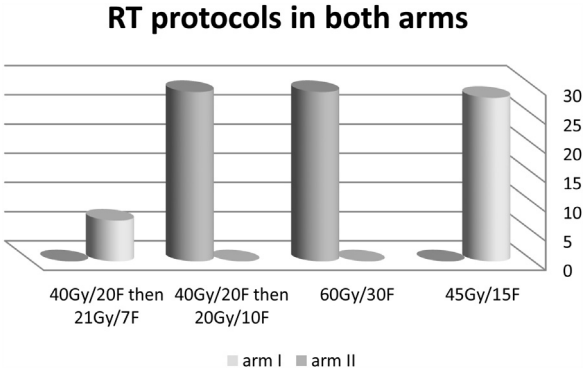


**Fig. 2.** Techniques of RT in both arms.

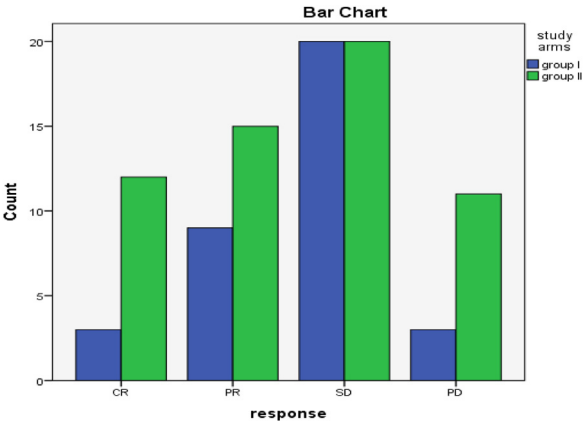


**Fig. 3.** Distribution of patterns of response between both arms with no significant difference (P = 0.104).

**Table 4**
PFS among patients with GBM in both study arms.

| Survival | PFS (months) | |
|---|---|---|
| | Arm I | Arm II |
| Mean ± SE | 7.305 ± 0.81 | 9.92 ± 0.861 |
| 95% CI | 5.717-8.89 | 8.23-11.6 |
| Median ± SE | 6 ± 0.408 | 10 ± 1.65 |
| 95% CI | 5.2-6.8 | 6.77-13.2 |
| log-rank, P value | Chi-Square = 2.936, P = 0.087 | |

Data expressed as mean ±SE, median ± SE, 95% CI, log- rank.

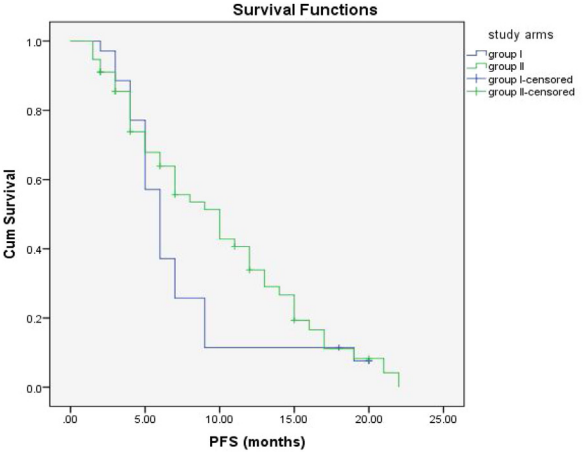


**Fig. 4.** Kaplan-Meier estimates of PFS among study arms with no significant difference, log rank = 2.936 P = 0.087.

**Table 5**
Overall survival among GBM patients in both arms.

| survival | OS (months) | |
|---|---|---|
| | Arm I | Arm II |
| Mean ± SE | 10.03 ± 0.971 | 11.48 ± 1.01 |
| 95% CI | 8.13-11.93 | 9.51-13.46 |
| Median ± SE | 9 ± 0.557 | 11 ± 1.43 |
| 95% CI | 7.91-10.09 | 8.19-13.80 |
| log-rank, P value | Chi-Square = 0.790, P = 0.374 | |

