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REVIEW OPEN ACCESS

Infant Embryonal CNS Tumors: Molecular Insights and Treatment Considerations for Contemporary Pediatric Neuro-Oncology

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ABSTRACT

Background: Embryonal tumors comprise the majority of malignant central nervous system (CNS) neoplasms diagnosed in children under 3 years of age. Compared with their counterparts in older children, these tumors exhibit distinct molecular biology and a more aggressive clinical phenotype, while their management is complicated by the heightened vulnerability of the developing brain to acute toxicity and long-term sequelae from surgery, chemotherapy, and radiotherapy.

Objectives: To summarize the contemporary understanding of infant CNS embryonal tumors, including molecular classification, treatment paradigms, and emerging therapeutic strategies, and to outline a framework for molecularly driven, risk-adapted management.

Design and Methods: We performed a narrative review of published cooperative-group, consortium, and single-institution trials in medulloblastoma, atypical teratoid/rhabdoid tumor (AT/RT), embryonal tumor with multilayered rosettes (ETMR), pineoblastoma, and other infant CNS embryonal entities, integrating findings with the 2021 WHO Classification of CNS Tumors and recent DNA methylation- and next-generation sequencing-based subclassifications.

Results: Molecular profiling has reshaped diagnosis and risk stratification across all infant embryonal entities, identifying clinically actionable subgroups (e.g., SHH-I/II in medulloblastoma; AT/RT-TYR, -SHH, -MYC; ETMR with C19MC or *DICER1* alterations; pineoblastoma molecular subgroups). Multimodal regimens that delay or avoid craniospinal irradiation have achieved durable survival in favorable-risk SHH-activated medulloblastoma, while outcomes remain poor for Group 3 medulloblastoma, ETMR, pineoblastoma, and metastatic AT/RT. Investigational targeted and immunotherapeutic strategies, intraventricular methotrexate, proton-beam radiotherapy, and cerebrospinal fluid liquid biopsy are increasingly being incorporated into risk-adapted approaches.

Conclusion: Molecularly driven, risk-adapted clinical trials and international collaborative registries are essential to advance care for infants with CNS embryonal tumors, with the dual goals of improving survival and reducing treatment-related neurodevelopmental morbidity.

1 | Introduction

Central nervous system (CNS) tumors are the most common solid neoplasm in children; however, cases presenting in children under 3 years of age constitute a minority [1–3]. Within this age group, infant CNS tumors represent a distinct and rare subset that poses significant diagnostic and therapeutic challenges. Among these, embryonal tumors comprise the majority of malignant cases [1, 4]. Biologically, these tumors exhibit a more aggressive phenotype than their counterparts in older children, contributing to poorer outcomes.

Management of infantile CNS embryonal tumors is further complicated by the heightened risk of acute toxicity and long-term sequelae associated with conventional treatments such as surgery, chemotherapy, and radiation therapy (RT). While recent advances in tumor biology have provided insights into their molecular underpinnings, therapeutic innovation has lagged; however, ongoing research initiatives aim to bridge this gap [4, 5].

Recent molecular advances, including next-generation sequencing (NGS) and DNA methylation profiling, have enabled more precise tumor classification and risk stratification [5, 6]. In this review, we summarize the current understanding of infant CNS embryonal tumors with a focus on molecular characterization and the evolving treatment landscape. This is a narrative review. We searched PubMed/MEDLINE for English-language articles published through 2025, using combinations of terms including "infant," "medulloblastoma," "atypical teratoid/rhabdoid tumor," "embryonal tumor with multilayered rosettes," "pineoblastoma," "CNS embryonal tumor," "methylation profiling," and "radiation-sparing therapy." We prioritized cooperative-group, consortium, and single-institution clinical trials, the 2021 WHO Classification of CNS Tumors, and recent methylation- and sequencing-based subclassification studies, supplemented by review of references within selected articles. Study selection was based on relevance to infant and young-childhood disease rather than a formal systematic-review protocol.

2 | Diagnosis

Historically, the diagnosis of CNS embryonal tumors relied primarily on neuroimaging and histopathological assessment [7]. However, molecular profiling has now become an integral component of the diagnostic workflow. The previously used umbrella term, "CNS primitive neuroectodermal tumor (PNET)," has been replaced with the broader classification of CNS embryonal tumors. This transition reflects the integration of histologic features with molecular data to achieve greater diagnostic precision [5, 8]. The fifth edition of the World Health Organization (WHO) Classification of CNS Tumors (2021) formally incorporates these methodologies, establishing molecular characterization as a standard for tumor classification (Figure 1) [5].

Immunohistochemistry (IHC) remains a cornerstone of histopathologic evaluation, often serving as a surrogate for underlying molecular alterations in pediatric CNS tumors. However, certain genetic aberrations may not produce detectable protein-level changes, limiting the sensitivity of IHC in some contexts [9, 10]. In contrast, NGS panels enable comprehensive profiling of numerous genes simultaneously, identifying both single-nucleotide variants and gene fusions—alterations that are particularly prevalent in pediatric CNS neoplasms [11].

