Expert Review of Molecular Diagnostics

ISSN: 1473-7159 (Print) 1744-8352 (Online) Journal homepage: https://www.tandfonline.com/loi/iero20

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To cite this article: Bryan K. Li, Salma Al-Karmi, Annie Huang & Eric Bouffet (2020): Pediatric embryonal brain tumors in the molecular era, Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2020.1714439

To link to this article: https://doi.org/10.1080/14737159.2020.1714439

Accepted author version posted online: 09 Jan 2020.

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Molecular Diagnostics*

DOI: 10.1080/14737159.2020.1714439

Pediatric embryonal brain tumors in the molecular era

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Abstract

INTRODUCTION: Embryonal brain tumors (EBTs) are highly aggressive malignancies predominantly affecting children. They include medulloblastoma (MB), atypical rhabdoid/teratoid tumors (ATRT), pineoblastoma (PB), embryonal tumor multiple rosettes (ETMR)/*C19MC*-altered tumors, and newly recognized embryonal tumors with *FOXR2* activation or *BCOR* alteration.

AREAS COVERED: This review will provide a comprehensive overview and updated of the literature on each of these EBTs. The evolution from location- and histopathology-based diagnosis to more specific and robust molecular-based classification schemes, as well as treatment modalities, will be discussed.

EXPERT OPINION: The subgrouping of EBTs with multi-omic profiling has had important implications for risk stratification and discovery of targetable driver pathways. However, these innovations are unlikely to significantly improve survival among high-risk patients until robust preclinical studies are conducted, followed by validation in biology-informed clinical trials.

Keywords: Atypical teratoid/rhabdoid tumor ATRT, C19MC-altered tumors, Embryonal tumor, Embryonal tumor multiple rosettes ETMR, Medulloblastoma, Pediatric brain tumor, Pediatric cancer, Pineoblastoma, Primitive neuroectodermal tumor PNET

Article highlights

- EBTs are aggressive malignancies primarily seen in children.
- EBTs include entities such as medulloblastoma, ATRT, pineoblastoma, ETMR/*C19MC*-altered tumors, and embryonal tumors with *FOXR2* activation or *BCOR* alteration.
- Diagnosis and treatment of these entities are evolving from being based on location/histopathology towards more recently established molecular classification schemes.
- Specific molecular markers have expanded or enabled the recognition of certain EBTs (loss of *SMARCB1*/INI1 for ATRTs and alteration of the C19MC amplicon for ETMRs).
- Multi-omic profiling have uncovered subgroups for several types of EBTs with distinct clinical and molecular features.
- These revised classification methods may have an emerging role for risk stratification, but the introduction of much-needed novel targeted therapies is still under evaluation.
- Primitive neuroectodermal tumor PNET

1. Introduction

Pediatric brain tumors are the leading cause of cancer-related death and disability in children. Primary brain tumors, which are the most common solid tumors of childhood, comprise a spectrum of diseases [1]. Of these, 15-20% are embryonal brain tumors (EBTs), a group of highly aggressive cancers that mostly affect young children [2, 3, 4]. Though classically exhibiting the small round blue cell morphology of extra-CNS embryonal tumors, they can show varying degrees of differentiation. Historically, the classification of EBTs was based on primary location and histology. For example, medulloblastoma (MB) is an EBT that arose in the infratentorial compartment [5]. Atypical teratoid/rhabdoid tumors (ATRT) presented anywhere in the CNS but classically had distinctive histologic features resembling extra-CNS malignant rhabdoid tumors. Other EBTs presenting above the tentorium were called supratentorial primitive neuroectodermal tumors (sPNET), except for pineoblastoma (PB) which arose from the pineal gland [6]. However, the identification of specific molecular markers expanded the recognition of distinct entities with overlapping locations and histology among other EBTs: loss of function alterations of *SMARCB1*/INI1 or *SMARCA4*/BRG1 became a specific marker for ATRTs, while amplification of an embryonic stem cell-enriched miRNA cluster at chr 19q13.42 (C19MC) characterized a highly aggressive C19MC-altered tumors/embryonal tumor multiple rosettes (ETMR) [7, 8, 9, 10]. Since then, genomic, transcriptomic, and proteomic (i.e. multi-omic) profiling on large collections of EBTs have revealed additional heterogeneity, with newly proposed subgroups characterized by distinct molecular drivers. While the separation of MB into four subgroups (WNT, SHH, group 3, group 4) has generated a schema for molecular risk stratification and informed preclinical studies of targeted therapies, the rarity of other EBTs provides additional challenges [6, 11]. The following review will provide an overview of each type of EBT, describing its

clinicopathologic characteristics, specific molecular markers and their significance, and general treatment strategies.

