Abstract  Introduction: High-grade gliomas account for 15-20% of intracranial tumors in the pediatric population, usually with poor prognosis for overall survival. Objective: To identify prognostic factors for overall survival and local control in patients diagnosed with intracranial high-grade gliomas managed with conformal radiotherapy. Patients and methodology: This retrospective study assessed all high-grade glioma-diagnosed patients treated with radiotherapy at the Federico Gómez Children’s Hospital over the period 2008-2013 by means of a review of medical records, imaging files, and treatment plans. Results: The analyzed patients (n = 18) had a median age of five years. The most common localization was infratentorial. Histologies found were glioblastoma multiforme and anaplastic astrocytoma. Of the analyzed patients, 44.4% received surgical management owing to the lesion localization and their performance status. All patients received radiotherapy with > 54 Gy total dose with or without chemotherapy. Local control rate was 94.4% and median overall survival was 13 months. With regard to surgical management for gross tumor resection, subtotal tumor resection, and no resection, five-year overall survival was 100, 50, and 36%, respectively (p = 0.04). The patients showed overall survival improvement with radiotherapy total dose > 54 Gy and standard fractioning. Conclusion: In the present study, surgical gross resection and management with standard external beam radiotherapy at doses > 54 Gy were found to be predictive factors for overall survival in pediatric patients diagnosed with intracranial high-grade gliomas. (creativecommons.org/licenses/by-nc-nd/4.0/).
INTRODUCTION

Central nervous system tumors are at third place in incidence among all solid tumors, with a rate of 29.7 per million at the pediatric age. Astrocytomas are the most common glioma subgroup, and involve 40-50% of intracranial tumors in the pediatric population. The high-grade group is comprised by anaplastic astrocytoma (with or without oligodendroglial component) and glioblastoma multiforme (GBM). High-grade astrocytomas or gliomas are infrequent in the pediatric population, accounting for 15-20% of intracranial tumors.

The etiology of high-grade glioma (HGG) has not yet been fully determined, but factors associated to its carcinogenesis are known, including exposure to ionizing radiation, as well as its genetic, molecular, histological, clinical, and therapeutic characteristics, which even have been shown to be prognostic factors for disease-free survival (DFS) and overall survival (OS)\(^2\). The HGG clinical features are generally related to its localization, as in the case of the supratentorial area, where usually it can cause compression or obstruction of the ventricular system and produce hydrocephalus and usually symptoms consistent with intracranial hypertension such as headache, nausea, and vomiting. The presence of dysphasia, hemiparesis, and tonic-clonic seizures with focalization according to the primary site has been correlated with the degree of rapid progression, which confers poor prognosis in terms of OS. In the case of infratentorial localization, more related to posterior fossa involvement, cerebellar mutism, and positional vertigo involvement or dysfunction, there can also be signs and symptoms associated with hydrocephalus and intracranial hypertension\(^14\). The study technique with the highest diagnostic sensitivity and specificity is contrasted magnetic resonance imaging (MRI), where adequate assessment should be with at least T1-weighted sequences with and without contrast for lesions with heterogeneous solid component and irregular borders, with enhancement after the contrast medium is applied, as well as centrally predominating areas of necrosis and calcification. To assess edema, T2/FLAIR-weighted reconstruction is used. In case the resource of multi-parametric MRI is available, functional MRI should be performed with spectroscopy, perfusion, and diffusion for better diagnosis of tumor activity by imaging\(^6\).

Initial standard treatment for HGG is multimodal, with extensive surgery or gross total resection being the cornerstone at any age. In children older than three years, it will be supplemented with standard radiotherapy adjuvant management at doses not higher than 60 Gy and/or chemotherapy\(^6\)\(^15\)\(^16\). Late toxicity, such as neurocognitive or neuroendocrine alterations and vasculopathy, should be evaluated when the treatments are offered\(^11\).

The role of adjuvant chemotherapy remains controversial in patients older than three years since its use has been suggested to improve the prognosis in terms of DFS, but not of OS, or it increases it modestly, as assessed in reports of the Cancer Pediatric Group with the scheme based on lomustine, vincristine, and prednisone\(^14\). However, there is conflicting evidence in pediatric patients, with temozolomide management concomitant with radiotherapy having been assessed in pediatric patients with no benefit in terms of DFS or OS\(^15\)\(^17\), as well as in patients with recurrent HGG on the prolonged scheme of 90 mg/m\(^2\) for 21 days for four weeks with no OS benefit in the phase II trial by Nicholson\(^13\), et al. in contrast with trials where an impact on local control (LC), DFS, and OS is reported, as in the study by Stupp, et al.\(^16\), although in this trial most patients were adults.