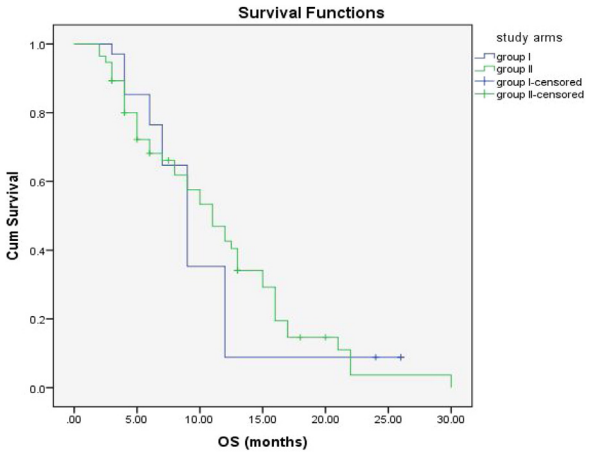


**Fig. 5.** Kaplan-Meier estimates of overall survival among GBM patients in both study arms, log rank = 0.790, P = 0.374.

**Table 6**
Possible prognostic factors for PFS and OS in arm I.

| Prognostic factor | PFS | OS |
|---|---|---|
| Age | r = −0.317, P = 0.06 | r = −0.365, P = 0.034 |
| Sex | P = 0.518 | P = 0.668 |
| KPS | r = 0.048, P = 0.786 | r = 0.035, P = 0.843 |
| Primary size $cm^2$ | r = −0.128, P = 0.484 | r = −0.244, P = 0.164 |
| NLR | r = 0.058, P = 0.742 | r = 0.03, P = 0.869 |
| Eloquency | P = 0.033 | P = 0.039 |
| Focality | P = 0.216 | P = 0.003 |
| Pattern of enhancement | P = 0.347 | P = 0.519 |
| Type of surgery | P = 0.244 | P = 0.045 |
| Response | P = 0.002 | P<0.0001 |

Data analyzed using Spearman correlation, Mann-Whitney U test, Kruskal-Wallis test for significance.

it did not reach the significance level for PFS. In addition, a significant impact of GBM site on PFS and OS was found, with significantly better OS for patients with unifocal lesions than those with multifocal lesions. Our results also demonstrated that patients who had undergone tumor resection attained better OS but tumor resection alone was not sufficient to attain a better PFS (P = 0.244). As expected; patients who developed higher response achieved significantly better PFS and OS, Table 6.

Multiple linear regression test for different prognostic factors of OS:

In order to predict the relative contributions of different independent predictors in the total variance of OS for arm I patients, we performed the multiple linear regression test with quality of prediction of 0.728. This model showed a significant effect of different prognostic factors on the variance of OS (P = 0.04) with F ratio equal to 2.358

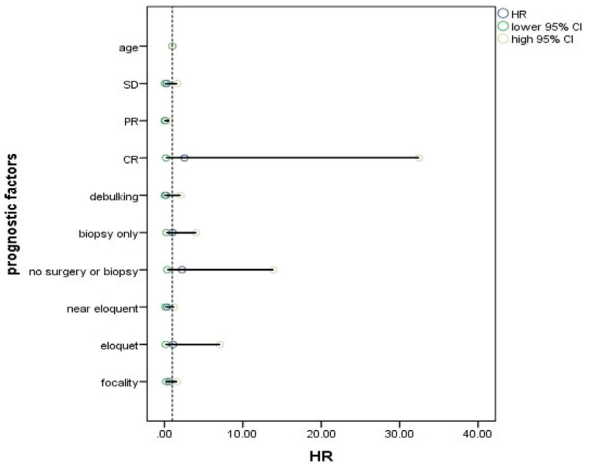


**Fig. 6.** HR, for different prognostic factors of OS, showed an increasing risk of death with eloquent sites, no surgery, biopsy only, and increasing age, and a decreasing risk of death with improving the response.

Model Summary for OS

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df 1 | df2 | Sig. F Change |
| 1 | .728[a] | .530 | .305 | 4.58994 | .530 | 2.358 | 11 | 23 | .040 |

a. Predictors: (Constant), KPS, pattern of enhancement, focality, protocol of treatment, eloquency, primary size cm2, sex, age, response, type of surgery, KPS
b. Dependent Variable: OS (months)

We found that only the type of surgery had a significant effect on mean survival when all other variables were held constant. This effect was positive indicating that increasing the extent of resection improved survival, although in a previous table we found significant differences in mean survival with different response patterns implicating that the effect of response on mean survival was attributed to other prognostic factors, Table 7.

