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Glioblastoma Multiform: Analysis of Patients Treated with Radiotherapy at King Abdulaziz University Hospital

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Abstract. Treatment of Glioblastoma Multiform typically involves maximal surgical resection, followed by adjuvant radiation therapy. In this study, all patients with GBM treated with radiation therapy after initial surgical intervention at King Abdulaziz University Hospital were reviewed. From April, 2000 to December 2002, 13 patients were treated, 9 (69%) males and 4 (31%) females. Two (15%) patients had near complete resection, one (8%) had biopsy only and 10 (77%) had partial resection. Radiation therapy was given on palliative intent in 10 (77%) patients with dose of 24-30 Gy, and 3 (23%) cases treated radically with dose of 54-60 Gy. Radiological follow-up after 6-8 weeks from completion of radiation therapy showed complete response in 8%, partial response in 38%, stable disease in 8%, disease progression in 38% and 8% did not have their radiologic evaluation. Evaluation after one year showed overall survival rate was 36%, the median survival time was 9.5 months; the median time to disease progression was 6 months. Radiation therapy provided good palliation for these patients.

Keywords: Glioblastoma multiform, Radiation therapy, Palliation.

Introduction

In spite of the substantial advances in the field of oncology due to improvements in the neuroradiology, neurosurgical techniques, and novel

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methods to deliver radiation therapy, the outcome of newly diagnosed Glioblastoma Multiform (GBM) has improved little. The median survival time remains 10 to 12 months; the 2-year survival rate is under 10%. The outcome in these patients continues to be related to prognostic factors more than the type of therapy[1].

Prognosis of these patients is affected by the presence of multiple tumors and patient's related factors, like extent of disease, patient's performance status, and degree of neurological deficit. Changes in treatment protocols have so far attributed little to preventing mortality from uncontrolled local disease[2].

The initial treatment of GBM is maximal surgical resection with minimal damage to the surrounding normal brain tissue[3]. Many trials have reported a modest improvement in local control and survival for those patients who had adjuvant radiation therapy after surgical resection when compared to those who had surgery alone[4]. A limited improvement in survival was noted in those patients who were given the addition of systemic chemotherapy to postoperative radiation therapy[5].

The aim of this study was to review the clinical presentation and treatment results of patients with GBM referred to the radiotherapy unit of King Abdulaziz University Hospital (KAUH).

Patients and Methods

All patients with histological proven GBM treated at the Radiotherapy Unit, KAUH from April 2000 till December 2002 have been reviewed. Evaluation included patient's age, sex, performance status using Eastern Cooperative Oncology Group (ECOG) scale[6], whether or not the patient presented with increased intracranial tension, presence or absence of cranial nerve palsy, and any neurological deficits.

Extent of disease was evaluated by computerized tomography (CT) scan or magnetic resonance imaging (MRI), criteria included: tumor size, degree of edema around the lesion and presence or absence of midline shift.

Types of surgeries included biopsy, partial resection, or complete resection. Patients with a performance status of III/IV by ECOG received postoperative palliative radiation therapy as 30 Gy in 10 fractions, 300 cGy daily fractions over 2 weeks. The planning target volume was as the edema around the tumor plus 2 cm margin. Patients with performance status of I/II by ECOG scale received radical postoperative radiotherapy. The radiation therapy was delivered in two phases, the planning target volume for Phase One included the edema around the tumor plus 2 cm margin and was treated to 46 Gy in 23 fractions, 2 Gy per fraction per day over 4.6 weeks, then Phase Two to boost the tumor with 2 cm margin to a total dose of 60 Gy. The dose was calculated by 3D using CT planning system (Cad plan) and patients were treated by Varian 2100c linear accelerator.

Patients were followed up at 6-8 weeks after radiation therapy by CT scan / MRI to evaluate response. Complete response (CR) was defined as complete disappearance of the previously seen lesion, partial response (PR) was defined as reduction of more than 50% of the lesion, stationary disease (SD) was defined as no change or less than 50% reduction of the lesion and disease progression (DP) was defined as increase of the lesion size, or the appearance of new lesions. After the initial assessment, patients follow up was arranged every 3 months for the first 2 years, then bi-annually for the next 3 years, then per annum for 5 years. At each visit, a clinical and radiological assessment is done with the same assessment criteria mentioned before. At any time, if patients developed neurological deficits or manifestations of increased intracranial symptoms they were subjected to full clinical and radiological assessment.

Descriptive statistics were used and the overall survival (OS) was determined by Kaplan-Meier method. Overall survival was measured from the date of histological diagnosis till last follow-up or death of the patient.

