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Research Article

A Retrospective Analysis of High-Grade Glioma Cases Treated in Menia Cancer Center and Gharbia Cancer Society Egypt in the Period from 2008-2014

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Abstract

Aim: To compare results of treatment of Glioblastoma Multiform (GBM) at Menia Cancer center and Gharbia Cancer society in Egypt with the internationally recognized results.

Patients and Methods: The data of 122 patients with GBM treated in the period between 2008 and 2014 were collected including patients' evaluation, data of irradiation process, use of chemotherapy and follow up data. The GTV was delineated at the contrast-enhancing edge of the tumor on postsurgical enhanced T1-weighted MRI scans fused with planning CT. CTV46 = GTV + 25mm, CTV 60 = GTV +15mm. PTV: A 5 mm margin was added to the CTV.

Results: The Follow up period ranged between 1-60 months with a median follow up of 7 months. Median survival time for all patients was 10.6 months and mean survival was 17.2 months. Overall survival at 6 month was 72.8%, at 12 months was 40.3% and at 24 months was 21.8%. The independent prognostic factors in this study were tumor grade, performance status and radiation dose. Two years overall survival was better in grade 3 than grade 3 (p=0.001). one year progression free survival(PFS) was higher in patients with grade 3 and those who have Karnofsky Score (KS)>70% (p=0.001).

Conclusion: Performance status of the patient is a crucial factor in treatment, as it affects prognosis and treatment decision. Implementation of new radiotherapy techniques is highly encouraged to achieve more effective & precise dose delivery with limitation of treatment toxicity.

Keywords: Radiotherapy; GBM

Introduction

In Egypt, there is no clear data about the incidence of high grade gliomas in the population, but in National Cancer Institute (NCI), this group constituted only 0.21% of total malignancy with a slight adult predominance of 54.44% and no sex predilection (50% each). The low number of such tumors could be attributed to the lack of neurosurgery practice at NCI [1]. Malignant astrocytoma; glioblastoma multiform (WHO grade IV), and anaplastic astrocytoma (WHO grade III) are still the most common primary cerebral neoplasms in adults. These highly invasive tumors have a strong predilection for cerebral hemispheres. Glioblastoma Multiform (GBM) comprises 80% of malignant gliomas. While malignant astrocytoma's compromise only 2% of all adult tumors at a rate of 5 cases per 100,000 adults per year, their malignant nature makes them the fourth greatest cause of cancer death [2].

A recursive partitioning technique was applied to an analysis of 1578 patients accrued to three successive Radiation Therapy Oncology Group (RTOG) trials [3]. Age, histological appearance, Karnofsky performance status (KPS), mental status, duration of symptoms, neurological functional class, extent of surgery, and

radiation dose were identified as significant partitioning covariates. Six patient classes were defined with different prognosis as favorable (classes I and II), intermediate (classes III and IV) and poor (classes V and VI). A subsequent reanalysis of data in glioblastoma patients showed no statistical difference between class V and VI with a median survival of 7.5 months [4]. Neurologic symptoms and signs affecting patients with glioblastomas can be either general or focal and reflect the location of the tumor. The most common symptom experienced by patients is headache. Alternatively, patients may present with generalized symptoms of increased Intracranial Pressure (ICP), including headaches, nausea and vomiting, and cognitive impairment. Seizures are another common presenting symptom.

MRI with and without contrast is the study of choice. These lesions typically have an enhancing ring observed on T1-weighted images and a broad surrounding zone of edema apparent on T2-weighted images. Several pathological studies have clearly shown that the area of enhancement does not represent the outer tumor border because infiltrating glioma cells can be identified easily within, and occasionally beyond, a 2-cm margin [5]. Positron Emission Tomography (PET) scans and magnetic resonance (MR) spectroscopy can be helpful to identify glioblastomas in difficult cases, such as those associated with radiation necrosis or hemorrhage. A study by Piroth et al., found that O-(2- [(18) F] Fluoroethyl-L-tyrosine (FET) PET to measure tumor volume after surgery has a strong prognostic impact [6].

