ORIGINAL ARTICLE

Clinical Risk Factors Affecting Survival of Primary Cerebral Malignant Astrocytoma at a University Hospital in Western Saudi Arabia

MOHAMMED BANGASH

Section of Neurological Surgery, Department of Surgery, King Abdulaziz University
P.O Box 42806 Jeddah 21551, Saudi Arabia

ABSTRACT

Objective: *Malignant astrocytomas are the most aggressive tumors affecting the brain. The natural history of survival of malignant astrocytomas differs significantly between anaplastic astrocytoma and glioblastoma multiforme (1). The clinical risk factors affecting the survival of malignant astrocytomas are scarcely studied (2). The aim of this study is to describe the clinical risk factors affecting the survival of malignant astrocytomas at king abdulaziz university hospital in Jeddah.*

Materials and Method: *From January 2004 to December 2008, medical files of patients with a diagnosis of anaplastic astrocytoma and glioblastoma multiforme were retrospectively reviewed. Only those with characteristic pathologic findings suggestive of malignant astrocytomas were enrolled. Demographic data and clinical manifestations with outcome were analyzed. All data were processed using SPSS 16 software (SPSS Inc., Chicago Illinois).The data were analysed for age, symptoms, signs and clinical risk factors influencing the survival of both tumours. Differences with $p < 0.05$ were considered significant.*

Results: *Forty eight cases were evaluated. The number of anaplastic astrocytoma was 15 (31.25%) and the number of GBM was 33 (68.75%). The mean age for glioblastoma multiforme was 55.3 ± 27.5 years. The mean age of anaplastic astrocytoma was 27.4 ± 21.3 years. Risk factors that worsen the prognosis were: A- old age $p = .00002$, B- Vomiting $p < .02$, C- Numbness $p < .0001$, D- Cranial nerves abnormalities $p < .0004$ and E- Abnormal mental status $p < .003$.*

Conclusion: *Clinical risk factors affecting the survival negatively of patients with malignant astrocytomas are age, presentation with vomiting, numbness, abnormal mental status and abnormal cranial nerves examination.*

Keywords: *Anaplastic astrocytoma, glioblastoma multiforme, clinical, risk factors, Jeddah, Saudi Arabia.*

Abbreviations: *Anaplastic astrocytoma (AA), glioblastoma multiforme (GBM), clinical risk factors, Malignant astrocytoma (MAS).*

INTRODUCTION

Astrocytomas are brain tumors that originate from the glial cells. They represent a wide variety of tumors, ranging from benign tumors to malignant tumors. WHO classification for astrocytomas is a widely used system. It is based on the pathological features of the tumors (cell proliferation, mitosis, nuclear atypia and neovasculization). **Grade I** is a benign tumor (such as pilocytic astrocytoma) where there is cell proliferation only with no malignant features. **Grade II** is a benign tumor (such as fibrilary astrocytoma) where there are two neoplastic features. **Grade III** is a malignant tumor (such as anaplastic astrocytoma "AA") where there are three neoplastic features. **Grade IV** is the most malignant tumor (glioblastoma multiforme "GBM") where there are all four features of the malignant neoplasm. Malignant astrocytomas (MAS) refer to the grades III and IV.

Anaplastic astrocytoma (AA) represents about 4.3% of all brain tumors. While glioblastoma multiforme (GBM) represents about 22.6% of all brain tumors (3).

The natural history of survival of MAS differs significantly between AA and GBM ranges from two months to eight years.[1]

The outcome of astrocytoma varies, where it is favorable for benign types and fatal for the malignant types. The treatment options for MAS are **surgery**, **chemotherapy** and **radiotherapy**. The **Prognosis** is influenced by age, symptoms' duration, mental status and performance status. A truly complete resection, which is a recognized independent prognostic factor, is not possible and recurrence in the surgical cavity is common.[4] The clinical risk factors affecting the survival of MAS are scarcely studied.[2]

The aims of this study are (a) to describe the clinical features of malignant astrocytoma and (b) to describe the clinical risk factors affecting the survival of malignant astrocytoma at king abdulaziz university hospital (KAUH) in Jeddah.

MATERIALS AND METHOD

From January 2004 to December 2008, medical files of patients with a diagnosis of anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM) were retrospectively reviewed. Only those with characteristic pathologic findings and radiological features suggestive of MAS were enrolled. Demographic data and clinical manifestations were reviewed and analyzed. The outcome was recorded.