Results

The total number of patients was thirteen, 9 (69%) males and 4 (31%) females. The median age was 51-years-old (range: 43-73 years). The performance status was III in 10 (77%) patients, I in 2 (15%) patients and II in one (8%) patients. Ten (77%) patients presented with increased intracranial pressure and 4 (31%) patients had cranial nerve palsy. The average tumor size was 6 cm and it ranged from 2.9 to 7.5 cm, peritumor edema was marked in 10 (77%) patients with midline shift.

Two (15%) patients had total gross resection of the tumor, 10 (77%) had partial resection and one (8%) patient had biopsy only. Nine (69%) patients had palliative radiotherapy and 4 (31%) had radical radiotherapy.

Radiation toxicity is summarized in Table 1.

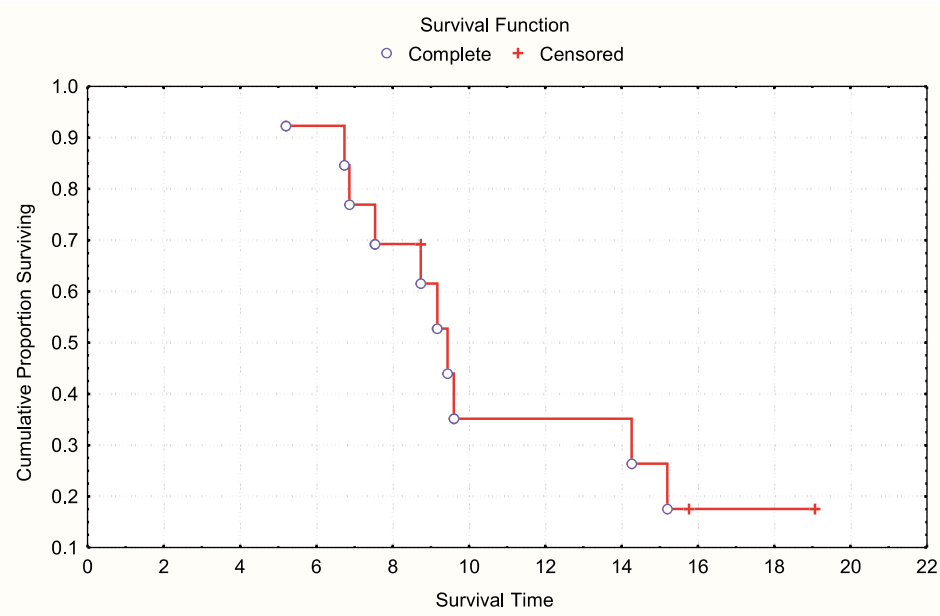
Table 1. Radiation therapy related toxicity (Radiation Therapy Oncology Group scale).

Toxicity	G0	G1	G2	G3
Nausea	22%	0	54%	24%
Vomiting	54%	0	31%	15%
Headache	46%	15%	31%	8%
Alopecia	0	0	62%	38%

Tumor response at 6-8 weeks follow-up was radiological CR in one (8%) patient, PR in 5 (38%), SD in 1(8%), DP in 5 (38%) and one (8%) patient had no radiological assessment.

During patients' follow-up: 4 (31%) patients showed stable disease (SD) and 9 (69%) showed disease progression (DP). At the end of follow-up, only 3

(23%) of 13 cases were still alive, while 10 patients (77%) had died of their disease. Overall survival rate at one year was 36%, the median survival time was 9.5 months, and the median time to disease progression was 6 months. The survival rate is shown in Fig. 1.



Complete: patients who died.
Censored: patients who were living on their last follow up.

Fig. 1. Overall survival curve for the patients in the study.

Discussion

GBM is considered a relatively uncommon malignancy within the overall oncology referrals to cancer centers, with an average incidence of 2.6 cases/100,000 populations per year[7]. Regional figures for its incidence showed also a low incidence rate as shown by Cancer incidence report in Saudi Arabia (year 1994-1996)[8]. The overall incidence of brain tumors was 0.2 cases /100,000 population which represented 4.4% of all cancer referrals. In Egypt; GBM cases represented only 18.2% of all gliomas cases during the period 1968-1980 and around 32.8% during the period 1981-1991[9]. However the overall incidence of brain tumors in the same center had been found to be only 6% as compared to other types of cancer[10]. Thirteen cases of GBM were referred to the Radiotherapy Unit at KAUH during the 2 year period 2000-2002. The aim of that study was to evaluate the treatment results of patients with GBM referred to the Oncology Center at KAUH during that period.

Surgical treatment ranged from biopsy to partial or complete surgical resection. Data from 3 prospective studies including a total of 645 patients with GBM were reviewed for the influence of extent of surgery on survival; surgical treatment consisted of biopsy only in 17% of cases, partial resection in 64%, and total resection in 19% of cases; it was found that the median survival was longer for those who had either total resection (11.3 months), or partial resection (10.4 months) when compared to those who had biopsy only (6.6 months), the difference in survival among the 3 groups was not statistically significant[11]. In Meta analysis from a series that compiled a data from 20 studies of 5,691 patients, only 4 studies found a relation between the extent of surgery and survival[12]. In the current study; the majority of cases (77%) had partial resection.