2. Medulloblastoma (MB)

MB is the most common EBT and most common malignant tumor of childhood [5]. Historically, due to histologic resemblance, MB and other EBTs were considered collectively as intracranial PNETs [12]. However, identification of *SMARCB1*/INI1 loss a defining marker for ATRT removed a subset of EBTs that had been misdiagnosed as MB [13]. Later use of gene expression-based profiling confirmed MB as a separate entity from other EBTs that may also arise in the cerebellum [14]. The current 2016 WHO classification of CNS tumors defines MB based on both histology and molecular features [5]. Four histologic classes are recognized: classic, desmoplastic/nodular, MB with extensive nodularity (MBEN), and large cell/anaplastic (LCA). In parallel, four molecular classes of MB with distinct clinic-pathological features are also recognized: wingless (WNT)-activated, sonic hedgehog (SHH)-activated, group 3, and group 4 MB [15, 16, 17, 18]. The latter two are collectively considered as non-WNT/non-SHH MB as there is some overlap seen in molecular clustering analyses [5]. Recent whole proteome analysis has also reflected this four-molecular group classification [19, 20]. Clinical tools for determining a molecular group are increasingly being implemented and include immunohistochemistry, global gene expression or DNA methylation profiles [11, 12, 21], and gene set expression panels [22, 23]. Recently, substantial collections of MB with gene expression and/or DNA methylation-based microarrays indicate further subtypes within the four groups [24, 25, 26]. Further, emerging clinical analyses is providing insight for improved risk prognostication among subsets of patients within each group.

Due to the severe neurocognitive sequelae from radiation exposure in young children, current therapy for MB generally divides patients by an age division of 3 years old at diagnosis, and into average and high-risk groups [27]. Localized cases with gross tumor resection (GTR) ($\leq$1.5cm^2 of residual disease) are considered average risk, while those with metastatic disease and/or less than GTR are high-risk. Tumors with diffuse anaplasia histology have also been considered high-risk [28]. Therapy begins with maximal upfront resection. For children >3 years old, this is followed within 4-6 weeks by craniospinal irradiation (CSI) of 23.4 Gy for average risk and 36 Gy for high risk cases, and further local irradiation (boost) to the tumor bed or posterior fossa to a total dose of 54-55 Gy. Adjuvant chemotherapy may be initiated during or after radiotherapy, and generally consists of combinations of cyclophosphamide, lomustine, cisplatin, carboplatin, etoposide, and vincristine [29, 30, 31, 32]. In an effort to omit or delay radiotherapy for patients <3 years old, high-dose intravenous methotrexate (MTX), intraventricular MTX, and/or intrathecal MTX or mafosfamide have also been used [33, 34, 35, 36, 37]. Alternatively or in combination, multiple rounds of high-dose chemotherapy with autologous stem cell rescue have also been employed for this age cohort [38, 39], as well as older children with high-risk disease [40]. While an international consensus has been reached for risk stratification based on the four subtypes of MB, its clinical applicability is still being evaluated in ongoing prospective clinical trials (SJMB12/NCT01878617, PNET5/NCT02066220) [11, 41].

2.1 WNT MB

This subgroup is defined by activation of the WNT signaling pathway and accounts for approximately 10% of MB cases [5]. Often found invading into the fourth ventricle, it is thought to arise from cells in the dorsal brain stem that originate from the lower rhombic lip [42, 43]. Nearly all have classic histology, and are very rarely anaplastic [5]. Prognosis is excellent with 5-year survival rates of

>95% across multiple trials in patients under 16 years of age [12]. The favorable outcome of WNT tumors has led to localized cases occurring in patients <16 years old being considered low risk in the most recent 2016 consensus [11]. Current efforts are focused on de-intensifying treatment via dose reduction for CSI (to 18 Gy) and adjuvant chemotherapy (SJMB12, PNET5, and NCT02724579 trials).

WNT tumors are associated with two signature molecular markers: activating, somatic mutations in *CTNBB1* (β-catenin) in 85-90% of tumors, and monosomy 6 in 85% of tumors [25]. However, 10-15% of cases lack either of these features, which should prompt genetic testing as pathogenic germline variants of *APC* (i.e. Turcot Syndrome) have been observed. Other reported somatic mutations affect *TP53* (12% of cases), *SMARCA4* (25%), and *DDX3X* (50%) [12]. In contrast to SHH-activated MB, *TP53* mutations are not prognostic [44].

