Pediatric brainstem glioma:
treatment influence on survival rate-
systematic review

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LITHUANIA, Kaunas. 2017 m.
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1. **Summary (English):**

Ignacio González Bautista.
Pediatric brainstem glioma: treatment influence on survival rate- systematic review.

*Research aim:*
The aim of this study is to compare the treatment influence on survival rate in pediatric patients suffering from brainstem glioma. This systematic review analyses previous performed studies which compare different treatment strategies which are used nowadays in clinical practice and their outcomes in terms of survival-rate, also analysing the major different types of brainstem gliomas and their outcomes.

*Objectives:*
The objective of this systematic review, through comparison of different treatment strategies, evaluates the best option that can be chosen when managing brainstem glioma in children, and the outcomes to be expected from each treatment, with a special remark on the two major types of brainstem gliomas: Low-grade gliomas (LGG) and High-grade gliomas (or diffuse intrinsic pontine gliomas (DIPG)).

*Methodology:*
Through the use of major scientific databases (Ovid Medline, Embase, Pubmed) and searching of the needed terms seeking the adequate studies, a quantity of 18 studies have been chosen and compared with each other to obtain a comparison of the treatments used in the management of brainstem glioma.

*Study participants:*
The study participants reviewed in this study is 592 excluding participants of systematic reviews.

*Research results:*
The comparison of the studies did not find a significant improve in survival between new and conventional treatment techniques.

*Conclusions:*
No differences in overall survival differences have been found with the novel therapeutics used for the treatment of brainstem glioma, although diagnostic methods have evolved and new and promising therapeutical options are being evaluated nowadays.

*Recommendations:*
Further studies have to be done in the field of pediatric neurooncology regarding this type of tumors since the actual treatment options do not provide a sufficient improvement in terms of survival, mainly focusing on individually-based techniques and focusing in new therapies which can have a potential curative effect of this tumors and providing a remarkable difference in survival of this patients.

*Conflict of interest:*
The author reports no conflicts of interest.
2. Introduction

Brainstem gliomas are arising with a higher incidence in children than in adults [20,21]. They represent a big challenge for the physicians who have to face this kind of tumors, because of the rapid manifestation of symptoms as well as the fast progression of them along with quick deterioration of life quality with a high mortality risk. The main problem of these tumors relies on the fact that no curative treatment has been found nowadays for the diffuse gliomas, which represent up to 80% of the seen brainstem tumors in children. The treatment goal is to provide a disease progression free period where the relief of the symptoms can improve the life quality of the patients, having in mind that symptoms will follow eventually and lead to patient death in a relative short period of time.

In this systematic review, I tried to focus on the treatments used for brainstem gliomas in children, paying special attention on those representing the vast majority (the diffuse tumors) and comparing them in terms of survival benefits found. My intention was to obtain an insight on which treatment is more effective and also consider alternative or additional treatments which could make up a difference in terms of survival of the patients since, unfortunately, tends to be really low and the impact for the family and the patient tends to be really huge because of the aggressiveness of this disease along with the tedious process of treatments that they have to follow. Improve the quality of life of the patient among with significantly increasing his/her survival should represent the main goal of the health system workers involved in this type of disease nowadays, from any healthcare and research institution involved.
3. Aim and objectives of the thesis

The aim of this thesis is to evaluate the treatment options for brainstem glioma patients and provide a personal insight of which treatments are effective.

Objectives:

1. Present the variety of treatment options given for brainstem gliomas.
2. Assess its effectiveness in terms of survival rate.
3. Discuss on which would be the “best treatment option” given in such patients.
4. Formulate a conclusion according to all the collected data.
4. Literature review

Brainstem tumors account for 10-20% of all brain and CNS tumors in children and adolescents [10,21,31], being the 3rd most common site of tumor appearance with slightly higher prevalence in noted in males according to some studies, while others accepting an equal prevalence among both sexes. According to WHO (World Health Association) [18], 4 grades of brainstem glioma are established according to histological appearance (see table 1), based on the presence of nuclear atypia, appearance of vascular proliferation, mitoses and necrosis (necrosis being typically seen in the grade 4: glioblastoma multiforme). Other classifications are possible [16,23].

