Treatment Outcome of Supratentorial High Grade Astrocytoma and Glioblastoma Multiform

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Abstract

Purpose: The study was initiated to obtain epidemiologic data and information on anatomic distribution, clinical features and treatment results in patients with primary supratentorial anaplastic astrocytoma and glioblastoma multiform.

Patients and Methods: Between January 2000 and January 2006, 113 primary high grade astrocytoma patients were eligible to evaluate clinical features.

Radiotherapy was received by all patients whether gross total tumor excision had been carried out or not. External beam radiation therapy was delivered at 2Gy once daily to the intracranial lesion and surrounding oedema with 2-3cm safety margin all around with a dose of 4000cGy/20 fraction in 4 weeks, followed immediately by a booster localized field to intracranial bed proper to a dose of 2000cGy/10 fraction in 2 weeks using 60Co photons.

Results: A total of 58.4 patients had anaplastic astrocytoma and 41.6 of the cases, had glioblasloma multiform. The most common site of origin was the temproparietal region (31.8%). Large tumors (>5cm) accounted for the majority (75.2%). Seventy one percent of primary high grade astrocytoma patients had a duration of symptoms of >9 months. Most primary supratentorial anaplastic astrocytoma and glioblastoma multiform patients had objective radiological response (52.13%) to treatment. Among all our patients, sex, perfor- mance status, duration of symptoms, histologic grade, tumor size and extent of surgery were significant prognostic factors for OS.

Conclusion: High grade astrocytoma is heterogeneous disease. Histopathology of the tumor, sex, performance status, tumor size, duration of symptoms and extent of surgery were the most important significant prognostic factors. The number of patients with high grade astrocytoma did not allow for detailed analysis. Large studies are needed for primary supratentorial anaplastic astrocytoma and glioblastoma multiform with new treatment modalities to improve survival in these patients.

Key Words: Supratentorial high grade astrocytoma – Anaplastic astrocytoma – Glioblastoma multiform – Surgery – Radiotherapy.

Introduction

PRIMARY brain tumors occur with an approximate incidence of 17,000 new cases per year in the United States. The associated 13,000 deaths per year from primary brain tumors account for 2% of all cancer mortality. The frequency of primary brain tumors show an increase with age: 4/100'000 at age younger than 10 years, versus 70/100,000 for ages older than 70 years [1].

Although the exact nature of the carcinogenic events leading to primary brain tumors induction is not known, experimental evidence suggests an accumulation of genetic alterations leading to the acquisition of a malignant phenotype thought to involve activation of cellular oncogenes and loss of cellular tumor suppressor genes [2].

Astrocytomas are the most common primary brain tumors. Collectively these neoplasms account for about 75% of primary malignant brain tumors. Glioblastoma rarely occurs in people younger than 15 years, but dramatically increases after the age of 45. The incidence of most glial tumors, other than glioblastoma multiforme actually decreases with increasing age. There is some concern that the incidence of glioblastoma multiforme is increasing in the elderly population Davis et al., [3] although incorrect ascertainment preceding the widespread availability of computed tomography (CT) scans in the late 1970s and magnetic resonance imaging (MRI) in the 1980s may account for some of the presumed increase in incidence [4].

Survival for patients with malignant gliomas remains poor despite multimodality treatment. Five year survival is 29.7% for anaplastic astrocytomas and 3.4% for glioblastoma, according to the Central Brain Tumor Registry of the United States [5].
According to Gharbiah cancer registry total cases of brain and central nervous system tumor 2000-2002 [6] is 362 cases representing 3.1% of all incident cancers Male to female ratio is 1.2: 1 mean age for males 41.7 year and for females 36 years. Astrocytoma represent 47.3% of centenal nervous system (CNS) tumor, gliomas 33.9%, medulloblastomas 10.5% and ependymomas 8.3% [6].

In addition to tumor grade, however, several other factors influence the survival. In 1993, Curran and colleagues performed a recursive partitioning technique to analyze survival in 1578 patients entered in three Radiation Therapy Oncology Group malignant glioma trials from 1974 to 1989. Six prognostic classes were identified based on age, histology, Kamofsky Performance Score, mental or neurological status extent of surgery and radiation dose. Survival ranged from 4.6 to 58.6 months among these classes [7].

Patients and Methods

From January 2000 through January 2006, every patient with a primary supratentorial anaplastic astrocytoma and glioblastoma multiform reported in Clinical Oncology Department, Tanta University Hospital was considered eligible to evaluate the clinical features of this disease.