Pathology Specimen

The pathologic diagnosis included 33 GBMs and 15 AA. The diagnosis was determined with specimens removed at surgical resection or biopsy, according to the WHO criteria, by general pathologists at KAUH. The specimens were obtained from both enhanced and non-enhanced areas of each tumor with reference to three-dimensional contrast material – enhanced MR images by using a neuro-navigational system (Brain Lab Vector Vision neuronavigation system, Germany) during surgery or biopsy. Routine histo-pathological tests were done (hematoxylin and eosin) and special immune-histochemistry studies (GFAP and Ki-67 / MIB-1) for all patients.

Postoperative Treatment

After surgery, all the patients subsequently received radiation therapy according to the protocol of our hospital. For AAs, local brain irradiation of 72 Gy for 30 days (5 days a week for 6 weeks) was delivered with the **hyperfractionation** method (1.2 Gy delivered twice a day). For GBM, whole-brain irradiation of 30 Gy for 15 days (5 days a week for 3 weeks) was delivered with the conventional method, and afterward, localized irradiation of 30 Gy for 10 days (5 days a week for 2 weeks) was delivered with the **accelerated hyperfractionation** method (1.5 Gy delivered twice a day). All the patients were evaluated at monthly outpatient examinations.

Statistical Analysis

All collected data were processed using SPSS 16 software (SPSS Inc., Chicago Illinois). The data were summarized as the mean ± standard deviation unless otherwise indicated. Univariate analysis of pooled data was performed with the Student t test and Wilcoxon rank-sum (Mann – Whitney test) for continuous parametric and nonparametric variables, respectively, and the χ^2 test (or Fisher exact test) for categorical variables. The correlation was made between the age, clinical presentation, treatment and the outcome using Pearson correlation test. The cumulative survival was computed using the Kaplan – Meier method. Survival time was calculated from the time of diagnosis to the date of death or the end of 2008. The effect of variables on the survival time was evaluated by Log Rank test. Stepped Cox regression test was used for the multivariate analyses. Differences with $p < 0.05$ were considered significant.

The ethics committee of King Abdul Aziz university Hospital, Jeddah, Saudi Arabia approved this retrospective study without requiring patients' consent.

RESULTS

Malignant Astrocytoma (MAS) Statistics

Total of 48 cases admitted to KAUH from January 2004 to December 2008 were evaluated.

Tumor Pathology:

The number of AA was 15 (31.25%), all patients were confirmed with pathological studies.

The number of GBM was 33 (68.75%), all patients were confirmed with pathological studies.

Age

The mean age for GBM was 55.3 ± 27.5 years. The mean age of AA was 27.4 ± 21.3 years.

There was a bimodal distribution of age where it peaks at age of 0-10 and between ages of 60-80 years.

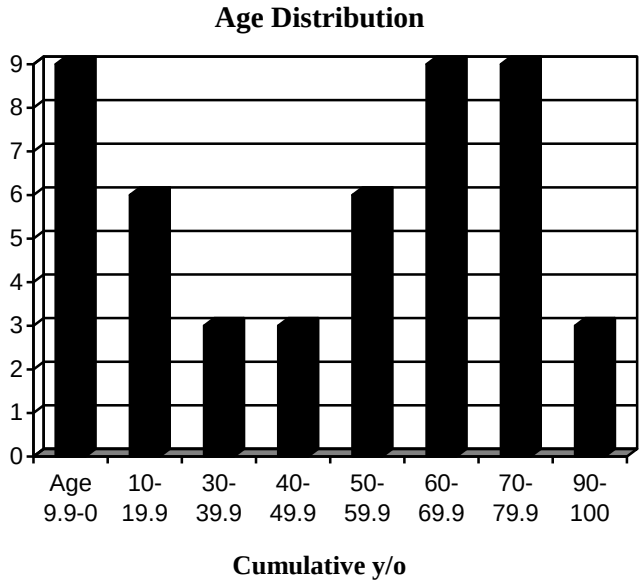

Figure 1: *Histogram shows the age distribution of MAS patients.*

Sex

The number of male patients is 18 (37.5%) and the number of female patients is 30 (62.5%).

The male to female ratio is 1:1.6.

Number of male patients affected by glioblastoma multiforme (GBM) was 12 (66.67%) of all males in the study .The number of female patients affected by GBM was 21(70%) of all females in the study.

The number of male patients affected by AA was 6 (33.3%) of all patients in the study. The number of female patients affected by anaplastic astrocytrma (AA) was 9 (30%) of all female patients.

About two thirds of the affected patients were females and about one third was males.

Clinical Manifestations

Symptoms

The most common presenting symptom for Malignant astrocytoma (MAS) was headache 24 (50%) followed by seizure 12 (25%) and weakness 12 (25%).