Upon doing the Cox regression test for factors increasing the hazard of death, subsequently shortening survival, we detected an unfamiliar finding as the hazard of death increased with increasing probability of CR but with an insignificant effect (HR = 2.548, P = 0.471) that could be explained by the small number of patients achieved CR (n = 3). Interestingly, the hazard of death decreased as the probability of PR increased (HR = 0.066, P = 0.014), the hazard of death increased with mulifocality, eloquent brain, no surgery and only biopsy as illustrated in Table 8, Figs. 6.

### 6.2. *Side effects between both arms*

No significant differences in different side effects between both arms as illustrated in Table 9.

## 7. Discussion

Glioblastoma multiforme is by far the most common primary brain tumor accounting for 17% of all intracranial tumors. From the clinical and biological point of view, GBM includes a rather heterogeneous group of tumors that vary by site of origin, histopathological features, tumor microenvironment,[13] and genetics. It is usually resistant to different lines of treatment including radiotherapy, chemotherapy, and targeted therapy with overall survival rates ranging from few months to years, rendering it invariably lethal. The standard treatment of this tumor up till now comprises surgical resection of the tumor, postoperative radiotherapy with concomitant temozolomide, followed by adjuvant TMZ therapy. This treatment regimen is, right now, the most effective one as it increases the median overall survival from 12 months with RT alone to 14.6 months. Therefore, the percentage of survived patients for 2 years increases from 10.4% to 26.5%.[14]

Despite all the advancements and developments in radiotherapy and chemotherapy, they are still insufficient to provide a cure for those unfortunate patients with GBM, and the current practice relies mainly on surgical excision to improve survival and QoL in those patients.

Three-dimensional conformal fractionated RT to a total dose of 60 Gy in 30 daily fractions of 2 Gy each is considered standard and employed based on the results from previous studies.[15] GBM is characterized by rapid doubling time so that the utilization of protracted RT schedules harbors theoretical drawbacks of enhancing cell repopulation that has previously been translated into up to additional 10% of patients developing DP.[16,17]

HFRT offers the advantages of achieving an increased cell-killing effect by the delivery of a higher dose per fraction over a shorter time frame, and of reducing the effect of accelerated tumor cell repopulation by shrinking the RT treatment time. Based on these observations, several studies have been designed to assess the effectiveness of HFRT within multimodal treatment approaches utilizing concurrent and adjuvant TMZ after maximal tumor resection,[18–20] the preliminary results of these studies were encouraging with a median survival of 20 months achieved in some of them and low incidence of neurologic toxicities.

There is no agreement about the dose of HFRT utilized in these studies. In a published pilot study done by Terasaki et al.,[18] median survival of 15.6 months was achieved when a dose of 45 Gy/15 fractions with concurrent and adjuvant TMZ was delivered. Although our study was not comparable to Terasaki as we reported a lower median survival of 9 months, we achieved ≥1-year OS of 34.3% and OS ≥2-year in 8.6% (3/35), which were not reported by Terasaki.

The mean PFS demonstrated in our results did not differ between the control arm (9.9 ms) and the study arm (7 ms) with no significant difference (P = 0.087) approaching the PFS achieved by Pierna Navarria et al., for both the control arm (standard arm received 60 Gy / 30 fractions and PFS of 7 ms) and the study arm (60 Gy/15 fractions and PFS of 10.9 ms) implicating that increasing the total dose and dose per fraction did not lead to a marvelous improvement of survival.[21]

The greater benefit on survival was achieved by those patients in our study who were younger than 50 years of age, which came with agreement with Pierna Navarria et al.

