Chapter 7
High-Grade Tumors of the Brainstem (Except DIPG)

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Abbreviations

ATRT	Atypical teratoid rhabdoid tumor
CCNU	Lomustine
CNS-PNET	Central nervous system primitive neuroectodermal tumor
DIPG	Diffuse intrinsic pontine glioma
ETMR	Embryonal tumor with multilayered rosettes
FISH	Fluorescence in situ hybridization
GBM	Glioblastoma
HDC	High-dose chemotherapy
IDH1	Isocitrate dehydrogenase-1
IMRT	Intensity-modulated radiation therapy
MGMT	O^6-methylguanine–DNA methyltransferase
MRI	Magnetic resonance imaging
OS	Overall survival
PCV	Vincristine
PFS	Progression-free survival
PTEN	Phosphatase and tensin homolog
WHO	World Health Organization

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7.1 Adult Malignant Brainstem Tumors

7.1.1 Introduction

Hare and Wolf (1934) discussed intramedullary tumors of the brainstem, based on Cushing's clinical documentation of brainstem tumors [1]. White (1963) evaluated a series of 44 patients accumulated over 31 years at the Neurological Institute in New York, and the mean age of the patients was 42 years (range is 17–68 years); most of those who were studied pathologically had astrocytic tumors of various grades [2]. The clinical presentation and course of patients in this adult brainstem glioma series was comparable to the pediatric series studied earlier at the same institution [2]. Adult brainstem gliomas are rare tumors (~2%) and are slightly more common in males in their 30s [3]. Over 60% of adult brainstem tumors are found in the pons, about a quarter of them are found in the medulla oblongata, and the rest are encountered in the midbrain [4]. It is also important to note that brainstem lesions that are diffuse have a wide differential, including tumors such as gliomas and lymphomas, vasculitis, brainstem injury, infections, central pontine myelinolysis, amongst others [5].

7.1.2 Clinical Presentation

Brainstem gliomas in adults are subdivided based upon clinicopathological and radiographic characteristics: diffuse intrinsic, low-grade brainstem gliomas; focal, malignant brainstem gliomas; focal tectal gliomas; and exophytic growing tumors [4]. The focus of this section is not on the diffuse tumor type, but all other types of tumors, which are less frequent: focal malignant brainstem gliomas (~25%), tectal gliomas (~3–8%) and other brainstem tumors (~15%) [4]. The clinical signs correlate with the anatomy of the lesion, and these include cranial nerve dysfunction (87% of patients), gait disturbances (61% of patients), and long-tract signs (~58% of patients). Headaches and raised intracranial pressure symptoms are variable in this patient group [5]. Patients older than 40 with a higher pathological grade and a non-Caucasian ethnicity have been identified as unfavorable prognostic factors [6]. In a study conducted by Dellaretti and colleagues, the histological grade was a significant prognostic factor in terms of patient survival [7].

7.1.3 Imaging and Histopathological Diagnosis

7.1.3.1 Focal Malignant Brainstem Gliomas

These tend to be localized, discrete masses, and can occupy <50% of the greatest dimension of the brainstem [4]. These tumors occur in patients older than 40 and are characterized by the rapid onset and progression of brainstem dysfunction [8].

Radiographically, these tumors have been described to exhibit ring-like enhancement of contrast that is ill-defined (Fig. 7.1) [4]. Neuropathology of these tumors is often consistent with anaplastic astrocytomas (World Health Organization (WHO) Grade III) or glioblastomas (GBM) (WHO Grade IV tumors) [9, 10]. As suggested by the high grades of these tumors, the prognosis is poor and median survival is 12.5 months [8]. Molecular markers that should be checked for these tumors include: O^6-methylguanine–DNA methyltransferase (MGMT), phosphatase and tensin