<table>
<thead>
<tr>
<th>WHO GRADING</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Juvenile pilocytic astrocytoma</td>
</tr>
<tr>
<td>G2</td>
<td>Diffuse astrocytoma</td>
</tr>
<tr>
<td>G3</td>
<td>Anaplastic astrocytoma</td>
</tr>
<tr>
<td>G4</td>
<td>Glioblastoma multiforme</td>
</tr>
</tbody>
</table>

*Table 1: WHO ranging of brainstem glioma (with histological types examples).*

There is now tendency to classify the tumors according to the molecular profiling. For example, the tumors with mutated IDH1 (IDH stands for isocitrate dehydrogenase) and IDH2 have better outcomes than the gliomas with wild-type IDH [6]. These is because the first two promote the cellular accumulation of HIF-1α (hypoxia-inducing factor), promoting cell death. Also, codeletions of Chromosome 1p and 19q along with an IDH1 mutation indicates an oligodendroglioma in Grade 1-3 gliomas.

For pediatric diffuse gliomas, a newly defined entity termed diffuse midline glioma, H3 K27M-mutant is characterized by K27M mutations in the histone H3 gene, a diffuse growth pattern and a midline location. This newly defined entity occurs primarily in children, but can be seen in adults [11,20], and includes tumors previously referred to as diffuse intrinsic pontine glioma (DIPG).

From all the diagnosed brainstem tumors, we can also differentiate them into two major groups according to location. In the first group, which represents the 15-20% of those brainstem tumors, have characteristics of focal glial tumors, and they are more commonly seen in the medulla or midbrain, tending to be low-grade (benign), sometimes in association with NF-1 (neurofibromatosis 1) [16], and with better prognosis which is mainly related to the tumor biology and the degree of surgical accessibility, and usually with an indolent clinical course [30].
The second group, the remaining 80%, represents those diffuse tumors, usually located in the pons [29], englobed in the group of high grade gliomas (HGG), commonly seen as diffuse intrinsic pontine gliomas (DIPG), which have a malignant, diffuse and a very poor prognosis (see figure 1) [21].

The cause of this tumors is unknown. A genetic link is suspected although still not found. For example, increased incidence of brainstem glioma has been observed in patients with neurofibromatosis (usually low-grade). Other causes such as radiation like in radiated children suffering tinea capitis infection or radiotherapy-induced neoplasms. This implies that gene mutations, either acquired or inherited, are the causative agent in the appearance of those tumors and have an influence on the outcomes. For example, tumors that overexpress p53 protein and have high proliferation index as well [2], tend to have worse outcomes. Some receptors such as the VEGF (vascular endothelial growth factors) receptors tend to overexpress on those tumors which exhibit a higher rate of invasion and growth by promoting the angiogenesis, such as in the supratentorial glioblastomas [2]. The EGFR (endothelial growth factor receptors) are present in about 25% of glioblastomas and are important in the growth of these neoplasms.

Fig. 1: Illustration demonstrating various locations of brainstem tumors. A. denotes the tectal plate; B, the focal intrinsic midbrain; C, the focal intrinsic pontine; D, the dorsal exophytic pontine; E, the diffuse pontine; F, the focal intrinsic medullary; and G, the dorsal exophytic medullary.
as well [14]. Recurrent activating ACVRI mutations are also seen in DIPG gliomas [28]. Other mutations have been identified [33].

The signs and symptoms that can derive from these tumors are various, being headache, motor deficits and visual complaints the most common in children. Since this area is hosting some control centers and nucleus, and represents a passage of long tracts as well at is close close to cranial nerves, it’s affection can lead to many symptoms, which are summarized into a “triad” (1. Cranial nerve deficits; 2. Long tract signs and 3. Ataxia of trunk and limbs). Rare clinical presentations such as acute brainstem haemorrhage can appear [36].

Being precise in the location of the tumor gives us information about the clinical appearance of the tumor. For example, tectal lesions tend to cause hydrocephalus by blocking the passage of cerebrospinal fluid in the 4th ventricle. The pontine and cervicomedullary lesions tend to show long tract and cranial nerve signs.

The diagnosis of this tumors begins with the imaging studies and its correlation with the previously described clinical symptoms (Karnofsky Performance Status Scale (KPS) [25,34]), and CT and MRI [3,10,23] are the most commonly used, being the last one the most appropriate method of use because of better accuracy (unless contraindicated). Other methods such as CSF and arteriography help in the diagnosis and differential diagnosis process. Tissue biopsy option depends on the morphological aspect of the tumors, being those with focal, cystic, exophytic, clear margins characteristics those in which the biopsy is more feasible. In the case of diffuse tumors, the feasibility of biopsy is nowadays under discussion [4].

