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**Cervicomedullary gliomas in pediatric age: a systematic review of the literature and tertiary care center experience**

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Short Title: Cervicomedullary gliomas in children

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**Abstract**

**Introduction**. CMG are usually low-grade tumors often found in pediatric age. Histological findings, treatments and classification have been much the same for 40 years, although histological and molecular classifications have largely been developed for other pediatric CNS tumors. The management and treatment of pediatric CMG is still conducted by many authors according to their anatomical location and characteristics, independently from histology.

**Methods**. We conducted a literature review in PubMed (Medline) to identify relevant contributions about pediatric CMG published until December 31st, 2021. We also analyzed a series of 10 patients with CMG treated from 2006 to 2021 at IRCCS Istituto Nazionale dei Tumori. The aim of the present review is to see whether and how the diagnosis, treatment and classification of cervicomedullary gliomas (CMG) in children have developed over time, especially in the context of molecular advancements, and to analyze our single center experience in the last 15 years.

**Results**. Thirty articles have been included in the review. Articles have been divided in two historical periods (1981-2000 and 2001-2021) and data from different series were analyzed to see how much the management and treatment of pediatric CMG have changed during years. Analysis of our series of 10 patients affected by CMG was also performed to compare it with the literature.
**Discussion**. Management and classification of CMG in children has not dramatically changed during years. However, new insight from molecular diagnostics and target therapies and development of radiological, neurophysiological and radiotherapy techniques have updated treatment modalities in the last 20 years. Treatment modalities and their innovations have been reviewed and discussed. Further studies are needed to standardize and customize treatment protocols for these tumors.

**Introduction**

For a long time, brainstem tumors were believed to be a homogeneous group of tumors with a poor prognosis. Due to the high incidence of surgical morbidity and mortality connected to the location of these tumors, surgery did not initially play a major role in their management while radiotherapy (RT) was the treatment of choice, despite partial benefits. [1]

In 1980, Hoffman et al. [2] described a "dorsally exophytic" group of brainstem gliomas as a distinct subgroup that might be amenable to surgical resection. Epstein and McCleary classified non-exophytic brainstem gliomas as diffuse, focal, and cervicomedullary tumors. [3] While diffuse intrinsic tumors were always malignant and surgery was unable to improve prognosis, focal and cervicomedullary gliomas localized in the low brainstem and upper cervical spinal cord were often histologically low-grade indolent tumors and suitable for surgical resection with potential clinical benefits. Since then, surgery has been generally considered of primary importance in the treatment of CMG with the aim to achieve a maximal safe resection, not necessarily gross-total or subtotal. [1,4]. Some series considered also the role of biopsies to obtain histopathological and molecular diagnosis. [5]

Advances in neuroimaging have led to a better description and classification of brainstem tumors, some of which have particular radiological characteristics that can suggest a more aggressive approach. The increasing role of intraoperative neuromonitoring progressively led to a safer surgical technique.

Interestingly, the advances in molecular diagnosis, which significantly impacted on other pediatric tumors, did not involve similarly CMG. In fact, anatomical classification of CMG still plays a primary role in their management.

The aim of our review is to highlight neurosurgical and neuro-oncological state of the art about the heterogeneous group of gliomas of the cervicomedullary junction (CMG) to see whether and how their treatment has been changed during years. We furthermore report our single-center experience.

**Materials and Methods**

We reviewed all patients treated from 2006 to 2021 at the IRCCS Istituto Nazionale dei Tumori (Milan, Italy) for cervicomedullary glioma, examining symptoms at presentation, disease extension, treatments and outcomes. We then ran a search in PubMed (Medline) for literature on the treatment of cervicomedullary glioma in children published up until December 31$^{st}$, 2021. The search was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [6], and only articles in the English language were considered, with no restrictions regarding publication status. The following sequential keywords were used: "cervicomedullary tumors children", "cervicomedullary gliomas children", "cervicomedullary junction children", "pediatric cervicomedullary tumors", "cervicomedullary children", "pediatric cervicomedullary" and "medulla glioma children". Our inclusion criteria were the following: articles in English language, articles including not duplicated CMG cases, period of publication up to December 31$^{st}$, 2021. Our exclusion criteria were: articles being pure reviews (containing no new cases) and editorials; in case of a series of articles by the same working group, we evaluated the possibility of inclusion of the same patients in multiple papers and we thus included for analysis only the latest research excluding the previous reports; papers focusing only on histopathological analyses and/or radiological findings; articles on post-mortem findings; studies on tumors and conditions other than gliomas of the cervicomedullary region; and studies on adult populations.

**Results**

Our literature search in PubMed found 95 articles using the keywords "cervicomedullary tumors children", and using the words "cervicomedullary gliomas children" identified 52 articles within this first set (51 duplicated). The search for "cervicomedullary junction children" identified 153 papers (47 of which were duplicates, and 106 were new). Searching for "pediatric cervicomedullary tumors" revealed 43 studies (39 of them duplicates, while 4 were new), while searching for "cervicomedullary children" identified 279 papers (202 duplicates and 77 new). Using the keywords "pediatric cervicomedullary" found 125 articles (112 of them duplicates, and 13 new). The terms "medulla glioma children" pinpointed 175 studies (19 duplicates, and 156 new). Another 17 articles emerged as eligible from a review of the references in the previously identified articles.