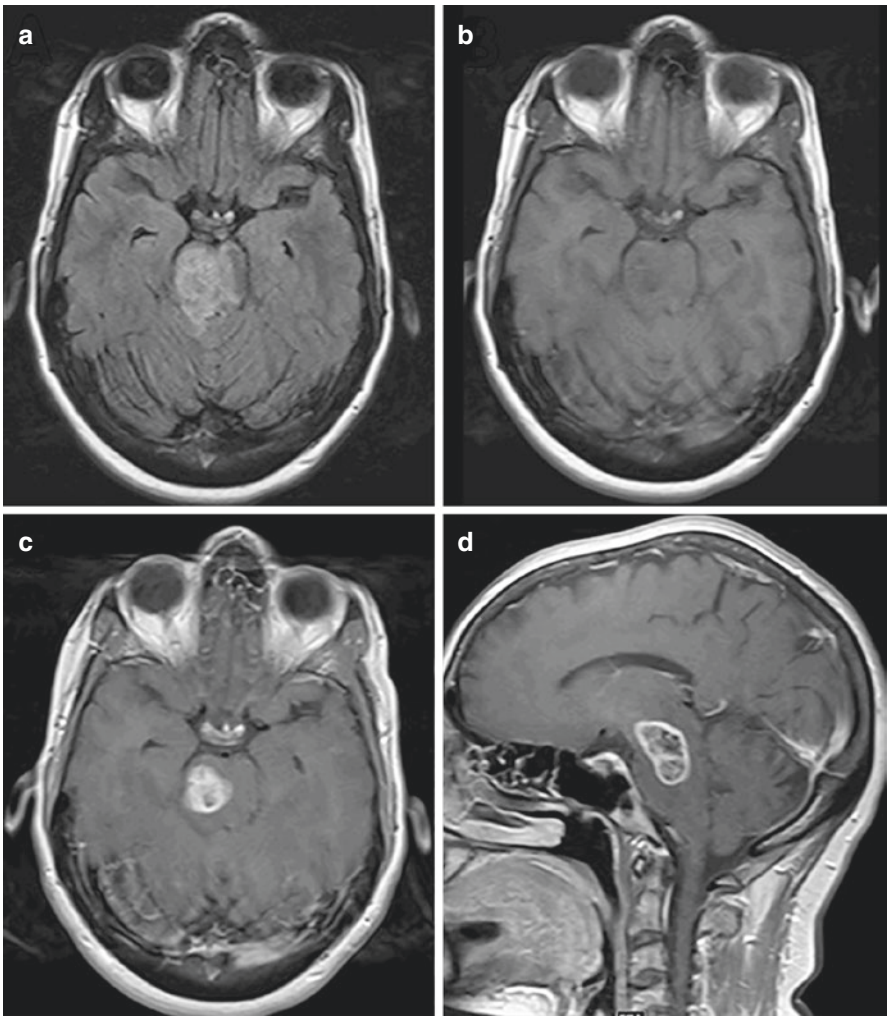

Fig. 7.1 Midbrain and pontine high-grade glioma. (**a**) Fluid-attenuated inversion recovery (FLAIR) demonstrates an expansile mass in the right anterior midbrain and pons. (**b**) Pre- and (**c**, **d**) post-contrast T1-weighted images show a mass with heterogenous and avid enhancement with central necrosis. This mass was treated as a high-grade glioma without biopsy