According to the study protocol for evaluation of treatment, patients who were older than 75 years and/or presented with second malignancies, had missing confirmation of histologic subtype, or had comorbidity prohibiting therapy were excluded from the study.

Diagnostic and staging procedures:

The diagnostic work-up included patients’ history, physical and neurological examination, blood work (liver enzymes, alkaline phosphatase, creatinine and RBC and WBC count), computerized tomography and/or MRI of brain, chest X-ray and abdominal ultrasound evaluation. Formalin-fixed specimens and histopathological examination of the tumors were done for all patients. In cases of tumor resection, the extent was analyzed retrospectively based on operating sheets and histopathologic certificates.

Study design and treatment strategy:

We decided to perform a nonrandomized retrospective study as for supratentorial anaplastic astrocytoma and glioblastoma multiform, the scarcity of the disease would not allow the accrual of enough patients for a valid statistical analysis.

Protocol radiotherapy and surgery was obligatory as follows:

**Surgery:**

Surgical procedure was performed in all patients these operations, included: Biopsy in 72 patients, subtotal excision in 27 patients and gross total excision in 14 patients.

**Radiation therapy:**

External beam radiation therapy was delivered at 2Gy once daily to the intracranial lesion and surrounding oedema with 2-3cm safety margin all around with a dose of 4000cGy/20 fraction in 4 weeks, followed immediately by a booster localized field to intracranial bed proper to a dose of 2000cGy/10 fractions in 2 weeks using $^{60}$Co photons.

All bilateral or median cerebral hemispheric tumors are treated with parallel-opposed lateral portals. Treatment of unilateral hemispheric tumors is planned and performed according to location. Frontal lesions encompassing only the anterior parts of the lobe treated with anterior and lateral isocentric beams and the dose distribution may be optimized with wedges in either or both beams.

Midcerebral tumors (posterior frontal or anterior parietal) treated with parallel-opposed anterior and posterior portals as well as with lateral portals.

Posterior parietal or occipital lesions treated with posterior and lateral isocentric beams, both suitably wedged for dose homogenization. Lesions in the temporal lobe tip are treated with lateral portals.

**Criteria for response and follow-up procedures:**

Response quality was evaluated by CT and/or MRI brain to evaluate the former tumor bed. A complete response (CR) required the absence of any radiologically visible tumor. Partial response was considered to be a $>50$ decrease in tumor area (calculated by multiplying the longest diameter by the greatest perpendicular diameter) or in the case of multiple lesions, a $>50$ decrease in the sum of the products of the perpendicular diameters of these lesions. Progressive disease was defined as a greater than 25% increase in the size of the target lesion or in a case of several target lesions, a greater than 25% increase in the sum of the products of the perpendicular diameters of these lesions or the appearance of any new lesions. Stable disease was defined as a bidimensionally measurable decrease of less than 50% or increase of less than 25% in the sum of the products of the largest perpendicular diameters of the measurable lesion.
Follow-up brain CT scans and/or MRI were obtained after the initial, 4000-cGy dose of radiation, three months after the completion of treatment and then every six months thereafter. At each follow-up, evaluation consisted of pertinent medico history, physical and neurological examination. Median follow-up for the entire group was 10 months (range 2-32 months).

Statistical methods:
The date of final analysis was January 2006. Patients were stratified according to histological grade (supratentorial anaplastic astrocytoma versus glioblastoma multiform).

SPSS version 11.0 was used for data management. Kaplan Meier method estimated overall survival. Log rank test compared survival curves with p value $<0.05$ considered significant. Overall survival was measured from the day of starting treatment to the time of death or to last follow-up.

Results
Between January 2000 and January 2006, the total number of patients eligible for this study was 113. Patient characteristics are listed in Table (1). The two histologic grade subtypes were evenly distributed according to stratified patient characteristics.

