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Original Paper

Modality of Radiotherapy and Overall Survival in Pediatric Diffuse Brainstem Gliomas: Implications for Resource-Constrained Settings

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ABSTRACT

Background: Childhood diffuse brainstem glioma (dBSG) is a rare tumor with a poor prognosis. Any tumor-directed surgical intervention is difficult. Magnetic resonance imaging forms the mainstay of diagnosis and radiation therapy has remained the backbone of therapy. In this study, we compare the outcomes of conformal radiotherapy with conventional therapy in the context of resource-constrained settings.

Methods: In this retrospective analysis, conducted between 2010 and 2019, all pediatric patients with a diagnosis of dBSG were analyzed. The survival data were calculated in months from the date of diagnosis. Survival differences between variables were compared using the Log-rank test and the risk of death was calculated using Cox regression analysis.

Results: A total of 20 patients (11 males, 55%) with a diagnosis of dBSG were included. Median age at diagnosis was 6.5 years. No surgical resection or biopsy was done in any patient. Fifteen (75%) patients received radiotherapy and only 4 (20%) patients received additional chemotherapy. Five (25%) patients did not receive any form of anti-cancer therapy. Median overall survival (OS) was 8 months (95% CI 5.2–10.8). Females were at a higher risk of death than males. Children treated with radiotherapy had a longer OS than untreated children; however, the modality of radiotherapy employed or the addition of chemotherapy did not affect the OS.

Conclusion: Radiotherapy, irrespective of the modality, increases the survival of children with dBSG in resource-poor settings. Additionally, socioeconomic concerns need to be addressed in the management of these tumors, especially in the case of female children.

LAY SUMMARY

Childhood diffuse brainstem glioma (dBSG) is a rare tumor with a poor prognosis. Any tumor-directed surgical intervention is difficult. Magnetic resonance imaging forms the mainstay of diagnosis and radiation therapy has remained the backbone of therapy. In this 10-year retrospective study, we compare the outcomes of conformal radiotherapy with conventional therapy in the context of resource-constrained settings. A total of 20 patients with a diagnosis of dBSG were included with a median age at diagnosis of 6.5 years (5.25–8.75). No surgical resection or biopsy was done in any patient. Fifteen (75%) patients received radiotherapy and only 4 (20%) patients received additional chemotherapy. Five (25%) patients did not receive any form of anti-cancer therapy. Median overall survival (OS) was 8 months (95% CI 5.2–10.8). Females were at a 3.4-fold (95% CI 1.0–12.1) higher risk of death than males. Children treated with radiotherapy had a longer OS than untreated children; however, the modality of radiotherapy employed or the addition of chemotherapy did not affect the OS. Radiotherapy, irrespective of the modality, increases the survival of children with dBSG in resource-poor settings. Additionally, socioeconomic concerns need to be addressed in the management of these tumors, especially in the case of female children.

KEYWORDS: brainstem, chemotherapy, conformal radiotherapy, conventional radiotherapy, diffuse, glioma

INTRODUCTION

Each year, nearly 300 000 cases of pediatric cancer are diagnosed worldwide [1]. Central nervous system (CNS) tumors are the second most common, accounting for about one-fifth of all cancers in this age group [1]. In the USA, they account for the most common cancer-related death (∼25%) in children [2]. As per global data, brainstem gliomas (BSGs) comprise about 10% of all primary CNS tumors in children and adolescents (0–19 years) [3]. However, there is a higher proportion of BSG cases (around one-fourth of all CNS tumors) reported from India [4]. The precise etiopathogenesis of these tumors remains largely elusive. In patients with neurofibromatosis-1, BSGs are the second most frequently encountered brain tumors [5]. The clinical diagnosis of BSG is based on characteristic features on magnetic resonance imaging (MRI) [6]. MRI has become the imaging investigation of choice in the characterization of BSG (hyp/iso-intense on T1; hyperintense on T2-weighted images). Despite a marked improvement in survival of children with cancer for many decades [7], the prognosis of patients with diffuse BSGs (dBSGs) remains bleak [8]. Due to its structural complexity and integrated brain functions, any surgical intervention involving the brainstem (diagnostic or therapeutic) is difficult and patients often receive a radiological diagnosis only. Due to its rarity, there is a paucity of data on comparative treatments, with conformal radiotherapy (CRT) usually being the standard of care [9]. The ability to employ CRT may be limited in developing countries and access to high precision stereotactic surgical interventions is often far-fetched due to technical and logistic constraints. We, therefore, aim to compare the influence of conventional radiotherapy with non-conventional radiotherapy on the outcome of dBSGs managed non-surgically. In the context of resource-constrained settings, conventional radiotherapy may be more cost-effective and less technically demanding.