2.2 SHH-activated MB

SHH-activated tumors account for approximately 30% of MB cases. They often present in the cerebellar hemisphere and are proposed to arise from cerebellar granule neuron precursors originating from the rhombic lip [5, 42]. SHH tumors includes a majority of MB with desmoplastic/nodular or MBEN histology, as well as a smaller proportion with classic histology, and rarely LCA histology.

The 2016 WHO classification divides SHH cases based on the mutational status of the tumor suppressor *TP53*. Germline or somatic mutations are seen in 30% of SHH cases, and is associated with a very poor prognosis [41, 44]. These mutations frequently co-occur with amplifications of *GLI2* and/or *MYCN*, and chromothripsis (chromosome shattering) seen in unstable genomes [45]. In infant cases, mutations in *PTCH1* and *SUFU* are common, occurring as germline in 25% and 20% respectively [12]. Therefore, genetic testing is warranted for infant cases for *PTCH1* (i.e. Gorlin syndrome/nevoid basal-

cell carcinoma syndrome) or *SUFU*, and for *TP53* (i.e. Li-Fraumeni syndrome) in childhood cases. In contrast, adult SHH tumors have a higher mutation load and are associated with somatic mutations of *PTCH1*, *SMO*, *TERT* promoter, and *IDH1* [12, 46, 47, 48]. Reflecting this heterogeneity in age and mutations, recent studies by Cavalli et al. indicate further molecular segregation of SHH tumors into an additional four subtypes [24].

The current consensus classification designates SHH tumors with *MYCN* amplification or metastatic disease as high-risk, those with *TP53* mutations as very high-risk, and all others as standard-risk. Newer SHH pathway-antagonists (ex. SMO inhibitors vismodegib and sonidegib) show some promise among relapsed or refractory cases [49]. However, its use may be limited in non-adult cases due to pathway activation downstream of *SMO* (via *SUFU*, *GLI2*, *MYCN* mutations) that is often seen in infant and childhood cases [46], as well as concerns of premature osseous fusion among skeletally immature patients [50].

2.3 Group 3 MB

Group 3 tumors account for approximately 20% of MB cases [5]. They arise in younger children, comprising 45% of infant cases and are frequently (40-50%) metastatic at diagnosis [5, 12, 16]. The primary tumors frequently present in the fourth ventricle adjacent to the brainstem. Most non-WNT/non-SHH (i.e. group 3 and 4) MBs have classic histology. However, MB with the uncommon LCA histology are usually group 3 tumors [5].

This group is transcriptionally characterized by GABAnergic and photoreceptor pathway activation. They are considered copy number-driven tumors, as only rare somatic nucleotide variants including mutations of *SMARCA4*, *CTDNEP1*, *MLL2* have been reported [12]. Amplification of *MYC* is

seen in 10-20% of cases, frequently as a gene fusion with *PVT1* secondary to complex rearrangements of chr 8q24. Broad chromosomal arm level-changes are common, notably isochromosome 17q (i17q), seen in 40% of cases. Aberrant enhancer associated *GFI1* activation related to focal alterations of chr 1 and 9 are seen among 20% of cases [43]. Recent proteomic studies have revealed a subset of group 3 tumors are characterized by *MYC* activation through either gene amplification or interestingly, an increase in post-translational modification of MYC that altered its half-life and transcriptional activity [19]. Preclinical data from targeting this pathway using BET/bromodomain inhibitors, which target MYC and MYCN-associated transcription activity, have shown promise [51, 52].

The prognosis of group 3 MB is poor overall, with high-risk features being infancy, metastatic disease, and *MYC* amplification in metastatic cases [5, 12, 41, 53, 54, 55]. However, patients with non-metastatic disease treated with CSI appear to have an intermediate outcome [41]. Based on promising preclinical studies, the additional use of the antifolate pemetrexed and nucleoside analog gemcitabine [56] is currently being evaluated in SJMB12 for select group 3 and 4 patients.

2.4 Group 4 MB

Group 4 tumors are the most common subgroup, accounting for 40% of all MB [5]. It is predominantly seen in children age 5-15 years [57]. They are associated with longer pre-diagnostic intervals and present with disseminated disease in 30-40% of cases [58]. Overall, group 4 tumors have an intermediate outcome, with metastasis being a negative prognostic feature [12, 26, 59]. Patients with localized disease who received radiation appear to do very favorably (5-yr progression-free survival/PFS >95%) [41].