On treatment options (see figure 3), three of them represent the main and most effective options to treat brainstem gliomas, which are the focal radiotherapy [3,24], chemotherapy and surgical resection, having in ming that none of them has proven curative in the case of most aggressive gliomas, but palliative by reducing the symptoms and ameliorating the clinical picture of the patient as well as the life quality that comes with it, although no curative options have been found yet. The cerebrospinal fluid diversion may be needed in cases of hydrocephalus [23] and targeted therapy (i.e. BRAF kinase inhibitor).

The focal radiotherapy [1,24] establishes as the cornerstone of treatment, in terms of reduction of clinical progression of symptoms, providing usually transient clinical improvement, and with conventional dosage ranges from 54-60 Gy (Grays) [11], with doses up to 72 Gy when hyperfractionation modality is
used, having in mind that there are not reported significant differences between conventional and hyperfractionated radiotherapy in terms of overall survival (OS) and progression free survival (PFS) in cases of patients with DIPG however, hyperfractionated radiotherapy has shown to reduce the time of treatment completion (3 weeks with hyperfractionated vs. 6 weeks with conventional modality [27,35]), radiotherapy is also not considered the best option in the case of low-grade gliomas considering the long-term sequelae. Corticosteroids (Dexamethasone) are usually given concomitantly to reduce tumor and postsurgical as well as radiotherapy-induced edema. Ancillary procedures such as cerebrospinal fluid diversion is done in hydrocephalus patients. Complications can appear.

Chemotherapy is usually given before or after radiotherapy [8,9,15], or even in concomitance with radiotherapy, usually as a therapy adjuvant, preferably entering the patient into a clinical trial, since there is discussion about the difference in survival between patients using chemotherapeutic agents along with the radiotherapeutic option [29,31], also having in mind the complications derived from the toxicity of those agents (lymphopenia, neutropenia, thrombocytopenia, infection, leukopenia, nausea) and treatments [27], during drug-induction as well as during maintenance.

Conventional agents such as Temozolomide [1,7,15,34] and Carboplatin/Vincristine are used [17], the first one, Temozolomide having shown an improved outcome in children <3 years of age [3], as well as increased effectivity in the cases of glioblastoma multiforme (GBM) although significant OS has not been seen with the use of those agents.

Antioangiogenesis agents such as thalidomide and bevacizumab (VEGF-specific recombinant, humanized monoclonal antibody that binds to and inhibits VEGF from binding to its receptors, preventing endotelial proliferation) have been used in HGG such as GBM, anaplastic astrocytoma, gliosarcoma and DIPG, but it has not conferred survival benefits as well [12,25,29,31].

Surgical resection [4,5] of tumor being achieved in some cases, although before, brainstem tumors scared neurosurgeons and gross total resections were not practised as much as nowadays. Surgery is performed in conjunction with radiotherapy (showing more adverse effects if given early vs. delayed [26]) or chemotherapy, or even both [5,15,23], and as said before, it is not required for diagnosis in cases of diffuse tumors, being more feasible in cases of focal tumors such as exophytic tumors (like the dorsal exophytic tumors protruding into 4th ventricle, causing symptoms such as hydrocephalus), cystic tumors, and enhancing tumors with clear margins which exert a space-occupying effect.
Other procedures such as percutaneous esophagostomy (PEG) may be needed on those patients with difficulties in swallowing and diminished gag reflex, or patients with multiple upper respiratory infections, pneumonia, or altered voice may need postoperative ventilatory assistance.

From the treatment, other complications such as developmental and growth delay are seen in children, as well as cerebral herniation, deep cerebral vein thrombosis, meningitis, paralysis/paresis, radiation necrosis, hypopituitarism/hypothyroidism, bone marrow suppression and cognitive dysfunctions.

Further following of the patients after treatment requires periodic neuroimaging studies such as MRI (unless contraindicated) to assess response to therapy and progression of disease. Contact between doctor, family and patient is crucial to monitor worsening of signs or symptoms, on inpatient as well as outpatient care.
The prognosis for LGG remains good since they are resectable in most of the cases. In the cases of HGG the prognosis remains very poor, with a survival being in the media 7-16 months (even under treatment) since the time of diagnosis in the worst cases like in the pontine gliomas [10,11,25,29].