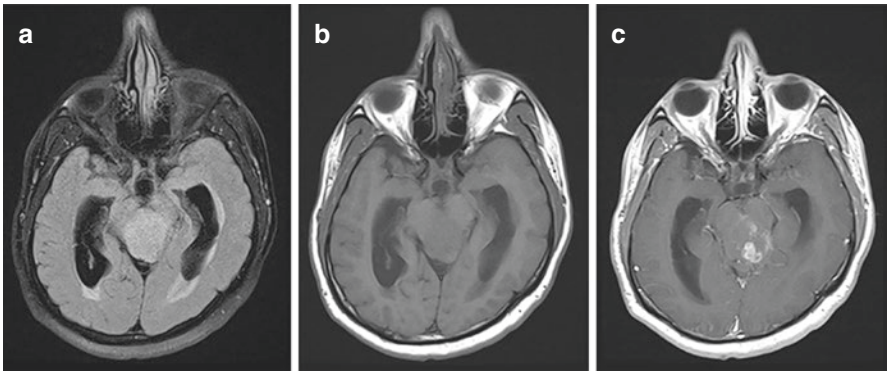

Fig. 7.2 Midbrain and tectal glioblastoma (biopsy-proven). (**a**) FLAIR demonstrates an expansile mass in the superior aspect of the midbrain and tectum. (**b**) Pre- and (**c**) post-contrast T1-weighted images show a mass with heterogenous and avid enhancement

homolog (PTEN) loss, R132H isocitrate dehydrogenase-1 (IDH1) mutation, epidermal growth factor receptor vIII variant, histone H3.3, and activating A receptor type 1 mutations [4].

7.1.3.2 Focal Tectal Gliomas

The presentation is often innocuous and can be incidentally identified. The most common presentation is headaches, and patients are found to have obstructive hydrocephalus. Due to their clinical presentation and radiologic appearance (Fig. 7.2), surgical biopsy is often deemed unnecessary. If biopsied, they tend to be WHO Grade II oligoastrocytomas, and higher grades are exceedingly rare [9]. These types of tumors are typically indolent and are associated with a more favorable prognosis. In a recent review, survival has been around 84 months irrespective of tumor treatment [4].

7.1.3.3 Other Brainstem Gliomas

These include dorsally exophytic brainstem gliomas, oligodendrogliomas, and glial tumors associated with Neurofibromatosis type 1. Note that in adults, these exophytic gliomas are usually contrast-enhancing and highly aggressive, thus surgical resection and pathologic evaluation is key, if possible [4].

7.1.4 Chemotherapy

Unfortunately, the role of chemotherapy in treating adults with brainstem gliomas is unclear. Salmaggi et al. described a retrospective analysis of 20 patients who received either temozolomide (18 patients received 75 mg/m^2 temozolomide during

radiation, followed by adjuvant temozolomide 200 mg/m^2), and the 2 other patients received combined procarbazine, lomustine (CCNU) and vincristine (PCV) (procarbazine 75 mg/m^2 days 8–21, CCNU 110 mg/m^2 on day 1, and vincristine 1 mg/m^2 on days 8–28) with radiation (48–54 Gy in 1.8 Gy fractions) [3]. Only 50% of these patients had disease stabilization by imaging, and the patients who received PCV had grade 3 and 4 myelotoxicity, in addition to 6 of the patients who received temozolomide who also had the same level of myelotoxicity. At the time of recurrence, the role of chemotherapy is even less clear, the use of PCV, carboplatin, cisplatin, salvage bevacizumab, etoposide and paclitaxel have been reported, and these options cause significant chemotoxicity in patients, who need to be carefully monitored [4].

7.1.5 Conclusion

Brainstem gliomas are just as heterogeneous in terms of genetic complexity as their supratentorial counterparts [11]. In adult brainstem gliomas, the most significant gene alterations are IDH1 and H3F3A(K27M). One hopes that more targeted therapies are an option in the future, as opposed to concomitant radiation and temozolomide, and during recurrent salvage radiotherapy. The rarity of IDH1 mutations in brainstem gliomas is also emphasized in an earlier work by Theeler et al. [12]. Interestingly, in 1998, Landolfi et al. mentioned that adults with brainstem gliomas fare better in terms of survival than children [13]. In addition, they recommended that patients with tectal or cervicomedullary tumors can be managed by observation alone, and very little has changed in terms of current management since these authors initially recommended this conservative strategy.