Signs

The most common presenting sign for malignant astrocytoma was weakness 24 (50%) followed by abnormal reflexes 15 (31.25%).

Duration of Symptoms

The mean time for duration of symptoms was 1.4 ± 1 month for anaplastic astrocytoma (AA) and 3.28±5.2 months for GBM.

Table 1: *Count and percentage of the symptoms encountered with MAS.*

Symptom	Count	%
Headache	24	50%
Nausea	6	12.5%
Vomiting	9	18.75%
Seizure	12	25%
Numbness	3	6.25%
Weakness	12	25%
Blurred vision	3	6.25%
Unsteady gait	5	10.42%

Table 2: *Count and percentage of the signs encountered with MAS.*

Sign	Count	%
Altered mental status	12	25.00%
Weakness	24	50%
Cranial nerve abnormality	12	25%
Pupil abnormality	3	6.25%
Coordination abnormality	3	6.25%
Reflexes abnormality	15	31.25%
Speech abnormality	3	6.25%

Surgical Treatment

All patients (48) underwent surgical interventions; 27 (56.25%) biopsy only and 21 (43.75%) craniotomy for resection. The decision regarding which procedure to be performed depended on the patients' level of consciousness, the location of the tumor (superficial or deep) and radiological appearance of the mass (suggestive of MAS or not).

Outcome

The mean time of survival for anaplastic astrocytoma (AA) was 29.6 ± 22 months (95% CI18.4 – 40.7). The mean time of survival for the GBM is 4 ± 7.3 months (95% CI 1.4 – 6.5).

Risk Factors

Age: The older the patient the worse the prognosis is. F (1, 46) = 0.3, p = .00002.

Where age of 46.6 (95% CI = 38.29 – 54.96) years was shown to be a demarcation age since patients < 46.6 years survived more than one year and patients > 46.6 years survived less than one year (95% CI = 6.76-17.24).

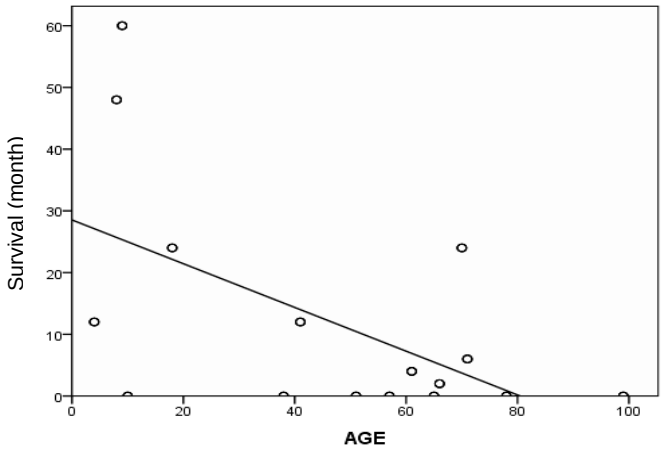

Figure 2: *Correlation between age (years) and survival (months).*

Vomiting presence worsens the prognosis r (48) = .3, p < .02.

Patients presented with vomiting survived less than one year (95% CI = 6.76 – 17.24), and patients presented without vomiting survived more than one year.

Numbness presence worsened the prognosis r (45) = .64, p < .0001

Patients presented with numbness survived less than 10 nonths (95%CI = 4.8 – 15.2).

Cranial nerves abnormalities worsen the prognosis r (48) = .49, p < .0004.

Patients presented with abnormal cranial nerves examination survived less than 10.2 months (95% CI = 4.9 – 15.5).

Abnormal mental status worsen the prognosis r (45) = .42, p < .003.

Patients presented with abnormal mental status examination survived less than 10.0 months (95% CI = 4.8 – 15.3).

Effect of Treatment on Survival

Radiotherapy alone was an independent factor that prolong the survival of both types of MAS F (1, 46) = 0.2, p = .0007.

For MAS the survival was affected significantly with combined treatment (surgery, chemotherapy and radiotherapy). χ^2 (1, N = 48) = 8.64, p = .003.