Because of the infiltrative nature of GBM, even gross total resection is associated with a high recurrence rate, and adjuvant radiation therapy is indicated to improve local control.

Many studies demonstrate the importance of postoperative irradiation as shown by Andersen[13] in a prospective randomized trial of patients with GBM treated with surgery only (57 cases) versus those treated with surgery and postoperative radiation therapy (51 cases); the median survival was statistically higher (23 weeks) in irradiated patients as compared to those who had surgery alone (15-weeks) P value < 0.005. Walker *et al*.[4], demonstrated in a prospective randomized trial that those patients treated with postoperative irradiation (93 patients) had a better median survival (36 weeks) if compared to those who had surgery alone (42 patients), whose median survival was 14-weeks, a statistically significant difference (P = 0.001). Recently, a meta-analysis of six randomized trials detected a significant survival benefit favoring post operative radiation therapy versus no radiation therapy, risk ratio; 0.81, 95% confidence interval; and P value < 0.0001[14].

Before the development of conformal radiation therapy, whole cranial irradiation (WCI) was given to patients; its efficacy was evaluated by researchers such as Coffey *et al*.[15] who found that those patients with GBM treated with WCI with radiation doses > 50 Gy had a median survival of 27-weeks which was much higher than those treated with WCI at doses less than 50 Gy (11-weeks). The usual radiation dose given to patients with GBM who would be treated with WCI ranged from 50-60 Gy, and the median survival of those patients treated with doses between 50 and 60 Gy of WCI is the same as shown by Walker *et al*.[16] the median survival for those patients treated with whole cranial irradiation at doses of 50, 55 and 60 Gy were 28-, 36-, and 42-weeks, respectively.

The rational of using limited field radiation therapy in GBM is that, 80-90% of cases of recurrent GBM after WCI were located within 2 cm of the original tumor[17].

Sheline *et al*.[18] reported a median survival of 10-months for GBM using limited volume radiation therapy which was comparable with that seen in patients treated with whole cranial irradiation. Wallner *et al.*[19] documented that more than 90% of treatment failure were due to tumor recurrence at original site.

Radiation therapy dose when limited volume is used is 56-60 GY in 28-30 fractions which resulted in a one year survival of 39% and 18-month survival of 18%[20]. Dose escalation above 60 Gy did not result in any improvement in disease control or survival as shown by Scott *et al.*[21] compared in a randomized prospective study 520 patients with GBM who received either 72 Gy / 60 fractions / 6 weeks (hyper-fractionated arm) or 60 Gy / 30 fractions / 6 weeks (standard arm); the median survival for the two groups was 11 months and 12.2 months, respectively (P value = 0.44).

Chan *et al*.[22] treated 34 patients with supratentorial GBM with 90 Gy/45 fractions after initial surgical resection using 3 dimensional treatment planning system, not including peritumoral edema in the gross tumor volume (GTV), and the planning target volume (PTV) was designed with 2.5 cm around the GTV, using intensity modulated radiation therapy technique and giving the radiation through 5-6 non-coplanar fields. The median survival was only 11.7 months and the 1- and 2-year survival rate was 47.1% and 12.9%, respectively.

Chemotherapy has been used in GBM, in the Brain Tumor Study Group (BTSG) trial (protocol 69-01) patients post-surgery had either supportive care, carmustine, whole cranial irradiation (WCI), or WCI and carmustine. The median survival for the two groups of patients who had WCI and WCI with carmustine was identical[4]. Deutsch *et al*.[23] reported BTSG protocol 77-02, 603 patients with GBM were randomized between 4 arms post surgery: arm I - carmustine plus conventional radiotherapy (60Gy/30 fractions/ 6 weeks); arm II - streptozocin plus conventional radiotherapy, arm III: carmustine and hyper-fractionated radiotherapy (66 Gy /60 fractions given as 1.1 Gy twice daily (BID) over 6 weeks); and arm IV - conventional radiotherapy with misonidazole as radiosensitiser followed by carmustine. The median survival of the 4 arms was similar about 10-months. Prados *et al*.[24] in a prospective randomized trial on 231 cases of GBM tried an accelerated hyperfractionation (70.4 Gy /44 fractions, 1.6 Gy per fraction given as twice daily fractions) alone or with chemotherapy (DiFluoroMethylOrnithine – DFMO) vs. conventional radiation given as 59.4 Gy /33 fractions, 1.8 Gy per fraction alone or with DFMO, the median survival for the 4 groups of patients were 10-, 10.5-, 9.2-, and 4-months, respectively. The difference was not statistically significant (P = 0.48). Other studies confirmed the lack of benefit from chemotherapy[10,25].