There have been also identified several prognostic factors, such as age <40 at onset, duration of symptoms before diagnosis longer than 3 months, KPS ≥70, low-grade histology, absence of contrast enhancement and “necrosis” on MRI [25,29].
5. Research methodology and methods

A total of 18 studies which focused on the treatments used for brainstem glioma were studied and data and conclusions were taken from them. Through the use of major scientific databases (Ovid Medline, Embase, Pubmed) and searching of the needed terms seeking the adequate studies, studies have been chosen and compared with each other to obtain a comparison of the treatments used in the management of brainstem glioma. Studies show some different modalities of treatment used nowadays for the management of brainstem glioma and the outcomes derived from it. The sample of studied people (excluding two analysed systematic reviews) is 592 (n=592).

From the studies which I compared all of them have less than 10 years (2007-2017), except two studies which I added, being those from 1996 and 2006. I considered relevant to include those studies for different reasons. The study from 1996 (J. Slotman et al.) seemed relevant because it used hypofractionated radiotherapy [24,27,35] which is nowadays used and even considered the cornerstone of brainstem glioma treatment, showing that no big improvement of treatment modality has appeared since then, and survival rates have not changed significantly in the last 50 years [25,31]. The study from 2006 was a systematic review which compared relevant studies since 1984, again showing similar outcomes.
6. Results

The data extracted from the studies give us a table (see table 2) which compares all the 18 previously mentioned studies, showing the survival conclusions of each study, all of them going around the main treatments seen on the previous diagram (see figure 2).

The main comparison is made between the treatment and the survival conclusions. As we can see, the main indicators for longer survivals are the type of glioma (low grade vs. high grade), obviously tending to see longer survivals in the patients with gliomas with lower grade of development, showing that the structures adjacent to the tumors are less damaged on those cases than in the cases where the gliomas are of higher grades. This translates in better outcomes for low grade gliomas than high grade gliomas in terms of survival. This is also due to the fact that lower gliomas tend to have a higher chance of resectability, and respond better to the adjuvant therapies such as the chemotherapy. In the case of the higher grade tumors the area involved tends to be more diffuse and total resectability is not feasible in most of the cases, although the development of techniques of biopsy (such as the stereotactic biopsy [4]) have increased the feasibility of biopsy of those tumors which would give histological information about the tumor and can give the possibility to doctors to look for better targeted treatments according to the histological type of tumor [5,19]. However, even the possibility for biopsy of those tumors have not given yet an insight on how to target genetic or molecular routes in a way that would really give a significant difference in terms of survival outcomes, and improve prognosis in low-grade gliomas as well [22].

Data from the type of diagnostic method was extracted also to provide information on what has to be the way of diagnosing those tumors, which comprises mainly the clinical symptomatology derived from those tumors and confirmation through more specific methods such as radiological or histological diagnosis.