<table>
<thead>
<tr>
<th>Table (1): Patient characteristics.</th>
<th>Anaplastic astrocytoma</th>
<th>Glioblastoma multiform</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patient</td>
<td>66</td>
<td>47</td>
</tr>
<tr>
<td>Age</td>
<td>18-69</td>
<td>22-67</td>
</tr>
<tr>
<td>Mean</td>
<td>40.9</td>
<td>45.9</td>
</tr>
<tr>
<td>Median</td>
<td>38</td>
<td>50</td>
</tr>
</tbody>
</table>

**Clinical presentation:**
- Increased intracranial tension: 43 (65.2), 38 (80)
- Neurological Deficit (hemipsresis): 39 (59.1), 28 (59.6)
- Vision defect: 17 (26), 16 (34)
- Seizures: 18 (27.3), 19 (40)

**Duration of symptoms:**
- ≤3 Months: 53 (80), 27 (57.1)
- >3 Months: 13 (20), 20 (42.9)

**Site:**
- Single site:
  - Temporal: 6 (9), 5 (10)
  - Parital: 15 (23), 6 (13)
  - Frontal: 2 (3), 4 (8)
  - Corpus callosum: 2 (3), 3 (7)
- Multiple sites:
  - Temproparital: 22 (33), 14 (30)
  - Frontoparietal: 13 (20), 6 (13)
  - Parieto-occipital: 6 (9), 9 (19)

**Karnofsky performance status:**
- >80: 8 (12.12), 5 (10.63)
- <80: 58 (87.87), 42 (89.36)

**Extent of surgery:**
- Biopsy: 38 (57.6), 34 (72.3)
- Subtotal: 19 (28.8), 8 (17)
- Gross Total: 9 (16.3), 5 (10.6)

**Pre-operative tumor size:**
- ≥5 cm: 47 (71), 38 (81)
- <5 cm: 19 (29), 9 (19)

**Postoperative tumor size:**
- ≥5 cm: 40 (61), 30 (64)
- <5 cm: 26 (39), 17 (36)
**Treatment compliance:**

Most patients (57.6% in the anaplastic astrocytoma arm and 72.3% in the glioblastoma multiform arm) underwent biopsy. Only 9 patients (13.6% in the anaplastic astrocytoma arm and 5 patients (10.6%) in the glioblastoma multiform arm underwent gross total excision (Table 1). All patients were treated by external beam radiation therapy which was delivered at 2Gy once daily to the intracranial lesion and surrounding edema with 2-3cm safety margin all around with a dose of 4000cGy/20 fraction in 4 weeks, followed immediately by a booster localized field to intracranial bed proper to a dose of 2000cGy/10 fraction in 2 weeks using $^{60}$Co photons.

**Acute toxicity:**

The most common features of toxicity in both groups were nausea and/or vomiting independent of changes in intracranial pressure in 29 of those with anaplastic astrocytoma versus 36% of those with glioblastoma multiform particularly with posterior fossa irradiation and alopecia within the irradiated areas which was permanent in 23% of those with anaplastic astrocytoma versus 31.9% of those with glioblastoma multiform. Radiation dermatitis was usually mild and treated with topical hydrocortisone if necessary.

**Late toxicity:**

The most serious late reactions to radiation therapy were radiation necrosis in 6.1% of those with anaplastic astrocytoma versus 8.5% of those with glioblastoma multiform and blindness in 3% of those with anaplastic astrocytoma versus 8.5% of those with glioblastoma multiform. Inclusion of the middle ear was associated with vestibular damage in 9% of those with anaplastic astrocytoma versus 19% of those with glioblastoma multiform.

**Response to treatment and survival:**

Table (2) shows the complete response rates of the primary tumor following therapy of 113 Patients. Four of them were complete responders (3.53%) after therapy. The rest of the patients (109) who had persistent tumor and who were evaluated for response $8$ (7.07%) exhibited tumor progression. While 55 patients (48.6) underwent partial radiological response.

The anaplastic astrocytoma arm was associated with more clinically complete and partial responses (Table 2) than the glioblastoma multiform arm (66.66% versus 31.9%).

<table>
<thead>
<tr>
<th>Radiological response (R.S.)</th>
<th>Anaplastic astrocytoma</th>
<th>Glioblastoma multiform</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete (R.S.)</td>
<td>4 6.06</td>
<td>0 0</td>
<td>4 3.53</td>
</tr>
<tr>
<td>Partial (R.S.)</td>
<td>40 60.6</td>
<td>15 31.9</td>
<td>55 48.6</td>
</tr>
<tr>
<td>Stationary response</td>
<td>22 33.3</td>
<td>24 51.0</td>
<td>46 40.7</td>
</tr>
<tr>
<td>Tumor progression</td>
<td>0 0</td>
<td>8 17.02</td>
<td>8 7.07</td>
</tr>
</tbody>
</table>

The higher response rate following treatment in the anaplastic astrocytoma was associated with a significant better (overall survival) OAS ($p<0.001$) Fig. (1).