7.2 Pediatric Malignant Brainstem Tumors, Excluding Diffuse Intrinsic Pontine Gliomas (DIPG)

7.2.1 Introduction

Neoplasms that arise in the brainstem account for 10–15% of pediatric brain tumors [14, 15]. The majority of these tumors (80%) are DIPG, with the remainder being predominantly focal low-grade gliomas. Thus, non-DIPG pediatric malignant brainstem tumors are exceedingly rare. In one retrospective review from a single institution, non-DIPG malignant brainstem tumors constituted less than 5% of all pediatric brainstem tumors [16]. Non-DIPG malignant histologic types of the brainstem in children have been recognized as either: (1) high-grade glial neoplasms (~60%), including WHO Grade IV glioblastoma (GBM) or WHO Grade III anaplastic astrocytoma, oligodendroglioma and ganglioglioma, occurring within the midbrain,

medulla or eccentrically displaced within less than one-third of the pons (non-DIPG); or (2) embryonal tumors (~40%), including atypical teratoid rhabdoid tumor (ATRT), embryonal tumor with multilayered rosettes (ETMR), and what had previously been classified as central nervous system primitive neuroectodermal tumor (CNS-PNET) [14–16]. In 2016, the WHO classification for CNS tumors removed CNS-PNET as a unique histological entity based on evidence from molecular profiling studies showing that the majority of these tumors are actually a diverse group of other known histologic entities, including high-grade gliomas (HGG) [17, 18]. Furthermore, according to the 2016 revised WHO classification, midline gliomas that harbor H3K27M mutation are now considered a single histologic entity termed as diffuse midline glioma (WHO Grade IV), irrespective of location, further blurring what constitutes a DIPG from a non-DIPG. Thus, the precise histologic types of malignant non-DIPG brainstem tumors and their incidence are unclear. Individual case reports have also described the presence of astroblastoma and angiocentric glioma in the brainstem of children [19, 20]; however, this review will attempt to summarize the key features in the diagnosis and management of the most commonly encountered non-DIPG pediatric malignant brainstem tumors.

7.2.2 Clinical Presentation

The mean age of non-DIPG brainstem tumors in children has been reported to be approximately 7.5 years (peak age range is 5–10 years), with the majority (90%) occurring in those less than 18 years of age [14–16]. The tumor location is either the pons or pontocerebellar junction in over half of the cases, followed by the medulla or pontomedullary junction (~20%), and finally the midbrain (~15%) [14–16]. Nearly half of the cases will have an exophytic portion of the tumor on imaging [15]. The most common presenting signs and symptoms relate to tumor location within the brainstem, irrespective of histology, and include cranial nerve deficits, pyramidal tract signs, and ataxia [14–16, 21]. In general, patients typically present with progressive neurological symptoms of short duration.

7.2.3 Imaging and Histopathological Diagnosis

7.2.3.1 High-Grade Gliomas (HGG)

The majority of non-DIPG HGG of the brainstem will present in the middle cerebellar peduncle junction or pontomedullary junction (80–90%); however, it is unclear whether the HGG tumors in these locations that harbor the H3K27M mutation, a hallmark of DIPG, would now be considered eccentrically displaced "atypical-appearing DIPG" given the 2016 WHO re-classification of H3K27M-mutated diffuse midline gliomas as a single entity [17]. The remaining HGG (10–20%) occur in the midbrain.