Transcriptionally, this group exhibits activation of neuronal and glutaminergic pathways [12]. Like group 3 tumors, they are thought to be copy-number driven tumors. 80% of cases have i17q and is associated with high-risk disease [16, 17, 26, 60]. Notably, loss of chr 11 is a favourable marker and denotes low-risk disease among non-metastatic tumors [11, 59]. Other common alterations include inactivating mutations of histone demethylase *KDM6A* (13% of cases), and amplifications of *MYCN* (6.3%) and *CDK6* (5-10%) [12, 17, 57, 61]. Tandem duplications of *SNCAIP* (10.4%) have been seen and appears mutually exclusive to *MYCN*/*CDK6* amplification. In contrast to SHH tumors, *MYCN* amplification is not a negative prognostic marker in group 4 MBs [59, 62]. Recent transcriptional and proteomic studies have suggested the cell of origin arises in the nuclear transitory zone of the developing cerebellum and is characterized by *ERBB4-SRC* signaling, a druggable target [20, 63]. However, there remains a paucity of pre-clinical models (i.e. representative cell lines and mouse models) for this group, impeding the development and validation of new therapies [12].

3. Atypical teratoid/rhabdoid tumors

ATRTs are highly aggressive pediatric EBTs characterized by loss of function alterations of *SMARCB1*/INI1, and more rarely, *SMARCA4*/BRG1, both keys components of the SWI/SNF chromatin remodeling complex [64, 65, 66]. They exhibit a wide variation in morphology, ranging from classic rhabdoid features (eccentric nuclei, prominent nucleoli, abundant eosinophilic cytoplasm with globular inclusions) to blander cells with abundant cytoplasm but less nuclear atypia. Most tumors also contain epithelial, primitive neuroectodermal, or mesenchymal features. Small round blue cell components are seen in two-thirds of cases, historically making them difficult to distinguish from MB and then-termed CNS-PNETs [67]. However, the initial recognition of a highly recurrent focal deletion or translocation

of 22q11.2, later found to be *SMARCB1*, as well as rarer alterations of *SMARCA4* among ATRTs, led to its classification as a separate entity by the WHO in 2000 [8, 13, 64, 66].

The incidence of ATRT is difficult to assess accurately due to its relatively recent recognition [13, 68]. With this caveat, current estimates report that it accounts for 1-2% of all pediatric brain tumors [5, 69]. Strikingly, it is the most common malignant brain tumor in children < 6 months of age, and 75% of cases occur in children < 3 years of age [70]. They can present anywhere in the CNS: most commonly in the cerebral hemisphere or posterior fossa, and more rarely (1-7% of cases) in the spinal cord [71, 72, 73]. As germline mutations of *SMARCB1* (seen in up to a third of cases) and *SMARCA4* have been widely reported, genetic testing and counseling should be performed [65, 74].

Survival data is largely based on retrospective data with widely heterogenous cohorts and treatment regimens. With this important caveat, metastatic disease, seen in 14-21% of cases, is associated with a poor outcome [10, 71, 73, 75]. Young age (< 1-3 years) also appears to be a negative prognostic marker, likely due to restricted use of radiotherapy, higher rate of metastasis, and predisposition to other cancers due to germline mutations [10, 73, 76, 77, 78]. Supratentorial location is associated with a favourable outcome [76, 77, 79, 80].

Dismal outcomes (i.e. <10% event-free survival/EFS) were previously observed in older CCG9921 and POG9923 trials [78]. However, the more recent use of an intensified multimodal regimen (modified IRS-III) with conventional dose chemotherapy and intrathecal chemotherapy by the Dana-Farber group produced improved 2-year EFS and overall survival (OS) of 53% and 70% [76]. Alternatively, high-dose chemotherapy with autologous stem cell rescue may be used, with or without radiation, with overall long-term survival ranging between 23-50% [73, 81, 82, 83]. Indeed, similar preliminary results from the active prospective COG ACNS0333 trial have been reported with 2-year EFS/OS of 42%/53%, with those < 3 years old having a 2-year EFS/OS of 39%/48% [84].

Due to the lack of mutations beyond *SMARCB1* and *SMARCA4*, ATRT is believed to be epigenetically-driven via a disruption of the SWI/SNF chromatin remodeling complex [85, 86, 87, 88]. In normal developing tissues, SWI/SNF is thought to antagonize Polycomb Repressor Complex (PRC2)-mediated silencing of genes involved in embryonal differentiation [89]. Indeed, loss of *SMARCB1* has been shown to lead to elevated expression of PRC component *EZH2* and a repression of PRC2 targets via broad H3K27-trimethylation *in vitro* [89]. Further, initial studies by Birks et al. using expression microarray data identified a poor-survival sub-cluster characterized by high expression of BMP pathway genes (*BMP4, SOST, BAMBI, MSX2*) [90].