In patients younger than three years, after surgical treatment, radiotherapy will be reserved only for necessary cases such as disease progression and inadequate control with chemotherapy, owing to the late morbidity radiotherapy can confer. In case postponing radiotherapy is possible, chemotherapy management should be implemented with schemes based on lomustine, vincristine, prednisone, ifosfamide, carboplatin, and etoposide\(^16\)\(^21\).

The main purpose of the present study was to assess prognostic factors and their impact in terms of LC and OS in HGG-diagnosed patients on multimodal treatment at the Federico Gómez Children’s Hospital.

MAIN OBJECTIVE

To assess prognostic factors in terms of OS and LC in patients diagnosed with HGG managed with external beam radiotherapy at the Federico Gómez Children’s Hospital.

SECONDARY OBJECTIVES

To identify prognostic factors related to characteristics of the neoplasm in terms of localization, and with regard to the multimodal management and their impact on LC and OS.

MATERIAL AND METHODS

The present observational, retrospective study assessed all patients diagnosed with HGG over the period from 2008 through 2013 at the Department of Pediatric Radiotherapy of the Federico Gómez Children’s Hospital. Analyzed patients were those who met the following criteria:

Inclusion criteria:

- 0-17-year old patients.
- Patients with histological and/or imaging diagnosis of HGG (in case of brainstem localization), regardless of localization.
- Patients with a 60-100% Lansky score.
- Patients diagnosed with HGG who have received management with external beam radiotherapy and/or chemotherapy with ifosfamide/carboplatin/etoposide scheme and/or temozolomide in concomitant and/or adjuvant form.

Exclusion criteria:

- Patients with concurrent malignancy or history thereof within the previous five years (except for benign or genetic syndrome-related lesions).
- Patients with medically unstable conditions to receive external radiotherapy management (hemodynamically, neurologically, metabolically, or infectologically).
Techniques and procedures

Patients previously assessed by the neurosurgery department of the Federico Gómez Children’s Hospital and hospitals with an agreement therewith, with a diagnosis consistent with HGG by imaging or with histological corroboration by previous surgical manipulation.

Surgical treatment

Surgical procedures contemplated by the referral department in some patients were gross total resection or maximal resection (> 90%), subtotal resection (< 90%), and ventricular bypass drainage system placement according to each patient’s clinical context. The extension of the surgery was assessed by tomography or MRI 24-72 hours postoperatively.

Radiotherapy treatment

External beam radiotherapy treatment was provided with a linear accelerator (Varian System®), with 6 MV energy and Eclipse® planning system, version 7.3; in all cases, based on 3D conformal technique with coplanar and non-coplanar fields, with doses in the biological effect dose 50-60 Gy range. The GBM cases were defined as gross tumor volume (GTV) = tumor evidenced by imaging or contrast-enhanced surgical bed by MRI (previously fused), clinical target volume (CTV) 1 = GTV + FLAIR/T2 sequence-characterized perilesional edema + 1 cm margin, planning treatment volume (PTV) 1 = CTV1 + 3-5 mm; CTV2 = GTV + 1 cm margin, PTV2 = CTV2 + 3-5 mm. In the anaplastic astrocytoma cases and brainstem localization, GTV = tumor evidenced by contrast-enhanced MRI, CTV = GTV + 1 cm, PTV = GTV + 3-5 mm.

Fractioning for patients was mostly conventionally assigned and only in two cases was modified management decided with hypofractioning, due to uncertainty on patient neurological stability but, after improvement, dose escalation was contemplated, and the second phase was delivered with standard fractioning for a 60 Gy biological effect dose.

Chemotherapy treatment

Chemotherapeutical management was administered based on the following scheme:
- Ifosfamide: 2 g/m²/day, for one day;
- Carboplatin 30 mg/m², for three days;
- Etoposide: 100 mg/m², for two days
- Temozolomide at 100 mg/m² for five days at each cycle for at least six cycles.

In some hospitals with an agreement with our institution, chemotherapeutic management was not offered.

Surveillance

The surveillance scheme includes three-monthly skull contrasted MRI over the first year and every four months during the second year, every semester in the third year, and in both fourth and fifth year, annually or before this period for clinically necessary reason.

Data analysis

The statistical analysis was carried out using the GraphPad Prism® statistical package, version 6.0. Descriptive statistics was used to determine the median by population distribution type. To calculate and obtain the OS, the log-rank assessment was used, with different Gehan-Breslow-Wilcoxon tests. With regard to HGG by state in the country, as well as to the neoplasm intracranial localization distribution, a distribution graph determination was performed.