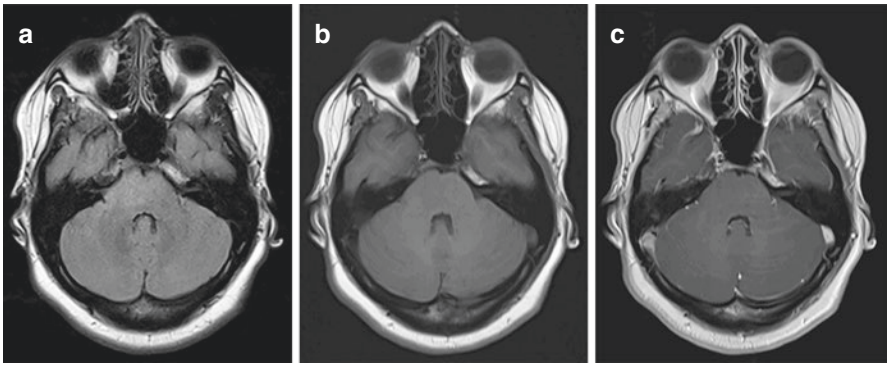

Fig. 7.3 Midline pontomedullary glioma, H3K27M-mutant. (**a**) FLAIR demonstrates an expansile mass in the right anterior and midline pons. (**b**) Pre- and (**c**) post-contrast T1-weighted images show a mass with no post-contrast enhancement. This lesion was biopsied and was found to be an H3K27M-mutated midline glioma

On magnetic resonance imaging (MRI), these tumors have the typical characteristics of HGG as in other locations (Fig. 7.3). The imaging features include heterogeneous signal intensities, prominent heterogeneous and ring-like enhancement with poorly defined margins, and multi-centricity or extra-axial metastases. Likewise, the histopathology of brainstem HGGs is identical to that of the corresponding Grade III and Grade IV HGGs in other locations. Histologic diagnostic features include infiltrative tumor cells with nuclear atypia, high mitotic activity, pseudopalisading necrosis, and florid microvascular proliferation.

7.2.3.2 Atypical Teratoid Rhabdoid Tumor (ATRT)

ATRT is a rare, highly malignant WHO Grade IV tumor that occurs in children and adults but has a predilection for infants, with 70% presenting in children <1 year old and 90% under the age of 3 years [22]. On MRI, ATRT is generally circumscribed, with heterogeneous contrast enhancement and signal intensity, usually secondary to areas of hemorrhage and necrosis (Fig. 7.4). Leptomeningeal spread is a common radiological finding, being present in approximately a quarter of cases at diagnosis [22].

Histological heterogeneity is characteristic of ATRT, with neuroectodermal, mesenchymal, and, rarely, epithelial differentiation being evident [22]. The neuroectodermal component can closely mimic medulloblastoma. Most ATRTs are composed of sheets of pleomorphic cells that typically have large nuclei with open, vesicular chromatin and prominent nucleoli, and a small-to-moderate amount of lightly eosinophilic cytoplasm. Many cases have at least focal rhabdoid morphology; however, the presence of rhabdoid morphology is not required for the diagnosis of ATRT [22].

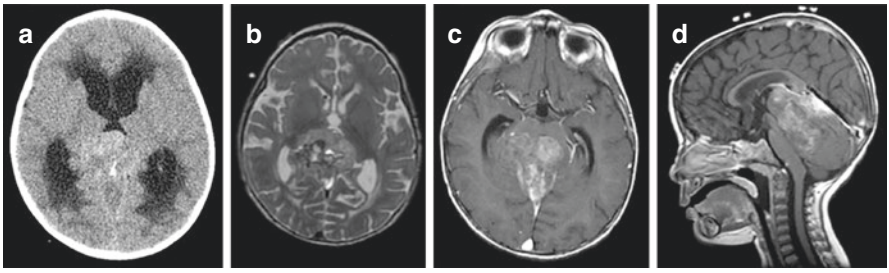

Fig. 7.4 Atypical teratoid rhabdoid tumor (ATRT). (**a**) Computed tomography (CT) image showing a hyperdense and partially calcified mass with obstructive hydrocephalus. (**b**) T2-weighted image demonstrates a markedly heterogenous mass. (**c**) Axial and (**d**) sagittal post-contrast T1-weighted images show a mass with heterogenous and avid enhancement involving the tectum and superior vermis with compression of the midbrain and pons