More recent studies have confirmed these findings and three epigenetic subgroups have been proposed, each with distinct expression signatures and pattern of *SMARCB1* alteration [86, 88]. While a consensus on subgroups is pending, those described by Torchia *et al.* (Group 1, 2A, and 2B) and Johann *et al.* (ATRT-SHH, -TYR, and -MYC) appear to correspond to one another. Group 1/ATRT-SHH has a neurogenic signature with prominent SHH (*MYCN, GLI2*) and NOTCH (*ASCL1, DLL1/3, HES5/6*) signaling. It is associated with focal *SMARCB1* alterations: point mutations and deletions. Group 2A/ATRT-TYR exhibits a mesenchymal/hindbrain (*OTX2, ZIC2/5*) and melanosomal (*TYR, MITF, DCT*) expression signature and is associated with both focal and broad alterations of *SMARCB1*. Group 2B/ATRT-MYC also has a mesenchymal signature, with upregulation of *MYC* and *HOXA/B/C* lineage genes. It is associated with broad deletions encompassing *SMARCB1*. Both Group 2A/ATRT-TYR and Group 2B/ATRT-MYC are characterized by high BMP signaling. The identification of subgroups with characteristic signaling pathways opens the door for further development of targeted agents. These will be crucial for the next generation of clinical trials as current therapies are approaching maximum tolerated intensities.

4. ETMR/*C19MC*-altered tumors

The histological entity known as embryonal tumor with abundant neuropil and true rosettes (ETANTR) was first described as a type of highly aggressive PNET affecting mainly younger children [91]. However, subsequent molecular studies revealed that ETANTR and a subset of sPNET, specifically ependymoblastoma (EPB) or medulloepithelioma (MEP), had recurrent amplifications of *C19MC*, an embryonic stem cell-enriched miRNA cluster located on chr 19q13.42 [9, 92, 93, 94]. On histology, multilayered pseudostratified rosettes are frequently observed. However, 20-25% of cases have no obvious rosette or neuropils, instead exhibiting variable differentiation or bland morphology. Reflecting these studies, any EBT with the *C19MC* amplification, regardless of histopathological features, is now classified as a C19MC-altered tumor/ETMR [5]. High expression of pluripotency genes *LIN28*/*LIN28B* is also seen [93], but is not specific to ETMR, as it is seen in 25% of ATRTs and 20% of high-grade gliomas (HGGs).

ETMRs share a distinct, highly lethal profile, with five-year overall survival estimated at <10% despite intensive multimodal therapy involving high-dose chemotherapy with autologous stem cell rescue [72, 93, 94]. They mainly arise in children under age 4 years (median 2.9 years) and more often in females. 65% of cases are localized at diagnosis but lower stage does not appear to confer a better outcome. Three-quarter of cases arise in the cerebral hemisphere. However, with more widespread use of FISH analysis for *C19MC*, these tumors have been identified in the cerebellum, brainstem, pre-sacral space, and pineal region, where they have previously been diagnosed as MB, HGG, or PB, respectively [93].

Exome sequencing studies have not demonstrated any other recurrent alterations among these tumors, suggesting the *C19MC* amplicon is indeed the major oncogenic driver [72, 95]. RNA sequencing studies have revealed recurrent gene fusions of *C19MC* to *TTYH1*, a chloride binding protein

with restricted expression to early embryogenesis, leading to high *C19MC* miRNA expression have been identified in both tumors with *C19MC* gains/amplifications and those without C19MC alterations [95]. This driver fusion may explain how EBTs with and without *C19MC* gains/amplification can still share methylation and expression profiles. Indeed, the fusion was recently implicated by Sin-Chan *et al.* in creating a highly oncogenic, feed-forward *C19MC-LIN28A-MYCN* circuit that entraps ETMRs in a primitive, highly proliferative embryonal phenotype [96]. Importantly, this circuit could be abrogated *in vitro* with MYC-targeting BET/bromodomain inhibitors, opening the possibility for further pre-clinical studies.

Improving the dismal outcome for these tumors will require several approaches. Its rarity necessitates continued international collaboration to collect tissue samples and clinical data for retrospective analyses. Discovery and validation of therapeutic targets is hampered by the paucity of available cell lines: only three are currently available and remain difficult to propagate. Thus, generation of new cell lines from freshly resected tissue, as well as a representative mouse model is a priority for future preclinical studies.

