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*Original Research Article*

# The Impact of Peripheral Enhancement in Magnetic Resonance Imaging on the Treatment Outcomes of Patients with Glioblastoma Multiform

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## ABSTRACT

**Background:** This study was done in clinical oncology and radio-diagnosis departments of Assiut University Hospital during a period of two years and involved patients' records presented to clinical oncology department from January 2013 to December of 2014.
**Patients and methods:** Only 25 cases with glioblastoma multiform (GBM) were eligible to be included in this retrospective study.
**Results:** 22 patients showed variable percentages of peripheral enhancement (PE) with a mean value of 62.8%. Decreased percentage of PE was associated with better response to standard treatment (*P*=0.001). The median progression free survival (PFS) and overall survival (OS) were 12 ± 1.2 months and 13±1.499 months respectively, PE was negatively correlated with survival (PFS and OS) with significant effect (*P*=0.03 and 0.000 respectively).
**Conclusion:** the percentage of PE had a significant prognostic impact on response and survival of GBM, but still the study needed to be evaluated in larger cohort studies to determine the accurate prognostic role of PE in GBM.
***Key words:*** glioblastoma multiform, survival, MRI, peripheral enhancement, prognostic factors.

## INTRODUCTION

Glioblastoma Multiform (GBM) is the most common primary malignant brain tumor, accounting for 40% of primary CNS Malignancies in adults. The incidence of GBM increases with age and approximately 50% of patients diagnosed with GBM are > 65 years old.

Age, performance status, extent of resection, and neurologic function at the time of presentation are known prognostic factors. Despite aggressive surgery, radiotherapy, and chemotherapy; the prognosis is very poor especially in elderly patients with an overall survival less than one year.

GBM can be classified into primary and secondary, primary GBM occurs in patients older than 50 years with a short clinical history usually less than 3 months, while secondary GBM develops in patients younger than 45 years through a malignant progression from low grade astrocytoma to anaplastic astrocytoma over a mean time interval of 4-5 years indicating different genetic pathways are implicated in the pathophysiology of this tumor with a better prognosis in primary GBM than secondary type.

Molecular markers are important for tissue diagnosis and treatment guidance; less than 10% of patients carry isocitrate dehydrogenase gene mutation, and tumors carry this mutation have a more favorable prognosis. [1]

Epigenetic silencing of methyl-guanine methyl transferase gene promoter suggests inability of the tumor to repair the

chemotherapy–induced DNA damage [2] with improved outcome.

Temozolomide based chemoradiation and adjuvant temozolomide is the standard treatment for patients with GBM especially those less than 70 years of age, with significantly improved survival. [3]

We aimed from this study to determine the impact of percentage of peripheral enhancement on response and survival of patients with glioblastoma multiform treated with the standard temozolomide based chemoradiation followed by adjuvant 6 cycles of temozolomide.

## PATIENTS AND METHODS

This is a retrospective cohort study done mainly in clinical oncology and radio-diagnosis departments of Assiut University Hospital and involved patients with GBM presented to clinical oncology department during a period of two years from January 2013 to December 2014.

Patients' files were evaluated for the following data:

-Histological and radiological diagnosis of glioblastoma multiform

- History, clinical presentation, and preoperative MRI descriptions

-Treatment protocol received regarding radiotherapy (RT) dose and technique, chemotherapy received during and after RT

-The response to treatment was evaluated based on MacDonald criteria on MRI that was done after RT, mid-cyclic and at the end of chemotherapy, then regularly every 3 months over 2 years, MacDonald criteria [4] defined four categories of tumor response (complete response, partial response, stable disease, and progressive disease).

-Progression free survival (PFS), and overall survival (OS) were determined from these files

-preoperative MRIs with gadolinium contrast done at the time of diagnosis, were reviewed carefully by two readers to determine the percentage of peripheral enhancement i.e. the enhancing margin (the amount of the circumference with peripheral enhancement was determined on axial view images, and it was approximately estimated based on the value of the central angle included within this circumference, and expressed as percentage), peripheral enhancement was evaluated in T1 weighted and FLAIR images after contrast injection, fig. 1, 2, 3.

-GBMs without cystic component on MRI were excluded.