MATERIALS AND METHODS

A hospital-based retrospective observational study was conducted at the Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, India, which is the largest tertiary care cancer center in the region. It cares for ∼5000 cancer patients annually, and is the only referral center treating pediatric cancers in the region.

Between 2010 and 2019, all patients 0 to 19 years old with clinical and radiological diagnosis of dBSG were recruited from our Hospital-Based Cancer Registry. The diagnosis was based on MRI documented tumor epicenter within the brainstem, and not merely involvement of brainstem. All cases were

reviewed jointly by a team comprising of a radiologist, neurosurgeon, medical and radiation oncologists. Data recorded included age, gender, patient's presenting illness (symptoms/signs), radiological findings, surgical details (if any), radiation therapy and chemotherapy. Quantitative data were expressed using median (25th and 75th percentile); while qualitative data were expressed as number (percent). Overall survival (OS) was the time in months from diagnosis to death or last follow-up. Survival differences between variables were compared using the Log-rank test (p-value < 0.05 was considered significant). The risk of death was calculated using stepwise Cox regression analysis. The variables included in model building were age at diagnosis, gender, clinical presentation, tumor size, location of the tumor, presence/absence of necrosis or edema on imaging, placement of a ventriculoperitoneal shunt, and whether chemotherapy was employed. All statistical analysis was performed using Statistical Package for the Social Sciences software (SPSS, version 23, IBM corporation). We did not analyze treatment toxicity in these patients and long-term adverse effects of radiation were not assessed due to short survival.

RESULTS

A total of 20 patients with a diagnosis of dBSG were included in our study. The median age of presentation was 6.5 years (5.25–8.75) with a slight male preponderance ($n = 11$, 55%). Diplopia was the commonest presenting symptom ($n = 9$, 45%), followed by vertigo and headache (15% each). At presentation, half of the patients had altered sensorium on examination. In 16 (80%) patients, pons was the epicenter of the tumor. The median lesion size on MRI was 4 cm × 3.5 cm. No surgical resection or biopsy was done in any patient, a ventriculoperitoneal shunt was put in 3 (15%) patients (Supplementary Table S1).

In our cohort, 5 (25%) patients did not receive any form of anti-cancer treatment. Radiotherapy was given to the rest, while 4 (20%) patients received additional chemotherapy. Conventional radiotherapy was employed in 6 (40% of radiotherapy group) patients, intensity-modulated radiotherapy (IMRT) in 8 (53% of radiotherapy group) and 3D-CRT in 1 (7% of radiotherapy group).

All patients who did not receive any anti-tumor therapy succumbed to the disease within the first