In the column of treatment, radiotherapy with adjuvant chemotherapy seems to be the main and most effective way of management of those high grade tumors nowadays [32], even in combination with new therapeutical agents, although significant benefits have been seen in terms of overall survival, and moreover, there are also adverse effects derived from the use of them which also put under discussion the benefit/risk ratio derived from the use of those new therapeutical agents.
<table>
<thead>
<tr>
<th>Nr.</th>
<th>Study</th>
<th>Sample (n)</th>
<th>Type of gliomas</th>
<th>Diagnostic method</th>
<th>Treatment</th>
<th>Survival conclusions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ronghe et al. (2010)</td>
<td>16</td>
<td>Low-Grade Astrocytoma</td>
<td>Resection (total/subtotal)</td>
<td>Vincristine and Carboplatin Chemotherapy</td>
<td>All patients were alive at the date of last follow. Patients were followed for a median of 57 months (20–136 months)</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>D.I. Ueoka et al. (2009)</td>
<td>86</td>
<td>All types (Low grade/ High grade)</td>
<td>Biopsy / MRI</td>
<td>Seventy-eight patients (90.7%) underwent radiation therapy. Only four patients (4.7%) underwent chemotherapy</td>
<td>The median survival was 9 months</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>M.S. Zaghloul et al. (2014)</td>
<td>71</td>
<td>DIPG</td>
<td>MRI</td>
<td>HF (39 Gy/13 fractions in 2.6 weeks) vs. CF (54 Gy/30 fractions in 6 weeks)</td>
<td>The median and one-year overall survival (OS) was 7.8 months and 36.4 ± 8.2% for the hypofractionated arm, and 9.5 and 26.2 ± 7.4% for the conventional arm respectively</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>M.H.A. Jansen et al. (2012)</td>
<td>973</td>
<td>DIPG</td>
<td>Biopsy / MRI</td>
<td>Hypofractionation of radiotherapy / Neo-adjuvant chemotherapy / Temozolomide / Other chemoradiotherapy (Vincristine-etoposide, tamoxifen and an intensified chemotherapy protocol) / Non-cytotoxic radiosensitizers (inhaled carbogen, motexafin gadolinium / Anti-angiogenic therapy (temozolomide or celecoxib-etoposide) / Targeted therapy (tyrosine kinase inhibitors, tipifarnib, PDGFR, imatinib, gefitinib, erlotinib) / Non-published completed and ongoing trials</td>
<td>No clear improvement in survival has been achieved in DIPG during recent years</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>S. Bailey et al. (2013)</td>
<td>43</td>
<td>DIPG</td>
<td>Clinico-radiological</td>
<td>Radiotherapy and concomitant temozolomide (75 mg/m2) after which up to 12 courses of 21 d of adjuvant temozolomide (75–100 mg/m2) were given 4 weekly</td>
<td>Median survival was 9.5 months (range 7.5–11.4 months)</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Darren Hargrave et al. (2006)</td>
<td>973</td>
<td>DIPG</td>
<td>Biopsy / MRI</td>
<td>Same treatment techniques analyzed in M.H.A. Jansen et al.(2012)</td>
<td>Overall, outlook is poor and nearly all children eventually die: most studies showed a median survival time of shorter than 1 year.</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>J. L. Frazier et al. (2009)</td>
<td>NN</td>
<td>DIPG</td>
<td>Biopsy / MRI</td>
<td>Systemic therapy administered prior to, concomitantly with, or after radiotherapy</td>
<td>Standard treatment for these high-grade neoplasms has consisted of conventional fractionated radiotherapy, and the response to these ancillary therapies has been transient at best, providing a progression-free survival benefit with no effect on overall survival</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>Broniscer et al. (2008)</td>
<td>10</td>
<td>DIPG</td>
<td>Clinico-radiological</td>
<td>Four patients initially were observed only. All patients received therapy, which consisted of radiation therapy (RT) (n 5 2), RT and chemotherapy (n 5 6), or chemotherapy only (n 5 2)</td>
<td>Four patients have died of tumor progression after a median interval of 0.7 years from diagnosis (range, 0.5–3.7 years) (Table 1), and 6 patients have survived for a median of 2.3 years (range, 0.9–8 years). The current study demonstrates that young age at diagnosis (&lt;3 years) may be associated with a better outcome. Six of our patients have survived for at least 2 years despite the use of therapy that is ineffective in older children with similar tumors.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Tene A. Cage et al (2013)</td>