Additionally, DNA methylation profiling has emerged as a highly robust diagnostic tool. Although genome-wide methylation arrays interrogate hundreds of thousands of CpG sites, the CNS tumor classifier assigns tumors to defined methylation classes using a comparatively small subset of the most informative, class-discriminating CpG loci [5, 12]. While DNA methylation profiling is a powerful classification aid, methylation classes do not always correspond uniquely to individual tumor entities, and cases with overlapping histologic or molecular features can remain diagnostically ambiguous. For example, methylation-based classification can reliably distinguish medulloblastoma subgroups (e.g., Group 3 vs. Group 4) and has facilitated the recognition of newly defined embryonal tumor entities driven by FOXR2, BCOR, or CIC alterations [4, 5].

3 | Surgical Considerations in Infant Embryonal CNS Tumors

Surgical resection remains a cornerstone of management for infant embryonal CNS tumors; however, it is uniquely challenging in this population. Infants, particularly those younger than 1 year of age, have limited circulating blood volume, increasing the risk of intraoperative hemodynamic instability with even modest blood loss [13]. Careful preoperative planning, availability of blood products, and coordination with pediatric anesthesia teams are essential to mitigate these risks.

Hydrocephalus is frequently present at diagnosis, particularly in posterior fossa tumors, and often requires temporizing measures such as external ventricular drainage or ventriculoperitoneal shunting prior to or following tumor resection.

The extent of resection remains an important prognostic factor in several embryonal tumor types, particularly medulloblastoma; however, this must be balanced against the risk of neurologic morbidity [14]. Tumor location plays a critical role in surgical decision-making, as lesions involving eloquent brain regions or deep midline structures carry a higher risk of postoperative deficits.

Importantly, infants demonstrate greater neuroplasticity than older children, allowing for some degree of functional recovery following surgical injury. Nevertheless, aggressive resection should not come at the expense of significant neurologic compromise. In select cases, staged resection or second-look surgery may be considered to optimize extent of resection while minimizing morbidity.

Molecular and histologic subtype should also inform surgical aggressiveness. Sonic hedgehog (SHH)-activated