Previously mentioned studies showed that aggressive treatment modalities were not of additional benefit to these patients. Thus, a hypofractionated schedule of radiation therapy was adopted for these patients, considering the

palliative nature of treatments and the aggressive course of the disease. Hoegler and Davey[26] and Thomas *et al.*[27] used palliative radiation therapy course of 30Gy/ 6 daily fractions and 30 Gy /10 daily fractions respectively, the median survival ranged beween 4-8 months with an acceptable toxicity profile; results similar to those reported with prolonged fractionations schedules[18,19,28] in a prospective randomized trial which compared 3 different fractionation schedules in 155 patients with GBM: either 66 Gy/33 fractions versus 40 Gy/ 8 fractions (5 Gy / fraction), or 28 Gy/ 4 fractions (7 Gy per fraction), the median survival was 7-, 5.6-, and 6.6-months, respectively, no difference in survival was noted among the 3 groups.

The current study is a retrospective review of GBM cases treated at KAUH, 77% were treated surgically with partial resection as compared with 65% (Prados *et al*.[24]) and 74% (Grossman *et al*.[1]). Sixty-nine percent of patients in this study received irradiation on palliative basis (30 Gy/10 fractions) due to poor performance status (ECOG performance scale III/IV) with a median survival of 9.5 months, and a 1 year survival rate of 36%. Hulshof *et al*.[28] found that the median survival for patients treated with 40 Gy/ 8 fractions or 28 Gy/ 4 fractions, were 7- and 5.6-months, respectively. McAleese *et al*.[30] in a comparative study of hypofractionated radiation (using 30 Gy/6 fractions / 2 weeks) to GBM patients versus conventional method of 60 Gy /30 fractions /6 weeks found that median survival was higher among the conventional arm but was not statistically significant. Chang *et al*.[29] in a higher dose schedule (50 Gy/20 fractions at 2.5 Gy per fraction) found that the median survival was 7 months. In centers that treat on a radical basis like Brandes *et al*.[31] patients received 59.4 Gy/ 33 (1.8 Gy per fraction) either alone (arm I) or with chemotherapy procarbazine, lomustine and vincristine (arm II) or with temozolomide (arm III), the median survival of the whole group was 7.2 months without any statistically significant difference between the 3 groups.

Radiation toxicity, in the current study was acceptable with gastrointestinal Grade II (GII) nausea in 54% of patients, vomiting GII in 31%, headache GII in 31%. The toxicity profile of hypofractionated radiation therapy in GBM has been found to be acceptable in other studies as that shown by Chang *et al*.[29], and McAleese *et al*.[30].

Conclusion

Hypofractionated radiation therapy is an acceptable treatment modality in patients with poor performance GBM with an acceptable toxicity profile. It is more convenient to the patient and reduces the cost of treatment. It is recommended to study the hypofractionated irradiation in a larger number of patients with a longer follow-up.

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الورم الدبقى متعدد الأشكال : دراسة للمرضى المعالجين بالأشعة بجامعة الملك عبدالعزيز

ياسر عبد العزيز بهادر

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جـــدة – المملكة العربية السعودية

المستـخلص. عـلاج الورم الدبقى المتـعـدد الأشكـال عـادة مـا يكون بالاستئصـال الجـراحى ، ويتبـعـه العـلاج بالأشعـة . فى هذه الدراسـة قـمنا بمراجـعـة جميع حـالات الورم الدبقى المعـالجـة بالأشـعـة فى جامـعـة الملك عـبـدالعزيـز خلال الفـتـرة من إبريل ٢٠٠٠م إلى ديسـمبـر ٢٠٠٢م . ثلاثة عـشـر مـريضًـا، ٩ منهم (٦٩٪) ذكـورًا ، و٤ مـنهم (٣١٪) إناثًا. ١٥٪ كـان بالاستئصال الجراحى كاملاً، وواحدًا (٨٪) أخذت عينة فقط و٧٧٪ كان الاستـئصـال جزئيًـا . العـلاج بالأشـعـة أعطي بشكل خـفـيف لـ ٧٧ ٪ من المرضى ، وبشكل جذرى لـ ٣٣٪ .

تمت متـابعة المرضى بعد ٦–٨ أسـابيع من أخذ الإشـعـاع ، الاستـجـابة كـانت كلية في ٨ ٪ ، وجـزئـية في ٣٨ ٪ ، ومـسـتـقـرة في ٨٪ ، وزاد حـجم الورم في ٣٨ ٪ ، و٨ ٪ لم نستطع تقييمهم.

متـوسط الحـياة للمـرضى كان ٩,٥ شـهـرًا و٣٦ ٪ منهم كـانوا على قـيـد الحياة لمدة سنة .