RESULTS

A total of 102 patients diagnosed with glioma, out of which 18 patients (17.6%) had HGG, were assessed by the Radiotherapy Department of the Federico Gómez Children’s Hospital of Mexico over the period from 2008 through 2103. Most assessed patients came from Mexico City (then Distrito Federal) and the State of Mexico (Fig. 1).

Median age of the patients diagnosed with HGG-related intracranial lesions was five years, with no gender being predominant (Table 1), and the most common localization was infratentorial, specifically in the brainstem in 10 patients (55.6%). The reported histologies of the patients were anaplastic astrocytoma and GBM.

With regard to the management of patients amenable to surgical treatment, eight patients (44.4%) underwent surgery, with the procedure being gross tumor resection in four subjects (22.2%). Those patients who were not offered initial surgical management owing to localization or any other limitation were offered external radiotherapy management.

All patients (n = 18) received external beam radiotherapy and/or concomitant or adjuvant chemotherapy based on the ifosfamide/carboplatin/etoposide and/or temozolomide scheme. In some patients, external radiotherapy had a protracted prolongation owing to concomitant management-associated comorbidities, as well as to increased intracranial hypertension, which was improved with ventricular bypass valve changes.

Local control analysis

In most patients, adherence to post-treatment follow-up was not adequate, mainly owing to economic reasons, which limited the attainment of control imaging studies, with only initial local control data being obtained, but not an ade-
quate follow-up thereof in order to be able to objectively establish the disease-free interval for all analyzed patients. In patients where control follow-up imaging data could be collected after the completion of the external radiotherapy treatment with 54-60 Gy doses, partial response was observed at 6-8 months in 50%, with subsequent stability of the disease status until death, and only in three cases was a complete response obtained at 15 months of treatment completion and, hence, a DFS of 100% at three years.

Overall survival analysis

Information on survival could be obtained from all patients, and therefore the analysis was performed, which yielded a five-year OS of 37%, with a median of 13 months (Fig. 2).

Subsequently, different patient and neoplasm-inherent factors were analyzed in order to assess their effect on OS. No correlation of OS with age was made because in the series there were no patients younger than three years, neither was it made with molecular alterations because these were not assessed.

The factors that were observed to have an influence on OS in this case series were: surgical intervention, external radiation therapy dose, and radiotherapy treatment type of fractioning.

With regard to the surgical procedure, an 18-month OS of 100 vs. 50 vs. 36% was obtained for gross total resection, subtotal resection, and no surgical intervention, respectively (Fig. 3). Overall survival was increased with external radiotherapy doses higher than 54 Gy, with median survival of 19 vs. 7 months with lower doses, \( p = 0.0002 \) (Fig. 4A and 4B).

In the assessment of the fractioning type, an improvement in OS was found with standard fractioning, with a median of 20 vs. 10 months; \( p = 0.02 \) (Fig. 5).

<table>
<thead>
<tr>
<th>Table 1. Patient and disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Gender (male:female)</td>
</tr>
<tr>
<td>Genetic alterations or syndromes:</td>
</tr>
<tr>
<td>- Type 1 neurofibromatosis</td>
</tr>
<tr>
<td>Localization:</td>
</tr>
<tr>
<td>- Supratentorial (parietal and temporal lobes)</td>
</tr>
<tr>
<td>- Infratentorial (brainstem and posterior fossa)</td>
</tr>
<tr>
<td>Histology (suggested by imaging and pathology):</td>
</tr>
<tr>
<td>- Anaplastic astrocytoma</td>
</tr>
<tr>
<td>- Glioblastoma multiforme</td>
</tr>
<tr>
<td>Clinical findings:</td>
</tr>
<tr>
<td>- Headache</td>
</tr>
<tr>
<td>- Cranial nerve alteration</td>
</tr>
<tr>
<td>- Ataxic gait</td>
</tr>
<tr>
<td>- Seizures</td>
</tr>
<tr>
<td>Surgical management:</td>
</tr>
<tr>
<td>- Gross tumor resection (95-100%)</td>
</tr>
<tr>
<td>- Subtotal resection (&lt; 95%)</td>
</tr>
<tr>
<td>- None</td>
</tr>
<tr>
<td>Management with external radiotherapy (fractioning):</td>
</tr>
<tr>
<td>- Modified</td>
</tr>
<tr>
<td>- Standard</td>
</tr>
<tr>
<td>Radiotherapy total dose:</td>
</tr>
<tr>
<td>- Lower than 54 Gy</td>
</tr>
<tr>
<td>- Equal to or greater than 54 Gy</td>
</tr>
<tr>
<td>Chemotherapy:</td>
</tr>
<tr>
<td>- ICE scheme</td>
</tr>
<tr>
<td>- Temozolomide scheme</td>
</tr>
<tr>
<td>- ICE with temozolomide scheme</td>
</tr>
<tr>
<td>- None</td>
</tr>
</tbody>
</table>

Gy: Gray; ICE: Ifosfamide-Carboplatin-Etoposide-based chemotherapy scheme.
Factors such as tumor histology and management with chemotherapy were also analyzed, but none of these factors was found to impact on OS.