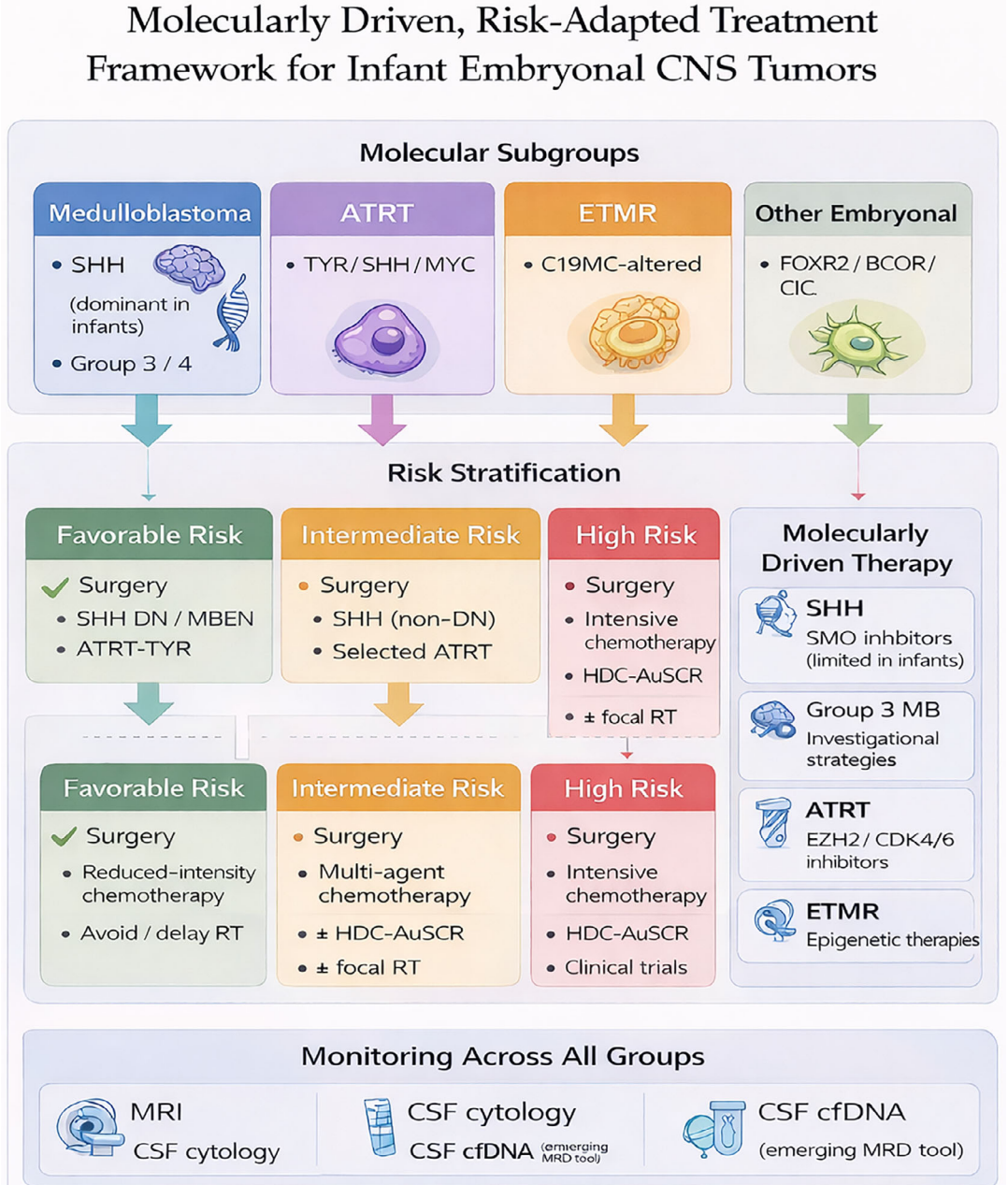

FIGURE 1 | Molecularly driven, risk-adapted treatment framework for infant embryonal central nervous system (CNS) tumors. Infant embryonal CNS tumors are increasingly managed using integrated molecular and clinical risk stratification. Major tumor types including medulloblastoma, atypical teratoid/rhabdoid tumor (AT/RT), embryonal tumor with multilayered rosettes (ETMR), and other embryonal tumors are first defined by molecular profiling. These subgroups are subsequently stratified into favorable-, intermediate-, and high-risk categories based on molecular features, extent of resection, and metastatic status. Treatment strategies are then tailored accordingly, with de-escalation approaches for favorable-risk disease to minimize long-term toxicity, and intensification strategies for high-risk tumors incorporating high-dose chemotherapy, radiotherapy, and clinical trial enrollment. Emerging molecularly targeted therapies and cerebrospinal fluid (CSF)-based liquid biopsy approaches are expected to further refine risk-adapted treatment and longitudinal disease monitoring. *Image created with Biorender*.

medulloblastomas with nodular desmoplastic or extensively nodular (MBEN) histology are exquisitely chemosensitive and can be cured with chemotherapy-based regimens alone; in this setting, attempting gross total resection (GTR) at the expense of neurologic morbidity is not warranted, and a more conservative, function-preserving approach is appropriate [14, 15]. Recognizing these favorable-risk features intraoperatively, or anticipating them from imaging and pathology, can therefore guide a less aggressive resection.

Given the rarity of many embryonal tumor types outside of medulloblastoma, these surgical principles are broadly applicable across entities and emphasize a tailored, multidisciplinary approach.

4 | Radiotherapy Considerations in Infants

Radiotherapy (RT) plays a critical role in the management of embryonal CNS tumors but is approached with caution in infants due to the profound risk of neurocognitive, endocrine, and developmental toxicity [16, 17]. As such, most contemporary treatment strategies aim to delay, reduce, or avoid RT in children younger than 3 years of age through the use of intensive chemotherapy regimens.

When RT is required, the timing and modality are carefully considered. Focal radiotherapy may be introduced in select cases, particularly in children approaching 3 years of age or in those with residual or progressive disease. Craniospinal irradiation (CSI), while highly effective for disease control in embryonal tumors such as medulloblastoma, is generally deferred in infants and reserved for relapse or refractory disease due to its substantial long-term toxicity profile. Emerging data suggest that carefully selected patients, including those with favorable-risk, nonmetastatic molecular profiles, or older infants approaching 3 years of age with localized residual disease may benefit from reduced-dose or delayed CSI strategies; however, this remains an area of ongoing investigation [18].

Proton beam therapy has increasingly become a preferred modality in pediatric neuro-oncology, particularly in infants and young children. Compared to conventional photon radiation, proton therapy offers superior dose conformality with reduced exit dose, thereby minimizing radiation exposure to surrounding normal tissues [19]. This is particularly relevant in the developing brain, where reductions in off-target radiation may translate into improved neurocognitive and endocrine outcomes [20].

While long-term comparative data remain limited, early clinical experience supports the use of proton therapy as a means to reduce treatment-related morbidity without compromising oncologic efficacy [21]. As access to proton therapy expands, it is likely to play an increasingly central role in the management of infant CNS tumors.

5 | Tumor Types

5.1 | Medulloblastoma

Medulloblastoma (MB) is the most common embryonal brain tumor in children, representing approximately 12% of all pediatric CNS tumors and about 9.2% of brain tumors in children under 4 years old [22]. Medulloblastoma arises in the posterior fossa; however, its cell of origin varies by molecular subgroup, with SHH tumors typically arising from granule neuron precursors in the cerebellar hemispheres, while WNT tumors originate from the dorsal brainstem. Group 3 and Group 4 tumors are thought to arise from distinct progenitor populations within the cerebellum [23, 24]. Historically, clinical risk stratification has been based on factors such as the presence of anaplastic histology, extent of surgical resection, and metastatic disease at diagnosis [25]. Advances in molecular profiling over the past decade have revealed MB as a heterogeneous disease entity with distinct biologic subgroups, additionally contributing to risk stratification [4, 26].

