Journal of Clinical Neuroscience 44 (2017) 34–46

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review article

# Ganglioglioma of brain stem and cervicomedullary junction: A 50 years review of literature

M. Burhan Janjua [a,*], Iryna Ivasyk [a], David J. Pisapia [b], Mark M. Souweidane [a]

[a] Department of Neurological Surgery, Weill Cornell Medical College and New York Presbyterian Hospital, 525 East, 68th Street, New York, NY 10065, United States
[b] Department of Pathology, Weill Cornell Medical College and New York Presbyterian Hospital, 525 East, 68th Street, New York, NY 10065, United States

ARTICLE INFO

*Article history:*
Received 13 March 2017
Accepted 13 June 2017

*Keywords:*
Brain stem ganglioglioma
Imaging characteristics
Extent of resection
BRAF V600E mutation status

ABSTRACT

Gangliogliomas are rare low-grade brain tumors composed of both neoplastic glial and neuronal cell elements. The treatment modalities are relatively different in this location and hence factors affecting outcome are poorly understood. We identified 142 brain stem GG patients across 46 studies. The average age was 11.4 years with significant difference b/w males and females under the age of 20 ($p = 0.001$). 100% of tumors in the CMJ while, 72% of type I and 86% of type II tumors demonstrated contrast enhancement. 72% of type I and 86% of type II tumors demonstrated contrast enhancement. All BRAF mutation positive tumors demonstrated contrast enhancement. Medulla and pons was the most favorable location followed by medulla alone, and the CMJ. In all tumors "gross total resection" (GTR, 16%), "subtotal resection" (STR, 48%) or "partial resection" (PR, 36%) was achieved. Most subtypes II and III were partially resected (86% and 66%), while, subtype I underwent STR (66%). Only 55% of the patients were positive for the BRAF V600E mutation. The overall survival dropped from 50% at 24 to 10% at 60 months, postoperatively. Through this review, we found that an early diagnosis, location, and with the imaging characteristics are vital part of the preoperative planning. Surgical resection is highly dependent on location in the brain stem with radical resection only limited to the most contrast enhancing portion of these tumors. BRAF V600E mutation status should be considered to allow the possibility of targeted therapy in case of a residual tumor and/or regrowth.



## 1. Introduction

Ganglioglioma (GG) is an exceedingly rare brain tumor composed of both neuronal (ganglion cell types) and glial cell elements [1]. These neoplasms comprise of 1–10% of all CNS tumors in pediatric population, and only 6% tend to occur in the supratentorial compartment with the predominant involvement of the temporal lobes (more than 70%) while, 15% of them occur in the infratentorial compartment [1–4]. Additionally, among posterior fossa gangliogliomas (GGs) tendency to involve the brainstem is considerably high [5–9]. The incidence is relatively higher in the younger population between the age of 10–20 years [10]. The treatment modalities for these tumors are limited, especially if they arise in the brainstem (BS) where complete surgical resection is not possible. Moreover, BS-GGs present acutely with a short prodrome of clinical symptoms, relatively high mortality rate when compared to the cerebellar or cerebral GGs and a decreased progression free survival (PFS) [6,7,11].

While considering different treatment options, surgery is the treatment of choice with a preferable goal of a gross total resection (GTR), if feasible. However, the involvement of eloquent structures preclude gross total resection. GTR is more easily achievable in cerebral gangliogliomas rather than BS-GGs, and is the only predictor of a long term disease free survival [5,12–16]. Among infratentorial GGs, cerebellar involvement is considered less challenging due to the hemispheric involvement and more amenable to the resection. But, its extension to the cerebellar peduncles (brachium conjuctivum, brachium pontis, and restiform body), and/or BS renders resection incomplete and hence affects the survival substantially [7,8,17].

Additionally, the literature is reminiscent of quite a number of reports of recurrence despite the advancement in stereotactic image guidance yielding a confirmed complete resection [18,19]. Due to the rarity of these tumors, the data are scarce to assess the epidemiology, factors affecting outcome and accurately predict the risk of recurrence in pediatric population. Another caveat is the small number of pediatric surgical case series comprising of mix

* Corresponding author at: Pediatric Neurosurgery Fellow Weill Cornell Medical College and New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, United States.
*E-mail addresses:* burhan167@yahoo.com, mburhanj@gmail.com (M.B. Janjua).

http://dx.doi.org/10.1016/j.jocn.2017.06.021
0967-5868/

histological grades yielding a limited statistical analysis [20–22]. Classically, GGs are considered as WHO Grade I or II. The degree of anaplasia and/or necrosis within the glial cell component increases the grade to III or IV [22]. Recurrent tumors cause considerable patient morbidity because they require further therapies including additional surgery, radiation, and/or chemotherapy. The management of brainstem GGs becomes very challenging depending upon its grading, location, and the extension. Among other treatment modalities offered, BRAF V600E mutation has been reported in BS-GGs with few therapeutic implications. Therefore, we compared the age, gender, presenting symptoms, imaging characteristics, treatment options, BRAF V600E mutation status, and prognosis. The primary objective of this retrospective review is to identify association of demographic features, clinical features, location and other predictors of survival in patients with BS-GGs including cervicomedullary junction GGs (CMJ).

## 2. Methods

We have conducted a detailed retrospective review to identify all patients with BS-GGs and/or CMJ who were diagnosed from 1966 to 2016. We used MEDLINE literature search utilizing keywords "ganglioglioma of brainstem" or "ganglioglioma of cerebellomedullary junction". All patient variables comprising of demographics, presenting symptoms with or without the presence of raised intracranial pressure or hydrocephlaus, any CSF diversion procedure if performed, location of lesion in BS and/or CMJ with or without the involvement of cerebellar peduncles, imaging features with or without the contrast enhancement, biopsy or autopsy procedures if performed, the extent of surgical resection, histological grading, adjuvant or salvage radiation therapy, chemotherapy, BRAF V600 E mutation status, documented follow up, and the overall survival were recorded. All clinical case reports and/or series comprising of either de novo or recurrent cases of GGs of cerebrum, cerebellum, or spinal cord below CMJ were excluded from the final analysis.

We also present an interesting case of GG of CMJ with a short prodrome of her sensory and subtle motors symptoms. The presentation, imaging details, initial thought process and preoperative planning have been discussed. We have described our surgical approach in detail due to the location of the tumor. The histological features of the tumor have been shown and documented. We have also discussed our limitations of resection due to diffuse nature of the lesion consistent with the mixed intensity on imaging.

## 3. Statistical details

For univariate analysis a Chi-square ($\chi^2$) and Fisher exact *t*-test were used for changes of significance among categorical variables. Using the Kaplan-Meier method and population proportion approximation, we examined associations between different variables and assessed survival among these patients. In specific, the 95% confidence intervals (CIs) for proportions were calculated following a normal binomial proportion confidence interval approximation. While, the Kaplan-Meier method was used to determine follow up and the overall survival differences. The *t* test was used to compare mean age within each defined categorical variable. The margin of error was calculated utilizing 95% confidence interval. The overall statistical significance was determined if the p-value was <0.05. All data was analyzed and visualized utilizing Microsoft Excel (2013) and Matlab (version 8.5.0.197613 (R2015a)).

## 4. Case report

A 24 year old left handed dominant female presented with a sudden onset of dysesthetic symptoms of left upper extremity, more specifically in the dermatomes of C2-C6 distribution, followed by poor dexterity of left hand one week later. There was no history of headaches, blurry vision, tinnitus, change in mental status, behavior, changes in taste, hearing difficulty, nausea, emesis, weakness in either extremity, any bowel/bladder incontinence, swallowing difficulty, central sleep apnea, dizziness or ataxia. On presentation, she had a completely non-focal neurological exam. After a week of persistent symptoms, she consulted a neurologist who prescribed an MRI brain and cervical spine with and without contrast which revealed an enhancing, expansile mass extending from the right inferior brachium pontis to the dorsal medulla, cervicomedullary junction to the upper cervical spine. The mass was poorly defined, with intermediate pre-contrast T1 and heterogeneous mildly hyperintense T2 signal intensity. A focal exophytic portion was also seen in the right dorsal medulla. Primarily, the peripheral and dorsal enhancement extended caudally along the cervical spinal cord to the mid C3 level, with small regions of the ventral enhancement were also seen at the C1-C2 junction. The caudal extension of intramedullary T2 hyperintensity was seen up to the level of C5-C6 level. A spinal syrinx was observed on the left of the central cord with a maximum of 5 mm in diameter at the level of C4. However, no leptomeningeal enhancement was seen in the lower cervical spinal cord. No restricted diffusion was noticed within the confined boundaries of the lesion. There were coarse foci of hypointensity with associated positive phase contrast on quantitative susceptibility map imaging in the right dorsal medulla and craniocervical junction consistent with chronic internal blood products. Peripheral hemosiderin staining was seen at the craniocervical junction (Fig. 1). These radiographic findings were concerning for a lesion/inflammatory mass in the CMJ. A lumbar puncture was initially recommended to rule out any inflammatory etiology involved. Cerebrospinal fluid (CSF) cell count, glucose, protein, gram stain and culture studies were pristine. CSF flow cytometry was inconclusive. These results were not concerning for inflammation nor malignancy. Further studies, including a positron emission tomography (PET) scan of brain and skull base including cervical spine were completed. These revealed an inconspicuous 5-fluorodeoxyglucose (FDG) uptake at the level of the CMJ corresponding to the enhancing mass seen on MRI scan, favoring a primary neoplasm, however, another etiology for the findings such as tumefactive demyelination or BS encephalitis may have had a similar imaging appearance and could not be excluded. There was a poor FDG uptake revealing any avid disease involved (Fig. 2A & B).