5. Pineoblastoma

PB is a rare but aggressive EBT that arises in the pineal gland, the intracranial neuroendocrine organ that secretes melatonin for the regulation of sleep-wake cycles. Reported in less than 1% of pediatric brain tumors [1], it accounts for a third of tumors that arise from the pineal parenchyma [97]. As other EBTs may also present in the pineal region and share overlapping histology, specific markers to exclude these entities should be performed (loss of *SMARCB1*/INI1 or *SMARCA4*/BRG1 for ATRT, and *C19MC* amplification +/- *LIN28* expression for ETMR/*C19MC*-altered tumors). Other lesions

arising in the pineal region include lower grade pineal lesions (pineocytoma, pineal parenchymal tumors of intermediate differentiation/PPTID, and papillary tumor of the pineal region/PTPR), germ cell tumors, and HGGs.

Historically, PB has been treated alongside sPNET using high-risk MB protocols, complicating PB-specific survival analyses. Optimal therapy regimens are not established, although prospective consortia studies showed improved survival for older children with intensified multi-modal approaches [98, 99, 100] often consisting of upfront resection, craniospinal irradiation with local boost, and multiple cycles of high-dose chemotherapy with autologous stem cell rescue. A recent large clinical retrospective study identified the lack of upfront radiotherapy, age <4 years, and metastatic disease as negative prognostic factors, while high-dose chemotherapy (HDC) was not associated with outcome [101]. Overall long-term survival rates have been reported to be approximately 50-65%, with younger patients (age <5 years) faring much worse (15-40%) [102, 103]. However, more favourable outcomes for patients ≥3 years with no metastasis or bulky residual disease (i.e. average-risk) treated with SJMB03 or similar regimens were recently reported (5-year PFS and OS both 100%) [104]. Reassuringly, these patients received reduced-dose CSI of 23.4 Gy with focal boost, followed by four cycles of high-dose chemotherapy (cisplatin/cyclophosphamide/vincristine) with autologous stem cell rescue. In contrast, high-risk patients, who instead received increased-dose CSI of 36 Gy still did poorly (5-year PFS/OS 56.5%/60.3%).

The rarity of PB has impacted discovery of specific markers for it. PB is associated with germline mutations of *RB1*, where it presents in association with retinoblastoma (termed trilateral retinoblastoma) [105], and *DICER1* [106, 107], a cancer predisposition syndrome associated with pleuropulmonary blastoma, cystic nephroma, and other tumors of the ovary and thyroid. *DICER1* encodes an endonuclease involved in the generation of miRNA, a key cellular mechanism used to

regulate gene expression, particularly in embryonal development [108, 109]. Related to this, a recent molecular analysis of 23 PB samples by Snuderl et al. reported recurrent deletions of *DROSHA*, another endonuclease also involved in miRNA biogenesis, in a quarter of cases [110]. Although disrupted miRNA biogenesis has been seen in other cancers [108], whether it is a driver in PB is yet to be confirmed. Alterations of chr 1, and complete or partial loss of chr 9, 13, 16, and 22 have also been observed among limited numbers of sporadic cases [111, 112, 113, 114]. No recurrent mutations involving *TP53* or *CDKN1A* have been reported, though overexpression of *UBE2C*, *SOX4*, *TERT*, and *TEP1* have been described [115, 116, 117]. Similarly, overexpression of genes involved in proliferation (*PRAME*, *CD24*, *POU4F2*, *HOXD13*) have been reported in PB [117].

Recently, independent analyses of much larger collections of PB by three research groups have segregated this tumor into as many as five subgroups with distinct molecular and clinical features [104, 118, 119]. While a combined analysis of datasets remains pending, two subgroups have recurrent loss-of-function alterations of miRNA biogenesis genes (*DICER1*, *DROSHA*, *DGCR8*), affect older children and adolescents [104, 118, 119], and are associated with an OS of 70-100% [118]. Two high-risk (OS 29-38%) [118] infant subgroups have either recurrent inactivation of the *RB1* tumor suppressor [104, 118, 119] with copy number gain/amplification of the oncogenic microRNA cluster *miR-17/92* [118], or gain/amplification of the *MYC* oncogene [118, 119]. A separate subgroup appears to overlap with lower-grade PPTIDs [104, 118, 119], with hotspot mutations in *KBTBD4* [118], a CUL3 ubiquitin ligase adaptor involved in protein degradation, but otherwise few chromosomal copy number changes. It is associated with patients of adolescent to adult age and an intermediate prognosis (80% OS) [118].