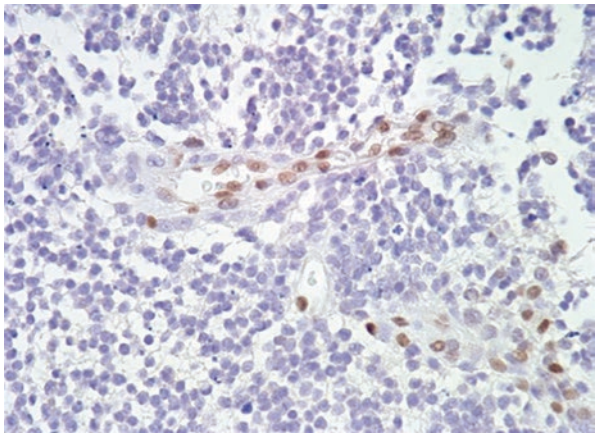

Fig. 7.5 Atypical teratoid rhabdoid tumor (ATRT). Immunohistochemistry demonstrates loss of INI1 expression in tumor cells, while native endothelial cells retain staining (brown) for INI1

Unlike other CNS neoplasms, ATRTs demonstrate remarkable uniformity in genetic alterations of the *SMARCB1* locus on chromosome 22q11.2 [23]. Reported alterations include homogenous and heterozygous deletions, loss of heterozygosity, and mutations of *SMARCB1,* especially in exons 5 or 9 [23]. Since loss of expression or function of INI1 is thought to be a key molecular event in the formation of ATRT, demonstration of its loss or mutation is a reliable way to diagnose ATRT in patients who present with an embryonal brain tumor (Fig. 7.5). Use of fluorescence in situ hybridization (FISH) along with genomic sequencing permits identification of more than 75% of ATRTs [24]. While there are embryonal brain tumors that exhibit histologies that are consistent with ATRT but positive immunohistochemical staining for the *SMARCB1* protein, INI1, these are considered even more rare and are thought to represent only 2% of all ATRTs [25]. ATRTs that retain wild-type *SMARCB1* and its protein product often have a mutation in *SMARCA4* and its related chromatin modeling protein, BRG1, which, along with *SMARCB1*, is an

important component of the SWI/SNF complex, which plays an important role in lineage specification and stem cell maintenance [26].

7.2.3.3 Embryonal Tumor with Multilayered Rosettes (ETMR) and Historical Central Nervous System Primitive Neuroectodermal Tumor (CNS-PNET)

Recent identification of focal amplification of a micro-RNA cluster on chromosome 19q13.42 (C19MC) has led to a new designation of ETMR (ETMR, C19MC-altered), which encompasses medulloepithelioma, ependymoblastoma, and the previously-described entity, embryonal tumor with abundant neuropil and true rosettes (ETANTR) [27, 28]. ETMR occurs in young children, with a mean age of about 2 years, reaching up to almost 5 years, with a female predominance of around 2:1 female-to-male ratio. The most common MRI appearance is a heterogeneously-enhancing, well-circumscribed, solid mass [29].

The histological appearance consists of islands of embryonal tumor cells in a sea of neuropil-like matrix, forming luminal or "ependymoblastic" rosettes (Fig. 7.6). The ependymoblastic rosettes appear in both the hypo- and hyper-cellular areas, and are formed of multi-layered, elongated tumor cells that are arranged radially around a well-defined, round to slit-like lumen. Similar to nodular medulloblastomas, ETANTR tumor cells show varying levels of differentiation, from embryonal within the areas of cellularity to neurocytic, and even occasionally ganglionic, within the hypocellular areas. Although the undifferentiated cells within the clusters generally fail to stain for neuronal or glial markers, NeuN, synaptophysin and neurofilament staining can be strong within the more differentiated cells of the neuropil-like areas.