Sequential imaging studies revealed no resolution of the enhancement pattern, suggesting neoplasia as the most likely diagnosis. Almost 2 weeks after first initial clinic visit the surgical intervention to biopsy the lesion was offered to the patient including all benefits and risks of the procedure involved. The patient opted for surgery. She was taken to the operating room, and following the administration of general anesthesia, the patient was placed prone on the operating room table. The electrophysiological monitoring (EOM), including lower cranial nerves, motor evoked potentials (MEP), somatosensory evoked potentials (SSEPs), were set up prior to the procedure. Following local infiltration, a midline incision was created extending from the suboccipital region down to the spinous process of the upper cervical spine. A subperiosteal dissection was performed via a submuscular dissection. Utilizing a combination of the rongeurs and a high-speed air drill, C1 and partial C2 vertebral laminectomy were performed. A suboccipital craniectomy was performed with a midline burr hole and bilateral semilunar drilling of the suboccipital bone. With this, the dural exposure was completed. A midline durotomy was created to expose the cervicomedullary junction. Utilizing standard microsurgical technique, the arachnoid was sharply incised to expose the subarachnoid space. Immediately apparent was that the upper cer-

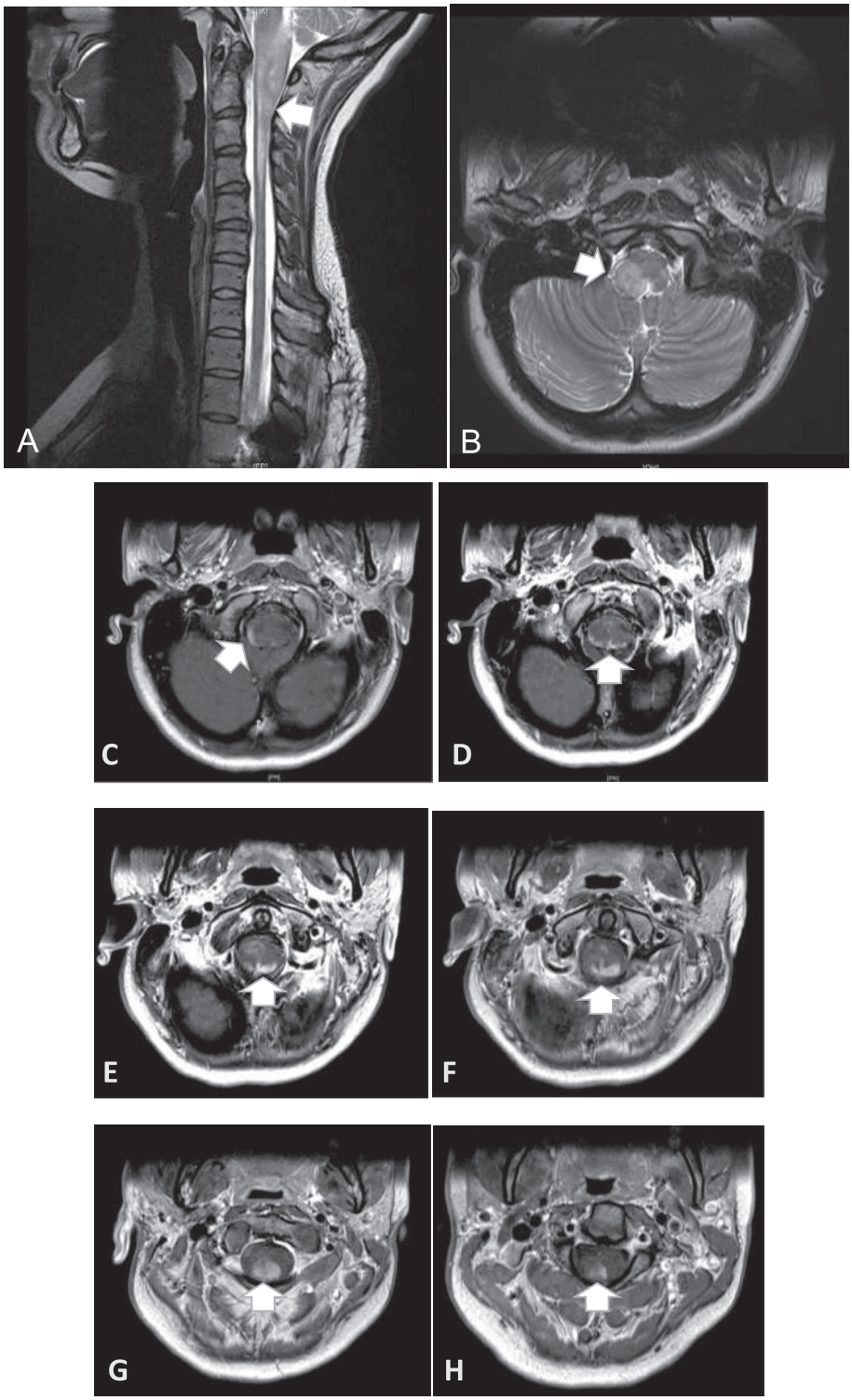


**Fig. 1.** (A and B are pre-contrast sequences, while, C and H are post-contrast sequences.) A-B. T2 hyperintense expansile mass (white arrow) is seen extending from right brachium pontis to the C3 vertebral body. C-H. Peripheral enhancement can be seen extending from dorsal to the ventral aspect of the cervical segment of spinal cord.

vical cord appeared expansile. Additionally, a white opaque tissue was noticed just underneath the right cerebellar tonsil. Utilizing standard microsurgical technique, a cerebellar medullary fissure dissection was performed reflecting the cerebellar tonsils superiorly and laterally. The midline aperture of the 4th ventricle was in full view with no noted abnormality. Dissecting the interarachnoidal plane more laterally, the cerebellar hemisphere was mobilized away from the upper cervical cord at the CMJ. This whitish opaque tissue was investing the pial vasculature (Fig. 3A-D). The main tributary (tonsilomedullary segment) of the sight sided posterior inferior cerebellar artery (PICA) was identified. Based on the anatomical position of the enhancing portion of this mass, that segment of PICA was utilized as an anatomical landmark. With this, a sharp dissection was utilized on the pia just above the tonsil-

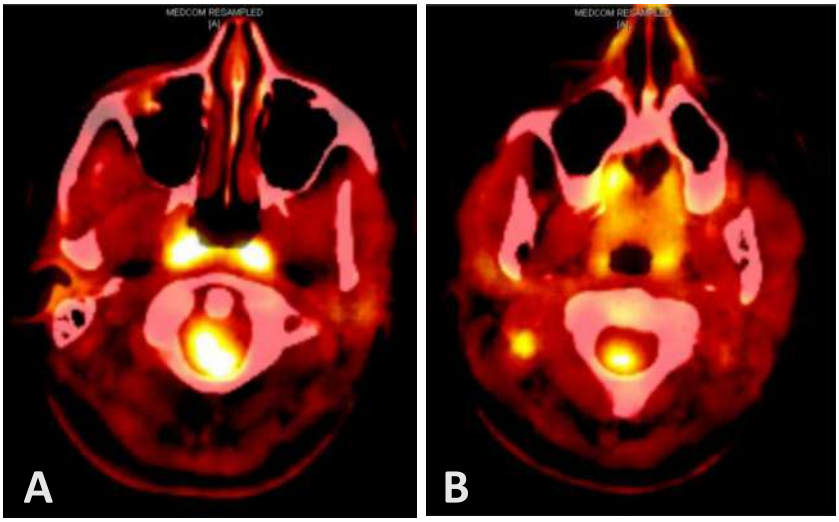


**Fig. 2.** (A-B). PET scan images depicting an increase in FDG update in the cervicomedullary junction.

lomedullary segment of the PICA. Care was taken not to disrupt any tissue with coagulation. Specimens measuring approximately $2 \times 3$ mm were sent both for frozen and permanent section (Fig. 3E-F).

The intraoperative frozen section was consistent with an infiltrating glial neoplasm. Although the grade could not be further specified, the specimen did not have a frozen appearance consistent with a juvenile pilocytic astrocytoma. Thus, it was felt that diagnostic sampling was accurate and within the lesion. Once hemostasis was confirmed, the dura was then closed with a patulous xenographic duraplasty to afford a wider decompression given the expansile nature of the mass (Fig. 3G-H). Similarly, the suboccipital bone was not replaced in an effort to provide a decompressive suboccipital craniectomy which could accommodate the increased growth of the neoplasm. Fibrin sealant was used on the dural closure lines and the wound was closed in a multilayered fashion. The patient tolerated the procedure without complications and was transferred to the ICU for an immediate 48 hours after surgery. The postoperative course was uncomplicated, the patient had intact light touch, vibration, and proprioception sensation after surgery and no cranial nerves paresis, cerebellar signs of incoordination or motor weakness. She was discharged home in a stable condition on postoperative day 4. Upon one month follow up, she still had residual dysesthetic symptoms with some improvement in her hand dexterity movements. Although, the initial frozen section revealed juvenile pilocytic astrocytoma but the final pathology was consistent with the ganglioglioma grade I (Fig. 4).

## 5. Results

Through our literature search we were able to identify 142 brain stem GG patients across 46 studies published over the last 50 years (between 1966 and 2016). Data regarding each patient's presenting age, symptoms, imaging characteristics, tumor location, extent of resection, tumor histology, and the mutation status are documented based on gender difference. All values are in the percentages with the margin of error was calculated from 95% confidence interval (Table 1). The rest of the data from these studies are summarized below.

## 6. Presenting age

The age of patients raged from 1 day to 59 years with an average of 11.4 years [95% C.I. 9.5 years to 13.3 years]. The distribution was heavily skewed towards the younger ages with the majority of patients being under the age of 20, a couple of patients in their twenties and only a handful above the age of 30. When separated by gender, the average age was 10.9 years for males and 12.0 years for females and there was a statistically significant difference in age distributions for patients under the age of 20 ($p = 0.001$) (Fig. 5). Furthermore, there were no reports of females post menopause, with the oldest female patient being 36, meanwhile, multiple cases of older male patients in their 40 s and 50 s have been reported.