6. Other embryonal brain tumors

Historically, the diagnosis of CNS-PNET or sPNET was generally applied to all EBTs that presented in the supratentorial compartment. A notable exception to this applied to PB (though itself occasionally labelled as a pineal region PNET). The recent discovery of specific molecular markers for now separate entities (ATRT and C19MC-altered tumors/ETMR) formerly under the umbrella of CNS-PNET/sPNET have since left a heterogenous group of tumors without robust identifying features. The uncertain nature of this group is reflected in the definitions of medulloepithelioma (without C19MC-alterations), CNS neuroblastoma, CNS ganglioneuroblastoma, and CNS embryonal tumor, NOS in the 2016 WHO classification [5]. Given our evolving understanding of these entities, the use of retrospective data to interpret this group's clinical features and prognosis remains challenging. With this caveat, historical reports of non-pineal CNS-PNETs depict an aggressive disease primarily affecting young children [6]. Among 37 non-infant (age >3 years) cases of institutionally diagnosed non-pineal CNS-PNETs treated in CCG trial 99701, five-year PFS/OS was 39%/44%.

However, global expression or epigenetic profiling may help delineate this heterogenous group and allow more accurate prognostication. In COG trial ACNS0332, the use of global DNA methylation profiling to establish a molecular tumor type revealed that among 31 patients with locally diagnosed non-pineal CNS-PNET, a striking 22 (71%) cases represented other entities not intended for trial inclusion, including 18 (58%) cases of HGG [98], suggesting that a significant proportion of historic non-pineal CNS-PNET may be misdiagnosed HGG or other entities [103, 120, 121]. Patients with a molecular diagnosis of CNS-PNET or PB also had far better outcome (5-year EFS/OS: 62.8%/78.5%) than those with HGG (5-year EFS/OS: 5.6%/12.0%), who despite more intensive and potentially debilitating therapy, did no better than historical trends.

The increasing heterogeneity in this umbrella entity and recognition of candidate molecular signatures was shown in two previous molecular studies. Among 254 institutionally diagnosed CNS-

PNETs analyzed by Picard *et al*., nearly half (44%) were excluded after central pathology review, including cases that were reclassified at ATRT, ependymoma, and GBMs [72]. Of the remaining cases, transcriptional profiling and copy number analysis revealed three molecular groups. Group 1 consisted of C19MC-altered tumors with high *LIN28* expression. Groups 2 and 3 lacked recurrent copy number alterations but were enriched for oligoneural (*OLIG1/2*, *BCAN*, *SOX8/10*) and mesenchymal differentiation (*COL1A2*, *COL5A*, *FOXJ1*, *MSX1*) genes, respectively. Indeed, group 2 were associated with nuclear *OLIG2* immunostaining, suggesting that some of these tumors were malignant gliomas. Median survival in groups 1-3 in those age <4 years were 1.0, 0.8, and 2.7 years, while those >4 years were 0.5, 1.8 and 4.8 years. A later study by Sturm *et al.* analyzed 323 institutionally diagnosed CNS-PNET tumors using DNA methylation profiling [122]. Similarly, 196 (61%) tumors were re-classified as other tumor entities based on clustering analyses. Among the remaining cases, 77 (24%) formed four distinct clusters separate from other recognized tumors, which they proposed as new entities: CNS neuroblastoma with *FOXR2* activation (CNS-NB-FOXR2 or embryonal tumor with FOXR2 activation), CNS high grade neuroepithelial tumor with *MN1* alteration (CNS-HGNET-MN1) or *BCOR* alteration (CNS-HGNET-BCOR or embryonal tumor with BCOR alteration), and CNS-Ewing's family of tumors with *CIC* gene fusions (CNS-EFT-CIC). The CNS-NB-FOXR2 group closely mirrors the Group 2 CNS-PNETs described by Picard et al. [72, 122, 123]. While *FOXR2* fusion events were observed in 3/6 samples, unpublished data by Ho *et al.* have found similar FOXR2 fusions in a subset of HGG with *MYCN* activation [124]. The subgroup CNS-HGNET-MN1 largely corresponds to tumors with a histological diagnosis of astroblastoma, a less aggressive glial tumor. CNS-HGNET-BCOR and CNS-EFT-CIC tumors share gene alterations previously seen in extra-cranial malignant sarcomas and may represent local variants of the same entity [125, 126, 127]. Indeed, subsequent DNA methylation-based clustering show that CNS-EFT-CIC tumors cluster together with their extra-cranial counterparts [124].

