Clinicopathological features and treatment outcomes of brain stem gliomas in Saudi population

Yasser Bayoumi, Abdulrahman J Sabbagh, Reham Mohamed, Usama M ElShokhaiby, Ahmed Marzouk Maklad, Mutahir A Tunio, Ali Abdullah O Balbaid

AIM: To analyze experiences to identify treatment outcomes and prognostic factors in a Saudi population.

METHODS: Medical records of patients with brainstem gliomas treated from July 2001 to December 2012 were reviewed to identify treatment outcomes of surgery, radiation therapy and chemotherapy and associated prognostic factors in a Saudi population.

RESULTS: We analyzed 49 brain stem glioma (BSG) patients from July 2001 to December 2012; 31 of them were males (63.3%) with a median age of 12.6 years (range: 8-64 mo). Twenty-two patients (44.9%) had diffuse intrinsic pontine gliomas (DIPG) and 15 (30.6%) presented with focal/tectal BSG. Histopathology was available in 30 patients (61.2%). Median survival time for the whole cohort was 1.5 years. One and two year OS rates were 51.1% and 41.9% respectively. Two year OS rates for focal/tectal, dorsally exophytic, cervicomedullary and DIPG tumors were 60%, 33.3%, 33.3% and 13.6% respectively ($P < 0.0001$). Significant prognostic factors related to OS were age at diagnosis (worse for $> 18$ years) $P = 0.01$, KPS $< 70$ $P = 0.02$, duration of symptoms ($< 60$ d) $P = 0.002$, histology (better for favorable) $P = 0.002$, surgery (maximal resection) $P = 0.002$, and concurrent chemotherapy with radiation therapy in DIPG (better if given) $P = 0.01$.

CONCLUSION: BSG, especially the DIPG subgroup, had a dismal prognosis, needing more aggressive neurosurgical, radiation and chemotherapy techniques, while focal and tectal tumors were found to have a better prognosis.

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Key words: Brain stem glioma; Children; Adults; Saudi Arabia; Treatment outcomes
INTRODUCTION

Brain stem gliomas (BSG) account for about 10%-20% of all central nervous system tumors in children and 1%-2% in adults[1-2]. Traditionally, the term “brain stem glioma” was designed as a clinical diagnosis without histological confirmation because the morbidity for surgical intervention within the pons was high and the relevance of a histological diagnosis was low. With the advent of newer diagnostic modalities, BSG are now considered a heterogeneous group of tumors which are mainly divided into three categories according to treatment and prognosis[3]: (1) the dorsally exophytic and cervicomedullary tumors appear to benefit significantly from surgical resection[4]; (2) focal tectal glioma (solid or cystic) may be associated with a long history of symptoms and with neurofibromatosis type 1[5]; and (3) the largest subgroup of diffuse intrinsic pontine glioma (DIPG), in contrast, have a poor prognosis[6]. The DIPG subgroup clearly differs from focal, dorsally exophytic and cervicomedullary tumors on various points as DIPG is typically seen with rapidly progressing symptoms and signs comprising multiple erratic cranial nerve palsies, long track deficits, cerebellar symptoms and/or raised intracranial pressure with a median survival of 9 mo[6,7]. Gadolinium enhanced magnetic resonance imaging (MRI) allows easy confirmation of diagnosis for DIPG and high-grade BSG[8].

Surgery is the mainstay of therapy for focal, dorsally exophytic and cervicomedullary BSG; however, for DIPG the radiation therapy remains the standard treatment option[9,10]. Various chemotherapeutic agents investigated as monotherapy neoadjuvant agents (carboplatin or irinotecan) or as combination neoadjuvant chemotherapeutic agents (carboplatin, etoposide and vincristine or cisplatin, cyclophosphamide, etoposide and vincristine) have offered no significant improvements in overall and progression free survival rates[11,12]. Similarly, concurrent chemotherapeutic agents (etanidazole, topotecan, carboplatin and temozolomide) or high-dose chemotherapy followed by stem cell support have not shown any significant improvements in overall and progression free survival rates[11,14].

Our aim was to evaluate the frequency of BSG and to identify treatment outcomes of surgery, radiation therapy and chemotherapy and associated prognostic factors in a Saudi population.

MATERIALS AND METHODS

After formal approval from the institutional ethical committee, medical charts of patients with confirmed brainstem gliomas who were treated in our hospital were reviewed. Patients were selected if they met the following criteria.

Availability of a complete medical record: (1) demographic data [age at diagnosis, gender, main symptoms and duration, performance status according to Karnofsky Performance Scale (KPS) and main neurological signs]; (2) radiological characteristics of the tumors on MRI (T1 and T2-weighted images); and (3) surgical procedures including histopathological characteristics and other treatment modalities (radiation therapy and chemotherapy).