The search thus generated a total of 939 articles and 469 of them were considered for screening after duplicate removal (470). These 469 articles were initially investigated on the strength of their titles and abstracts with consequent exclusion of another 403 papers not meeting our abovementioned criteria. After reading the full texts of the remaining 66 articles, 36 were ruled out for the purposes of our systematic analysis for the following reasons: one focused only on histology and radiology; data were lacking in 4; histology, tumor site and/or patients' ages did not meet our inclusion criteria in 12; data on histology, treatment and follow-up in 16 studies

were not analyzed according to tumor site or did not distinguish among pediatric and adult cases; 3 papers because patients were probably duplicated in the latest research by the same working group. We opted to include 5 of these 36 articles in which involvement of the cervicomedullary region was evident by reviewing images provided by authors. [4,7–10] We thus had a final set of 30 articles to be included in our qualitative analysis (Supplementary figure 1 in the Supplementary material). We reported our findings in this article following the PRISMA Checklist (Supplementary table 1 in the Supplementary material).

*General findings*

The first description of a cervicomedullary glioma was reported by Epstein et al. in 1982 [11], although a group of brainstem gliomas characterized by a more benign and indolent course had already been identified (by Hoffmann, in 1980[2]). Reviewing the literature, a quite different number of articles were published in the two periods, each spanning about 20 years: 11 publications in the years 1981-2000 [4,7,12–20], and 19 in 2001-2021 **[8–10,21–36]** (Table 1 and Table 2). The total number of cases described in the various studies was 127. Some case series describing a number of cervicomedullary tumors were excluded from our analysis because the studies did not meet our inclusion criteria; therefore, in the analyzed periods an actual larger number of CMG could have been described.

*Literature series from 1981 to 2000*

Analyzing this period, there were 3 case series that included more than 2 cases, and a total of 63 patients presenting with a cervicomedullary tumor.

The histologies described were extremely various, including gangliogliomas, pilocytic astrocytomas and high-grade gliomas.

Surgery was the first treatment in the majority of patients, involving different extents of resections. Subtotal resection was described in 82.5% of cases, only a 9.5% of patients had a near or gross total resection. In 4 patients a biopsy has been performed (6%).

In only 6 patients RT was the first line of treatment, with delayed or no surgery. The use of intraoperative neurophysiological monitoring (IONM) was only described in few series. The concomitant use of RT and chemotherapy (ChT) in the single patient was an infrequent finding as a first-line treatment.

Overall survival was good for low-grade histologies. Deaths occurred in case of higher grade and progressive disease despite oncological therapies or postoperative complications. Mean follow-up and data are summarized in Table 1.

*Literature series from 2001 to **2021***

In these last 21 years, various groups have studied cervicomedullary gliomas. Three articles concerned small series of 3, 4 and 3 patients, respectively [10,33,36]. Two articles analyzed larger series of 9 [24] and 29 [28] cases. A total of 64 patients with cervicomedullary tumor were described during this period.

The pathology reports also included molecular analyses in some more recent cases: in particular 4 patients harbored BRAFV600E mutation and one patient had KIAA1549-BRAF mutation described. In a recent report by Sun and colleagues [35] IDH1 and BRAF mutation have been reported. Again, histology was variable, including the same diagnoses already mentioned in the previous two decades.

Surgery was performed in 63 patients. In 58% of patients a subtotal resection was described while in the 25% of cases a biopsy was the chosen treatment. Only a 17% of patients experienced a near total or gross total resection. The use of IONM was extensively reported.

Radiotherapy was the first-line treatment in 3 patients while chemotherapy in 1. Only 4 out of 19 articles (40 patients in total) described the concomitant use of RT and ChT as adjuvant therapy. Two patients received RT alone, in one case following surgical resection and in the other as first choice treatment. ChT alone followed surgery in 6 patients.

Data about overall survival, surgical comorbidities and deaths are summarized in Table 2 and show a general good outcome without clear differences from the series from 1981 to 2000.