5.1.1 | Molecular Subgroups and Histologic Correlation

MB are currently classified into four major molecular subgroups: WNT-activated, SHH-activated, and the non-WNT/non-SHH subgroups Group 3 and Group 4 [25, 26]. In children ≤3 years of age, SHH-activated tumors predominate, accounting for approximately 50%–60% of cases, while non-WNT/non-SHH Group 3 tumors comprise a substantial proportion (~30%–40%) and Group 4 tumors are comparatively uncommon in this age group [27]. In infants under 1 year of age, SHH-activated tumors involve over 90% of cases and typically lack *TP53* mutations [28, 29]. These molecular classifications strongly correlate with histologic subtypes: classic, desmoplastic/nodular (DN), medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic (LCA). DN and MBEN histologies are almost exclusively associated with SHH-activated MB, particularly subtypes SHH-I and SHH-II, and LCA histology is mostly found in those with Group 3 disease [30].

5.1.2 | Prognostic and Genetic Features

Molecular and histologic subtypes provide critical prognostic information and influence therapeutic strategies. Infants with SHH-activated MB generally have superior outcomes compared to those with Group 3 disease [27]. MBs are linked to germline mutations in genes such as *PTCH1, SUFU, GPR161, BRCA2, PALB2, ELP1*, and *TP53* [31]. In infants and young children (<3 years old) with SHH-activated MB, germline *PTCH1* and *SUFU* mutations are most common, with *SUFU* mutations frequently associated with nevoid basal cell carcinoma syndrome (i.e., Gorlin syndrome) [32, 33]. Childhood SHH-activated MB may also harbor germline *TP53* mutations, indicative of Li–Fraumeni syndrome, often co-occurring with somatic amplifications of *GLI2* and *MYCN* [31, 34]. These molecular alterations, along with chromosome 14q loss, portend a poor prognosis in SHH-activated tumors [35, 36]. Similarly, Group 3 tumors with *MYCN* amplification or isochromosome 17q represent high-risk disease [25, 37].

5.1.3 | Current and Historical Treatment Strategies

Historically, adjuvant chemotherapy has been the cornerstone of treatment for infant MB, with the primary objective of delaying or avoiding craniospinal irradiation (CSI) due to its well-documented neurocognitive, endocrine, and psychosocial consequences in the developing brain. Early regimens focused on maximizing systemic and intraventricular drug delivery, often incorporating high-dose chemotherapy with autologous stem cell rescue (HDC-AuSCR) and intraventricular methotrexate (IVT-MTX) (Table 1).

The HeadStart series of clinical trials (I–III) represented the first major North American effort to deliver radiation-sparing therapy to infants and very young children with MB [38, 39]. These protocols used multiple cycles of intensive induction chemotherapy with cisplatin, cyclophosphamide, vincristine, and etoposide followed by a single consolidation cycle of high-dose carboplatin, thiotepa, and etoposide with AuSCR. In HeadStart I and II, nonmetastatic patients achieved 5-year event-free survival

TABLE 1 | Medulloblastoma.

Study/Protocol	Treatment approach	5-year EFS	5-year OS	Key findings
CCG 99703	3 cycles intensive induction → HDC-AuSCR	70% overall; 86% SHH	—	Excellent outcomes in SHH-activated MB; established prognostic value of molecular subgrouping
COG ACNS0334	CCG 99703 backbone + high-dose methotrexate	Group 3: ~70% with HD-MTX vs. ~33% without; SHH: excellent EFS regardless of HD-MTX	OS not significantly different between arms; SHH tumors demonstrated uniformly high OS	Improved Group 3 response rates (63% vs. 30%); no OS benefit in SHH-activated MB
HeadStart I and II	Induction chemo + single AuSCR	52% overall; DN 67%; classic 42%	70% overall; DN 78%; classic 67%	DN histology best survival; gross total resection improved outcomes; residual disease worsened prognosis; TRM 14%
HeadStart III	5 cycles induction chemo → AuSCR	46% overall; DN 89%; classic/LC/A 26%–38%	62% overall; DN 89%; classic/LC/A 46%–53%	Outstanding DN survival, including some metastatic cases; TRM reduced to 2%; most survivors preserved neurocognition
HIT2000 (HIT-SKK)	Systemic + intraventricular methotrexate, no AuSCR	93% (SHH, nonmetastatic)	100% (SHH, nonmetastatic)	Exceptional SHH outcomes; poor survival in Group 3
COG ACNS1221	Systemic chemo without intraventricular methotrexate	—	—	Omission of IVT-MTX led to worse outcomes; trial closed early
SJYC07	Risk-adapted systemic chemotherapy alone	—	—	Suboptimal survival in high-risk subgroups

Abbreviations: CCG, Children's Cancer Group; COG, Children's Oncology Group; DN, desmoplastic/nodular; EFS, event-free survival; HDC-AuSCR, high-dose chemotherapy with autologous stem cell rescue; IVT-MTX, intraventricular methotrexate; OS, overall survival; SHH, sonic hedgehog.