The epicenter (main bulk) of the tumor was located in the brainstem (midbrain, pons and medulla oblongata) and diagnosis was either based on clinical history and characteristic MRI features or histopathological confirmation.

Exclusion criteria were: (1) the epicenter of the tumor was located in the thalamus, cerebellar peduncles or cervical spinal cord; and (2) suspicion of infection could not be ruled out on MRI in the absence of biopsy results.

Toxicity

The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 was used to score acute radiation and chemotherapy toxicity (< 90 d from the start of radiation therapy). The Radiation Therapy Oncology Group Late Radiation Morbidity Scoring Criteria was used to score radiation toxicity persisting beyond 90 d from the completion of radiotherapy.

Follow-up

Functional recovery after surgical and other treatment modalities was assessed. Radiological response to radiotherapy and chemotherapy was reported according to Response Evaluation Criteria in Solid Tumors (RECIST): (1) a complete response (CR), i.e., disappearance of all visible tumor; (2) a partial response (PR), i.e., a decrease of > 50% in the axial cross-section of the greatest surface area; (3) progressive disease (PD), i.e., > 25% increase in axial cross-section of the greatest surface area; or (4) stable disease (SD), i.e., all other situations.

Statistical analysis

The primary endpoints were functional recovery, response rates and the overall survival. Progression-free survival (PFS) was defined as the duration between the completion of treatment and the date of documented disease progression, death resulting from the cancer and/or last follow-up visit (censored). Overall survival (OS) was defined as the duration between the completion of
treatment and the date of patient death or last follow-up visit (censored). The probabilities of OS were determined with the Kaplan-Meier method and its 95%CI by the Rothman method. The comparisons for various endpoints were performed using the log-rank test. A P value of 0.05 was considered statistically significant. The multivariate analysis was used to test prognostic factors in multivariate analysis. Results are expressed with relative risk and its 95%CI. Statistical analyses were performed using the computer program SPSS (Statistical Package for the Social Sciences, version 17.0, SPSS Inc., Chicago, IL).

RESULTS
Study population
Between July 2001 and December 2012, 49 patients with BSG from the institutional database fulfilled the criteria and were analyzed.

Clinicopathological characteristics
Among forty-nine patients, the majority of the cohort consisted of children and adolescents (81.6%) with a median age of 12.62 years (range: 0.8-64). An age of >18 years at diagnosis was associated with a significantly shorter OS compared with a younger age (P = 0.0001) (Figure 1A). Median Karnofsky performance status (KPS) at diagnosis was 80 (range: 40-100). KPS < 70 was related to a shorter OS (P = 0.0001) (Figure 1B). Main symptoms at time of diagnosis were headaches (42.8%), diplopia or squint (38.8%), gait disturbance (34.7%), nystagmus (37.7%) and difficulty in swallowing or choking (26.5%). Mean duration of symptoms before diagnosis was 83.4 ± 47.5 d. Patients with short duration of symptoms (<2 mo) had poor OS (P = 0.04) (Figure 1C). Main neurological signs were cranial nerve palsies, mainly VI, VII, IX, X (65.3%), cerebellar dysfunction (51%), bilateral papilledema (38.8%), nystagmus (37.7%) and motor weakness (28.6%). Histopathological diagnosis was available in 30 patients (61.2%), mainly of astrocytic origin (23/28) and high grade (63.3%) (Table 1).

MRI characteristics at time of diagnosis
The main MRI characteristics are illustrated in Table 2.

On MRI, patterns were identified representing non-enhancing diffusely infiltrative tumors (54.5%), contrast-enhancing localized masses (33.3%) and tectal tumors (33.3%). Presumed necrosis on MRI, defined as a zone of irregularly shaped T1 hyposignal surrounded by contrast enhancement, was found in 5 (10.2%) patients.

Treatment characteristics
Thirty patients (61.2%) had surgery. Complete resection was done in dorsally exophytic (83.3%), focal tectal (66.7%) and focal (50%) tumors. Cerebrospinal fluid (CSF) shunts, including ventriculoperitoneal shunt, endoscopic third ventriculostomy and endoscopic ven-
in 14/32 patients (43.7%) and radical radiation therapy with and without chemotherapy was given in 18/32 patients (56.3%). Mean duration of time between surgery and starting radiation therapy was 25 d (range: 21-28).