<td>9 (Historical cohort study)</td>
<td>DIPG</td>
<td>MRI (most clearly visible on T2-weighted sequence)</td>
<td>Stereotactic biopsy</td>
<td>Stereotactic biopsy of brainstem tumors in pediatric patients carries a low associated morbidity.</td>
<td>4</td>
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<tr>
<td>10</td>
<td>Aghajan Y, et al. (2016)</td>
<td>1 (Clinical case)</td>
<td>High grade glioma</td>
<td>Clinico-radiological and biopsy (molecular and histopathological examination)</td>
<td>NN</td>
<td>Patient died 5 months after diagnosis</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td>Frappaz et al. (2008)</td>
<td>23 (Prospective trial)</td>
<td>DIPG</td>
<td>Clinico-radiological</td>
<td>Preradiation chemotherapy was given</td>
<td>The median survival was of 17 months. When survival is considered from time of radiotherapy in both groups, their representative curves superimpose (Fig. 3), suggesting that the 8-month difference in survival is due to chemotherapy.</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>Wolff et al. (2012)</td>
<td>31 (Retrospective chart review)</td>
<td>DIPG</td>
<td>Clinico-radiological</td>
<td>Different regimens: Etoposide (14) / Bevacizumab nimotuzumab irinotecan and, valproic acid (13 each). All of them under radiotherapy</td>
<td>The event free survival after a repeated treatment attempt varied between one month and one year</td>
<td>32</td>
</tr>
<tr>
<td>13</td>
<td>Cohen et al. (2010)</td>
<td>107</td>
<td>High grade glioma</td>
<td>All evaluable patients underwent central neuropathologic review</td>
<td>Concomitant chemoradiotherapy with temozolomide, followed by adjuvant chemotherapy with temozolomide</td>
<td>Temozolomide failed to improve outcome in children with high grade astrocytomas. MGMT overexpression was adversely associated with survival.</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>J. Slotman et al. (1996)</td>
<td>30 (Prospective, nonrandomized study)</td>
<td>Glioblastoma multiforme</td>
<td>Histological</td>
<td>Hypofractionated radiation therapy.</td>
<td>Median survival was 36 weeks (8.3 months)</td>
<td>27</td>
</tr>
<tr>
<td>15</td>
<td>Santhosh A. et al (2016)</td>
<td>25</td>
<td>Low-grade glioma</td>
<td>Clinical + Histopathological (23), MRI (2)</td>
<td>Resection/ Biopsy</td>
<td>The combination of skilled surgery, radiotherapy, and chemotherapy results in excellent survival of children with brainstem low-grade gliomas, with a 10-year 71% progression free survival and 100% overall survival.</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>R. Kebudi et al. (2012)</td>
<td>50</td>
<td>DIPG</td>
<td>Clinico-radiological</td>
<td>Radiotherapy + Concomitant/Adjuvant chemotherapy</td>
<td>The median survival time among all patients was 13 months (1–160 months)</td>
<td>15</td>
</tr>
<tr>
<td>17</td>
<td>Trent R. Hummel (2015)</td>
<td>27</td>
<td>DIPG/ HGG</td>
<td>Clinico-radiological for DIPG patients and histological for HGG patients.</td>
<td>Radiotherapy with concomitant Temozolomide (With resection (total/subtotal) or biopsy in some cases)</td>
<td>For DIPG patients, median overall survival (OS) was 10.4 months. For HGG patients, 3-year progression free survival and OS were 33 % (SE ± 14 %) and 50 % (SE ± 14 %), respectively.</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>G- Yazici et al. (2015)</td>
<td>63</td>
<td>HGG (Anaplastic astrocytoma(26) and Glioblastoma (37))</td>
<td>Clinico-radiological and histological</td>
<td>Surgery (GTR/others) + Radiotherapy + Concomitant/Adjuvant chemotherapy + TMZ</td>
<td>Median overall survival was 20.2 months. Survival was longer in patients with anaplastic astrocytoma (median survival of 37.4 months) than in glioblastoma patients (median survival 11.9 months). Comments: Patients in the present study that underwent GTR had significantly longer OS than patients with partial resection. Addition of chemotherapy (PCV/CCNU/vincristine [pCV]) to radiotherapy resulted in prolonged EFS in children with high-grade astrocytoma, as compared to radiotherapy alone; the difference was greatest in children with glioblastoma.</td>
<td>34</td>
</tr>
</tbody>
</table>