(EFS) and overall survival (OS) rates of approximately 52% and 70%, respectively. Desmoplastic/Nodular (DN) histology was associated with superior outcomes, with EFS of 67% and OS of 78%, compared to classic histology, where EFS and OS were 42% and 67%, respectively. GTR correlated with improved survival, whereas residual disease was associated with worse outcomes. On HeadStart II, metastatic patients who received high-dose methotrexate (12 g/m^2) during each cycle of induction, as listed above, with no change in the consolidation regimen, resulted in a 5-year EFS and OS of 45% ± 11% and 53% ± 12%, respectively. HeadStart III, a prospective large Phase 2 trial, refined this approach with five induction cycles followed by consolidation with HDC-AuSCR. Among 92 MB patients, the 5-year EFS and OS for nonmetastatic and metastatic patients were 61% ± 8% and 77% ± 7% and 35% ± 7% and 52% ± 7%, respectively. Outcomes were particularly favorable in DN histology, with both EFS and OS at 89%, including in some metastatic cases, whereas classical and LCA subtypes had significantly lower survival (5-year EFS 26% and 38% and OS of 53% and 46% for classic and LCA cases, respectively). Notably, irradiation-free EFS was 78% for DN and 21% for non-DN MB patients, and treatment-related mortality decreased from 14% in HeadStart I/II to just 2% in HeadStart III, reflecting improved supportive care protocols. Long-term follow-up demonstrated preserved average to low-average neurocognitive function in most survivors, though some deficits in processing speed and adaptive functioning were observed. HeadStart IV further tailored therapy based on molecular subtype, age, and response (NCT02875314). All patients received either three or five cycles of induction as per HeadStart II based on disease response after Cycle 3. Low-risk patients (SHH-activated or WNT-activated) received only one cycle of HDC-AuSCR, while non-SHH/non-WNT subgroups were randomized to receive one versus three tandem cycles of HDC-AuSCR. Preliminary results showed that localized SHH-activated MB had superior outcomes even with only three cycles of induction and a single cycle of HDC-AuSCR consolidation (EFS 96.4% and 3-year OS 100%). Accrual is completed for this study, and final results are not publicly available at the time of this publication.

North American Cooperative Group protocol, Children's Cancer Group (CCG) 99703, employed three cycles of intensive induction chemotherapy followed by consolidation with HDC-AuSCR. This

approach achieved encouraging long-term outcomes, with 5-year progression-free survival (PFS) rates of 70% overall and 86% in SHH-activated MB, highlighting the prognostic importance of molecular subgrouping [40]. Building upon this, the Children's Oncology Group (COG) ACNS0334 trial investigated the addition of high-dose methotrexate to the induction phase. While methotrexate (MTX) significantly improved response rates in Group 3 patients (63% vs. 30%), it did not impact survival in SHH-activated cases, which maintained near 100% survival irrespective of MTX use [41–43].

In Europe, the HIT-SKK regimen was designed to avoid or defer CSI in young children (<4 years old) with nonmetastatic MB. It incorporated systemic chemotherapy (vincristine, cyclophosphamide, etoposide, carboplatin, and high-dose MTX) with serial IVT-MTX via an Ommaya reservoir without HDC-AuSCR. In the HIT2000 study, nonmetastatic SHH-activated MB patients under 4 years achieved outstanding 5-year PFS and OS rates of 93% and 100%, respectively, without RT [28]. However, outcomes for non-SHH subtypes, particularly Group 3, remained poor with a 5-year PFS of 37% and a 5-year OS of 62%. Neurocognitive outcomes were worse for patients with metastatic disease, classic/LCA histology, and/or patients exposed to CSI. Processing speed and psychomotor deficits were still observed in survivors who received chemotherapy with IVT-MTX alone, but significantly better than those who received CSI. Of note, leukoencephalopathy (mostly Grade 1 and 2) was observed in approximately 57% of patients secondary to IVT-MTX, but was not independently associated with worse neurocognitive outcomes.

The importance of intraventricular therapy in radiation-sparing strategies was further highlighted by COG ACNS1221, which evaluated an intensive systemic chemotherapy backbone similar to HIT-SKK, but omitted IVT-MTX in young children with newly diagnosed medulloblastoma. This trial was closed earlier due to inferior EFS compared with historical controls, particularly among non-SHH molecular subgroups [30]. These findings suggest that systemic chemotherapy alone may be insufficient for durable CNS disease control in the absence of radiotherapy or other consolidative therapies.

The SJYC07 Phase II study explored risk-adapted treatment in three groups (low-risk, intermediate-risk, and high-risk) based on molecular stratification, metastatic status, and extent of resection. Multi-agent induction was given to all patients (MTX, vincristine, cisplatin, and cyclophosphamide plus vinblastine in the high-risk group), followed by consolidation based on risk group: the low-risk group received two cycles of cyclophosphamide, carboplatin, and etoposide, intermediate-risk patients received focal RT, and high-risk patients received topotecan and cyclophosphamide-based chemotherapy. Maintenance therapy was then given with cyclophosphamide, topotecan, and erlotinib. Suboptimal survival was noted for all groups, with a 5-year EFS for the low-risk group of 55.3%, intermediate-risk group of 24.6%, and high-risk group of 16.7%. Similar to prior studies, outcomes for the SHH-activated subgroup were significantly better than Group 3 or 4, with 5-year PFS 51.5% versus 8.3% and 13.3%, respectively [44].