**One-Year overall survival rate was 54% for patients with tumor size <5cm but dropped to 24% for patients with tumor size >5cm (Fig. 2). The difference was statistically significant $p=value <0.001$.**

![Fig. (1): Survival rate of all patients according to histological grade.](image1)

![Fig. (2): Survival rate of all patients according to tumor size.](image2)
Among the 71 male patients, the overall actuarial survival was significantly better than among the 42 female patients. One-year overall survival rate was 46% for male patients but dropped to 26% for female patients ($p<0.001$) Fig. (3).

The one year survival rate was 71% for patients with gross total resection Vs. 52% for patients with partial resection and 26% for these subjected to biopsy only. The difference was statistically significant ($p<0.001$) (Fig. 5).

One year overall survival rate was 100% for patients with performance status $\geq 80$ Vs. 50% for patients with performance status $<80$.

Among the 80 patients with duration of symptoms $\leq 3$ months, the overall actuarial survival was significantly better than among those 33 with duration of symptoms 3 months one-years overall survival rate was 46% for patients with duration of symptoms $\leq 3$ months but dropped to 27% for patients with duration of symptoms $>3$ months ($p<0.001$) (Fig. 4).

The one year survival rate was 38% Vs. 36% for patients $\geq 40$ years and those $<40$ years respectively. The difference was statistically insignificant ($p=value >0.05$) (Fig. 6).

**Proportional-hazards analysis:**

Multivariate and univariate analyses were used to provide quantitative estimates of the association of the following seven clinical and pathological tumor factor with overall survival in the 113 studied patients: Clinical tumor size ($<5cm$ Vs. $>5cm$) ($p<0.001$), the presence or absence of gross total tumor resection ($p<0.001$), duration of symptoms $\leq 3$ months ($p<0.001$), age of the patient ($p=>0.05$), performance status $\geq 80$ Vs. $<80$ ($p<0.001$), sex
(p=<0.001) and the tumor grade (anaplastic astrocytoma Vs. glioblastoma multiforme) (p=<0.001). Thus this analysis of overall survival showed that clinical tumor size the presence or absence of gross total tumor resection, duration of symptoms, performance status, sex as well as the tumor grade all approached statistical significance (p=<0.001).

Discussion

This retrospective study included 113 patients with supratentorial high grade astrocytoma presented at Clinical Oncology Department, Tanta University Hospital during the period from January 2000 to January 2006.

The principle prognostic factors and their effect on results of treatment were retrospectively evaluated in these patients.

In this study the mean age was 43.7 years for the whole study group which was lower than that reported by Stuart et al., [8] who reported a mean age of 55 years.

The mean age of patients with glioblastoma multiforme and anaplastic astrocytoma in this study was 40.9 and 45.9 respectively and this was lower than reported by Laws ER., et al., [9] who reported mean age of 45 years and 58 years for anaplastic astrocytoma and glioblastoma multiforme respectively, also Burger et al., [10] reported mean age of 56 years and 46 years for anaplastic astrocytoma and glioblastoma multiforme respectively. The median age was 42 years which is lower than that reported by Magrini et al., [11] who reported median age of 59 years. This may be due to environmental factors.

In this study the majority of patients were male and constituted 62% of all cases which is comparable to Stuart et al., [8] and Magrini et al., [11] where male sex constituted 67% and 61% respectively.

In our study anaplastic astrocytoma compromised 58.4% and glioblastom multiforme compromised 41.6% of all cases. Taizo N and Kiyoshi [12] reported anaplastic astrocytoma in 32% and glioblastoma multiforme in 68% of all cases. Jermic et al., [13] and Rao et al., [14] reported that glioblastoma multiforme compromised 77% and 61% of all cases respectively.

As regard to clinical presentation 71.6% of our patients presented with symptoms of increased intracranial tension, this was similar to the finding of Burger et al. [10].

The majority of our patients 71% had duration of symptoms <3 months before the diagnosis, which is comparable to Walker et al., who reported 60% of his cases.

In our study only 11.5% of all cases had performance status > 80 Kamofsky performance scale which were worse than that reported by Gene et al., [15] who reported performance status in > 70 in 67% of all cases while Nieder et al., [16] reported median Kamofsky performance score 70. This can be explained by the better general condition and earlier diagnosis of the patients in those studies.

The majority of our patients 62% had tumor size >5cm, this figure is similar to Chang et al., [17] but Magrini et al., [11] reported 52% of all cases >5cm.