*Fondazione IRCCS Istituto Nazionale dei Tumori series*

Ten patients with cervicomedullary tumor, 5 males and 5 females, were treated from 2006 to 2021 (Table 3). Their age at diagnosis ranged from 2 months to 16.3 years (mean 5.97, median 4.35). The location of their tumors was limited to the cervicomedullary passage in 3 cases; it extended from the medulla to C2 in 4 cases, and from

C2 to C4 in another 2 cases; and it was widely disseminated (from the medullary-pons junction to the level of the first thoracic vertebral body) in one patient. Follow-up after first radiological diagnosis ranged from 4 to 121 months (median 73 months).
Histology was available for all cases: 4 pilocytic astrocytomas; 3 gangliogliomas (only one tested and found mutated for BRAFV600E); and 3 low-grade gliomas (2 glioneuronal tumors, and 1 glial tumor not otherwise specified), 2 of them revealing no molecular mutations, while 1 showed an ALK rearrangement never described before. All histologies were centrally reviewed.
The first-line approach was surgery for all 10 patients: 6 had a diagnostic biopsy and 4 a subtotal surgical resection (STR). Six patients received first-line chemotherapy (ChT), consisting of Cisplatin and Etoposide. Four patients out of the six treated by ChT relapsed and received second-line treatment that was RT in 2 patients and ChT in the other 2. Four patients didn't require any further oncological treatment.
Generally, patients were able to conduct their normal everyday activities with neurological impairments in some cases. In details, three patients had a normal neurological examination at the end of the treatment period, 4 had a motor impairment ranging from partial to complete paresis while one patient is suffering for delayed motor development and hemiparesis. One patient continued to suffer from multiple motor tics that have led to diagnosis. A percutaneous endoscopic gastrostomy and a tracheostomy were necessary in two cases.
In one case a rapid neurological deterioration led to death after progressive disease and *ab-ingestis* pneumonia at 7 years after diagnosis despite multiple retreatments for relapse.

**Case report**

The infant was born at a gestational age of 37+5 with respiratory distress and evidence of abnormal head and eyes movements. After the onset of epilepsy at 45 days of life, brain magnetic resonance imaging (MRI) (Fig. 1 a, b) showed a wide area with a pathological signal stretching from the ponto-mesencephalic junction through the cervical medulla, with surrounding edema and mild contrast enhancement. No hydrocephalus was documented. Auditory evoked potentials were pathological on the right side.
At 2 months of age, the patient underwent surgical biopsy at the Department of Neurosurgery of San Gerardo Hospital, Monza (Italy). Histological analysis and central pathological review concluded for a mixed glioneuronal low-grade cervicomedullary tumor. Molecular and genetic investigations didn't reveal any specific target. A ventriculo-peritoneal shunt was implanted to treat delayed hydrocephalus.
Given the surgical findings, neuro-oncological treatment was proposed according to the protocol for low-grade gliomas adopted at the Fondazione IRCCS Istituto Nazionale dei Tumori [37]. A regimen consisting of low-dose cisplatin (25 mg/m$^2$/day) and etoposide (100 mg/m$^2$/day) was administered in ten three-day cycles, achieving a good volume reduction on MRI performed after 6 months, and a stable disease control up to 18 months of age. When MRI revealed progressive disease (PD) at 18 months of age, second-look surgery with subtotal resection through a telovelar approach was proposed. Continuous IONM was performed to monitor brainstem and cervical spine functions. The previous histological diagnosis was confirmed, and none of the known mutations were ruled out.
Central breathing anomalies and acute desaturation events subsequently developed, requiring inpatient medical support. A new MRI revealed further PD (Fig. 1 c, d). Given the tumor's aggressive behavior with rapid clinical worsening, RT was proposed. The patient received 54 Gray to the lesion, including the brainstem and right cerebellar hemisphere, using conventional fractionation (1.8 Gray/fraction) administered with IMRT V-MAT (Intensity-Modulated Radiation Therapy and Volumetric-Modulated Arc Therapy) technique. A few weeks after the RT ended, a tracheostomy was needed due to chronic respiratory distress. The response to RT was satisfactory and no further progression was seen on imaging. The latest follow-up MRI, performed 25 months after the end of RT (Fig. 1 e, f), showed stable disease. The child's current neurological status was characterized by a sixth right cranial nerve deficit, a mild and rapidly improving right hemiparesis with delayed motor development. No cognitive impairment has been documented as yet.

**Discussion**

An extensive use of molecular and genetic classifications for the majority of pediatric brain tumors has reformed the oncological management of certain pathologies (e.g. medulloblastoma) [38]. Despite this, some subgroups of tumors remain classified by localization, although they may show a certain variability in histologic diagnosis. This is particularly true for gliomas of the cervicomedullary junction, whose management and treatment modalities have remained similar in the last 40 years. Recently, some molecular and genetic information have been

highlighted (e.g. BRAF mutations) with promising results in selected cases [26]. Surgical management (considering different extension of resection or biopsies) still maintains a primary role, together with adjuvant chemotherapy and radiotherapy. Considering the selected literature and analysis of our own data, this treatment scheme has been quite homogenous despite histological heterogeneity. At the best of our knowledge, this scenario represents the current state of the art in the management of cervicomedullary gliomas with an increasing percentage of patients undergoing biopsies in the last 20 years (25% vs 6%).