## 7. Presenting symptoms

The most commonly reported symptoms in our review appeared dysesthesia, motor weakness and lower CN palsies, each of which was experienced by 80–90% of patients. In general, a larger fraction of female patients experienced each one of these symptoms as opposed to male patients, but a statistically significant difference was only seen in dysesthesia ($p = 0.048$). Other common symptoms included ataxia, headaches, incoordination, respiratory distress, vocal changes and sleep delay (Fig. 6A-B). Out of these symptoms, females were significantly more likely to experience respiratory distress ($p = 0.039$), and vocal changes ($p = 0.050$).

The distribution of symptoms experienced also varied by the age of onset (Table 2). The most commonly associated symptoms appear to be present at all ages, with dysesthesia being least common between the ages of 11–15 and motor weakness being least common in older patients. Adolescents (age 11–15) and young children (age 0–5) are the most likely to experience respiratory distress and vocal changes, meanwhile pre-adolescents (age 6–10) and older patients (age greater than 15) are more likely to experience ataxia. Incoordination is noted as a symptom in 50% of patients aged 6–10 and is rarely seen in any other age group. Finally, headache only appears as a symptom in patients older than 10 years and syncope appears more often in the oldest patients.

## 8. Imaging and histological findings

Studies in which imaging was conducted were pooled to analyze the contrast enhancement of various tumors. Contrast enhancement also varied slightly based on tumor location (Table 3, and Fig. 7A). Fraction of contrast positive tumors dropped off with age (Fig. 7B, and Table 2) and appeared to have no relationship

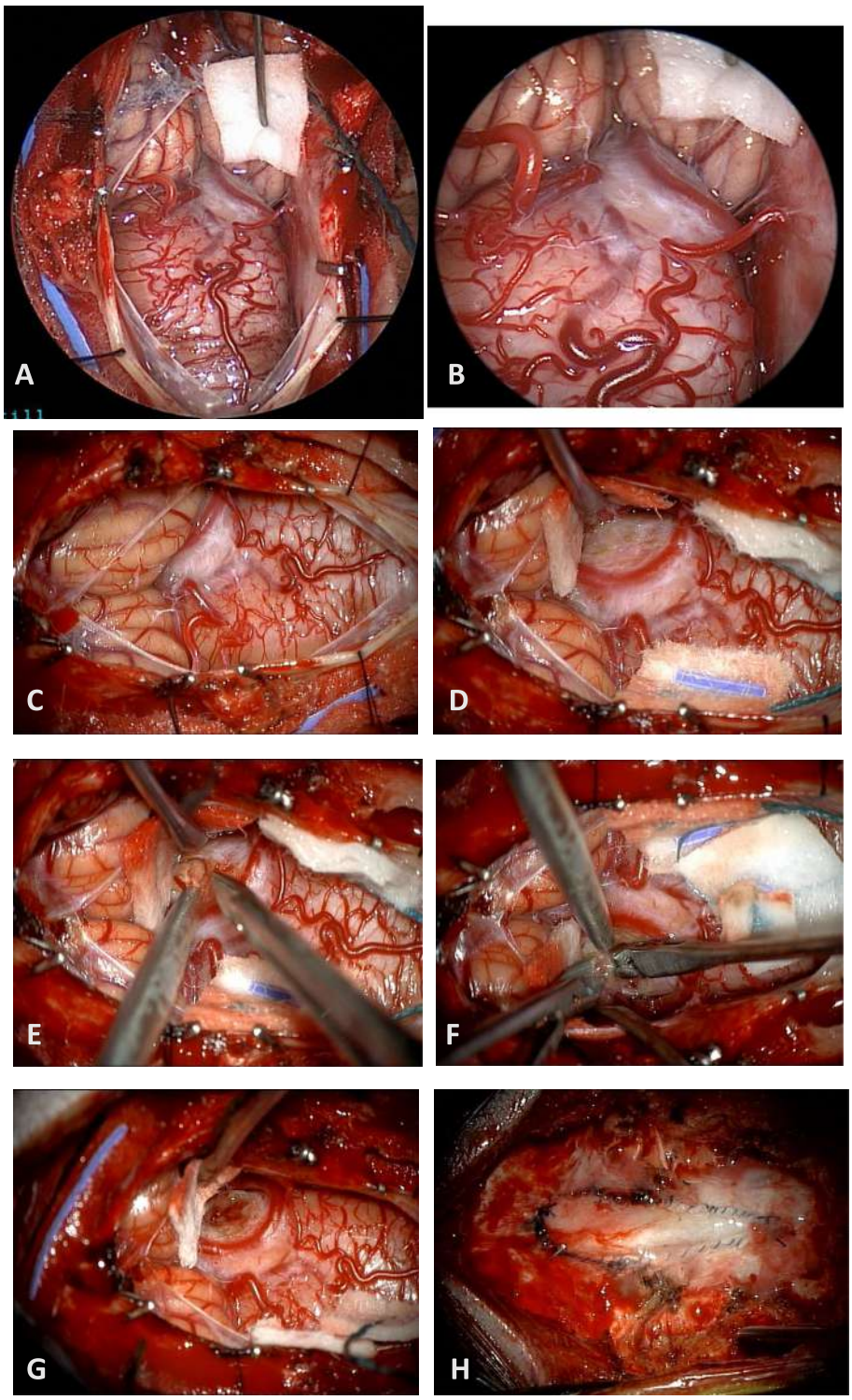


**Fig. 3.** (A-H) Intraoperative details entailing the infiltrative and expansile appearance of cervicomedullary junction (CMJ) ganglioglioma. The site of biopsy was selected based on most contrast enhancing portion of tumor lateral to the right sided tonsilomedullary segment of posterior inferior cerebellar artery (PICA). Note figures A and B with higher magnification.

with gender. Notably, 100% of tumors in the cervicomedullary junction being contrast positive. When looking at histological variables, 72% of type I and 86% of type II tumors were contrast enhancing; no data was available for type III. All of the BRAF mutation positive tumors were contrast positive, as opposed to 67% of negative ones.

## 9. Tumor location

The majority of the cases involved both the medulla and the pons, with the second most common involving just the medulla alone. Interestingly, very few cases reported involved the pons without medullary involvement as well. The least common tumors

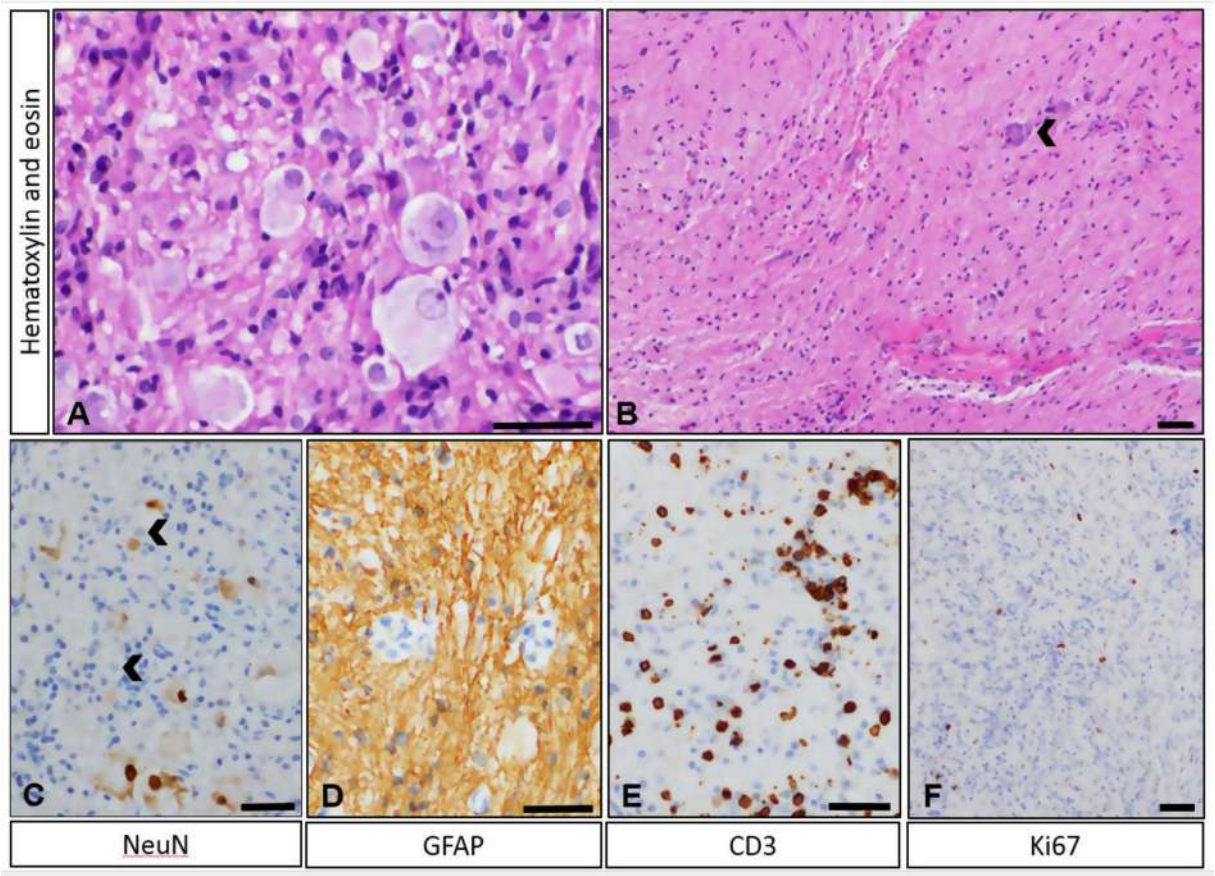


**Fig. 4.** H&E-stained sections show dysplastic appearing ganglion cells (A) and areas demonstrating predominantly glial features (B) with only an occasional ganglion cell (B, arrow). Immunohistochemical stains shows variable NeuN expression (C), with some cells showing moderate to strong staining and other neurocytic cells that are entirely negative (C, arrows). GFAP staining highlights the fibrillary glial component (D). Characteristic of these tumors is a lymphocytic infiltrate, here with a prominent CD3-positive T cell component (E). In keeping with lower grade biologic potential, these tumors often demonstrate only limited proliferative indices, as measured by Ki67 (MIB1) staining (F). All scale bars = 50 μm.

in our analysis involved the midbrain of brainstem. Furthermore, roughly half of the cases included the cervicomedullary junction and a third involved the cerebellopontine angle. There was no statistical significance between tumor locations when separated by gender or age (Fig. 8A-B). Patients with additional cerebellum involvement tended to be younger (8.1 years) than those without documented cerebellum involvement (12.4 years $p = 0.0097$). Interestingly, out of the patients with cerebellar involvement, males (5.1 years) tended to be much younger than females (11.6 years, $p = 0.0026$).