Surgery remains the most effective method for achieving rapid symptoms control and rapid cytoreduction. In this study 64% of all cases were subjected to biopsy, 24% were subjected to subtotal resection and 12% were subjected to gross total resection. Taizo and Kiyoshi [12] reported 25.7% of cases underwent gross total resection, 35.6% underwent subtotal resection and 38.6% underwent biopsy.

Magrini et al., [11] reported 25% underwent biopsy, 21% partial resection and 44% radical resection. This can be explained by early detection and good surgical procedure available for treatment of these patients.

Prognostic variables can be divided into patient characteristics, tumor characteristics and treatment related variables. Patient characteristics include age, sex, performance status and durations of symptoms.

In our study there was no statistically significant difference in survival rate between patients aged <40 years and those >40 years one and two years survival rate for patients aged <40 years were 36% and 10% respectively and for patients aged >40 years were 38% and 11% respectively. This could be explained by small number of patients and imbalance in performance state and tumor grade between both groups, Burger et al., [10] reported that the inverse relation between the increasing age and decreasing survival could be due to diminishing resistance of the host accelerating malignancy of the neoplasm or both.

Age as prognostic factor affecting survival was reported by Brada et al., [18] Backner et al., [19], Prados et al., [20] and Levin et al., [21]. All of them...
reported that younger patients are associated with better survival rate.

As regard sex there was significant difference in survival rate between male and female in favor of male. Male showed survival rate of 46% and 16% at 1 and 2 years respectively in contrast to 26% and 2% at same time interval for female.

Magrini et al., [11] reported that male was related to worse survival. While most of studies didn't consider gender as prognostic factor [22,23].

As regard performance state and its association with survival there was significant difference in survival rate between cases who had performance status >80 Kamofsky performance scale and cases who had performance status <80. Survival rate were 100% and 33% at 1 and 2 years respectively for the first group in contrast to 50% and 11% for the second group Kowalczyk et al., [21]. Yeh et al., [24] reported performance status as prognostic factor and its association with survival. Performance status has also shown to consistently affect survival in both NCCTG (North Central Cancer Treatment Group) and Brain Tumor Study Group trials [19].

In our study as regard the duration of symptoms there was significant difference between patients with duration of symptoms <3 months and those who had duration more than 3 months. The one year survival rate was 46% for patients with duration >3 months and 27% for patients with duration <3 months. Gehan et al., [25] reported that, long duration of symptoms lengthen the survival, possibly because of slower tumor growth.

In this study the histopathology was one of the most important prognostic factors with significant difference of survival rate in favor of anaplastic astrocytoma over glioblastoma multiforme. Survival rate was 48% and 18% at 1 and 2 years respectively for anaplastic astrocytoma in contrast to 23% and 0% respectively at same time interval for glioblastoma multiforme, these results were comparable with that reported by Kowalczyk et al., [21]. The analysis of 10 NCCTG and Mayo Clinic trials reported by Buckner et al. [19] with histology data of 1368 patients has also shown a significant survival difference between anaplastic astrocytoma and glioblastoma multiforme (p value <0001).

In this study tumor size was another prognostic factor that affect survival rate there was significant difference in survival rate between patients who had tumor size <5cm and those with tumor size >5cm, 1 and 2 years survival rates were 54% and 25% respectively for patients who had tumor size <5cm and for patients who had tumor size >5cm were 24% and 4% respectively. Magrini et al., [11] reported 1 and 2 years survival rate of 29% and 9% respectively for patients who had tumor size >5cm this finding runs in accordance with our results.

Treatment related variable analyzed in this study was the extent of surgery, in this study there was significant difference in survival rate between patients who had just biopsy and those who subjected to either sub or gross total excision in favor of the latter however there was no statistically significant difference in survival rate between patients who had subtotal excision of their tumor and those treated by gross total tumor excision. Laws et al., [9] reported that patients who underwent biopsy had worse survival outcome than patients who underwent resection. The importance of extent of surgical resection was also documented by Nitta and Sato [12], Sanwaya et al., [26] and Lacroix et al., [27].

In general to allow better comparison between anaplastic astrocytoma and glioblastoma multiforme larger prospective studies are needed. Evidence-based treatment for high grade astrocytoma will require prospective randomized trials comparing efficacy and toxicity. Because of the complex relationship between treatment efficacy and toxicity and the diverse assumptions and expectations for treatment held by patients with cancer, the comprehensive measurement of health status has become an important and appropriate component of many clinical trials. In conclusion future researches allowing newer treatment modalities to improve survival in these patients are recommended.

References