Histologically, the most common types of cervicomedullary tumor are pilocytic astrocytomas and gangliogliomas; high-grade gliomas have rarely been described. Both gangliogliomas and pilocytic astrocytomas are low-grade, slow-growing neoplasms with a low-to-moderate cellularity. [26,27]

Little is known about cervicomedullary gliomas from a genetic and molecular point of view. BRAF gene mutations have recently been described in low-grade gliomas. The most frequent is a mutation at codon 600 (BRAFV600E), which characterizes a large proportion of brainstem gangliogliomas. A variety of other genetic alterations (RAF1 fusion, KRAS or NF1 mutation, FGFR mutations or fusions) have been described in gangliogliomas without a clear clinical correlation. [26,39,40] Best-known alteration for pilocytic astrocytoma concerns the presence of the KIAA1549–BRAF fusion gene, which is common in sporadic pilocytic astrocytomas and is used as a diagnostic marker with a developing oncological role. KIAA1549–BRAF fusion in circumscribed lesions suitable for higher extension of surgical resection has been associated with excellent survival rates and low rate of progression disease. [41–43] Other BRAF, KRAS [44] or PTEN [45] mutations, and polysomy of some chromosomes have occasionally been documented without an actual role on treatment and outcome of CMGs. [46]

Independently from the histological subtype, all these tumors are characterized by a peculiar centrifugal growth pattern influenced by anatomical boundaries that limit neoplastic spread [12,24,47]: pontomedullary decussating fibers prevent a cranial extension to the pons, while crossing fibers from the lower brainstem serve as a barrier to limit spread to the caudal spinal cord. Their development towards the fourth ventricle can be explained by the lower resistance of the ependyma that leads these tumors to be dorsally exophytic. [48] The peculiar growth pattern of cervicomedullary tumors and their tendency to become exophytic in the fourth ventricle suggest the possibility of surgical excision, even pursuing gross-total or near-total resection. Malignancy or more invasive growth patterns, with invasion of the brainstem and spinal cord, can limit the feasibility of surgical management due to high risk of surgery-related comorbidities [3,28] and little or no impact on overall survival. [49]

Radiological characteristics of cervicomedullary tumors vary considerably, making it difficult to distinguish different histopathological entities. [50] Neuroradiological studies usually demonstrate a solid mass at the cervicomedullary junction with possible extension to the fourth ventricle, strong and almost homogeneous enhancement on MRI and computed tomography (CT) studies. [27,51] Advanced preoperative MRI studies, particularly diffusion tensor imaging (DTI), have progressively led to a better definition of tumor's relationship with the normal anatomy, facilitating surgical planning and improving outcomes. [22]

Improved surgical techniques, and the intraoperative use of ultrasound, MRI and IONM, have reduced the surgery-related morbidity [52], meaning that a large proportion of patients could safely undergo the above-mentioned subtotal or near-total resections. [53] In particular, IONM plays **a** significant role in preserving brain functions and ensuring a consequently better quality of life. Permanent alterations on IONM during posterior fossa surgery usually involve cranial nerves function and correlate with a postoperative deficit with a sensitivity and specificity of up to 95% and 85%, respectively. Analysis of the available data suggests that IONM has gained in the last 20 years a primary role in the surgical management of these tumors, helping in minimizing morbidity and preserving function in critical brain areas. [54] Stereotactic biopsies have been reported as a minimally invasive surgical option to obtain histopathological characterization with low morbidity and mortality [55] but necessarily followed by ChT or RT. From the present analysis of the literature, it is evident an increased percentage of biopsies in the last 20 years (25% vs 6% in the period 1981-2000). In our opinion, this could be due to the progressive introduction of molecular therapies and their reported promising results that not necessarily require larger surgical resections.

As most cervicomedullary tumors are low grade, the overall survival (OS) is favorable despite the risk of recurrence. [19,28] The progression-free survival (PFS) and OS rates at 5 years after surgery are of 45-65% and 85-89%, respectively. [28,53]

The role of ChT and RT in the treatment of low-grade cervicomedullary tumors is still debated and no specific neuro-oncological protocols have been yet introduced. After wider surgical resection, a wait-and-see approach is still commonly adopted.

Chemotherapy is an adjuvant therapy, or it may be attempted as a salvage treatment for recurrent or progressive tumors. Although it can lead to disease stabilization, ChT alone affords only a partial benefit, with a mean 5-year PFS of 30-40%. [28,56] Vincristine and carboplatin-based schedules were used in the international SIOP-LGG 2004 protocol, and therefore in the majority of reported series of CMG. ChT was preferred to RT in younger patients. [49]

The introduction of BRAF inhibitors (e.g. dabrafenib and vemurafenib) has shown positive results in the treatment of low grade gliomas in children with a significant response rate in terms of cytoreduction and overall survival. Despite their efficacy, a paradoxical activation of RAS/MAPK signaling pathways with a failure in treatment have been shown in patients treated with BRAF inhibitors and presenting KIAA1549-BRAF or in BRAF wild-types. In these cases, the use of MEK inhibitors has been reported with promising results. Moreover, different studies are ongoing for investigating the role of ALK, ROS1 and NTRK inhibitors which have shown anti-tumoral activity in tyrosine receptor kinase (TRK) altered lesions, even if rarely described in pediatric low grade gliomas (pLGG). Trials are also reported to assess the role of FGFR inhibitors in pLGG. [57–60]