**Table 2: Comparison of treatment and survival effect**
7. Discussion

The studies analysed provide an insight on how the treatment should be given nowadays depending on the type of tumor we are facing, and the expected survival derived from its use. However, it is also seen that there is consensus on how the treatment options can provide benefits depending on the moment given meaning that proper early diagnosis is crucial to slow disease progression and worse survival outcomes.

The present study shows that nowadays, the survival goes around the year for the most aggressive cases using the main therapeutical options, with or without concomitant treatments, being seen higher survivals on some studies, and which could show statistical differences, but having in mind that risks of misinterpretation of outcome data are substantial and that harmony is urgently needed between eligibility criteria and statistical endpoints.

Also is important to consider the advantages of the treatment options in terms of hospitalization means and time invested in receiving the treatment, since every second matters with this disease and trying to provide a good quality of life for those patients, as well as “time out of the hospital” should be maximized in order to avoid as much as possible traumatic experiences for the patient as well as for relatives.
8. Conclusion

Since brainstem glioma in pediatric patients represents a “big headache” for the medicine nowadays because of the big impact that supposes for the family as well as for the pediatric patient, the main discussion which has to be put on the table is how to really change the outcome of this devastating and insidious disease, which through comparison of the previous 20 years, has not seen a very significant improvement in terms of real survival benefits for the patient, remembering that no treatment has shown a benefit over conventional radiotherapy (other than reduced treatment completion with hypofractionated radiotherapy [27,35]) and although diagnostic and therapeutical options widen, as well as quality of life of patient tends to be better, new therapeutical options have to be focused on stopping the progression of the disease and provide a real difference in overall survival of the patients.

This also translates for adults whom suffer from high grade brainstem gliomas, which also tend to have bad outcomes, and curative treatment has not been found for them as well, where observation is better than intervention in some cases (more conservative approach) [20]. Further prospects for the future require the focus on targeted therapies [19,23] but also individual therapies directed for each case of patients, also with multidisciplinary team (neurologists, radiologists, oncologists, pathologists, researchers, and so on) which can provide the most effective treatment in each case and finally see real benefits from the therapy given.

Let’s hope new methods of treatment arise in the future which will change the “1-year mean overall survival” with the actual treatments and we can be able to say that the treatment doctors are giving is curative.
9. Literature list


### 10. Abbreviations list

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>B-raf proto-oncogene</td>
</tr>
<tr>
<td>BSG</td>
<td>Brainstem glioma</td>
</tr>
<tr>
<td>CCNU</td>
<td>Lomustine</td>
</tr>
<tr>
<td>CF</td>
<td>Conventional fractionated (radiotherapy)</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>DIPG</td>
<td>Diffuse intrinsic pontine glioma</td>
</tr>
<tr>
<td>EGFR</td>
<td>Endothelial growth factor receptor</td>
</tr>
<tr>
<td>GBM</td>
<td>Glioblastoma multiforme</td>
</tr>
<tr>
<td>GTR</td>
<td>Gross total resection</td>
</tr>
<tr>
<td>Gy</td>
<td>Grays (radiation units)</td>
</tr>
<tr>
<td>HF</td>
<td>Hyperfractionated radiotherapy</td>
</tr>
<tr>
<td>HGG</td>
<td>High-grade glioma</td>
</tr>
<tr>
<td>HIF</td>
<td>Hypoxia-induced factor</td>
</tr>
<tr>
<td>IDH</td>
<td>Isocitrate dehydrogenase</td>
</tr>
<tr>
<td>KPS</td>
<td>Karnofsky performance scale (score)</td>
</tr>
<tr>
<td>LGG</td>
<td>Low-grade glioma</td>
</tr>
<tr>
<td>MGMT</td>
<td>O6-Methylguanine-DNA methyltransferase</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NF</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PCV</td>
<td>Procarbazine/Lomustine/Vincristine (chemotherapy regime)</td>
</tr>
<tr>
<td>PEG</td>
<td>Percutaneous esophagostomy</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression free survival</td>
</tr>
<tr>
<td>TMZ</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</table>
11. Terms

- **Brainstem:**
  - The stem-like part of the base of the brain that is connected to the spinal cord. The brain stem controls the flow of messages between the brain and the rest of the body, and it also controls basic body functions such as breathing, swallowing, heart rate, blood pressure, consciousness, and whether one is awake or sleepy. The brain stem consists of the midbrain, pons, and medulla oblongata.

- **Glioma:**
  - Type of tumor that occurs in the brain and spinal cord. Gliomas begin in the gluey supportive cells (glial cells) that surround nerve cells and help them function.

- **Ataxia:**
  - An inability to coordinate voluntary muscular movements that is symptomatic of some central nervous system disorders and injuries and not due to muscle weakness — called also incoordination.

- **Cystic:**
  - Enclosed in a cyst. A cyst is a closed sac having a distinct membrane and developing abnormally in a cavity or structure of the body.

- **Exophytic:**
  - Tending to grow outward beyond the surface epithelium from which it originates.

- **Stereotactic biopsy:**
  - Stereotactic brain biopsy is a minimally invasive procedure that uses this technology to obtain samples of brain tissue for diagnostic purposes.

- **Hydrocephalus:**
  - Abnormal buildup of cerebrospinal fluid (CSF) in the ventricles of the brain. The fluid is often under increased pressure and can compress and damage the brain.