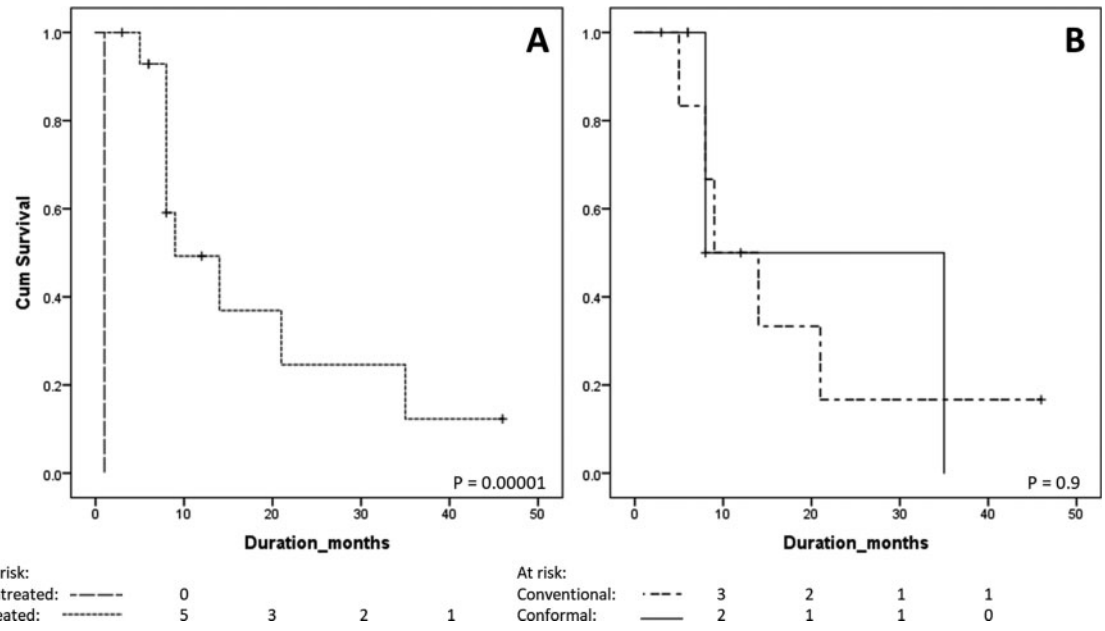

Fig. 1. Comparative Kaplan-Meier survival curves of patients in our cohort. (**A**) Survival benefit of radiotherapy with/without chemotherapy over untreated patients. (**B**) Comparison of OS in patients treated with different modalities of radiotherapy. p values have been calculated using the Log-rank test.

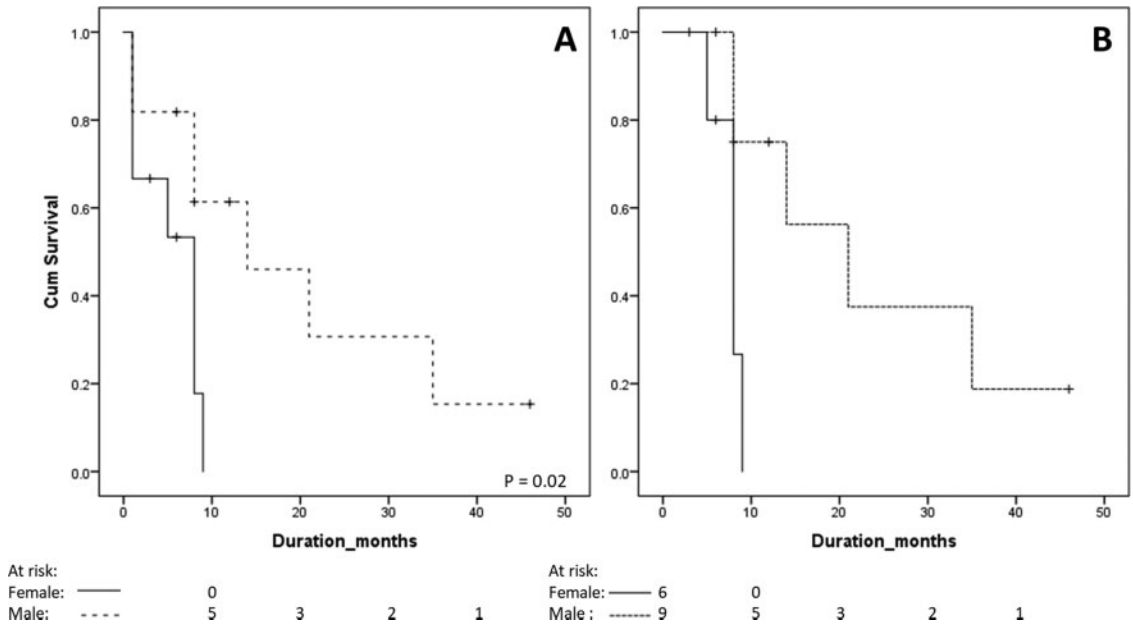

Fig. 2. Comparative Kaplan–Meier survival curves of patients stratified by gender. (**A**) All patients included (treated and untreated). (**B**) Patients treated with radiotherapy (irrespective of the modality) with/without chemotherapy. *p* values have been calculated using the Log-rank test.

month of presentation; whereas, in the rest, median survival was 9 months [95% confidence interval (CI) 1.1–16.9 months] (Fig. 1A). The addition of chemotherapy did not result in any difference in the OS of the patients.

In the conventional radiotherapy cohort, five out of six patients (83%) succumbed to the illness, whereas, in the non-conventional radiotherapy group 4 out of 9 (44%) patients had died at last follow-up; however, there was no difference in the OS as the conventional radiotherapy group has a higher median duration of follow-up (Fig. 1B).