Similarly, gene targeted therapies and immunotherapeutics, which have already shown a role in the treatment of high grade gliomas, have been mentioned in the literature and could turn out to contribute in preventing progression/recurrence of pLGG such as the majority of CMG. [61]

Radiotherapy is typically used to treat recurrent/progressive tumors in selected cases. Combining RT with surgery is clearly effective in controlling disease and has a positive impact on PFS. Tumors that are RT-resistant and progress early on have a more aggressive biology and carry a poorer prognosis. [62] Concerns about the use RT as a first-line treatment relate to its possible sequelae, given the young age of the patients involved. There have been sporadic reports supporting the use of stereotactic radiosurgery (SRS) and Gamma Knife (GK), with a reported limit in the treatment of lesions extending to the cervical spine region. [63–65] Results from the literature show a comparable results in term of response to treatment when compared to standard RT which is more frequently associated with stable diseases [65]. When compared to RT, SRS and GK groups of patients show an apparent increase in number of collateral minor adverse effects with major complications limited to few cases. [65–67]. New technological advances in SRS and GK techniques have been introduced during the years with promising results. [68]

**Conclusions**

Reviewing the literature and considering our own case series, an actual lack of novelty emerged in the practical management and treatment of cervicomedullary tumors in the last 40 years. The good results obtained with surgery and adjuvant therapies, the usually low-grade nature of these tumors and the good overall survival have probably limited innovations in the last years. The case described although atypical because congenital and with extension of the tumor to cerebellar peduncles was intended to summarize the state of the art and the possible problems of managing cervicomedullary tumors in children.

The introduction of higher resolution imaging and the extensive use of intraoperative neuromonitoring in the last 20 years have led to a safer surgical approach with lower postoperative morbidity. Moreover, the increasing use of molecular target therapies (e.g. inhibitors of the MAP kinase pathway in patients with BRAFV600E mutations) has recently been considered for cervicomedullary tumors with promising results. Further experiences are needed to verify efficacy of recently introduced molecular targeted therapy and to better describe their role in the treatment of cervicomedullary tumors.

## Statements

### Statement of Ethics
Ethical approval was obtained at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, April 20th, 2021 (protocol INT88/21). Written informed consent was obtained from the participants' parents for publication of the details of their medical cases and accompanying images.

### Conflict of Interest Statement
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Data Availability Statement
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

### Author Contributions
Andrea Trezza: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing; Camilla de Laurentis: data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing; Veronica Biassoni: writing and data collection- review & editing; Giorgio G. Carrabba: writing - review & editing; Elisabetta Schiavello: data curation, investigation, methodology, writing – review & editing; Francesco Canonico: writing – review & editing; Paolo Remida: writing – review & editing; Alessandra Moretto: writing – review & editing; Maura Massimino: validation, supervision, writing – review & editing; Carlo Giussani: conceptualization, validation, supervision, writing – review & editing.

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**Figure Legends**

**Fig. 1. Serial MRI images about the case report.** Sagittal post-contrast T1-weighted and sagittal T2-weighted MRI images (July 2016) showing a wide area of pathological signal clearly involving the ponto-mesencephalic junction and extending to the cervical region, with swelling of the surrounding anatomical structures (a,b). Coronal and axial T2-weighted MRI images (April 2019) showing recurrence of the disease (c,d). Sagittal and axial T2-weighted MRI images (October 2020) showing response to RT and no further progression of disease (e,f).