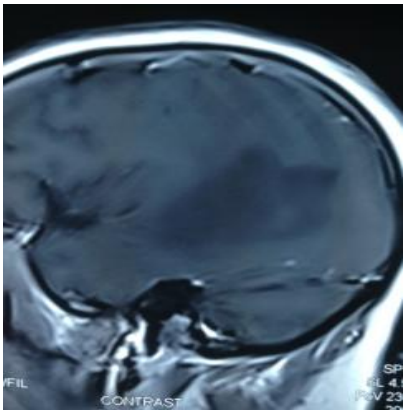

**Fig. 1: T1 image of MRI of GBM of parieto-occipital region without PE of middle aged female diagnosed by biopsy**

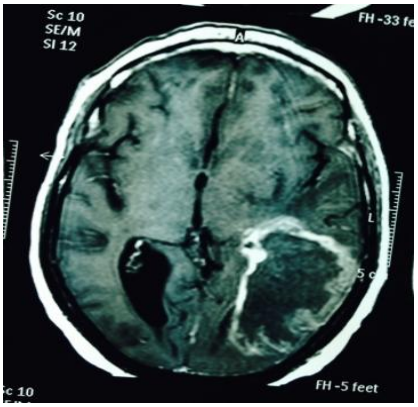


**Fig.2: T1 image of GBM with 100% PE and diagnosed by MRS**

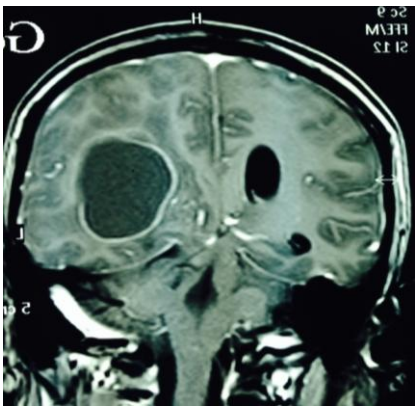

**Fig.3: T1 image of GBM with 80% PE diagnosed by biopsy of a middle aged female**

### Statistical analysis

All data were analyzed using SPSS ver. 21, *P*-value of 0.05 was considered significant with 95% confidence interval, Pearson correlation was used to find the relationship between PE and survival, Anova test, log rank test were used to determine the significance, Kaplan-Meier method [5] was used to determine PFS and OS, the response to treatment were determined based on MacDonald criteria.

PFS was calculated from time of diagnosis to evidence of disease progression on MRI (but not pseudo-progression), and OS was calculated from time of diagnosis to last time the patient was seen or death.

## RESULTS

Only 25 cases with glioblastoma multiform were included in this retrospective study. Clinical data of these patients were demonstrated in the following table (table 1), with a median age of 46 years, male more than female with a sex ratio of 1.08:1, lateralization of clinical picture was predominantly to the right side in 64% of patients with a median duration of symptoms 2.5 months, 24% of patients had no biopsy and the diagnosis in these patients was made depending on clinical data and imaging by MRI spectroscopy.

**Table (1): clinical characteristics of 25 patients with glioblastoma multiform.**

| Characteristic | Number | Percentage (%) |
|---|---|---|
| **Age** | | |
| median±SD | 46±1.3 | |
| mean±SE | 45.9±2.6 | |
| min-max | 21 ys-80 ys | |
| **Sex** | | |
| Male | 13 | 52% |
| Female | 12 | 48% |
| **Duration of symptoms** | | |
| median±SD | 2.5 ± 2.08 ms | |
| min-max | 1-8 ms | |
| **lateralization** | | |
| right side | 16 | 64% |
| left side | 8 | 32% |
| none | 1 | 4% |
| **Type of surgery** | | |
| Biopsy only | 10 | 40% |
| Debulking | 5 | 20% |
| Subtotal excision | 4 | 16% |
| No biopsy | 6 | 24% |
| **Regularity of treatment** | | |
| Regular | 20 | 80% |
| Irregular | 5 | 20% |

### 2- Tumor characteristics based on MRI

MRIs used in this study to calculate percentage of PE were gadolinium contrasted MRIs that were done before surgery or diagnostic MRS Right side of the brain was more commonly affected with glioblastoma multiform in 64% of cases, eloquent areas of the brain were slightly more involved by the tumor in 56% of patients, no peripheral enhancement in MRIs of 12% of patients, and the mean value of PE in the remaining 88% of patients was 62.8%.

**Table (2): MRI characteristics of 25 patients with GBM**

| MRI characteristic | Number | % |
|---|---|---|
| **Side** | | |
| Rt side | 16 | 64% |
| Left side | 8 | 32% |
| Central | 1 | 4% |
| **Brain area** | | |
| Eloquent brain | 14 | 56% |
| Non eloquent brain | 5 | 20% |
| Near eloquent brain | 6 | 24% |
| **Peripheral enhancement** | | |
| No PE | 3 | 12% |
| With different percentages of PE | 22 | 88% |

### 3- Radiotherapy and chemotherapy treatments of 25 cases of GBM

The most common RT dose received was 60 Gy/ 30 fractions/ 6 weeks in 72% of patients, all patients received temozolomide concurrently with RT whatever the dose received, and only one patient did not receive adjuvant temozolomide, 64% of patients completed 6 cycles of adjuvant temozolomide, table (3).