## 10. The extent of resection

We classified surgical procedures as "gross total resection" (GTR, 16%), "subtotal resection" (STR, 48%) or "partial resection" (PR, 36%). While comparing the extent of resection based on contrast enhancement, contrast enhancement was seen in more than 60% of patients across all three types of resections: GTR (75%), STR (86%) and PR (63%) (Fig. 9A). The majority of medullary tumors underwent subtotal resection (52%) while tumors involving the medulla and pons most often were partially resected (48%). All tumors involving only the pons underwent subtotal resection (Fig. 9B). Histologically, most subtype II and subtype III tumors were partially resected (86% and 66% respectively), and most subtype I underwent subtotal resection (66%) (Table 4).

## 11. BRAF V600E mutation

Among the studies, 55% of the patients that were tested for BRAF had positive mutation status, however, only 22% of all patients were tested, with no reported testing prior to 2014. All tumors with BRAF mutation were histologically classified as subtype I. The average age of BRAF+ patients was 7.9 years, and 9.7 years for those without, but no statistically significant difference was noted. Male patients with a BRAF+ mutation tended to present much younger (4.9 years) than females (13.3 years, $p = 0.0014$). Additionally, 88% of tumors which involved the cerebellum were BRAF+ ($n = 8$) (Table 4), specifically, these were found in five males under the age of 5 and two females aged 13 and 23 (Table 5).

## 12. Follow up and overall survival

Details of post procedural complications and follow up data for these patients has not been extensively documented. Furthermore, in most studies the reported patient's follow up or data on survival is relatively sparse. To our search, two years (24 months) after presentation, less than 50% of patients were continued to be followed, this percentage dropped to 25% at 40 weeks, and reached around 10% at 60 months (Fig. 10). The drop-off in patient's follow up appears to be largest and quick within the first 40 months and

**Table 1**
The gender difference based on presenting age.

| | Female | Male | Total [Margin of Error] |
|---|---|---|---|
| *Age* | | | |
| 0–10* | 38 | 66 | 52 [9] |
| 11–20* | 53 | 22 | 38 [9] |
| 21–30 | 8 | 5 | 6 [5] |
| >30 | 2 | 7 | 4 [4] |
| *Symptoms* | | | |
| Dysesthesia* | 100 | 69 | 80 [18] |
| Motor Weakness | 83 | 64 | 80 [10] |
| Lower CN palsies | 93 | 84 | 89 [7] |
| Ataxia | 29 | 15 | 21 [11] |
| Headaches | 17 | 15 | 16 [9] |
| Incoordination | 13 | 21 | 14 [8] |
| Respiratory Distress* | 46 | 18 | 29 [11] |
| Vocal Changes* | 46 | 21 | 31 [11] |
| Speech Delay | 0 | 12 | 7 [6] |
| Vomiting | 4 | 15 | 7 [7] |
| *Location* | | | |
| Medulla | 30 | 35 | 32 [8] |
| Pons | 5 | 12 | 7 [4] |
| Medulla & Pons | 60 | 49 | 58 [9] |
| Midbrain | 2 | 2 | 2 [2] |
| Medulla, Midbrain & Pons | 2 | 0 | 1 [2] |
| Brainstem | 0 | 2 | 1 [2] |
| CPA | 29 | 49 | 35 [11] |
| CMJ | 53 | 49 | 52 [10] |
| *Surgery* | | | |
| GTR | 16 | 18 | 16 [8] |
| STR | 40 | 50 | 48 [11] |
| PR | 44 | 32 | 36 [10] |
| *Imaging/Contrast* | | | |
| Contrast+ | 80 | 76 | 76 [10] |
| *Histology Subtype:* | | | |
| I | 80 | 66 | 67 [10] |
| II | 17 | 31 | 26 [9] |
| III | 3 | 3 | 8 [5] |

then, gradually levels off with some patients being followed for many years.

## 13. Discussion

Pediatric infratentorial GGs involving brainstem and cervicomedullary junction with or without the involvement of cerebellopontine angle or cerebellum, are exceedingly rare. Most of the available reports are with the limited case series, small number of patients of all ages and locations, a very little detail on course of the disease, imaging characteristics, follow up, treatment options, and the progression free survival. Therefore, it is cumbersome to draw an exact inference in order to assess the prognostic details of the disease. Nevertheless, with the limited information available we have tried to discuss the demographics, median age and gender difference, common presenting symptoms and location of these tumors. Very few studies have specifically looked and compared patients based on different regions of brainstem GGs to their presenting symptoms, signs, imaging characteristics, presence or absence of hydrocephalus, degree of resection and outcome variables. Our study is unique and first of its own type which included all previous studies on brainstem GGs and assessed different characteristics of this important pathology.

## 14. Clinical presentation

The clinical presentation of infratentorial GGs depends on the location and structures involved. The typical presentation of brainstem GGs is purely based on the segment involved, relative slow

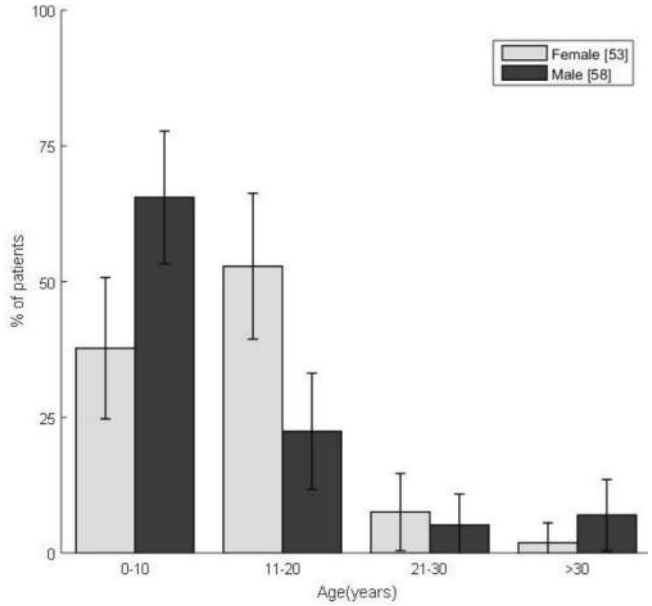


**Fig. 5.** The percentages of patients in different age ranges among males and females.

growth of the tumor, the degree of tumoral extent, with or without presence of upper cervical syrinx, and/or accompanying hydrocephalus. Common presentation includes numbness, sensory dysesthetic complaints, motor symptoms and signs of radiculopathy and/or myelopathy with or without the involvement of cranial nerve nuclei. Tumors with the predilection of cervicomedullary junction could present with lower cranial nerve dysfunction, sleep apnea, suboccipital or neck pain, progressive motor weakness, changes in gait, and hyper- or hyporeflexia [23]. Regardless of the presenting symptoms, as the tumor progresses and expands in a confined space a spectrum of symptoms and signs with an overlap could ensue. We specifically looked into separate subset of these symptoms in these patients and interestingly observed lower cranial nerve palsies as the common presenting symptom, followed by sensory dysesthesia, motor weakness, and ataxia (Fig. 6A). The gender differences based on presenting symptoms was noticeable clearly with the female predominance (Fig. 6B). Nonetheless, in previous studies, gender preference has been described closer to 1:1 among male to female without a specific age breakdown [5,6,11,12]. When looking at the age of tumor presentation, we found a male predominance among children under the age of 10, and female predominance among patients between the ages of 10–20 years and 20–30 years (Fig. 5).

## 15. Imaging characteristics

The radiological presentation of BS-GGs is an important part of the diagnosis and treatment planning. However, there is no specific or pathognomonic radiological features pertaining to these neoplasms. But the pattern of enhancement varies when comparing supratentorial to the infratentorial GGs. The supratentorial lesions are solid masses with an isolated enhancing mass, often associated with a cystic component [13,18,24], while the infratentorial in particular BS-GGs demonstrate patchy contrast enhancement [5]. Essentially, GGs are solid tumors and are similar to the other low-grade neoplasms. On computerized tomography (CT) scan imaging GGs frequently appear as a low-density lesion with an area of contrast enhancement, however, calcifications are relatively common in supratentorial GGs. Magnetic resonance (MR)