CNS-PNETs, which account for 1% of pediatric brain tumors, are a heterogeneous group of undifferentiated, highly malignant tumors that are histologically

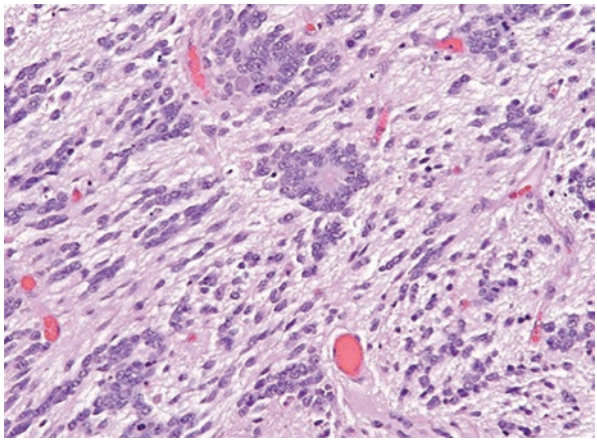

Fig. 7.6 Embryonal tumor with multilayered rosettes (ETMR). Although the hematoxylin and eosin stain demonstrates relatively low cellularity compared to other CNS malignancies, ETMR is a highly aggressive embryonal tumor

composed of neuroepithelial-like cells. MRI characteristics of CNS-PNETs include a focal intrinsic or exophytic non-enhancing brainstem tumor with low T1- and high T2-weighted signals [16]. Hydrocephalus and leptomeningeal dissemination are common presenting features. More recently, methylation profiling studies have found that CNS-PNETs do not cluster distinctly from other pediatric CNS tumors. Among the 323 analyzed CNS-PNETs, 61% were re-classified as another tumor type based on molecular profiling. Of the remaining CNS-PNETs, 11% clustered with known ETMRs, 15% formed small clusters that failed to associate with each other or with other known pediatric CNS tumors, and 24% formed four distinct, novel entities: CNS neuroblastoma with *FOXR2* activation (14%), CNS Ewing sarcoma family tumor with *CIC* alteration (4%), CNS high-grade neuroepithelial tumor with *MN1* alteration (3%), and CNS high-grade neuroepithelial tumor with *BCOR* alteration (3%) [18]. The 2016 WHO revised classification of CNS tumors thereby removed the term CNS-PNET; thus, the actual occurrence and distribution of these distinct entities within the brainstem is unknown.

7.2.4 Treatment and Outcome

It is estimated that the majority of children (>90%) with non-DIPG high-grade tumors of the brainstem can successfully undergo either surgical biopsy (open or stereotactic needle) or partial tumor resection as part of the initial management plan [14–16]. In the absence of non-surgical treatment, gross total resection of malignant brainstem tumors at the time of diagnosis is not feasible. The treatments administered, and the associated outcomes, are specific for the tumor type (as described below); however, survival in general is dismal for this group of patients as a whole, with at least one report describing a median overall survival (OS) of 6.4 months following the diagnosis, and only 31% of patients surviving more than 1 year [15].

7.2.4.1 Atypical Teratoid Rhabdoid Tumor (ATRT)

ATRT is an aggressive tumor that carries a poor overall prognosis. Published studies report a median survival from 8 to 17 months from diagnosis. Two factors that have repeatedly been associated with a poor outcome are age less than 3 years at diagnosis and the presence of metastatic disease [30]. Treatment considerations for ATRT of the brainstem would be the same as that for non-brainstem ATRT. The role of conventional versus high-dose chemotherapy (HDC) with autologous stem cell rescue remains controversial. At least two published studies reported a greater than 50% survival when patients with an ATRT were treated with a carboplatin-thiotepa-based HDC regimen [31]. The only prospective, front-line ATRT study using a modified rhabdomyosarcoma-type IRS-III regimen along with intrathecal chemotherapy and either focal or cranio-spinal irradiation reported a 2-year progression-

free survival (PFS) and OS of 53% and 70%, respectively [32]. Also controversial are the role and timing of radiotherapy; some clinicians consider radiotherapy as crucial to the treatment of ATRT, while others prefer to defer the use of irradiation due to its potentially devastating side-effects on cognition when used in young children [33]. Data from St. Jude Children's Hospital lend support to the early use of irradiation for ATRT [30]. Overall, newer treatment regimens have improved the prognosis for ATRT and led to a long-term cure in a minority of patients. Due to the paucity of cases, it is not yet known whether the outcome is significantly different in brainstem ATRT compared to ATRT in other locations.