**Table 3**

| | | |
|---|---|---|
| **RT protocol** | | |
| **Dose of RT** | | |
| 45 Gy/ 15 fractions | 6 | 24% |
| 54 Gy/ 27 fractions | 1 | 4% |
| 60 Gy/ 30 fractions | 18 | 72% |
| **Technique** | | |
| Involved field in 2 phases | 8 | 32% |
| Involved field in 1 phase | 5 | 20% |
| Whole brain followed by involved field | 12 | 48% |
| Temozolomide concurrently with RT | 25 | 100% |
| Adjuvant temozolomide | 24 | 96% |
| Number of cycles | | |
| 6 cycles | 16 | 64% |
| <6 cycles | 8 | 32% |

### 4- Response in 25 patients with GBM

The overall response rate (CR+PR) was 56% table 4.

**Table (4): Response in the study group**

| Response | Number % |
|---|---|
| CR | 6 24% |
| PR | 8 32% |
| SD | 6 24% |
| DP | 5 20% |

CR Complete remission, PR partial remission, SD stable disease, DP disease progression

## 5- PFS and OS of 25 patients with GBM

The median PFS for the study group was 12 months with 95% confidence interval (CI) (95% CI: 9.648-14.352 months), while the median OS was 13 months (95% CI: 10.062-15.938) (table 5, figures 4, 5)

**Table (5): Survival data of the study group**

| Survival | Mean ± SE | Median ± SD |
|---|---|---|
| PFS | 12.42 ± 1.893 ms | 12 ± 1.2 ms |
| OS | 13.760 ±1.696 ms | 13 ± 1.499 ms |

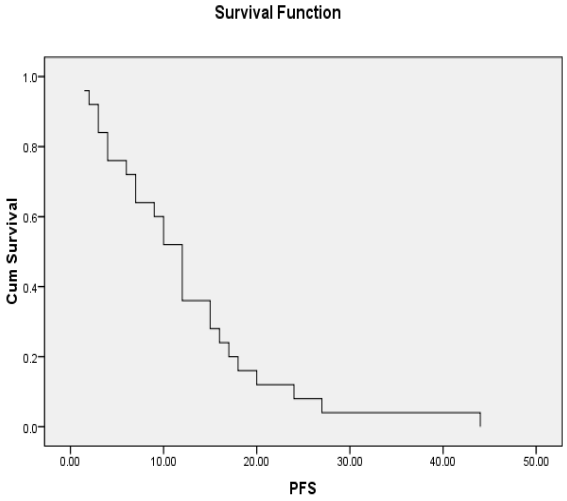


**Fig. 4: progression free survival of 25 patients with GBM**

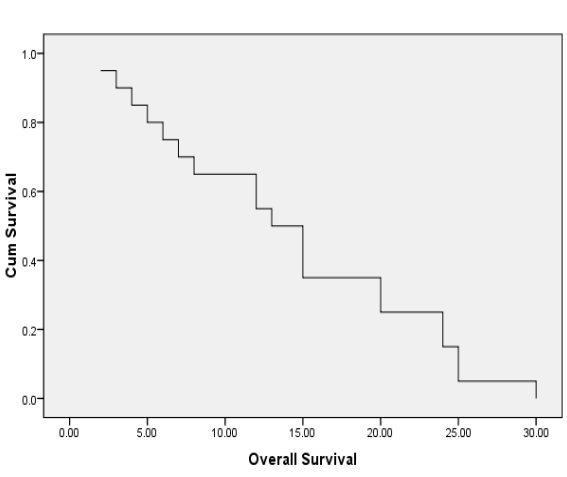


**Fig. 5: Overall survival (last follow up) of 25 patients with GBM**

## 6- Relation between peripheral enhancement (PE) and the type of response.

There was a significant effect of the size of peripheral enhancement on the type of response with better response obtained for those with smaller area of enhancement (table 6).

**Table (6): relation between the response and PE**

| Type of response | percentage of P.E *N Mean of PE* | significance |
|---|---|---|
| CR | 6 30% | |
| PR | 8 51.88% | P= 0.001 |
| SD | 6 87.5% | |
| PD | 5 90% | |

## 7- Relation between survival and the percentage of peripheral enhancement.

There was a negative moderate correlation between PE and PFS, as the smaller the percentage of PE the longer the PFS with significant effect ($P$ = 0.03). And a strong negative correlation between PE and OS with highly significant effect ($P$=0.000). (Fig. 6, 7. Table7).