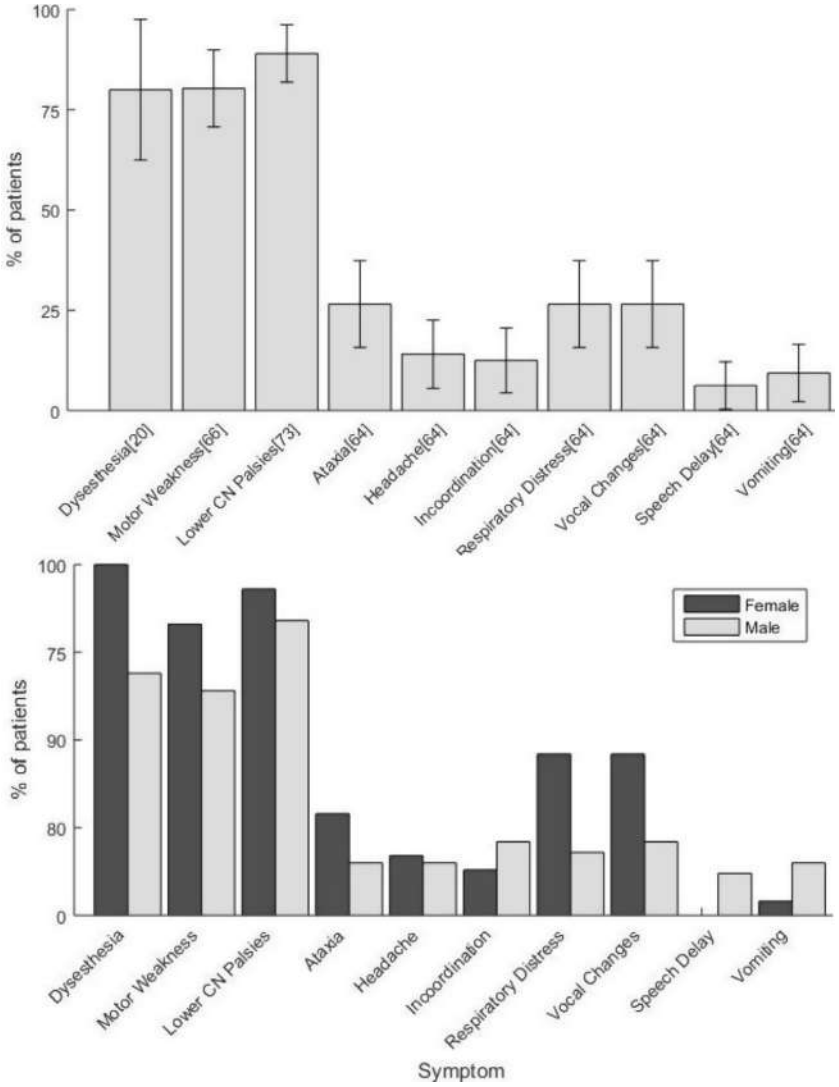


**Fig. 6.** The percentage of patients with the different presenting symptoms. The effect of gender difference on the percentage of patients with the presenting symptoms.

**Table 2**
The percentage of patients with the contrast enhancement on imaging based on age, location, histology, extent of resection and mutations status. Contrast positive sample size is in the parenthesis.

| Symptoms | Ages | | | |
|---|---|---|---|---|
| | 0–5 | 6–10 | 11–15 | >15 |
| Dysesthesia | 88 | 100 | 50 | 75 |
| Motor Weakness | 94 | 64 | 83 | 40 |
| Lower CN palsies | 100 | 85 | 77 | 83 |
| Ataxia | 12 | 40 | 0 | 45 |
| Respiratory Distress | 36 | 10 | 55 | 9 |
| Vocal Changes | 32 | 20 | 55 | 18 |
| Incoordination | 8 | 50 | 9 | 0 |
| Headache | 0 | 0 | 27 | 45 |
| Syncope | 0 | 0 | 0 | 27 |

imaging appearance is highly variable. On T1-weighted sequences, GGs appear with low or high signal intensity, whereas on T2-weighted images, they appear usually hyperintense. The contrast enhancement is heterogeneous on presentation with or without discontinues areas of mix signal intensity [3]. Tumors in cervicomedullary junction are infiltrative, expansile, solid without a cystic component predominantly with the dorsal exophytic component explained as "paintbrush" contrast appearance in few studies very similar to our case. These tumors are T2-hyperintense and do not restrict diffusion [9]. Rarely intratumoral hemorrhage could be seen in these tumors. Only 2 cases have been reported so far, low grade GG and anaplastic carcinoma (previously irradiated) respectively [14,25]. Based on our search more than 80% of patients less than the age of 20 years have demonstrated contrast enhancement on either CT or MRI scan imaging, however, this fraction dropped off to less than 40% for older patients (Fig. 7B). Interest-

**Table 3**
Tumor location and histology based on extent of surgical resection. Sample size is in the parenthesis.

| | % Contrast Enhancement on Imaging |
|---|---|
| *Age* | |
| 0–10 [37] | 86 |
| 11–20 [18] | 78 |
| >21 [8] | 38 |
| *Location* | |
| Medulla [20] | 75 |
| Medulla & Pons [42] | 81 |
| Pons [3] | 33 |
| CPA [19] | 68 |
| CMJ [21] | 100 |
| *Histology Type* | |
| I [32] | 72 |
| II [19] | 80 |
| III [0] | n/a |
| *Extent of Resection* | |
| GTR [4] | 75 |
| STR [21] | 86 |
| PR [19] | 63 |
| *Mutation Status* | |
| BRAF+ [8] | 100 |
| BRAF− [9] | 67 |

ingly, based on presentation and imaging characteristics, dysembryoplastic neuroepithelial tumor (DNET), low-grade glioma, pleomorphic xanthoastrocytoma (PXA), and oligodendroglioma are considered strong differentials of the disease. Moreover, differentiating a BS-GGs from a glioma could be very challenging because of similar imaging characteristics. Both types of brainstem neoplasms are T1 hypointense, T2 hyperintense and does not restrict diffusion appear infiltrative and solid, however, BS gliomas have a little early contrast enhancement with more heterogeneous pattern is observed during later phase [26]. As mentioned earlier a dorsal exophytic "paintbrush" contrast enhancement pattern of enhancement could be taken as a differentiating feature favoring BS-GGs. Through our detail analysis, 100% of the tumors located at the cervicomedullary junction demonstrated contrast enhancement, while, contrast enhancement pattern is observed in around 75% of tumors located in medulla, medulla and pons and cerebellopontine angles; contrast enhancement was noticed in around 30% of tumors isolated in the pons (Fig. 7A).

## 16. Histopathological details

While discussing pathological findings under light microscopy, GGs are composed of neoplastic neurons and glial cells. These two components are heterogeneous and are generally intermixed, however, these two components could be separated, giving the appearance of a collision tumor. Neoplastic ganglion cells can be binucleated with prominent cytoplasmic vacuolation however, generally they have large nuclei with prominent nucleoli, Nissl substance and abundant cytoplasm [27,28]. The neoplastic glial component is astrocytic (fibrillary or pilocytic), rarely represents pleomorphic xanthoastrocytoma. At times, background fibrosis also supports the diagnosis of ganglioglioma [29]. WHO classification (2000) has categorized ganglioglioma as grade I or II tumor. These neoplasms classified as grade III only when anaplastic features are present in the glial component of the tumor. Less often gangliogliomas have been classified as grade IV based on changes (glioblastoma) in the glial cell component at an initial diagnosis; only 12 cases have been reported so far [30,31]. The distinguishing features from glioma is the presence of entrapped neural elements in ganglioglioma neoplasms. Additionally, some neurons may resemble neoplastic ganglion cells. However, the pathological differential diagnosis could further be narrowed with the expression of additional neuronal markers such as neurofilament, synaptophysin, and chromogranin A [29,32]. Synaptophysin is a transmembrane protein which causes an intense staining of the cell membrane of the neural elements in gangliogliomas.

Our case has clearly demonstrated the dysplastic appearing ganglion cells including areas with predominantly glial features with or without eosinophilic and lymphocytic infiltrate. Immunohistochemical staining was performed which revealed variable NeuN expression (C), with some cells demonstrating moderate to strong staining and other neurocytic cells that are entirely negative

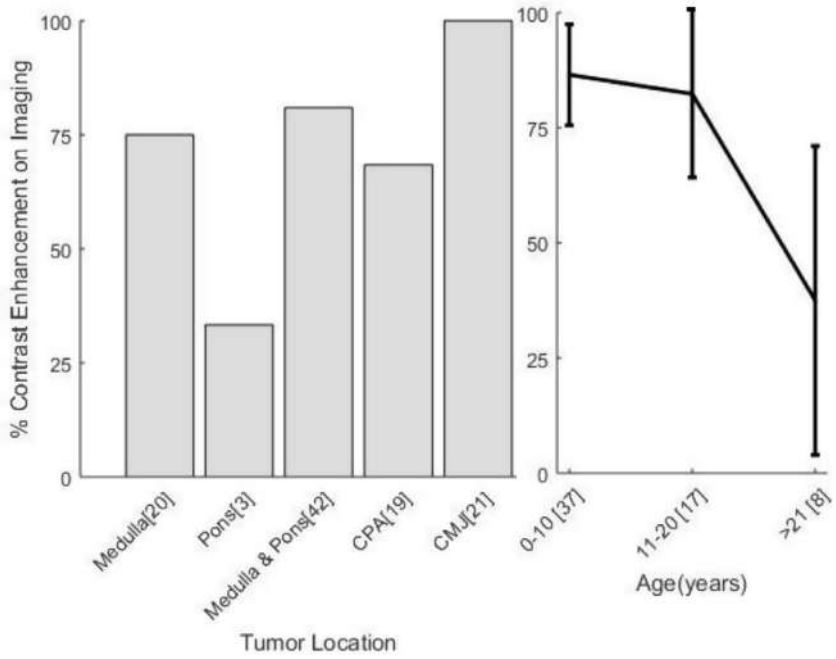


**Fig. 7.** The percentage of patients with tumor in different locations. The percentage of patients based on tumor with different histological grades.