Collectively, these data underscore the biological heterogeneity of infant MB and the need for molecularly driven therapy [45].

Taken together, these trials reveal both consensus and unresolved controversy. The clearest area of agreement is that for infant SHH-activated medulloblastoma with DN/MBEN histology, craniospinal irradiation can be safely deferred or avoided when intensive chemotherapy is combined with either intraventricular methotrexate (HIT-SKK) or high-dose chemotherapy with autologous stem cell rescue (HeadStart, CCG 99703). The corollary, established by ACNS1221 and SJYC07, is that omitting these local-control or consolidation elements yields inferior outcomes even in SHH disease, underscoring that conventional systemic chemotherapy alone is insufficient. Persistent areas of disagreement and uncertainty include the optimal consolidation strategy (intraventricular methotrexate vs. high-dose chemotherapy), the management of SHH-I versus SHH-II subtypes, and the near-uniformly poor outcomes of Group 3 disease, for which no current radiation-sparing approach is adequate. Cross-trial comparison is further complicated by differing age cut-offs, largely post hoc molecular reclassification, heterogeneous use of intraventricular methotrexate and high-dose chemotherapy, and varying endpoints (EFS vs. PFS), all of which warrant caution when interpreting the survival figures summarized in Table 1.

While these trials highlight that subgroups with DN/MBEN histology and SHH-activated can be cured with surgery and chemotherapy alone [15], CSI (sometimes in combination with surgery and chemotherapy) remains the mainstay of salvage treatment in cases of progressive and/or relapsed disease, especially in relapsed SHH-activated medulloblastoma, with over 50% of patients alive at 3 years post-relapse [46, 47].

SHH-activated medulloblastoma represents the predominant molecular subgroup in infants and is increasingly recognized as a biologically and clinically distinct entity. Recent studies have further stratified SHH tumors into subtypes (e.g., SHH-I and SHH-II), with emerging data suggesting differential therapeutic vulnerabilities [48].

Contemporary trials such as SJiMB21 (NCT05535166) are exploring risk-adapted approaches based on these distinctions, including de-escalation strategies for favorable-risk SHH-II tumors and incorporation of intraventricular methotrexate for SHH-I tumors while avoiding radiotherapy.

However, it is important to emphasize that most existing studies were not designed or powered to define outcomes based on molecular subtypes, and cohort sizes remain limited. As such, caution is warranted when extrapolating these findings into clinical practice, and treatment modifications should be pursued within the context of prospective clinical trials [28, 44] (Table 2).

5.1.4 | Emerging Investigational and Targeted Approaches

Smoothened (SMO) inhibitors, such as vismodegib, have been evaluated in SHH-activated MB, primarily as maintenance therapy in newly diagnosed patients (SJMB12) [49]. While initial responses were observed, resistance emerged rapidly, limiting long-term benefit. Similar findings were reported by the Pediatric Brain Tumor Consortium (PBTC) in recurrent SHH-activated MB

TABLE 2 | Ongoing and emerging clinical trials in infant embryonal CNS tumors.

Trial	Population	Design	Strategy	Primary endpoint
SJiMB21	Infant MB (SHH subtypes)	Risk-adapted	De-escalation (SHH-II), IVT-MTX (SHH-I), avoid RT	EFS/OS
NCI-2022-07099	Infant MB	Molecular stratification	Reduced intensity therapy	Survival, toxicity
SJATRT	AT/RT	Phase I/II	Alisertib ± chemo	Safety, response
PNOC031	Newly diagnosed ETMR	Prospective	Induction chemo + early focal RT	6-month PFS

Abbreviations: AT/RT, atypical teratoid/rhabdoid tumor; CNS, central nervous system; EFS, event-free survival; ETMR, embryonal tumor with multilayered rosettes; IVT-MTX, intraventricular methotrexate; OS, overall survival; PFS, progression-free survival; SHH, sonic hedgehog.

[50]. Immunotherapies including a measles oncolytic virus are also being studied for progressive/relapsed MB in children [51].

While SMO inhibitors such as vismodegib have demonstrated activity in SHH-activated medulloblastoma, their use in infants is contraindicated due to severe skeletal toxicity, including premature growth plate fusion and irreversible effects on bone development [52]. This limitation significantly restricts their applicability in this age group.

5.1.5 | Future Directions

Future clinical trials will incorporate molecular subtyping to guide risk-adapted therapy. These strategies are being operationalized by collaborative groups in concrete ways. De-escalation is being prospectively tested for favorable-risk SHH-II tumors (e.g., SJiMB21, NCT05535166), while intensification for high-risk disease, including the addition of intraventricular methotrexate for SHH-I tumors and incorporation of high-dose chemotherapy with autologous stem cell rescue for Group 3 and adverse-risk SHH tumors, is under active evaluation within COG and SIOPE/HIT-MED frameworks. Newer advances for disease monitoring may further refine therapy and improve outcomes in this heterogeneous disease.