Triventricular drain was performed in 28/49 patients (57.1%) to control raised intracranial pressure. Interestingly, 6/22 patients (27.3%) with DIPG underwent surgical debulking (Table 3). Postoperative radiation therapy was given in 14/32 patients (43.7%) and radical radiation therapy with and without chemotherapy was given in 18/32 patients (56.3%). Mean duration of time between surgery and starting radiation therapy was 25 d (range: 21-28).

### Table 1 Clinicopathological characteristics of cohort

| Character | Value |
|-----------|-------|
| Mean age at diagnosis (yr) | 12.62 (0.8-64) SD ± 13.42 |
| Gender | | 4/30 (13.3%) |
| Male | 31 (63.3%) |
| Female | 18 (36.7%) |
| According to age | | 5/30 (16.7%) |
| Children and adolescents | 40 (81.6%) |
| Adults | 9 (18.4%) |
| Duration of symptoms (d) | 83.4, SD ± 47.5 |
| Karnofsky Performance Status | 80 (50-100) |
| Symptoms at time of presentation | | 3 (6.1%) |
| Headache | 21 (42.8%) |
| Vomiting | 11 (22.4%) |
| Diplopia/ squint | 19 (38.8%) |
| Unsteady gait | 17 (34.7%) |
| Difficulty in swallowing or choking | 13 (26.5%) |
| Motor weakness/ paresis | 10 (20.4%) |
| Convolusions | 4 (8.2%) |
| Dysphonia/ dysarthria | 11 (22.4%) |
| Altered consciousness | 5 (10.2%) |
| Isolated facial paresis | 6 (12.2%) |
| Hearing problems | 3 (6.1%) |
| Fever | 2 (4.1%) |
| Failure to thrive | 1 (2.0%) |
| Neurological signs at time of presentation | | 15 (46.9%) |
| Mental status change | 8 (16.3%) |
| Cranial nerve palsies | 32 (65.3%) |
| Trigeminal | 2 (6.3%) |
| Abducens | 18 (36.3%) |
| Facial | 12 (37.5%) |
| Vestibulocochlear | 2 (6.3%) |
| Glossopharyngeal | 12 (37.5%) |
| Vagus | 8 (25.0%) |
| Motor deficit | 14 (28.6%) |
| Sensory deficit | 6 (12.2%) |
| Bilateral Babinski sign | 13 (26.5%) |
| Cerebellar signs | 25 (51.0%) |
| Nystagmus | 17 (34.7%) |
| Bilateral papilledema | 19 (38.8%) |
| Pathological diagnosis | | 13 (57.1%) |
| Yes | 30 (61.2%) |
| No | 19 (38.8%) |
| Radiological diagnosis | | 1 (2.0%) |
| Total dose (Gy) | 50.4-59.4 |
| Technique | | 15 (46.9%) |
| Concurrent | 12/23 (52.2%) |
| Neoadjuvant | 7/23 (30.4%) |
| Vincristine + carboplatin | 4/7 (57.1%) |
| High dose chemotherapy with stem cell rescue | 2/7 (28.6%) |
| Cyclophosphamide | 1/7 (14.3%) |
| Adjuvant/ salvage | 11/23 (47.8%) |
| BCNU + procarbazine + vincristine | 5/11(45.5%) |
| Vincristine + carboplatin | 4/11 (36.2%) |
| Irinotecan + bev acizumab | 2/11 (18.1%) |

### Table 2 Magnetic resonance imaging characteristics in our cohort of brain stem glioma n (%)

| Subgroups | Enhancement enhancing | Non-enhancing | T2W image hyper | Intensity mixed | Cystic | Solid | Mixed |
|-----------|-----------------------|---------------|-----------------|----------------|--------|-------|-------|
| Focal (12) | 17 (100) | - | 10 (83.3) | 2 (16.7) | 3 (25) | 6 (50) | 3 (25) |
| Focal tectal (3) | 2 (66.7) | 1 (33.3) | 1 (33.3) | 2 (66.7) | 3 (100) | 4 (66.7) | 2 (33.3) |
| Dorsally exophytic (6) | 4 (66.7) | 2 (33.3) | 3 (50.0) | 3 (50.0) | 4 (66.7) | 2 (33.3) |
| Cervicomedullary (3) | 2 (66.7) | 1 (33.3) | - | 3 (100) | 3 (100) | 19 (66.4) | 3 (13.6) |
| DIPG (22) | 10 (45.5) | 12 (54.5) | 10 (45.4%) | 12 (54.5) | 3 (25) | 6 (50) | 3 (25) |