The prognostic implications of these four subgroups are very limited by its small numbers, with the most data available for CNS-HGNET-BCOR and CNS-NB-FOXR2. The former appear to have a dismal outcome (3-year PFS/OS of ~40%/0%) [122], although other groups have reported some long-term survivors [128]. The latter appears to confer an intermediate prognosis (3-year EFS: ~ 65%)[122].

Further analyses with larger datasets of these rare tumors is needed to confirm these proposed groups and/or identify other robust markers that carry implications to treatment and outcome. Similarly, animal models will be needed to validate potential therapies that target specific alterations. For example, a recent zebrafish model of oligo-neural/CNS-NB-FOXR2 tumors was generated, which identified MEK inhibitor AZD6244 (Selumetinib) as a candidate drug for this proposed subgroup [123].

7. Conclusion

EBTs are a heterogenous group of aggressive cancers affecting primarily young children. While historically defined by location and histology, advances in our understanding of their biology have led to the discovery of newer EBT entities and specific diagnostic markers, and subgrouping with clinicopathologic significance. Therapy for EBTs remain very challenging. For those tumors with more favourable survival rates, significant lifelong disability and neurocognitive impairment are commonly observed. Overall outcomes among infants and children <3-4 years of age remain poor due to a combination of aggressive tumor biology and inability to use radiotherapy. These outcomes are unlikely to improve until novel upfront approaches, informed by rigorous preclinical studies, are implemented.

8. Expert opinion

The robust subgrouping of MB has created a new framework for prognostication and revealed additional biological heterogeneity that further informs outcome and opens avenues to targetable driver pathways [12]. Meanwhile, the discovery of specific molecular markers for ATRT and ETMR/C19MC-altered tumors has permitted these high-risk and aggressive malignancies to be distinguished from other EBTs when previously they were either not recognized or challenging to diagnose [6]. However, the rarity of non-MB EBTs has continued to limit the study of these rarer tumors. It has also challenged the creation of dedicated prospective clinical trials for these biological and clinically distinct entities. The continued collaboration and collection of rare EBTs, such as through the Rare Brain Tumor Consortium [129] and the development of representative cell lines and *in vivo* models will be critical to characterizing these entities as well as the discovery of their oncogenic mechanisms. These pathways and their drug targets may then be exploited in basket trials. Eligibility for this new type of prospective clinical trial is based on a common target rather than histology. Targeted therapies may fulfill a desperate need to improve both survival and reduce treatment-related morbidity. Indeed, outcomes for high-risk EBTs remain poor despite the use of intensive multimodal regimens already at the limit of patient tolerability. The new targeted agents will likely need to be employed upfront in combination with other targeted agents and/or conventional chemotherapies to prevent emergence of resistant clones of the primary tumor. The exact duration of targeted therapy and high cost also remain important concerns that will need to be addressed.

Global DNA methylation profiling has provided a powerful tool for researchers to elucidate the biology of many different cancer types. As demonstrated in COG trial ACNS0332, methylation profiling in CNS tumors may be an important complement (but not replacement) for conventional histopathology [98], particularly for determining eligibility for clinical trials and for diagnostic purposes at smaller centres that encounter fewer cases. However, widespread implementation will pose some challenges. It

would likely require the timely transfer of precious tumor material to a central processing institution. The receiving facility would require both laboratory and bioinformatic expertise to carefully handle samples and ultimately determine a reliable, molecular-based diagnosis using robust classifiers. These steps require significant start-up and on-going costs, which may become a barrier in resource-poor settings. Ongoing work to characterize the expression and mutation profile of methylation-defined entities may provide less costly diagnostic alternatives to DNA methylation profiling.

Other current studies are expected to reveal further insights into the biology of EBTs. For example, single-cell RNA sequencing, where the transcriptome of a tissue sample is sequenced at a single cell level, rather than bulk, has become an important tool to examine small sub-populations of tumors in detail. Uncovering this complex intra-tumoral heterogeneity has recently advanced our understanding of cell-of-origin and tumor-initiating cells in MB [130, 131, 132], which may provide new developmental pathways to target therapeutically. The technology has also helped characterize tumor-associated non-malignant cells, such as those of the immune system, in several common adult cancers [133, 134, 135], and may prove critical in understanding cancer progression and immunotherapy response.

Funding

This paper was not funded.

Declaration of interest

Bryan Li is funded by the Sick Kids Garron Family Cancer Centre Fellowship. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewers Disclosure

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

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