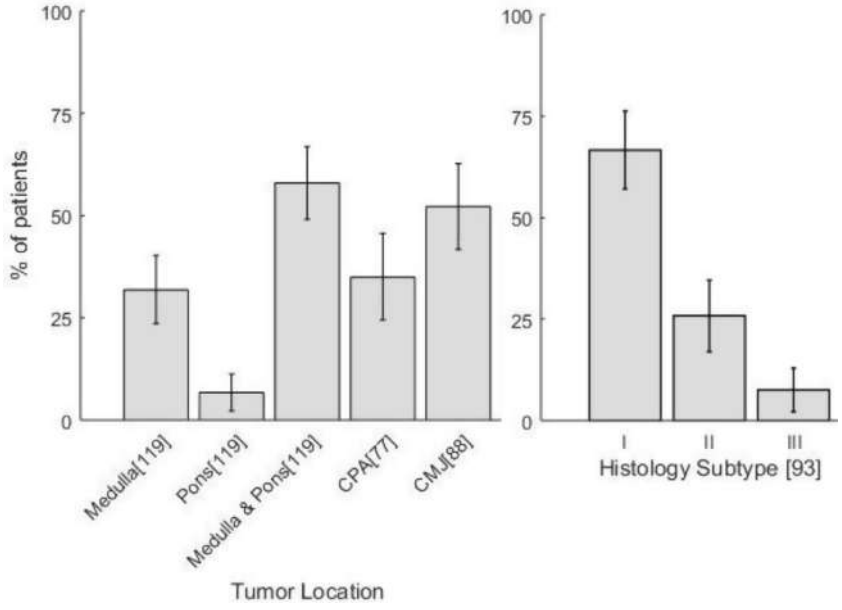


**Fig. 8.** A and B. The contrast enhancement seen based on tumor location and the presenting age.

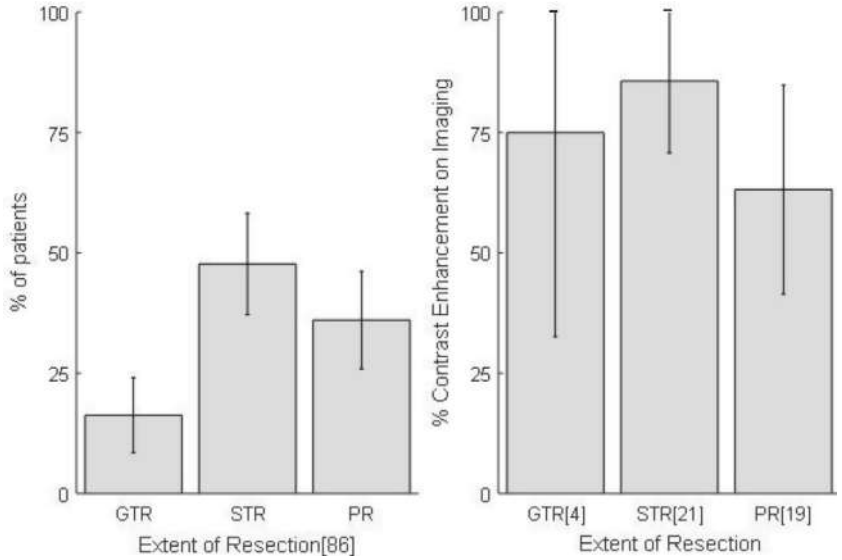


**Fig. 9.** The percentage of patients with the extent of resection. The extent of tumor resection based on contrast enhancement seen on imaging.

**Table 4**
Average ages and gender difference based on BRAF+ and BRAF− mutation status.

| | GTR | STR | PR |
|---|---|---|---|
| *Location* | | | |
| Medulla [21] | 10 | 52 | 38 |
| Medulla & Pons [42] | 12 | 40 | 48 |
| Pons [4] | 0 | 100 | 0 |
| *Histology Type* | | | |
| I [29] | 14 | 66 | 21 |
| II [18] | 17 | 22 | 61 |
| III [7] | 0 | 14 | 86 |

**Table 5**
The gender difference based on presenting age, symptoms, tumor location, extent of surgery, imaging characteristics, and the tumor histology. All values are in percentages with the margin of error calculated from 95% confidence interval.

| | BRAF+ | BRAF− |
|---|---|---|
| Female | 13.3 | 8.9 |
| Male | 4.9 | 10.8 |

(C, arrows). GFAP staining highlights the fibrillary glial component (D). Characteristic features of these tumors is a lymphocytic infiltrate, here with a prominent CD3-positive T cell component (E) (Fig. 4).

## 17. Different locations of brain stem gangliogliomas

The preoperative radiological characteristics are helpful in delineating the exact location of these tumors. Merely based on this information it is not possible to impart a true prognostic information. However, the location of these tumors in different parts of the brainstem could affect the surgical resection to a great extent and hence could affect the prognosis. According to our search

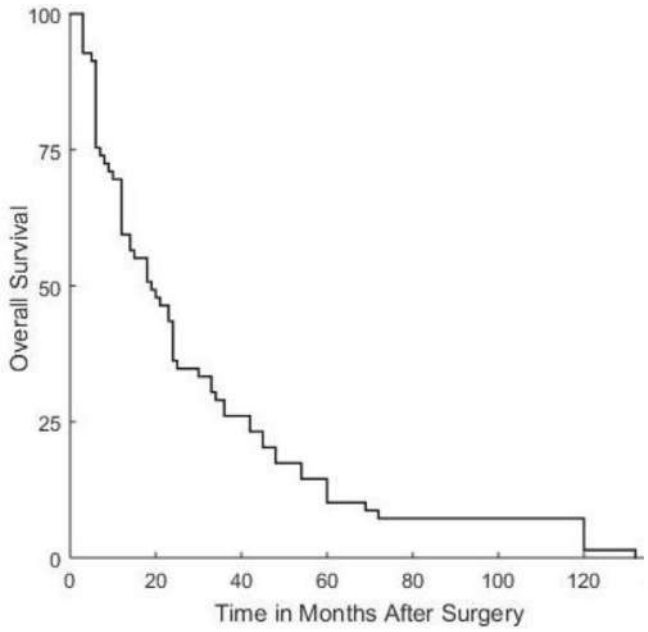


**Fig. 10.** Overall survival in months in all patients after resection of brain stem ganglioglioma.

about 60% of patients had involvement of medulla and pons while, around 55% had predominant involvement of cervicomedullary junction. Additionally, about 25–30% of patients presented predominantly with the involvement of medulla or cerebellopontine angle (CPA) alone and only 5–10% had a tumor isolated to the pons (Fig. 8A) We think different parts of brainstem location of these tumors is critical to an adequate diagnostic evaluation given their ability to accurately localize the lesion while planning on surgically resecting these tumors. This could be challenging while trying to preserve the eloquent structures and avoid being aggressive while excising these tumors upfront. Moreover, it is unclear if the observed difference in clinical outcome in brainstem GGs relates to the inability to completely excise the tumor given the unfavorable anatomical location or is due to the different biological characteristics between other locations of these tumors. While discussing the gene expression of these tumors, a microarray study on GGs have demonstrated a 256-fold increase in the expression of the neuropeptide prepronociceptin (PNOC); the protein product of a single largest upregulated gene implicated in neuronal growth. Nevertheless, a significantly weaker immunohistochemistry expression of PNOC was observed in non-brainstem GGs, while, all 7 brainstem GGs cases demonstrated a strong expression in neoplastic neurons [47].

## 18. Treatment paradigm for infratentorial gangliogliomas

Optimizing the acuity of disease is the first line of treatment due to the critical location of these tumors. Moreover, the expansile and exophytic nature of GGs and hydrocephalus, if present necessitates an emergent intervention. CSF diversion (ventriculoperitoneal shunt or endoscopic third ventriculostomy) should always be considered on an emergent basis when surgery is planned, electively. An endoscopic third ventriculostomy (ETV) is preferred way of treating hydrocephalus in this setting due to less morbidity involved with the procedure if expertise is available [33]. The surgical treatment been prioritized to address the supratentorial lesions to achieve a gross total resection (GTR) with a good outcome [7,14,15]. However, the optimal treatment of infratentorial tumors is a bit challenging. A good resection is achievable in the hemispheric tumors based on the location and the consistency of the lesion. However, the GGs of cervicomedullary (CMJ) are difficult to carve through the brainstem due to firm texture and its close proximity to the eloquent structures. Previously, only 5 cases had been reported where a subtotal resection (STR) was attempted [8,34,35]. Additionally, anecdotal evidence suggests dissecting around the most contrast enhancing exophytic area of tumor followed by close observation with the serial MR imaging without adjuvant treatment is a reasonable approach to address these lesions [8,24,36–39]. Another treatment rationale for the residual tumors is to recommend chemotherapy (CT) or radiotherapy (RT) right after surgery or only if any progressive disease was observed on serial imaging [4,7,18,40–42]. On the other hand, chemotherapy has not been truly successful and RT may cause malignant transformation of these tumors [43]. The true advantage of RT is equivocal. Other anecdotal evidence suggests it's benefit in patients with recurrence or a tumor histology depicting oligodendroglial cells or neoplastic cells with anaplastic features.