In a two-arm comparative observational study done by Lutterbach and Ostertag,[22] where 96 GBM patients older than 60 years were treated with HFRT of 42 Gy/12 fractions given to 50 patients and standard RT 60 Gy/30 fractions given to 46 patients, the median OS was 7.3 ms for the HFRT arm compared to 5.6 ms for the standard arm. We considered our results slightly better than those of Lutterbach and Ostertag, although the standard arm in our study achieved median survival of 11 ms, possibly because 68% of our control arm patients were less than 50 years implicating that younger patients achieved better results from standard 60 Gy/ 30 fractions.

Roa et al.[23] randomly assigned 100 GBM patients aged 60 years or older to CFRT (60 Gy in 30 fractions) or HFRT (40 Gy in 15 frac-

**Table 7**
Multiple linear regression test for different prognostic factors of OS.

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. |
|---|---|---|---|---|---|
| B | Std. Error | Beta | | | |
| (Constant) | 29.363 | 10.490 | 2.799 | .010 | |
| sex | 1.498 | 2.069 | .131 | .724 | .476 |
| age | −.088 | .069 | −.264- | −1.275- | .215 |
| focality | −.864 | 2.057 | −.076- | −.420- | .678 |
| eloquency | −3.002 | 1.664 | −.385- | −1.805- | .084 |
| patterns of enhancement | −2.398 | 1.731 | −.283- | −1.385- | .179 |
| KPS | −.197 | .158 | −.409- | −1.242- | .227 |
| type of surgery | 3.778 | 1.348 | .814 | 2.802 | .010 |
| primary size cm2 | −.075 | .047 | −.275- | −1.574- | .129 |
| response | −.530 | 1.484 | −.074- | −.357- | .724 |
| protocol of treatment | −4.465 | 2.314 | −.329- | −1.929- | .066 |
| KPS (<70 v.s. > 70) | 5.689 | 3.800 | .519 | 1.497 | .148 |

Dependent Variable: OS (months).

**Table 8**
Cox regression hazard model for OS.

| | B | SE | Wald | df | Sig. | Exp(B) | 95.0% CI for Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| **focality** | −.512 | .503 | 1.037 | 1 | .309 | .599 | .224 | 1.606 |
| **eloquency** | | | 5.801 | 2 | .055 | | | |
| eloquent | .070 | .962 | .005 | 1 | .942 | 1.072 | .163 | 7.060 |
| near eloquent | −1.070 | .650 | 2.705 | 1 | .100 | .343 | .096 | 1.228 |
| **surgery** | | | 3.657 | 3 | .301 | | | |
| no surgery | .806 | .931 | .749 | 1 | .387 | 2.238 | .361 | 13.882 |
| biopsy | .028 | .696 | .002 | 1 | .968 | 1.028 | .263 | 4.025 |
| debulking | −1.678 | 1.221 | 1.888 | 1 | .169 | .187 | .017 | 2.045 |
| **response** | | | 12.905 | 3 | .005 | | | |
| CR | .935 | 1.299 | .519 | 1 | .471 | 2.548 | .200 | 32.477 |
| PR | −2.723 | 1.114 | 5.977 | 1 | .014 | .066 | .007 | .583 |
| SD | −1.224 | .871 | 1.973 | 1 | .160 | .294 | .053 | 1.622 |
| age | .015 | .015 | 1.025 | 1 | .311 | 1.015 | .986 | 1.045 |

**Table 9**
Side effects of treatment protocols in both arms.

| side effect | Arm I | Arm II | Total (100%) | P value |
|---|---|---|---|---|
| anemia | | | | |
| grade 1 | 26(42.6%) | 35(57.4%) | 61 | 0.320 |
| grade 2 | 6(25%) | 15(75%) | 24 | |
| grade 3 | 3(37.6%) | 5(62.5%) | 8 | |
| neutropenia | | | | |
| grade1 | 25(39.1%) | 39(60.9%) | 64 | 0.740 |
| grade 2 | 8(38.1%) | 13(61.9%) | 21 | |
| grade 3 | 2(25%) | 6(75%) | 8 | |
| headache | | | | |
| mild | 30(39%) | 47(61%) | 77 | |
| moderate | 4(30.8%) | 9(69.2%) | 13 | 0.843 |
| severe | 1(33.3%) | 2(66.7%) | 3 | |
| cognitive function | | | | |
| no | 10(37.7%) | 18(64.3%) | 28 | |
| mild | 10(41.7%) | 14(58.3%) | 24 | 0.969 |
| moderate | 9(37.5%) | 15(62.5%) | 24 | |
| severe | 6(35.3%) | 11(64.7%) | 17 | |