DIPG: Diffuse intrinsic pontine glioma; VP shunt: Ventriculoperitoneal; ETV: Endoscopic third ventriculostomy; EDV: Endoscopic ventricular drain; IONP: Intra-operative neurophysiology; 3DCRT: Three dimensional conformal radiation therapy; IMRT: Intensity modulated radiation therapy; TMZ: Temozolomide; BCNU: 1,2-bis (2-chloroethyl) 1-nitrosourea.
The majority of cases (17/32) were treated with intensity modulated radiation therapy (Table 4). Among all 32 patients who received radiation therapy, the treatment protocol completion rate was 90% (95%CI, 85-100). Chemotherapy in an adjuvant or salvage setting was given mainly for the DIPG subgroup and patients with leptomeningeal dissemination which was seen in 5/49 patients (10.2%) (Table 5).

### Toxicity profile

Common acute grade 2 radiation induced toxicities were nausea and vomiting (30/32) and worsening of weakness (21/32). Grade 3 toxicities were nausea and vomiting (2/32) and worsening of weakness (4/32) and were treated with antiemetics and corticosteroids. Acute grade 2 otitis media was seen in one patient. Late toxicities at time of analysis were minimal and grade 2 skin pigmentation was seen in one patient. Common acute grade 3 chemotherapy induced toxicities were myelosuppression (5/23), thrombocytopenia (2/23), rash (1/23) and febrile neutropenia (5/23), of whom three had repeated episodes. No treatment related death was seen.

### Response rates

Clinical response of radiotherapy ± chemotherapy (defined as regression of cranial nerve palsies or weakness of the limbs or cerebellar symptoms for > 3 mo) was seen in 16/32 (50%) patients, confirmed by a neurologist. Radiological response was also evaluated in all patients and response rates according to RECIST were CR (0/32), PR (16/32), SD (6/32) and PD (11/32). The mean response time was 12 ± 8 mo (range: 7-30). The mean reduction of tumor volume was 50% and clinical benefit (PR + SD) was 68.7% for all patients. Clinical response of adjuvant chemotherapy was seen in 2/11 (18.1%) at the mean time of 5 mo (range: 4-18). Three months after chemotherapy, radiological PR was seen in two patients, SD in five (45.7%) and progressive disease in four cases (36.2%).

### Progression free survival and overall survival

Median survival time for the whole cohort was 1.5 years and 1, 2, 3 year OS rates for the whole cohort were 51.1%, 41.9% (29/49 died) and 23.1% (Figure 2). PFS rates at 1 and 2 years were 57.3% and 38.2% respectively. At 2 years, the OS rate for radiologically low grade (favorable) tumors was clearly high (57.1%) compared to high grade (unfavorable) in which the OS rate was 17.9% (P < 0.001) (Figure 3A). Furthermore, among the subgroups, two year OS rates for focal/tectal, dorsally exophytic, cervicomedullary and DIPG tumors were 60%, 33.3%, 33.3% and 13.6% respectively (P < 0.0001) (Figure 3B).

Two year OS rates for patients (14/30) with complete or maximal resection and patients (16/30) with incomplete resection or biopsy only were 53.8% and 27.8% respectively (P = 0.002) (Figure 3C).

### Tables

#### Table 3 Surgical resection in our cohort of brain stem glioma (n) (%)

| Subgroups   | Resection Complete | Incomplete/biopsy | VP shunt | ETV | EVD | IONP |
|-------------|--------------------|-------------------|---------|-----|-----|------|
| Focal (12)  | 6 (50.0)           | 6 (50.0)          | 3 (25.0)| 1 (8.3) | 2 (16.6)| 5 (41.7) |
| Focal tectal (3) | 2 (66.7) | 1 (33.3) | 2 (66.7) | 1 (33.3) | 1 (33.3) | 2 (66.7) |
| Dorsally exophytic (6) | 5 (83.3) | 1 (16.7) | 3 (50.0) | - | 2 (33.3) | 5 (83.3) |
| Cervicomedullary (3) | 1 (33.3) | 2 (66.7) | - | - | - | 2 (33.3) |
| DIPG (22)   | -  | 6 (27.3) | 11 (50) | 2 (9.0) | - | 1 (4.5) |

VP shunt: Ventriculoperitoneal; ETV: Endoscopic third ventriculostomy; EVD: Endoscopic ventricular drain; IONP: Intra-operative neurophysiology.