Upon initial diagnosis of Glioblastoma Multiform (GBM), standard treatment consists of maximal surgical resection, radiotherapy, and concomitant and adjuvant chemotherapy with temozolomide [7,8]. For patients older than 70 years, less aggressive therapy is sometimes employed, using radiation or temozolomide alone [9-11]. A study by Scott et al., found that elderly patients with glioblastoma who underwent radiotherapy had improved cancer-specific survival and overall survival compared with those who did not undergo radiotherapy treatment [12]. Recent evidence suggests that in patients over 60 years old, treatment with temozolomide is associated with longer survival than treatment with standard radiotherapy, and for those over 70 years old, temozolomide or hypo fractionated radiotherapy is associated with prolonged survival than treatment with standard fractionated radiotherapy. The improvement in survival with temozolomide is enhanced in patients with MGMT promoter methylation [13].

Stupp et al., [14] reported the final results of the randomized phase III trial for patients with glioblastoma who were treated with adjuvant temozolomide and radiation with a median follow-up of more than 5 years. Stupp et al., previously reported improved median and 2-year survival when temozolomide was added to radiation therapy in glioblastoma. Survival in the combined therapy group (i.e., temozolomide and radiation) continued to exceed that of radiation alone throughout the 5-year follow-up ($p < 0.0001$). Survival of patients who received adjuvant temozolomide with radiotherapy for glioblastoma is superior to radiotherapy alone across all clinical prognostic subgroups.

Median time to recurrence after standard therapy is 6.9 months [15]. For recurrent glioblastoma multiform, surgery is appropriate in selected patients, and various radio therapeutic, chemotherapeutic, biologic, or experimental therapies are also employed [16,17]. This is a retrospective analysis of high grade gliomas cases treated in Radiation Oncology Department at Menia Cancer Center and Gharbia Cancer Society at Egypt during the period between 2008 and 2014. All treatment data & results were collected and correlated with the different prognostic factors, in order to compare our results with the internationally recognized results.

Patients and Methods

This is a retrospective study of 122 patients with high grade gliomas treated in the Radiation Oncology Department, Menia Cancer Center, Gharbia Cancer Society during the period between 2008 and 2014.

i. Patients' evaluation was done including age, sex, date of diagnoses, presenting neurological manifestations, complete clinical examination including Karnofsky's performance score (KPS).

ii. Data of irradiation process; date, dose, method of planning, overall period of treatment, and mean dose to the target.

iii. Use of chemotherapy (Temodal), whether concurrent or adjuvant after end of radiation.

iv. MRI brain based follow up two to three months (after the end of treatment).

v. The date of last follow up and the status of the patient as regards local control & survival status.

Immobilization of patients using thermoplastic masks prior to treatment planning with their necks either in angle 0, hyper flexed or in prone position, according to tumor location. Serial C-T cuts was taken for the patient with I.V. contrast together with CT to MRI image registration was used. The GTV is delineated at the contrast-enhancing edge of the tumor (not edema) on postsurgical gadolinium enhanced T1-weighted MRI scans fused with planning CT. CTV46 = GTV + 25mm, CTV 60 = GTV +15mm. PTV: A 5 mm margin is added to the CTV.

3D planning

Treatment was given only to the PTV(s) using a 3-D conformal fields shaped to exclude as much of the normal brain and other critical structures as possible. The beam's eye view displays must be used to design beam apertures. Field arrangements will

be determined by 3-D planning to produce the optimal conformal plan in accordance with the volume definition used. Vertex and other non-coplanar fields was done to reduce dose to adjacent normal brain. The use of beam intensity modulation therapy is not allowed (except for wedges, compensating filters, and static beam shaping devices, such as MLC). The treatment plan used for each patient will be based on the treating physician's analysis of the volumetric dose including DVH analysis of the PTV and critical normal structures.

Statistical Analysis

Comparison of numerical variables between the study groups was done using Student t test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. Comparison between more than two groups was done using one-way analysis of variance (ANOVA) test when normally distributed and Kruskal Wallis analysis of variance test when not normally distributed.