In the entire cohort, males had a higher median OS [14 months (95% CI 0–28.7)] than females [8 months (95% CI 3.6–12.4)] (Fig. 2A) which translated to a 3.4-fold (95% CI 1.0–12.1) higher risk of death in females (stepwise Cox regression analysis). On subgroup analysis, in the treated group (radiotherapy with/without chemotherapy) the median OS in males was 21 months (95% CI 6.2–35.8) and in females, it was 8 months (95% CI 5.5–10.5 months). The risk of death was 5.6-fold (95% CI 1.0–31.3) higher in females on stepwise Cox regression analysis (Fig. 2B). Employing radiotherapy (irrespective of the type) and male gender were the independent predictors of outcome in our cohort. Other variables including the clinical features, size, MRI features, the dose of radiotherapy and location of the tumor did not influence the OS.

DISCUSSION

Initially considered a single group, BSGs are currently subtyped into two broad categories: dBSGs (>80% of all cases) and non-diffuse brainstem tumors, which have a more favorable prognosis [10]. About three-fourths of all BSGs occur in the first decade of life, peaking around 6–7 years. There is no recognized gender or racial predilection for dBSGs [11]. Our study also showed a similar profile at diagnosis. In about one-third, patients present with a triad of cranial nerve dysfunction, upper motor neuron signs and ataxia. However, the majority of patients present with only one of these signs, and only about 10% of patients present with hydrocephalus [12]. Symptom onset is usually brief (1–2 months) at diagnosis [13]. We observed cranial nerve palsy as the commonest presentation in our patients but had a relatively higher percentage of

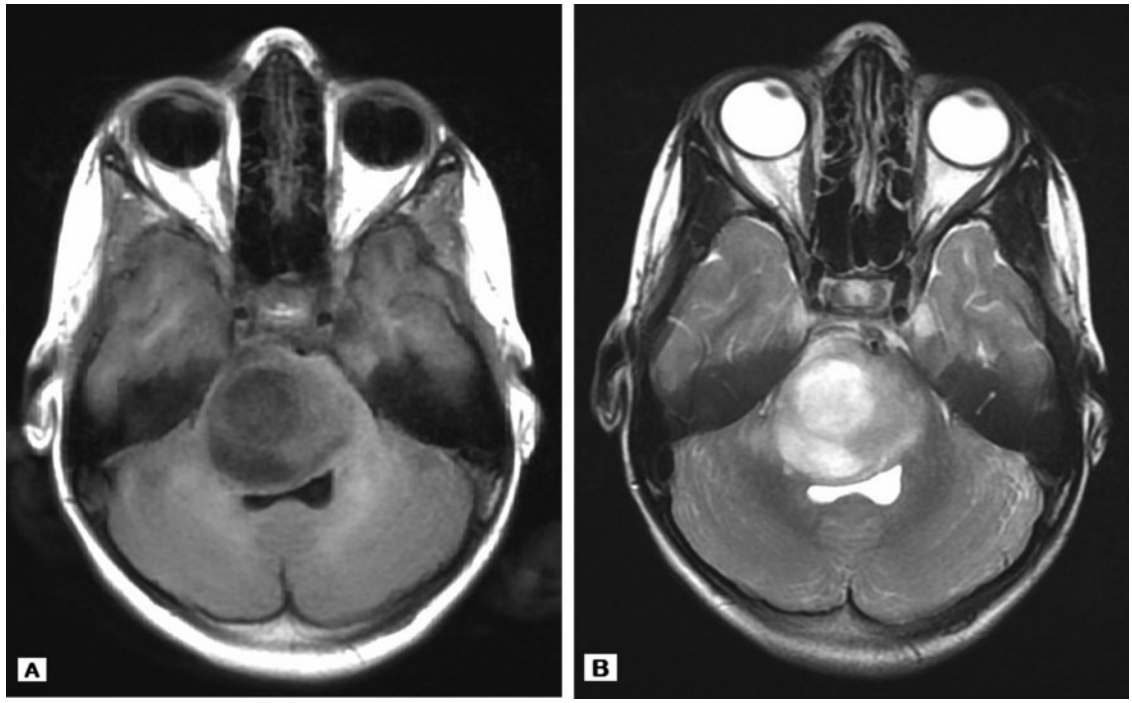

Fig. 3. Axial T1-weighted (**A**) and T2-weighted (**B**) images demonstrate a T1 hypointense and T2 heterogeneously hyperintense expansile mass lesion in pons in a 6-year-old female child. There is partial encasement of the basilar artery with effacement of the fourth ventricle. Also noted is the medial deviation of the right eyeball due to cranial nerve palsy.

patients having features of raised intracranial pressure as compared to what has been reported in the literature. This is possibly due to a more posterior extension of disease towards the fourth ventricle in our patients.