5.2 | Atypical Teratoid/Rhabdoid Tumor

Atypical teratoid/rhabdoid tumors (AT/RT) are highly aggressive embryonal CNS tumors that predominantly affect infants and young children. They account for approximately 1%–2% of pediatric CNS tumors overall, but represent roughly 10% of CNS tumors diagnosed in children younger than 1 year of age [53–55]. Most cases occur before 3 years of age, with a peak incidence between birth and 2 years [53]. The majority of AT/RTs arise in the posterior fossa (~70%), although tumors can also originate in the supratentorial compartment, including the diencephalon, cerebrum, and midbrain [56].

5.2.1 | Pathology and Molecular Features

Histologically, AT/RTs are characterized by rhabdoid cells with eosinophilic cytoplasm and prominent nucleoli, coupled with loss of SMARCB1/INI1 protein expression by immunohistochemistry [57]. Molecularly, these tumors almost universally demonstrate biallelic inactivation of *SMARCB1* on chromosome 22, typically through mutation and deletion, with less than 5% of cases driven by *SMARCA4* alterations [58]. Based on DNA methylation profiling, SMARCB1-deficient AT/RTs can be subclassified into three biologically distinct groups: AT/RT-TYR, AT/RT-SHH, and AT/RT-MYC [59]. The AT/RT-TYR subgroup, frequently associated with infratentorial tumors, has been linked to comparatively better outcomes in infants, though this does not hold true across all clinical contexts [60]. Despite these insights, molecular stratification has yet to be integrated into routine therapeutic decision-making.

5.2.2 | Germline Predisposition and Surveillance

Up to 55% of AT/RT cases in infants harbor germline mutations in *SMARCB1* and, less commonly, *SMARCA4*, conferring a diagnosis of rhabdoid tumor predisposition syndrome (RTPS) [54]. RTPS type 1, driven by germline *SMARCB1* mutations, predisposes patients to CNS, renal, and extrarenal rhabdoid tumors, necessitating intensive surveillance with regular brain and abdominal imaging [61]. *SMARCA4* germline mutations, while rarer, are associated with worse outcomes when present in AT/RT compared to *SMARCB1*-driven disease [62]. Genetic counseling and family screening are essential for all patients with confirmed RTPS.

Although AT/RT most commonly presents as an isolated CNS tumor, synchronous CNS and extra-CNS involvement, though rare, has been documented. Reports of approximately 30 such cases reveal nearly universal *SMARCB1* germline alterations, with outcomes remaining dismal despite multimodal therapy [63].

5.2.3 | Current and Historical Treatment Approaches and Outcomes

AT/RT have been associated with dismal prognosis, particularly in children under 3 years of age, with historical 5-year OS rates approximating 25% [64]. Recent prospective and cooperative group trials have introduced intensified multimodal strategies that have modestly improved outcomes, though survival remains suboptimal and treatment-related toxicity substantial (Table 3).

The landmark COG ACNS0333 trial represented the first prospective cooperative group effort dedicated to AT/RT. This regimen

TABLE 3 | Atypical teratoid/rhabdoid tumor.

Study/Protocol	Treatment approach	5-year OS /EFS	Key findings
COG ACNS0333	Intensive induction chemotherapy + HDC-AuSCR + risk-adapted RT	4-year OS: 43%, EFS: 37%	First prospective cooperative group trial dedicated to AT/RT; demonstrated improved survival compared with historical cohorts, supporting multimodal intensification
DFCI regimen	Surgical resection + anthracycline-based chemo + intrathecal therapy + RT	2-year OS: 70%, EFS: 53%	Improved short-term survival, but associated with substantial Grade 3–4 toxicity; limited feasibility in very young children
CCG 9921	Platinum-based chemotherapy + deferred/salvage RT	5-year OS: 29%, EFS: 14%	Early-generation regimen without high-dose chemotherapy; outcomes poor by modern standards
HeadStart I–III	5 cycles of induction chemo + HDC-AuSCR	3-year OS: 26%, EFS: 21%	Fewer than 25% of patients completed planned therapy due to toxicity or early progression; limited efficacy in AT/RT compared with medulloblastoma
EU-RHAB	Intensive multi-agent systemic chemotherapy ± intrathecal therapy; delayed or omitted radiotherapy in responders ($n = 143$)	5-year OS: 35%, EFS: 31%	Largest European experience; confirms persistent poor long-term survival despite treatment intensification; highlights need for novel, biology-driven approaches
Vienna MUV-ATRT	Multi-agent chemo + intrathecal therapy + HDC-AuSCR + focal RT	5-year OS: 100%, EFS: 88.9% (Cohort A, $n = 9$)	Small, highly selected cohort; exceptional outcomes attributed to aggressive, well-sequenced multimodal therapy; limited generalizability

Abbreviations: AT/RT, atypical teratoid/rhabdoid tumor; CCG, Children's Cancer Group; COG, Children's Oncology Group; EFS, event-free survival; HDC-AuSCR, high-dose chemotherapy with autologous stem cell rescue; OS, overall survival.

incorporated intensive induction chemotherapy, HDC-AuSCR, and risk-adapted RT based on age and disease extent. ACNS0333 reported a 4-year OS of 43% and EFS of 37%, demonstrating meaningful improvement compared to historical cohorts [65]. Importantly, the trial demonstrated that neither the presence of residual disease following induction therapy nor metastatic disease at diagnosis independently predicted inferior survival outcomes, suggesting that aggressive multimodal therapy may mitigate traditional high-risk features in AT/RT. Subsequent correspondence further explored outcomes among metastatic patients enrolled on ACNS0333, highlighting that a subset of children with metastatic disease achieved durable long-term survival, particularly when able to complete protocol-directed therapy including consolidation and radiotherapy [66].