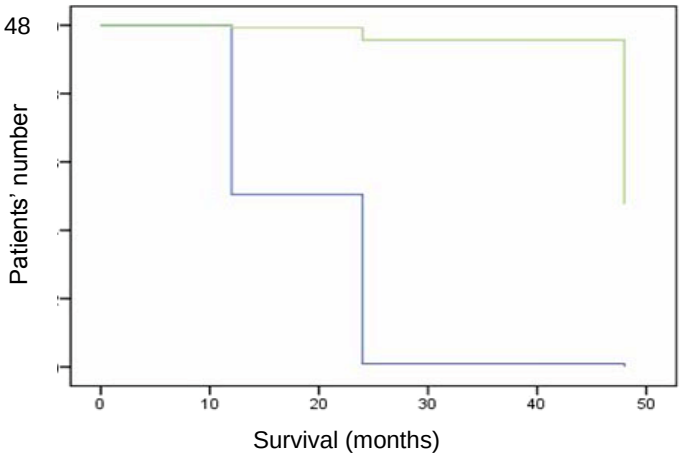

Figure 3: *Kaplan – Meier survival curve showing the survival of AA (upper line) in comparison with GBM (lower line).*

DISCUSSION

Gliomas are a heterogeneous group of neoplasm that comprises the majority of tumors originating in the central nervous system (CNS). In adults, the most frequently encountered of these are high – grade or malignant neoplasms of astrocytic lineage, ie, anaplastic astrocytoma (AA) and glioblastoma multiforme (GBM).[5]

The current study focuses on the malignant astrocytomas only as they represent one of the most common primary brain tumors.[6,7]

It is shown in this study that the patients' age falls into bimodal distribution. It peaks in the first and sixth decades of life. For the adult population the age is consistent with other study that showed almost the same age of involvement. The first decade of life involvement is mainly due to brain stem malignant astrocytomas. The patients ' age of anaplastic astrocytoma is significantly less than the GBM age (27 vs. 55 years)

that is consistent with another study that showed same results.[8] However, in this study the difference is almost half of the age between the two groups.

The sex distribution is almost the same. This is different from most of the literature documentation, where the male predominance is common.[9] This can be explained by the fact that the current study focuses only on the malignant astrocytomas without including other types of gliomas. However, this finding needs further evaluation.

The clinical presentation with headache and weakness is due to either increased intracranial pressure or direct tumor invasion to the brain tissues. The clinical findings in this study are in concordance with other articles[10-13] with this aspect.

The duration of symptoms shows less time period for the anaplastic astrocytoma by two months than GBM. This is the same range reported by the Tugcu et al.[6]

Age in this study is shown that younger patients survive longer than elderly patients, with patients less than forty six years survived more than one year. This finding is in line with the previously described literature.[14,15] The author observed a pattern of declining survival rates in patients with increasing age of the patient, that is in consistence with other study.[16]

Patients presented with **vomiting** survived less than other patients with no vomiting. This finding is most likely due to either increased intracranial pressure or brain stem invasion by the tumor. In either case, the survival is significantly affected due to fatality of both possibilities.

Presence of **numbness** affected the survival signifi-cantly. Where patients presented with numbness survived less than ten months.

Abnormal Mental status affects the survival. Patients with low mini mental status score survived less than normal mini mental status ones. This is a well established prognostic factor in the literature.[17-19] The current paper confirms this finding in our patients' population.

Abnormal cranial nerves upon admission worsen the prognosis. Patients with abnormal cranial nerves examination survived less than 10.2 months in comparison with intact cranial nerves. It is possible to be related to increased intracranial pressure or brain stem involvement.

Combined treatment with **surgery, chemotherapy and radiotherapy** prolonged the survival significantly that is well known in the literature.[20-23]

This is a retrospective study. Keeping in mind that this study focuses on clinical risk factors only, so follow up of the study cohort is not essential. However, a prospective study will increase the power of the evidence level of the findings in this article.

The patient's number limitation in this study represents a single institution experience. More patients can be recruited by conducting a multicentre study.

The Kanofsky performance scale is not emphasized on in this article, as it was well studied in other papers.[24-27] It is highly recommended to adopt a patients performance scale assessment upon admission of the patients to unify different assessment methods in the hospital, which is adopt it in many articles.[28-32]

This article may help the health care provider(s) to predict the survival of patients with MAS preoperatively. However, using advanced techniques will increase the accuracy of this prediction.[33]

CONCLUSION

Clinical risk factors affecting survival negatively of patients with malignant astrocytomas at King Abdul Aziz university hospital are age, presentation with vomiting, numbness, abnormal mental status and abnormal cranial nerves examination.

ACKNOWLEDGMENTS

The authors would like to thank Maha Daffa in medical records and Razan Mikwar in the IT department for their great help and effort in collecting the data for this article.

Address for Correspondence:
Mohammed Bangash MD, FRCSC
Assistant Professor, Section of Neurological Surgery,
Department of Surgery, King Abdulaziz UniversityP.O
Box 42806 Jeddah 21551, Saudi Arabia
E-mail: mhbangash@hotmail.com
Phone: + 966-2-6408222, ext.20344/18207
Fax: + 966-2-6408222, ext.20344

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