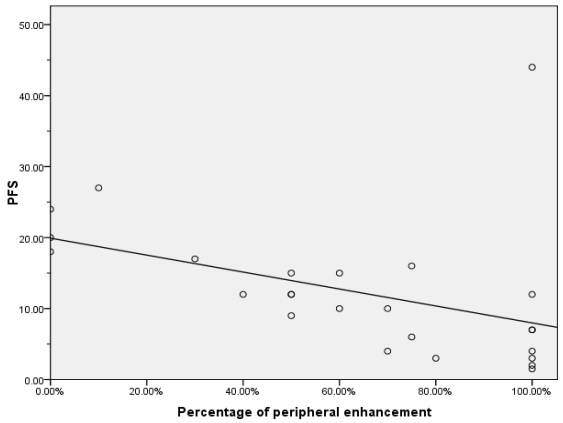


**Fig. 6: correlation between PFS and PE**

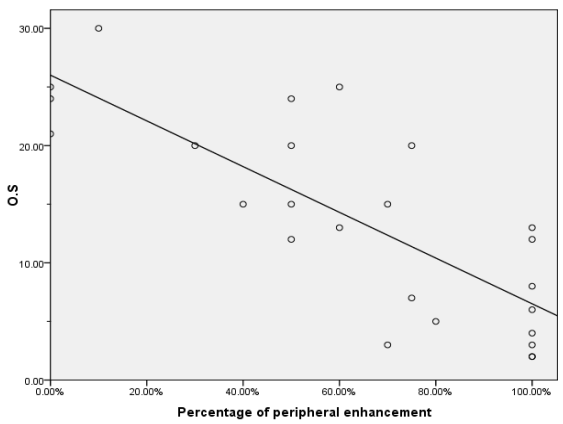


**Fig. 7: correlation between OS (last follow up) and PE**

**Table (7): Relation of peripheral enhancement and survival.**

| PE | PFS | OS (last follow up) |
|---|---|---|
| N =25 | | |
| Pearson correlation | -0.436 | -.0.794 |
| P (2-tailed test) value | 0.03 | 0.000 |

## DISCUSSION

Unfortunately; the management of GBM remains palliative including surgery, radiotherapy, and chemotherapy. The majority of patients have a short median survival with approximately 10% of patients survive about 5 years.

GBM is a rare tumor, however it contributes much to the total number of patients losing their lives in early ages, aggressive surgery followed by radiotherapy concurrently with chemotherapy then adjuvant chemotherapy is the current standard for long term survival in some patients but most patients have a poor prognosis.

Without therapy patients with GBM die within 3 months, but with optimal therapy the median survival is 14 months, [6] less than 25% of patients survive up to 2 years, and less than 10 % live up to 5 years.

In the current study; the median PFS and OS were 12 months and 13 months implicated comparability to previous results and failure of salvage therapies to prolong survival

The current standard of treatment of GBM is safe maximal resection followed by concurrent chemoradiation with temozolomide and radiotherapy dose of 60 Gy followed by 6-12 cycles of 5 days temozolomide.

The biological and molecular heterogeneity of the tumor, poor response to treatment, variability of signaling pathways and poor penetration of different treatment agents to blood brain barrier (BBB) contribute to failure of treatment and progression of the tumor. [7]

Important point in the assessment of a response to treatment is presence of a reliable end point. For GBM; OS, PFS, and response are valuable endpoints, response or no response is based on magnetic resonance imaging interpretations. [8]

The extent of tumor burden on MRI is assessed by the appearance and the size of enhancement on contrast-enhanced T1-weighted images. Contrast enhancement in GBM may suggest impaired blood brain barrier with leakage of contrast agents into the extravascular spaces. Tumor with relatively intact BBB may show no enhancement. Necrosis is the hallmark of glioblastoma and is caused by tumor hypoxia as a result of increased cell proliferation, mitotic activity, and insufficient tissue perfusion. On conventional contrast-enhanced T1-weighted images, tumor necrosis can be easily diagnosed as necrotic zones that are typically less enhanced, giving the tumor an appearance of irregular rim enhancing mass. Conventional MR imaging cannot accurately evaluate the invasive behavior of GBM due to overlapping of edema and tumor cells. However; conventional contrast-enhanced MR imaging is shown to be correlated with Ki-67 index up to 8.1% in gliomas with contrast enhancement as opposed to 2.0% in those without enhancement [9] and the mitotic activity or proliferation of gliomas is known to be significantly correlates with the prognosis. [10,11]

A complete tumor resection has meant to imply removal of the pre-operatively defined contrast-enhancing tumor areas. Whether such radical tumor resection exerts an influence on overall survival time or not is controversial but important studies show positive correlations. [12,13]

Determination of prognostic and predictive factors is essential for stratifications of patient cohorts with the aim to establish an individually customized and balanced therapy, the number of factors known to have an impact on life expectancy in malignant gliomas is very limited, so it is one of the tumors needs to be much more investigated to add more prognostic factors.

## CONCLUSION

This study tried to clarify a prognostic factor that may impact life expectancy as there were moderate to strong negative correlations between the percentages of enhancement of GBM margins and survivals (PFS, OS) with significant effect (P=0.03, P=0.000 respectively), but it was needed to be better evaluated on larger cohorts and in multiple oncologic centres as this study came from single centre.

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