Data expressed as number, percentage, Cramer's V test for significance.

tions) with localized field irradiation employed. The PTV included the enhancing primary tumor and surrounding edema with a 2.5 cm margin. The median survival was 5.1 months in the conventional RT group and 5.6 months in the HFRT group (p = 0.57). Our results were better than those of Roa et al. although no significant difference in median survival was achieved in all arms (Log rank = 0.790, P = 0.374).

Several studies[24–26] strongly considered the extent of surgical resection as a powerful prognostic factor affecting different outcome endpoints, and as expected; this was aligned with our results that declared mean survival of $13.6 \pm 8.5$ ms for those with tumor resection (P = 0.05)

A meta-analysis done by An-an Yin et al.[27] demonstrated no statistically significant variations in estimated statistics by variables like median age, the percentage of patients with a KPS $\geq$ 70, the percentage of male participants and sample size, with the exception of the percentage of patients who had undergone surgery. This variable seemed to be positively correlated with the survival benefits conferred by combined treatment ($P_{meta\text{-}regression} = 0.001$). Our results were contradictory to some extent to this meta-analysis, where significant negative correlation between age and OS (r=-0.365, P = 0.034) was detected, and in the multiple regression test, the extent of surgical resection was the only factor to have a significant impact on survival (P = 0.01).

Although no significant differences in different response patterns were found between both arms, more patients achieved an objective response rate of 46.6% in arm II vs. 34.3% in arm I, possibly due to 51.7% of arm II patients having undergone debulking and near-total resection compared with 34.3% in arm I.

45% of our study patients were older than 50 years of age; this could explain in part the development of moderate to severe cognitive impairment and grade 3 neutropenia, although many physicians were reluctant to treat elderly patients as aggressively as younger ones because of decreased tolerance to effective treatment, comorbidities, and poor physical condition, trying to treat them conservatively without surgery and with hypofractionated short courses of RT. Nevertheless, most toxicities reported in our study developed in those older than 50 years.

Some patients of our study arm were treated with the shrinkage field technique but without split course with an initial phase of 40 Gy/20 fractions treating the whole brain followed by a localized phase of 21 Gy/7 fractions. The employment of this technique was not associated with improved survival of our patients which was not comparable to that of the Johns Hopkins University, Baltimore, MD retrospective series[28] that recommended the SHORT regimen as an appropriate treatment option for most patients with malignant gliomas.

Although many studies of HFRT in GBM used suboptimal radiation doses, they reported efficacy comparable to CFRT, especially in poor-risk patients, but the therapeutic potential of HFRT schedules remained under close scrutiny as many authors believed that the use of more aggressive treatment protocols did not alter the outcomes. Some authors[29] strongly argued that the therapeutic efficacy of HFRT may indeed represent a true radiobiological effect. Likewise, Azoulay et al.[30] strongly considered HFRT 60 Gy/20 fractions to be a safe and short term approach sufficiently freestanding to achieve comparable survival to standard fractionation. Unlike most other tumors that follow the early-responding tissue pattern with RT, GBMs are relatively radioresistant and may respond more like late-responding neural tissue. About 50% of GBM carry mutated P53 tumor suppressor gene and it is known that tumors carrying that mutated gene behave like late reacting tissue when they are irradiated conventionally with a high degree of resistance and aggressiveness, subsequently they may gain benefit from hypofractionated protocols.

According to Cabrera et al.,[31] there is no supporting evidence up till now that conventionally fractionated RT (60 Gy/30 fractions) is superior to hypofractionated RT (40–45 Gy/15 fractions) and both are considered reasonable treatment options for elderly or frail patients, this conclusion was clearly evident in our results as there were no significant differences in the response patterns, PFS, and OS between both treatment arms.