Astrocytoma and ependymoma are the most common histological subtypes of brainstem tumors [14]; however, we included patients with classical radiological features of dBSG only (Fig. 3). Our results are, therefore, based on a broad anatomical depiction of the tumors, a scenario often encountered in resource-poor settings that lack the ability to perform stereotactic surgeries or biopsies. The role of guided biopsies in dBSGs is debatable, as additional information obtained from histopathological examination of the tumor may not lead to change in therapy or prognosis [15]. However, targeted therapy based on molecular details of the dBSGs may expand the significance of performing a biopsy [16]. Only a few centers in our subcontinent have the requisite logistic and technical expertise to employ stereotactic surgical interventions in pediatric dBSGs. Although there is no conclusive evidence of any survival benefit by subjecting patients with dBSGs to any surgical procedure [17, 18]; at times, surgery is performed as an ancillary procedure in patients with hydrocephalus that require cerebrospinal fluid diversion for relief of symptoms.

Radiotherapy remains the conventional modality of treatment and may lead to a neurological recovery in up to 85% of patients. A radiological response is often an accompaniment that permits the tapering of steroids [8, 19, 20]. Radiotherapy with or without chemotherapy was the only modality of treatment given to our patients which resulted in a higher median OS (8 months) as compared with untreated patients (none surviving >1 month) similar to that reported previously [19, 20]. The decision of not treating was based on caregivers' preferences or the Glasgow coma scale. However, in our patients, there

was no significant difference in the OS on comparing various doses of radiotherapy or the modality (conventional vs. conformal) employed. All patients received conventionally fractionated radiotherapy, and no hypo- or hyper-fractionation was employed in any patient in our cohort. Nonetheless, for patients with newly diagnosed diffuse gliomas in the brainstem, hypofractionated radiotherapy may offer non-inferior survival with shortening of treatment time compared with a conventional regimen [21]. This also reduces the number of anesthesia/deep-sedation sessions, which are often required in younger patients. For survival outcome, hyperfractionated radiotherapy was not superior to conventionally fractionated radiotherapy in a Pediatric Oncology Group trial in patients with diffuse intrinsic glioma [22]. Advanced radiation therapy procedures have improved treatment precision in pediatric CNS tumors. Even when CRT techniques are compared, patients who receive IMRT seem to have a longer OS than those who receive 3D-CRT [23]. However, in many developing regions, CRT has both availability and affordability constraints [24].

As in our cohort, the addition of chemotherapy to radiotherapy has not resulted in improved outcomes in dBSGs. When added to radiotherapy, temozolomide has not resulted in an improved survival rate and the median OS has ranged from 9 to 10 months [25, 26]. Only four patients received chemotherapy (one received concurrent and three patients received adjuvant temozolomide) in addition to radiotherapy in our patient population.

Another factor independently affecting survival in our patients was gender, with females having a higher risk of mortality. This is in contrast to what has been reported in literature where gender is unrelated to prognosis [14, 19, 27, 28]. The possible explanation for survival difference as a result of gender may be due to social factors which may affect parental choices in seeking medical care for cancers with a poor prognosis, especially in developing countries. Overall, in the pediatric population, it has been observed that the risk of death is higher in males in various tumor types [29]. Yet, there is little evidence on gender differences in survival by cancer type. Our results need to be interpreted with caution because of small sample size and single-center study design, which are the important limitations of our study.

Management of pediatric dBSGs in developing countries is challenging where socioeconomic factors additionally affect survival. In such scenarios, comparative studies analyzing various treatment modalities are scarce probably owing to the rarity of this tumor. An important strength of our study is a retrospective comparison of treatment outcomes in pediatric dBSG treated at our center over the past decade.

CONCLUSIONS

Treating dBSG patients with radiotherapy even with the conventional form should be encouraged which is especially important in resource-constrained settings. The impact of gender on the outcome is a source of significant concern and needs to be understood in a broader perspective, including the socioeconomic perspective, and preferably in a larger multicentric cohort of patients from developing countries.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

ETHICS APPROVAL

This work has not been published or is being considered for publication elsewhere. The study design has been approved by the SKIMS Ethics Committee (of our institution) and the work conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All patients who participated in this study have given informed consent.

DATA AVAILABILITY

The data utilized for the preparation of our article will be available on request.

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