Although we acknowledge the poor outcome results from BS-GGs, this current knowledge has been extrapolated from a small numbers of cases in the literature. A recent study has documented similar findings in 12 patients with BS-GGs, of which there were 8 recurrences and 4 deaths [6]. These results underscore the need for a novel therapeutic treatment in addition to the currently available modalities. Hence, treatment based on GGs subgroups and molecular profile could be an adjunct. BRAFV600E, is an established mutation targeted for the treatment of gliomas. Based on the histology the two subgroups of GGs have given some insight to the concept. Group 1, are classic GGs, while, group 2 have mixed features of pilocytic astrocytoma with foci of gangliocytic cells. Broadly speaking, more than 43% of group 1 GGs possess BRAF V600E mutation. However, more than 82% of Group 2 GGs have BRAF duplication or the BRAF gene fusion. Interestingly, group I tumors were mostly located in the medulla and the middle cerebellar peduncle without hemorrhage, necrosis, or cyst formation on MRI. The group II tumors were located mainly in the cerebellar vermis and the spinal cord and were very well circumscribed with signs of hemorrhage, necrotic and/or cystic degeneration. However, no information on the therapeutic management and the outcome was available [44]. The majority of BRAF mutations occur as a single amino acid substitution, which results in activation of BRAF's kinase function. In addition to the activating mutation of RAS-RAF-MEK-ERK-MAP kinase signaling pathway, the downstream targets such as MEK kinase inhibitors have similar therapeutic usefulness in patients who harbor BRAF V600E mutation. The kinase signaling pathway regulates cell function, replication, differentiation and apoptosis [45,46]. Inhibitors of kinase pathway have been considered as a potential target for therapy in these tumors [49,50]. Vemurafenib, is therefore, a competitive inhibitor that selectively recognizes the ATP binding domain of the BRAFV600E mutant and recognizes it as a selective target for therapy. Although, vemurafenib had previously been successful in treating melanomas, it has also shown promising results in a single case of BRAFV600E positive BS-GG [48]. Moreover, a recent case report of a BRAFV600E mutation positive recurrent cervicomedullary junction tumor previously treated with surgery and chemotherapy demonstrated a clinical and radiological response after 3 months of treatment and no recurrence was observed after 6 months of therapy [51]. Our analysis suggests that 55% of the GG patients had the BRAFV600E mutation, but the limitation was that only 22% of all patients were tested, with no reported testing prior to 2014. Interestingly, all tumors with BRAF mutation were histologically classified as subtype I and the average age of these patients appeared relatively young. Additionally, males with this mutation were much younger than the female counterparts. Since, the percentage of pediatric BS-GGs with BRAFV600E is sufficiently

high, all tumors should be tested for this mutation to at least allow for the possibility of targeted therapy in cases of residual or recurrent tumors.

The preoperative clinical status is an accessary determinant of the overall outcome. Therefore, early operative intervention is likely to yield better results [7]. Another important rationale is to maximize surgical resection in a staged fashion even for the BS-GGs. Imaging plays a critical role not only in the pre-operative planning but also during planned operation. As previously mentioned, contrast enhancement is considered an important landmark during surgery. Moreover, through our analysis we were able to observe more than 60% of contrast enhancement during diagnostic imaging in all three categories of extent of resection (GTR, STR, and PR). Additionally, use of neuronavigation can be very helpful in mapping these tumors and defining the tumor margin due to the solid nature of the lesion. Nonetheless, intraoperative neurophysiologic monitoring (IONM) is especially advocated for GGs of the BS and the CMJ when resection is planned [43]. In a case series of 9 brainstem GGs in children where the resection was targeted against the most contrast enhancing portion of the tumor, 2 cases were able to achieve GTR while, and 7 were able to achieve PR. This resulted in longer progression free survival without any intended treatment [5]. Therefore, surgical resection has been advocated for these tumors over biopsy and irradiation [7]. In a retrospective case series of 7 brainstem GGs patients, subtotal resection in 2 patients and partial resection was performed in 5 patients. No adjuvant therapy was given and no recurrence was observed in the residual lesions through serial MR imaging after 21–69 months of post-surgery follow up [37].

Our retrospective literature review entails 142 reported cases of BS-GGs over last 50 years. The optimal treatment of this rare disease is still indeterminate and the data is insufficient to draw a definitive conclusion. Moreover, duration of symptoms, the exact extent of tumor, operative planning merely based on imaging characteristics, different treatments instituted based on the location, lack of follow up imaging, presence or absence of hydrocephalus and any intervention utilized, postoperative recurrence and the treatment based on the histological grades, molecular testing, considerations on radiotherapy therapy versus salvage radiation therapy, role of chemotherapy, short follow up, and the lack of progression free survival are the nuances of the disease. Additionally, few autopsy cases have been reported so far and in most of these cases the tumor burden and the location in BS were the frequent association of sudden deterioration and death. The surgical management of cerebellar GGs varied among reported cases from biopsy to GTR [5,23,34,35,52–57]. Typically, cerebellar GG behave as pilocytic astrocytomas and should be totally resected, if safe. Rarely, they can be infiltrative and could resemble Lhermitte Duclos disease [38]. Due to the diffuse presentation, in some cases, a total excision cannot be advocated and an adjuvant treatment should be discussed according to the clinical status of the patient and the disease progression [58].

The outcome of BS-GGs in pediatric population is hard to assess. Most pediatric population results are inferred from large case series comprising of adult patients with a wide age range. Additionally, data regarding outcomes is very scarce, and if available only represents the amount of time over which patients were followed post-operatively. The number of patients being followed quickly drops off to half in the first two years after the surgery. The drop-off becomes more gradual over the next two years, when it reaches approximately 25% of patients and levels off (Fig. 10). Similarly, histopathological studies are derived from tumor samples largely based on adult data [1,5,9,10,16]. Another caveat is lack of a clear documentation of exact histological grade of these tumors in the literature which leaves a huge range of clinical outcomes for the grade I GGs and hence paradoxically improves the overall surgical outcome. However, the constant search for a novel treatment and the prognostic factors of the disease will improve risk stratification when considering surgical resection, adjuvant therapy, and other surveillance strategies especially for subtotally resected lesions.

## 19. Conclusion

BS-GG is an exceeding rare disease with a grave prognosis. The disease presents early in males but is relatively more common in females in an early adulthood. Due to the short prodrome, an early diagnosis along with the imaging characteristics are vital for preoperative planning. If coexistent at initial presentation, hydrocephalus demands an emergent CSF diversion procedure. Surgical resection is highly dependent on the location of these tumors. A radical surgical resection of the contrast enhancing portion of the lesion with an aim for to find safest possible plane is the optimal treatment strategy. Cerebellar GGs are more amenable to gross total resection than the BS-GGs, with a highly variable range of extent of resection. GGs of the cervicomedullary junction (CMJ) are firm, expansile, and infiltrative lesions with the exophytic portion of disease only amenable to a safe resection. However, based on our personal experience and a detailed literature review, only well-circumscribed enhanced parts of GGs, even if in the BS, can be removed safely with or without staged surgeries with a favorable outcome. Such a treatment strategy can offer a reassuring prognosis, since the role for adjuvant therapy is limited. Data is scarce regarding BS-GGs, with only a few large studies in the literature reviewing different treatment strategies and prognostic factors for outcome. Recent studies have identified and targeted BRAF V600E mutations in these tumors with some promise. The status for BRAF V600E mutation should be considered in all infratentotorial tumors, especially in BS-GGs to at least allow the possibility of some targeted therapy in case of a residual tumor and/or regrowth.

## Acknowledgements

I.I. was supported by a Medical Scientist Training Program grant from the National Institute of General Medical Sciences of the National Institutes of Health under award number T32GM007739 to the Weill Cornell/Rockefeller/Sloan-Kettering Tri-Institutional MD-PhD Program. This study is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

## References

[1] Pandita A, Balasubramaniam A, Perrin R, et al. Malignant and benign ganglioglioma: a pathological and molecular study. Neuro Oncol 2007;9:124–34.
[2] Zhang D, Henning TD, Zou L-G, et al. Intracranial ganglioglioma: clinicopathological and MRI findings in 16 patients. Clin Radiol 2008;63:80–91. http://dx.doi.org/10.1016/j.crad.2007.06.010.
[3] Blatt GL, Ahuja A, Miller LL, et al. Cerebellomedullary ganglioglioma: CT and MR findings. AJNR Am J Neuroradiol 1995;16:790–2.
[4] Zimmerman RA, Bilaniuk LT. Computed tomography of intracerebral gangliogliomas. J Comput Tomogr 1979;3:24–30.
[5] Baussard B, Di Rocco F, Garnett MR, et al. Pediatric infratentorial gangliogliomas: a retrospective series. J Neurosurg 2007;107:286–91. http://dx.doi.org/10.3171/PED-07/10/286.
[6] Donson AM, Kleinschmidt-DeMasters BK, Aisner DL, et al. Pediatric brainstem gangliogliomas show BRAF(V600E) mutation in a high percentage of cases. Brain Pathol 2014;24:173–83. http://dx.doi.org/10.1111/bpa.12103.
[7] Lang FF, Epstein FJ, Ransohoff J, et al. Central nervous system gangliogliomas. Part 2: clinical outcome. J Neurosurg 1993;79:867–73. http://dx.doi.org/10.3171/jns.1993.79.6.0867.
[8] Zhang S, Wang X, Liu X, et al. Brainstem gangliogliomas: a retrospective series. J Neurosurg 2013;118:884–8. http://dx.doi.org/10.3171/2013.1.JNS121323.