Age in our study was negatively correlated with PFS and OS with a significant impact ($r=-0.535$, $P<0.001$, $r=-0.506$, $P<0.003$, respectively), which came in alignment with different studies including Bambury et al.[32] However, the impact of NLR in our results was not clearly defined as it exhibited no correlation with PFS or OS and it was not consistent with the results of Bambury et al. who evaluated the impact of NLR in 84 patients with GBM and demonstrated that age over 65 years, gender, eastern cooperative oncology group performance status $\geq 2$, frontal tumor, extent of surgical resection, completion of the adjuvant chemoradiation protocol, and NLR > 4 was significantly correlated with overall survival.

In a retrospective study done by Niloofar Ahmadloo et al.[33] to determine the prognostic factors and treatment outcomes in 223 patients with GBM, patients with age $\leq$50 ys ($P<0.003$), and surgical resection ($P<0.009$) had significantly better overall survival. Our results agreed with Niloofar Ahmadloo et al. In addition, our study elucidated no impact of different radiation techniques utilized in our study arms which was comparable to Niloofar Ahmadloo et al. Important point in this retrospective study was the significantly better OS associated with those patients who had received a hypofractionated course of RT ($P<0.001$), which indirectly reinforced our study.

The anatomical relationship between the tumor and the eloquent cortex is pivotal as it is directly related to the amount of tumor that can be resected without permanent neurological disability.[34] Proximity to the eloquent cortex remains the strongest predictor for the ability to completely excise the tumor. Noneloquent cortex tumors are 11.8 times more likely to be excised than those located within the eloquent cortex; however, this was unclear in our study as about (51/98) 52.04% of the study patients had noneloquent tumors but with only (23/98) 23.5% of them having undergone near-total resection, possibly due to large size of the tumors (65.7% were $\geq$5 cm), and the concept of poor survival in those patients believed by many neurosurgeons.

The aggressiveness of this tumor is often reported by many oncologists in routine clinical practice, and up to 10% of GB patients discontinue the treatment due to rapid disease progression.[35] In this sense, the design of therapeutic strategies that aim at shortening the overall treatment time without decreasing efficacy or increasing toxicity is encouraged. Many published data demonstrated that short-course RT with concurrent TMZ and standard long-course CFRT are equivalent in terms of outcome and safety. These results have led to increased use of hypofractionated RT protocols to improve quality of life for elderly and fragile patients

Intuitively, most previous studies have focused on the utility of HFRT in elderly and frail patients, while in our study, we tried to prove the equality of HFRT in all age GBM patients to CFRT, especially for these tumors with disadvantageous radiologic characters and likely neurologic sequelae post-surgery. In this respect, Jablonska PA et al.[36] contemplated the use of 40 Gy/15 F as a valid option in the treatment of GBM with excellent compliance and manageable toxicities.

Our study suffered many limitations, including a small number of patients treated by our protocol. The small sample size was the crucial study limitation and, therefore, it was possible that some statistical associations were not found because of the small number of individuals, single-center study, heterogeneity of patients and tumor characteristics to some extent, and the absence of molecular factors including IDH type, and MGMT methylation. One important issue in our study and center was the use WBRT in phase one (40 Gy/20 fractions) with the potential consequences of changes in QoL, risk of late effects, and decline of neurocognitive function that were aggravated by TMZ necessitating the increase in steroid doses, opiods, and anticonvulsant therapy. However, pretreatment assessment of neurocognition of patients was lacking to assess the magnitude of this decline. Additionally, WBRT is still a standard of care in many situations including brain metastases with 4 or more metastatic deposits, adjuvant to brain focal therapies (surgery or stereotactic radiosurgery), and craniospinal irradiation.

Continuing improvements in understanding this aggressive and devastating tumor will allow investigators to better refine treatment in the future to further improve and extend the lives of GBM patients.

## 8. Conclusion

Our results show that HFRT with concurrent TMZ is a feasible therapeutic approach in patients with GBM, especially those with poor prognostic factors, assuring high treatment compliance and low toxicity rates. Dose escalation and reduction in overall treatment time are clear advantages of HFRT, while at least, the same survival rates as conventional fractionated RT are maintained.

## Conflict of interest

None.

## Financial disclosure

None.

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