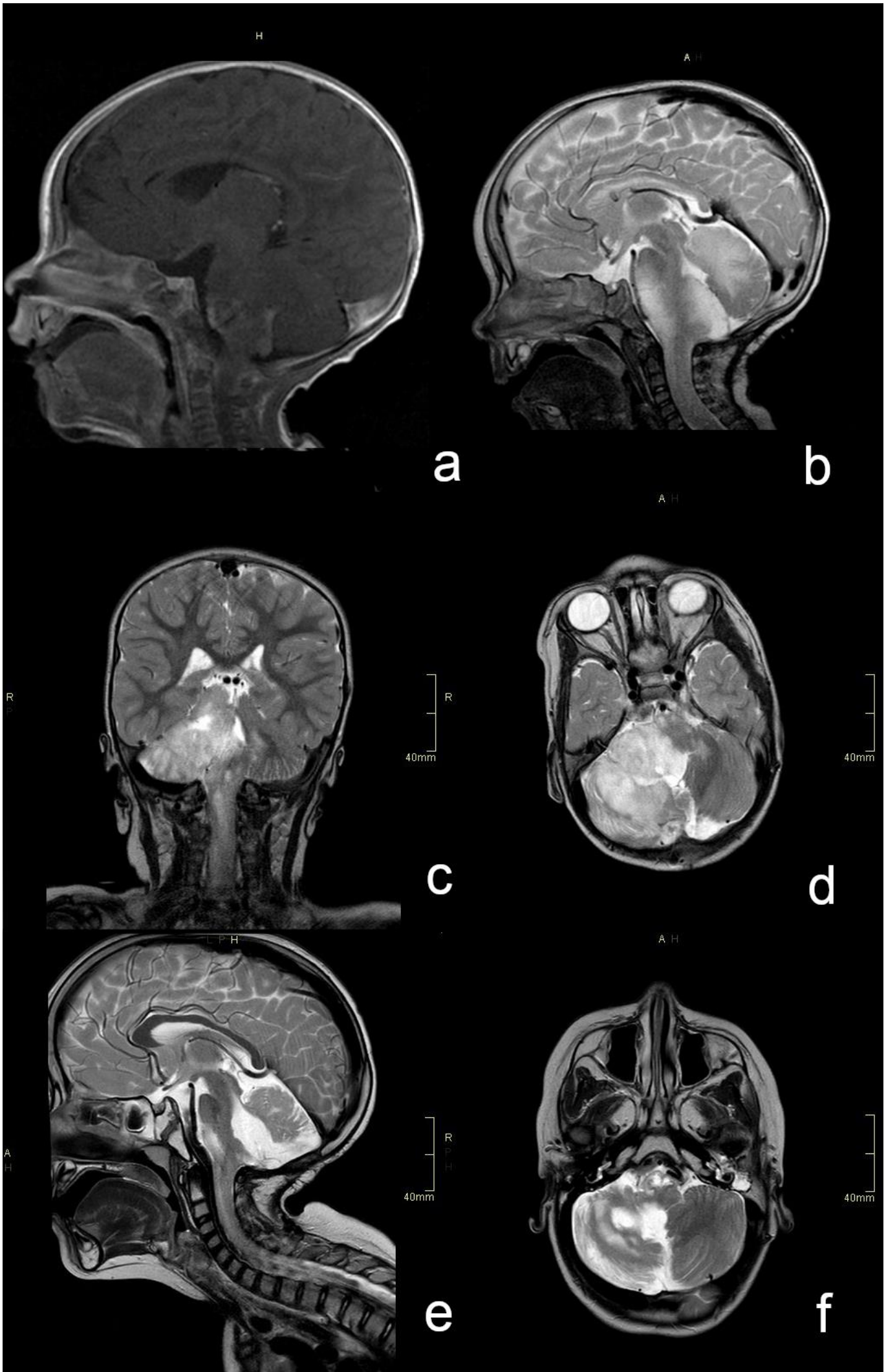
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**Table 1.** Publications about cervicomedullary glial tumors in children from 1981 to 2000.

| N. | Author | Year | Ref n. | N. pt | Age (y) | Histology | 1st treatment | Surgery | RT | CT | FU | Peculiarity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Epstein | 1988 | [13] | 24 | n/a | 16/24 GI-II astrocytoma; 4/25 GIII-IV; 4/24 GG | Surgery | STR | \ | \ | 6-60 months, improved for grade I, II and gangliogliomas; death 9-12 months for grade III-IV | IONM |
| 2 | Ahyai | 1990 | [4] | 2 | 8; 5 | astrocytoma | Surgery | STR | \ | \ | 1-20 months, improved | IONM |
| 3 | Khatib | 1994 | [14] | 2 | 20 mo, 30 mo | PA | Surgery | NTR | \ | \ | 26 months, 54 months | \ |
| 4 | Robertson | 1994 | [12] | 17 | 2-16 | LGA (10/17); GG (4/17); AGG (2/17); mixed LG oligoastro (1/17) | Surgery 11/17; RT 6/17 | GTR 2/17; STR 15/17 | 6/17 initially; 4/17 at progression | \ | 2 months- 13 years; 2/17 no recurrence, 13/17 SD, 2/17 died | IONM |
| 5 | Blatt | 1995 | [15] | 1 | 4 | GG | Surgery (VP shunt) | VP shunt; STR | \ | \ | n/a | \ |
| 6 | Hamilton | 1997 | [16] | 1 | 22 mo | PA | Surgery | STR | \ | \ | Recurrence 18 mo; new surgery | \ |
| 7 | Squires | 1997 | [17] | 1 | 21 mo | Low-grade astrocytoma (diffusely infiltrating) | Surgery | STR | \ | \ | Death at day 8 postop (aspiration pneumonia) | IONM |
| 8 | van Ouwerkerk | 1998 | [7] | 1 | 8 | Low-grade astrocytoma | Emergent surgery; then removal | GTR | 5040 Gy | \ | 5 years, slight deficit lower ccnn | IONM and US |
| 9 | Sawin | 1999 | [18] | 1 | 2 | GG | Surgery | GTR | \ | \ | 1 year, improved | Patient with NF2 |
| 10 | Young Poussaint | 1999 | [19] | 11 | 0.03-18 | PA (8/11), astrocytoma (2/11), gliofibroma (1/11) | Surgery | Biopsy 2/11, STR 9/11 | 5/11, 5400 cGy | 2/11, Vincristine, carboplatin | 0.2-11 years, 2/11 no residual; 7/11 stable; 1/11 increased; 1/11 died | \ |
| 11 | Nishio | 2000 | [20] | 2 | 3; 5 | PA | Surgery | Biopsy | 54 Gy; 50 Gy | yes | 5.1 year, stable; 0.5 years, died | IONM |