[9] Lindsay AJ, Rush SZ, Fenton LZ. Pediatric posterior fossa ganglioglioma: unique MRI features and correlation with BRAF V600E mutation status. J Neuro Oncol 2014;118:395–404. http://dx.doi.org/10.1007/s11060-014-1450-1.
[10] Demierre B, Stichnoth FA, Hori A, Spoerri O. Intracerebral ganglioglioma. J Neurosurg 1986;65:177–82. http://dx.doi.org/10.3171/jns.1986.65.2.0177.
[11] Dudley RW, Torok MR, Gallegos DR, Mulcahy-Levy JM, Hoffman LM, Liu AK, Handler MH, Hankinson TC. Pediatric low-grade ganglioglioma: epidemiology, treatments, and outcome analysis on 348 children from the surveillance, epidemiology, and end results database. Neurosurgery 2015;76:313–9.
[12] El Khashab M, Gargan L, Margraf L, et al. Predictors of tumor progression among children with gangliogliomas Clinical article. J Neurosurg Pediatr 2009;3:461–6. http://dx.doi.org/10.3171/2009.2.PEDS0861.
[13] Im S-H, Chung CK, Cho B-K, et al. Intracranial ganglioglioma: preoperative characteristics and oncologic outcome after surgery. J Neuro Oncol 2002;59:173–83.
[14] Im S-H, Chung CK, Cho B-K, Lee SK. Supratentorial ganglioglioma and epilepsy: postoperative seizure outcome. J Neuro Oncol 2002;57:59–66.
[15] Haddad SF, Moore SA, Menezes AH, VanGilder JC. Ganglioglioma: 13 years of experience. Neurosurgery 1992;31:171–8.
[16] Majores M, von Lehe M, Fassunke J, et al. Tumor recurrence and malignant progression of gangliogliomas. Cancer 2008;113:3355–63. http://dx.doi.org/10.1002/cncr.23965.
[17] Johannsson JH, Rekate HL, Roessmann U. Gangliogliomas: pathological and clinical correlation. J Neurosurg 1981;54:58–63.
[18] Johnson Jr JH, Hariharan S, Berman J, et al. Clinical outcome of pediatric gangliogliomas: ninety-nine cases over 20 years. Pediatr Neurosurg 1997;27(4):203–7.
[19] Chintagumpala MM, Armstrong D, Miki S, et al. Mixed neuronal-glial tumors (gangliogliomas) in children. Pediatr Neurosurg 1996;24(6):306–13.
[20] Smith NM, Carli MM, Hanieh A, Clark B, Bourne AJ, Byard RW. Gangliogliomas in childhood. Childs Nerv Syst 1992;8(5):258–62.
[21] Sutton LN, Packer RJ, Rorke LB, Bruce DA, Schut L. Cerebral gangliogliomas during childhood. Neurosurgery 1983;13(2):124–8.
[22] Liauw SL, Byer JE, Yachnis AT, Amdur RJ, Mendenhall WM. Radiotherapy after subtotally resected or recurrent ganglioglioma. Int J Radiat Oncol Biol Phys 2007;67:244–7.
[23] McAbee JH, Modica J, Thompson CJ, Broniscer A, Orr B, Choudhri AF, Boop FA, Klimo Jr P. Cervicomedullary tumors in children. J Neurosurg Pediatr. 2015 Oct;16(4):357–66.
[24] Zentner J, Wolf HK, Ostertun B, et al. Gangliogliomas: clinical, radiological, and histopathological findings in 51 patients. J Neurol Neurosurg Psychiatry 1994;57:1497–502.
[25] Jeevan DS, Neil JA, Mohan A, Tobias M. Hemorrhagic ganglioglioma of the posterior fossa: case report. Pediatr Neurosurg 2013;49:33–7.
[26] Ramos A, Hilario A, Lagares A, Salvador E, Perez-Nunez A, Sepulveda J. Brainstem gliomas. Semin Ultrasound CT MRI 2013;34(2):104–12.
[27] Burger PC, Scheithauer BW, Vogel FS. Surgical Pathology of the Nervous System and Its Coverings. 4 ed. New York: Churchill Livingstone; 2002. p. 264–70. 290–292.
[28] Silver JM, Rawlings III CE, Rossitch Jr E, Zeidman SM, Friedman AH. Ganglioglioma: a clinical study with long-term follow-up. Surg Neurol 1991;35:261–6.
[29] Miller DC, Lang FF, Epstein FJ. Central nervous system gangliogliomas. Part 1: pathology. J Neurosurg 1993;79:859–66.
[30] Dash RC, Provenzale JM, McComb RD, Perry DA, Longee DC, McLendon RE. Malignant supratentorial ganglioglioma (ganglion cell-giant cell glioblastoma): a case report and review of the literature. Arch Pathol Lab Med 1999;123:342–5.
[31] Matsuzaki K, Uno M, Kageji T, Hirose T, Nagahiro S. Anaplastic ganglioglioma of the cerebellopontine angle. Case report. Neurol Med Chir (Tokyo) 2005;45:591–5.
[32] Hirose T, Scheithauer BW, Lopes MB, Gerber HA, Altermatt HJ, VandenBerg SR. Ganglioglioma: an ultrastructural munohistochemical study. Cancer 1997;79:989–1003.
[33] Sainte-Rose C, Cinalli G, Roux FE, et al. Management of hydrocephalus in pediatric patients with posterior fossa tumors: the role of endoscopic third ventriculostomy. J Neurosurg 2001;95:791–7.
[34] Mickle JP. Ganglioglioma in children. A review of 32 cases at the University of Florida. Pediatr Neurosurg 1992;18:310–4.
[35] Milligan BD, Giannini C, Link MJ. Ganglioglioma in the cerebellopontine angle in a child. Case report and review of the literature. J Neurosurg 2007;107:292–6.
[36] Garrido E, Becker LF, Hoffman HJ, et al. Gangliogliomas in children. A clinicopathological study. Childs Brain 1978;4:339–46.
[37] Kim S-D, Kim JH, Lee C-Y, Kim H-W. Ganglioglioma in brainstem: case report and a review of literatures. J Korean Neurosurg Soc 2014;55:164–6.
[38] Takei H, Dauser R, Su J, et al. Anaplastic ganglioglioma arising from a Lhermitte-Duclos-like lesion. Case report. J Neurosurg 2007;107:137–42.
[39] Jallo GI, Freed D, Epstein FJ. Spinal cord gangliogliomas: a review of 56 patients. J Neuro Oncol 2004;68:71–7.
[40] Lagares A, Gómez PA, Lobato RD, et al. Ganglioglioma of the brainstem: report of three cases and review of the literature. Surg Neurol 2001;56:315–22. discussion 322–324.
[41] Haydon DH, Dahiya S, Smyth MD, et al. Greater extent of resection improves ganglioglioma recurrence-free survival in children: a volumetric analysis. Neurosurgery 2014;75:37–42.
[42] Mpairamidis E, Alexiou GA, Stefanaki K, et al. Brainstem ganglioglioma. J Child Neurol 2008;23:1481–3.
[43] Ng WH, Mukhida K, Rutka JT. Image guidance and neuromonitoring in neurosurgery. Childs Nerv Syst 2010;26:491–502.
[44] Gupta K, Orisme W, Harreld JH, Qaddoumi I, Dalton JD, Punchihewa C, Collins-Underwood R, Robertson T, Tatevossian RG, Ellison DW. Posterior fossa and spinal gangliogliomas form two distinct clinicopathologic and molecular subgroups. Acta Neuropathol Commun 2014;2:18.
[45] Kim G, McKee AE, Ning YM, Hazarika M, Theoret M, Johnson JR, Xu QC, Tang S, Sridhara R, Jiang X, He K, Roscoe D, McGuinn WD, Helms WS, Russell AM, Miksinski SP, Zirkelback JF, Earp J, Liu Q, Ibrahim A, Justice R, Pazdur R. FDA approval summary: vemurafenib for treatment of unresectable or metastatic melanoma with the BRAF V600E mutation. Clin Cancer Res 2014;20:4994–5000.
[46] Neuzillet C, Tijeras-Raballand A, de Mestier L, Cros J, Faivre S, Raymond E. MEK in cancer and cancer therapy. Pharmacol Therapeut 2014;141:160–71.
[47] Chan MH, Kleinschmidt-Demasters BK, Donson AM, Birks DK, Foreman NK, Rush SZ. Pediatric brainstem gangliogliomas show overexpression of neuropeptide prepronociceptin (PNOC) by microarray and immunohistochemistry. Pediatr Blood Cancer 2012;59(7):1173–9.
[48] Rush S, Foreman N, Liu A. Brainstem ganglioglioma successfully treated with vemurafenib. J Clin Oncol 2013;31(10):e159–60.
[49] Jacob K, Albrecht S, Sollier C, Faury D, Sader E, Montpetit A, Serre D, Hauser P, Garami M, Bognar L, Hanzely Z, Montes JL, Atkinson J, Farmer JP, Bouffet E, Hawkins C, Tabori U, Jabado N. Duplication of 7q34 is specific to juvenile pilocytic astrocytomas and a hallmark of cerebellar and optic pathway tumours. Br J Cancer 2009;101:722–33.
[50] Schindler G, Capper D, Meyer J, Janzarik W, Omran H, Herold-Mende C, Schmieder K, Wesseling P, Mawrin C, Hasselblatt M, Louis DN, Korshunov A, Pfister S, Hartmann C, Paulus W, Reifenberger G, von Deimling A. Analysis of BRAFV600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol 2011;121:397–405.
[51] del Bufalo F, Carai A, Figà-Talamanca L, Pettorini B, Mallucci C, Giangaspero F, Antonelli M, Badiali M, Moi L, Bianco G, Cacchione A, Locatelli F, Ferretti E, Mastronuzzi A. Response of recurrent BRAFV600E mutated ganglioglioma to Vemurafenib as single agent. J Transl Med. 2014;12:356.
[52] Chang T, Teng MM, Lirng JF. Posterior cranial fossa tumours in childhood. Neuroradiology 1993;35:274–8.
[53] Diepholder HM, Schwechheimer K, Mohadjer M, et al. A clinicopathologic and immunomorphologic study of 13 cases of ganglioglioma. Cancer 1991;68:2192–201.
[54] Mesiwala AH, Kuratani JD, Avellino AM, et al. Focal motor seizures with secondary generalization arising in the cerebellum. Case report and review of the literature. J Neurosurg 2002;97:190–6.
[55] Park S-H, Kim E, Son E-I. Cerebellar ganglioglioma. J Korean Neurosurg Soc 2008;43:165–8.
[56] Jay V, Squire J, Blaser S, et al. Intracranial and spinal metastases from a ganglioglioma with unusual cytogenetic abnormalities in a patient with complex partial seizures. Childs Nerv Syst 1997;13:550–5.
[57] Geyer JR, Schofield D, Berger M, Milstein J. Differentiation of a primitive neuroectodermal tumor into a benign ganglioglioma. J Neuro Oncol 1992;14:237–41.
[58] Puget S, Alshehri A, Beccaria K, Blauwblomme T, Paternoster G, James S, Dirocco F, Dufour C, Zerah M, Varlet P, Sainte-Rose C. Pediatric infratentorial ganglioglioma. Childs Nerv Syst 2015;31(10):1707–16. http://dx.doi.org/10.1007/s00381-015-2860-x. Epub 2015 Sep 9.