**DISCUSSION**

In the present study, the prevalence of HGG was assessed to be 17% in our pediatric population, which is similar to figures reported in the literature. Median age of the patients was five years, with no gender being predominantly affected and with infratentorial localization (specifically in the brainstem) being more common. Brainstem-located gliomas (55.6%) did not receive any surgical intervention or biopsy because these were diffuse lesions, with this being highly relevant since, by not being able to determine the glioma histological characteristics, there will always be higher uncertainty about the tumor behavior, as has been described in the world literature.
With regard to the determination of molecular and genetic prognostic factors (mutations, chromosomal alterations, or genetic syndromes) that have been reported in the world literature to have an impact on OS, in the present study it was not assessed because no molecular determinations or profiles could be carried out in our Institution, and only in one patient (5.6%) was the presence of type 1 neurofibromatosis syndrome established by clinical examination.

Surgical management with gross tumor resection was only possible in 22.2% and subtotal resection in 22.2%, and no surgical intervention was carried out in the brainstem-located cases. After surgical management, or in patients who were not candidates for it, external beam radiotherapy was immediately offered, mostly with conventional fractioning, with clinical improvement being observed at the end of radiotherapy treatment with an improvement in performance status. Patients were treated with a median dose of 54 Gy, with this dose being predominant owing to large volumes and at-risk organs restriction. External radiotherapy administration was concomitant and adjuvant with temozolomide, except in two cases (11.1%) where no chemotherapy was offered.

Local control assessment at follow-up could not be adequately determined in this study due to the failure to obtain imaging studies, as already commented in the results section, which impacted on the progression-free interval assessment. However, in patients where it could be assessed with post-treatment control studies, stable disease was observed at six months and, after eight months, there was partial response of at least 50%, and complete response in three cases at 15 months; in the remaining patients, stable disease was observed for up to 12 months until progression and death.

The patients who achieved a complete response at 15 months had a DFI of three years. It should be noted that these patients underwent at least subtotal resection and management with external beam radiotherapy at doses higher than 55 Gy, with adjuvant chemotherapy for up to six cycles and, in one case, in spite of the corroborated histological lineage being GBM, with subtotal resection and external radiotherapy with concomitant temozolomide and adjuvant ifosfamide/carboplatin/etoposide scheme, a complete response was achieved with a DFI of 42 months.

With regard to the 37% OS obtained in the present study at five years, this is slightly lower than that reported in the literature, probably owing to the high percentage of patients with no surgical intervention due to brainstem localization, although in the analysis of factors in the present study, the tumor localization factor did not statistically significantly impact on OS.

The factors that influenced OS in this study included the gross tumor resection, with its influence already being apparent at 18 months, with an important decrease of 50% when gross tumor resection was not achieved and a worse outcome when no surgical intervention was performed.

Another important factor that was assessed in the present study was external beam radiotherapy management, with doses higher than 54 Gy and standard fractioning favorably impacting on OS. Although the literature has only reported that the suggested dose is 55.8 Gy, a trend towards the dependence of OS on higher doses was observed in this study, as well as an OS improvement with standard fractioning, as previously proposed by authors such as Chan, et al. in 2002.

Although tumor histology has been reported to impact on OS by reducing it by 50% when GBM is compared with anaplastic astrocytoma, in this case series no such trend was observed, probably owing to the fact that GBM-diagnosed patients were surgically intervened with at least subtotal resection and received external radiotherapy management at a total dose of 60 Gy with standard fractioning and six cycles of concomitant chemotherapy.

Although chemotherapy did not statistically significantly modify OS as a single factor in this group of patients, it had at least an effect on disease stability, as has been observed in the literature.

CONCLUSION
In the present study, gross tumor resection and subsequent adjuvant management with external beam radiotherapy at a dose higher than 54 Gy and up to 60 Gy with standard fractioning were found to be the main overall survival prognostic factors in pediatric patients diagnosed with intracranial high-grade glioma.

REFERENCES