Ref: reference; pt: patients; y: years; mo: months; RT: radiotherapy; CT: chemotherapy; FU: follow-up; STR: subtotal resection; GTR: gross total resection; NTR: near total resection; VP: ventriculo-peritoneal; BCNU: carmustine; GG: gangliogliomas; AGG: anaplastic ganglioglioma; PA: pilocytic astrocytoma; LGA: low-grade astrocytoma; IONM: intraoperative neuromonitoring; US: ultrasound; ccnn: cranial nerves; NF2: neurofibromatosis; GI: grade I; GII: grade II; GIII: grade III; GIV: grade IV; (c)Gy: (centi)Gray; n/a: not available.

**Table 2.** Publications about cervicomedullary glial tumors in children from 2001 to 2021.

| N. | Author | Year | Ref n. | N. pt | Age (y) | Histology | 1st treatment | Surgery | RT | CT | FU | Peculiarity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | Fujisawa | 2005 | [21] | 1 | 2 | GG | Surgery | GTR | \ | \ | 18 months, improvement of BHS | postop Cyanotic Breath-Holding Spell. IONM |
| 13 | Phillips | 2005 | [22] | 1 | 9 | GG | Surgery | STR | \ | \ | Discharged 5 days postop | Advanced preop imaging and IONM |
| 14 | Klimo | 2006 | [23] | 1 | 15 | fibrillary astrocytoma | Surgery | n/a | yes | yes | 65 months | ETV for symptoms relief |
| 15 | Di Maio | 2009 | [24] | 9 | 1.7-11 | 5/9 GII astrocytomas, 2/9 PA, 2/9 LGG | Surgery 8/9, RT 1/9 | Various, 9/9 | 5/9 | 4/9 | 1.1-12 years, 5/9 alive, 4/9 died | Excluded focal medullary and dorsal exophytic tumors. Only true cervicomed gliomas included. IONM |
| 16 | Cheng | 2014 | [25] | 1 | 14 | GG | Surgery | GTR | \ | \ | 12 months, improved | IONM |
| 17 | del Bufalo | 2014 | [26] | 1 | 2.3 | GG BRAFV600E mutated | Surgery | Biopsy; then STR x2 | \ | SIOP LGG; then Vemurafenib | 6 months after last CT, reduced size of tumor, symptoms improved | IONM |
| 18 | Kim | 2014 | [27] | 1 | 10 | GG | Surgery | STR; EVD, VP shunt | \ | \ | 10 months, persistent lower cranial palsy and mild gait imbalance | Presentation with repetitive aspiration pneumoniae and seizures |
| 19 | McAbee | 2015 | [28] | 29 | 7 months–17 years | PA (12/31), gangliogliomas (8/31), angiocentric glioma (1/31); diffuse astrocytomas (4/31); GBM (3/31); HGG NOS (1/31) | RT (1/29), glioma; Surgery (28/29) | biopsy (12/31); GTR (3/31); NTR (1/31); STR (14/31)** | 21/31** | 14/31** | no recurrence in 17/31 (all LG, SD); recurrence in 14/31 (5 HG, 9 LG; 4 died, 2 PD, 8 SD)** | .2/31 ependymomas (excluded when possible) |
| 20 | Tanaka | 2015 | [8] | 1 | 9 | PA | Surgery | Biopsy | \ | Vincristine, carboplatin | 2 years, good clinical condition | Presenting as intractable hiccups |
| 21 | Conway | 2016 | [29] | 1 | 21 mo | astrocytoma | Surgery | STR | \ | Vinblastine | 17 months, stable size of tumor, persistent developmental delay | Diencephalic syndrome-like presentation |
| 22 | Yuge | 2016 | [9] | 1 | 3 | PA | Surgery | STR | \ | Vincristine, carboplatin | 3 mo, improved | Presentation with pathological crying and emotional vasovagal syncope |
| 23 | Champagne | 2017 | [10] | 3 | 1.5; 7 mo; 4 | PA | Surgery | STR | \ | \ | n/a | postop CWSW |
| 24 | Bahrami | 2019 | [30] | 1 | 3.5 | GG | Surgery | STR | \ | \ | 14 months, no progression | \ |
| 25 | Elmaraghi | 2020 | [31] | 2 | 11.9, 1.6 | GG; n/a | RT; CT | STR; none | 54 Gy; 2nd line | no; yes | 9.3, 36.9 months - deceased | \ |
| 26 | Labuschagne | 2020 | [32] | 2 | 3, 11 | PA, diffuse astrocytoma (?) | Surgery | GTR | \ | \ | 3 mo, no neurological deficits | Use of intraoperative 5-ALA, IONM |
| 27 | Oushy | 2020 | [33] | 4 | 16; 15; 15; 11 | GG: 1 BRAFV600E neg, 3 pos | Surgery | GTR 1/4; biopsy 3/4 | no (3/4); yes (1/4) | \ | 103 months, no progression (1/4); progression in 3/4 (FU 181, 159 months; 1 died after 8 months) | 1 excluded because not CMJ |
| 28 | Singh | 2021 | [34] | 1 | 7 | PA | Surgery | STR | \ | \ | n/a | Presented with congenital mobile atlantoaxial dislocation |
| 29 | Sun | 2021 | [35] | 1 | 10 | Astrocytoma GII, IDH1 R132H mutation and KIAA1549-BRAF fusion | Surgery | STR | \ | \ | 10 mo, improved | First time both IDH mutation and BRAF fusion |
| 30 | Rady | 2021 | [36] | 3 | 2-14 | LGG | Surgery | GTR, NTR, STR | \ | 2/3 | 5-years PFS 100% | \ |