For comparing categorical data, Chi square (C^2) test was performed. Exact test was used instead when the expected frequency was less than 5. Kaplan-Meier method was used to estimate overall survival and progression free survival as a function of time since start of treatment Comparisons between survival functions were performed by using the log rank statistic.

Results

The Follow up period ranged between 1-60 months with a median follow up of 7 months. Median survival time for all patients was 10.6 months and mean survival was 17.2 months. Overall survival at 6 months was 72.8%, at 12 months was 40.3% and at 24 months was 21.8% Figure 1.

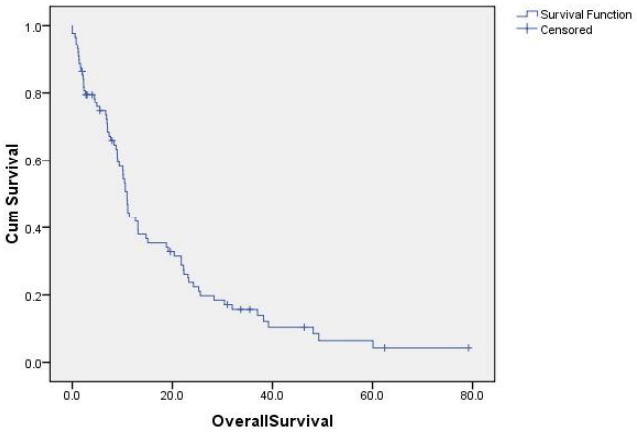

Figure 1: Overall survival for all patients.

Out of 122 patients in our study, only 94 patients received their scheduled treatment, and those patients only will be included in our survival analysis. On univariate analysis, we found that tumor grade, performance status, overall treatment period and radiation dose were statistically significant prognostic factors. There was a significant difference in overall survival regarding the grade of the tumor, where for grade III tumors, overall survival at 6,12& 24 months respectively were 80.3%, 54.8 % and 33.9% compared to 65.2%, 30.7% and 11.9% for grade IV tumors ($p < 0.001$) Figure 2 & Table 1.

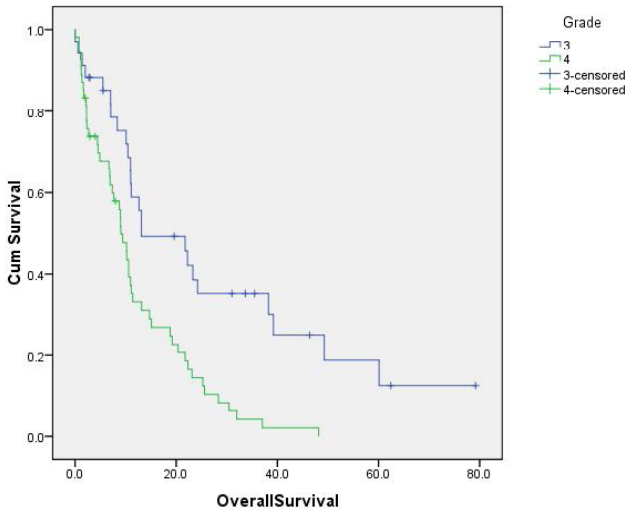

Figure 2: Overall survival according to tumor grade.

	No.	OS at 6 Month	Median OS ± SE	p-value
Whole group	94	72.8%	10.9 ± 4.54	
Grade of lesions				
Grade 3	41	80.3%	13.1 ± 2.8	<0.001
Grade 4	53	65.2%	9.1 ± 4.4	
Performance status				
> 70	41	93.3%	21 ± 0.65	<0.001
≤ 70	53	63.2%	6 ± 2.6	
Radiotherapy duration				
< 50 days	49	89%	15.1 ± 4.1	<0.001
>50 days	45	78.9%	10.4 ± 5.9	

Table 1: Overall Survival (OS) for all patients and relations to different prognostic factors at 6 months. (SE: standard error).

Progression free survival for grade 3 tumors at 6 & 12 months were 77.1 & 48.4% respectively compared to 61.4 & 25.9 % at 6 & 12 months for grade 4 tumors with p value < 0.001 Figure 3.