7.2.4.2 Embryonal Tumor with Multilayered Rosettes (ETMR) and Historical Central Nervous System Primitive Neuroectodermal Tumor (CNS-PNET)

Due to historically poor outcomes, children with CNS-PNET have been treated according to the high-risk arm of treatment protocols for medulloblastoma. Yet, 5-year survival has remained around 50–60% in children [34]. The median survival in patients with ETMR is 13 months from diagnosis, although clinical outcome has been accurately documented in only 48 patients to date [35]. In six patients with subtotal surgical resection and aggressive adjuvant therapy with radiation and/or chemotherapy, only one patient was reported alive without disease at 34 months after diagnosis following multiple resections and HDC [36]. Of the 48 cases reported to date, 6 children have survived beyond 30 months. The longest reported survival is 42 months [35]. Similar to other histologic entities, due to the rarity of this tumor type overall, it is unclear whether the outcome is different for brainstem ETMRs compared to ETMRs in non-brainstem locations. There is a case report of a 17-month-old boy with an ETANTR of the brainstem, and despite chemotherapy, the child died 3 months after initial diagnosis [37].

In a retrospective report of 83 children with brainstem CNS-PNETs treated between 1973–2013, the median OS was reported as 53 months [38]. A survival advantage was observed for patients older than 4 years of age, those who received surgery, chemotherapy and radiation, and those with gross or subtotal tumor resection. Another report described the outcome for 6 children with histologically-proven brainstem CNS-PNET and 2 with brainstem ependymoblastoma who were treated according to the multimodal HIT protocol therapy [21]. All patients had postoperative residual disease, including one with metastasis. All tumors progressed, with one exception, within 2.5–10.4 months. After progression, patients succumbed early to their disease resulting in a 1-year OS rate of 25%. The only surviving patient had a partially resected tumor, received chemotherapy and was reported without progression at 14 months after diagnosis [21]. With the recent evidence that the majority of PNETs are actually other known histologies, the optimal treatment and outcomes for each histologic type observed in the brainstem remains to be determined.

7.2.4.3 High-Grade Gliomas (HGG)

Treatment for HGG of the brainstem is identical to that for DIPG, namely, local irradiation of the tumor to 54 Gy in 1.8-Gy fractions using intensity-modulated radiation therapy (IMRT); this is administered alone, as standard therapy, or in conjunction with an investigational therapy on a clinical trial. As of yet, there has been no clinical benefit observed with any therapy apart from radiation. Multiple case reports indicate that secondary GBM with distinct histological features can arise after treatment for childhood medulloblastoma [39]. Other reports indicate that secondary HGG may result from malignant transformation of low-grade glial neoplasms, especially those harboring the BRAFV600E mutation and CDKN2A deletion [40]. Indeed, the majority of gangliogliomas of the brainstem have the BRAFV600E mutation, and HGG with this mutation may be treated with BRAF inhibitors on clinical trials evaluating the efficacy of these new agents [41]. The precise portion of these secondary HGG that arise in the brainstem secondary to radiation and/or underlying BRAFV600E mutation/CDKN2A deletion is unclear. However, secondary HGG of the brainstem appear to have a particularly dismal prognosis, with one report demonstrating median OS of 124 days compared to 6 months for the presumed primary HGG of the brainstem [15]. OS for brainstem HGG also appears to be worse than the median OS of 9–12 months for pediatric DIPG and HGG in non-brainstem locations [15].

7.2.5 Conclusion

Non-DIPG pediatric high-grade tumors of the brainstem are uncommon, but tend to occur in younger aged patients, almost always present with at least cranial neuropathies of short duration, and typically have a very poor prognosis, with relatively rapid disease progression despite multi-modality therapy. Larger prospective studies are needed, especially for the group of tumors that had been classified as CNS-PNETs, given the new molecular information indicating that these are actually composed of a highly diverse group of different histologic tumors.

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