Ref: reference; pt: patients; y: years; mo: months; RT: radiotherapy; CT: chemotherapy; FU: follow-up; STR: subtotal resection; GTR: gross total resection; NTR: near total resection; VP: ventriculo-peritoneal; EVD: external ventricular drain; BHS: Breat-Holding Spell; GG: ganglioglioma; AGG: anaplastic ganglioglioma; PA: pilocytic astrocytoma; LGG: low-grade glioma; GBM: glioblastoma; HGG NOS: high grade glioma not otherwise specified; IONM: intraoperative neuromonitoring; US: ultrasound; CT: computer tomography; NF2: neurofibromatosis; GI: grade I; GII: grade II; GIII: grade III; GIV: grade IV; (c)Gy: (centi)Gray; CSWS: cerebral salt wasting syndrome; 5-ALA: 5-aminolevulinic acid; IDH: isocitrate dehydrogenase; BRAF: v-raf murine sarcoma viral oncogene homolog B1; PFS: progression-free survival; n/a: not available. **the total is 31 because two were ependymomas, which were excluded.

**Table 3.** Cervicomedullary glial tumors treated at IRCCS Istituto Nazionale dei Tumori (Milan, Italy) from 2006 to 2021.

| N. | Sex | Age | Year | Location | Histology | Molecular analysis | 1st treatment | Surgery | RT | CT | OS | FU | Peculiarity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 16.3 | 2013 | M - C4 | PA | \ | surgery | STR | \ | \ | 93,00 | improved | \ |
| 2 | F | 13.6 | 2012 | M - C2 | PA | \ | surgery | STR | \ | \ | 98,00 | stable | \ |
| 3 | F | 4.3 | 2014 | CM | GG | \ | surgery | biopsy | \ | CDDP/VP | 73,00 | stable | \ |
| 4 | M | 7.8 | 2006 | M - C2 | GG | \ | surgery | biopsy | 50.5 Gy | CDDP/VP16 | 81,00 | multiple relapses, tracheostomy, death 7 years post diagnosis | \ |
| 5 | F | 3.1 | 2017 | M - C2 | GG, BRAFv600E pos, H3K27M neg | BRAFV600E | surgery | STR | \ | \ | 44,00 | stable emisyndrome | Favism |
| 6 | F | 3.2 | 2020 | CM | glial tumor NOS | ALK rearrangement (KIF5C-ALK fusion) | surgery | STR | \ | \ | 4,00 | stable emisyndrome | New ALK fusion |
| 7 | M | 6.5 | 2013 | M - C2 | PA | \ | surgery | biopsy | \ | CDDP/VP | 81,00 | emisyndrome, right ptosis, dysfonia, 12th cn deficit, nistagmus, Babinski | Ab ingestis pneumoniae + hiatal hernia |
| 8 | M | 0.3 | 2016 | CM | glioneuronal tumor with neuropilum isles | no H3K27, no BRAF, no p53 | surgery | biopsy | 54 Gy | CDDP/VP16; at relapse, vinblastine | 50,00 | 2 relapses, PEG+tracheo | \ |
| 9 | M | 4.4 | 2010 | M - C4 | PA | \ | surgery | biopsy | 54 Gy | CDDP/VP16, then CBDCA; at relapse, VCR/CBDCA - VCR/ACTD | 121,00 | 1 relapse, now stable | Presentation with bulbar laugh |
| 10 | M | 0.2 | 2016 | Pons - M - D1 | Low grade glioneuronal tumor | no H3K27 | surgery | biopsy | 54 Gy | CDDP/VP16 | 51,00 | 1 relapse, disequilibrium, exoforia right eye, Babinski | \ |

Age is in year and months. N: number; y: years; mo: months; RT: radiotherapy; CT: chemotherapy; OS: overall survival; FU: follow-up; STR: subtotal resection; GG: ganglioglioma; PA: pilocytic astrocytoma; pos: positive; neg: negative; Gy: Gray; CDDP: cisplatinum; VP(16): etoposide; CBDCA: carboplatin; VCR: vincristine; ACTD: dactinomycin.