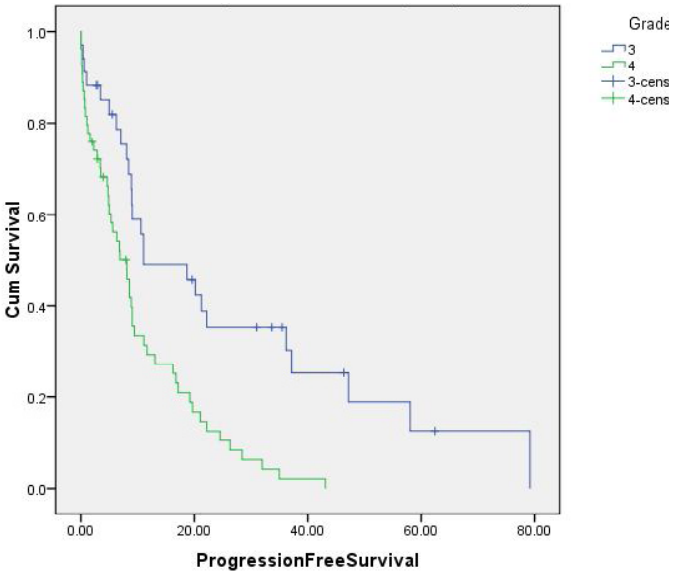

Figure 3: Progression free survival according to tumor grade.

Progression free survival was 93.2 & 71.0 % at 6 &12 months respectively for patients with KPS of > 70 % compared to 49.8 & 9.2% for those with KPS < 70 % Figure 4.

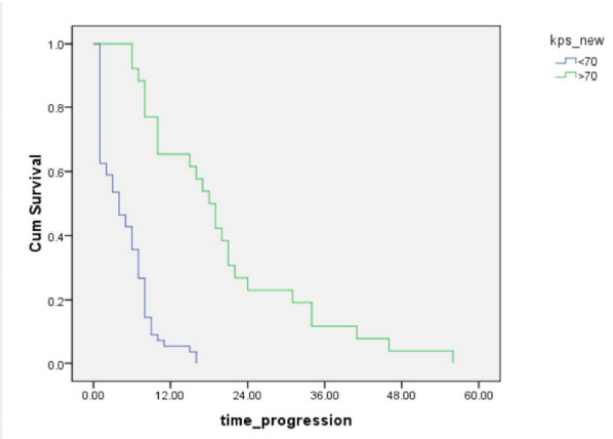

Figure 4: Progression free survival in relation to KPS.

Discussion

High grade gliomas remain a challenging issue for the oncologists despite the great advances in the multimodality approach; surgery, chemotherapy and radiation. The present work is a retrospective study involving 122 patients with high grade gliomas treated with multimodality therapy.

As regarding the grade, 53 patients were histologically WHO grade IV (56.38 %), while 43 patients were WHO grade III (43.62 %), which is consistent with other statistics that reveals that GBM is more common than malignant astrocytoma's as shown in Davis F et al., 1998 who demonstrated an 80 % incidence of GBM among malignant brain gliomas. Overall survival in this study was in accordance to several important. prognostic factors discussed in RTOG Recursive Partitioning Analysis (RPA) such as age, histology, Karnofsky performance status scale and radiation dose (Curran WJ Jr. et al., 1993). Regarding KPS, overall survival was significantly better for those with P.S > 70% compared to other groups, being 61.0% at 12 months, compared to 47.5 % for P.S < 70 %, these results are consistent with results obtained from RTOG RPA, which showed better survival in patients with better performance status (Curran WJ Jr. et al., 1993).

In our study, we found a correlation between overall survival and duration of treatment, which was statistically significant in the favor of duration less than 50 days compared to those received their planned treatment in a period more than 50 days, where OS at 6 months were 89 % and 78.9 % for both groups respectively with a significant p value (p< 0.001). Multivariate analysis of our statistical data confirmed the significance of tumor grade; radiation dose and KPS score regarding overall survival and progression free survival, while it was not significant for overall period of treatment.

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