#### Table 4 Radiation therapy in our cohort of brain stem glioma (n) (%)

| Subgroups   | Indication Postoperative | Radical | Technique 3DCRT | IMRT |
|-------------|--------------------------|---------|-----------------|------|
| Focal (12)  | 6 (50)                   | -       | 3 (50)          | 50.4-54 |
| Focal tectal (3) | 1 (33.3) | - | 1 (100) | 54 |
| Dorsally exophytic (6) | 1 (16.7) | - | 1 (100) | 54 |
| Cervicomedullary (3) | 2 (66.7) | - | 2 (100) | 50.4-54 |
| DIPG (22)   | 6 (27.3) | 16 (72.7) | 9 (40.9) | 13 (59.1) | 54-99.4 |

3DCRT: Three dimensional conformal radiation therapy; IMRT: Intensity modulated radiation therapy; Gy: Gray.

#### Table 5 Chemotherapy in our cohort of brain stem glioma (n) (%)

| Subgroups   | Neoadjuvant | Concurrent | Adjuvant/salvage |
|-------------|-------------|------------|------------------|
| Focal (12)  | -           | 3 (25.0)   |                  |
| Focal tectal (3) | - | - |                  |
| Dorsally exophytic (6) | - | - |                  |
| Cervicomedullary (3) | 1 (33.3) | - | 2 (66.6) |
| DIPG (22)   | 6 (27.3) | 1 (100) | 6 (27.3) |

DIPG: Diffuse intrinsic pontine glioma.
Median time of survival, one and two year OS rates for patients who were treated with postoperative (16/32) or radical radiation therapy (16/32) were 1.09 years, 50% and 17.9% respectively (Figure 4A). Patients treated with chemotherapy (neoadjuvant, concurrent or adjuvant/salvage) had a median survival time of 1.3 years and one and two year OS rates of 56.5% and 21.7% respectively (Figure 4B).

Multivariate analysis showed that for favorable tumors, important prognostic factors were: (1) age at diagnosis (worse for > 18 years); (2) KPS < 70; (3) histopathologically high grade; and (4) incomplete resection.

Important prognostic factors for unfavorable tumors including DIPG were: (1) age at diagnosis (worse for > 18 years); (2) KPS < 70; (3) histopathologically high grade; (4) radiological high grade (necrosis on MRI); and (5) no concurrent chemotherapy, as shown in Table 6.

DISCUSSION

BSG remains a therapeutic dilemma because of the location and heterogeneous biological behavior of these tumors, as seen in our cohort, comprised mainly of children and adolescents (81.6%). A median survival time of 1.5 years, one and two year OS rates of 51.1% and 41.9%, and clinical prognostic factors in our cohort were found to be in agreement with previously reported data\[15,16\]. We found no significant difference between
The subgroup of focal gliomas was the second most predominant in our cohort and these tumors were clearly found to be different from DIPG; however, the clinical picture was similar to DIPG. Complete removal in the majority of cases in our cohort reflected the improvement in median survival for such cases. Focal tectal gliomas constituted a small subgroup and these cases required CSF shunts for raised intracranial pressure, as reported by other studies. However, adjuvant radiotherapy can be criticized in children as such patients have been managed with a CSF shunt or observation alone for long periods.

The third most common subgroup of dorsally exophytic gliomas in our cohort were managed successfully with complete resection in the majority of patients. However, in contradiction to the literature, our patients had a shorter median survival. A possible explanation could be high grade histology and no adjuvant radiotherapy. A similar explanation for shorter median survival was also justified in our cohort of cervicomedullary glioma. Non-specific BSG, including medullary astroblastoma and pontomedullary BSG, had a similar clinical behavior and treatment outcome to DIPG.

In conclusion, brain stem gliomas have heterogeneous biological behavior. The DIPG subgroup had a dismal prognosis, needing more aggressive neurosurgical, radiation and chemotherapy techniques, while focal and tectal tumors were found to have a better prognosis.

**Table 6  Multivariate analysis of various prognostic factors in brainstem glioma**

| Variables                              | RR (95%CI) | P value |
|----------------------------------------|------------|---------|
| Age at diagnosis (> 18 yr)             | 3.0 (1.8-6.0) | 0.01    |
| KPS < 80                               | 3.3 (1.7-5.3) | 0.02    |
| Duration of symptoms (< 60 d)          | 6.7 (4.3-9.4) | 0.002   |
| Histopathology (high grade)            | 6.1 (3.5-10.2) | 0.002   |
| MRI characteristics (presence of necrosis) | 3.0 (1.9-5.9) | 0.01    |
| Incomplete resection for favorable tumors | 6.6 (3.9-12.2) | 0.002   |
| No concurrent chemotherapy with RT     | 3.1 (2.2-8.2) | 0.01    |

RR: Relative risk; CI: Confidence interval; KPS: Karnofsky performance scale; MRI: Magnetic resonance imaging; RT: Radiation therapy.
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