An alternative approach from the Dana-Farber Cancer Institute (DFCI) utilized upfront surgical resection followed by aggressive anthracycline-based systemic chemotherapy in combination with intrathecal therapy and RT. Although this protocol achieved encouraging 2-year OS and EFS rates of 70% and 53%, respectively, treatment was associated with high rates of Grade 3–4 toxicities, reflecting the challenges of balancing efficacy with tolerability in this population [67]. Subsequent experience with this regimen has not been uniformly reproducible. A recent report from an Egyptian cohort applying a similar DFCI-based treatment approach demonstrated inferior survival outcomes compared with the original series, highlighting significantly lower survival rates despite comparable treatment intensity [68].

Earlier regimens, such as the CCG 9921 protocol, relied on intensive platinum-based chemotherapy with deferred or salvage RT. Despite aggressive therapy, outcomes were poor, with 5-year OS and EFS of 29% and 14%, respectively [40, 69]. Similarly, the HeadStart I–III protocols were limited by significant toxicity and early disease progression, with fewer than 25% of AT/RT patients completing the intended regimen. Reported 3-year OS and EFS were 26% and 21%, respectively [70].

European treatment strategies utilized systemic chemotherapy combined with intrathecal therapy, with variable use of HDC-AuSCR and RT. Initial EU-RHAB registry data demonstrated 6-year OS and EFS of 45% and 46% in early cohorts [54]; however, an updated analysis of 143 patients reported 5-year OS and EFS of only 35% and 31%, respectively, underscoring the continued need for therapeutic innovation [71].

The Vienna MUV-ATRT regimen, which integrates multi-agent chemotherapy, intrathecal therapy, and HDC-AuSCR followed by focal RT, has produced some of the most striking results to date. In a small patient cohort (Cohort A, $n = 9$), this approach achieved 5-year OS and EFS of 100% and 88.9%, respectively, suggesting that optimized sequencing of intensive chemotherapy and RT may significantly influence outcomes [72].

While the Vienna MUV-ATRT regimen demonstrated excellent survival outcomes in a small cohort, these findings should be interpreted with caution given the limited sample size and lack of comprehensive molecular stratification. As such, the generalizability of these results remains uncertain.

Even in particularly challenging cases of metastatic AT/RT or those associated with rhabdoid tumor predisposition syndrome,

there is a clear survival advantage to using multimodal therapies, including HDC-AuSCR, RT, and intrathecal chemotherapy [63, 73, 74]. A meta-analysis of 130 children showed that HDC-AuSCR and RT independently improved OS in children with metastatic AT/RT [73].

Synthesizing across these trials, the area of greatest consensus is that intensified multimodal therapy combining high-dose chemotherapy with autologous stem cell rescue, intrathecal chemotherapy, and radiotherapy improves survival over historical regimens, and that radiotherapy and high-dose chemotherapy each contribute independently to outcome, including in metastatic disease. The principal controversies concern how much radiotherapy can be safely omitted or deferred in the youngest patients and whether molecular subgroup (notably the more favorable AT/RT-TYR) should guide that decision; molecular stratification has not yet been prospectively validated for treatment assignment. Cross-trial comparison is limited by small, heterogeneous cohorts, differing use and timing of radiotherapy, variable incorporation of high-dose chemotherapy, and inconsistent molecular annotation, which together explain the wide range of reported survival estimates in Table 3, for example, the exceptional but very small Vienna MUV-ATRT cohort versus the larger, more representative EU-RHAB experience.

5.2.4 | Emerging Therapeutic Strategies and Future Directions

Novel targeted and immunotherapeutic approaches are under active investigation. EZH2 inhibition with tazemetostat has demonstrated promise in INI1-deficient rhabdoid tumors, including AT/RT, particularly in the maintenance setting [75]. Additional agents under exploration include Aurora kinase inhibitors, immune checkpoint blockade (e.g., tiragolumab and atezolizumab, NCT05286801), and metronomic chemotherapy regimens such as MEMMAT (NCT01356290) [76, 77]. Recent data from the SJATRT study demonstrate that Alisertib is tolerable both as a single agent and in combination with chemotherapy; however, no significant improvement in survival outcomes has been observed to date [78].

Future studies aim to incorporate molecular profiling for risk stratification and treatment personalization, while registry-based initiatives like PNOC030 (NCI-2022-01992) seek to integrate real-world clinical and biological data to inform trial design and improve outcomes.

Two prospective trials illustrate the field's movement toward age- and risk-stratified, radiation-sparing strategies. The ongoing Phase III European trial SIOPE ATRT randomizes children aged 12–35 months between high-dose chemotherapy and conventional chemotherapy plus focal RT, treats infants younger than 12 months with high-dose chemotherapy without RT, and treats older children (≥36 months) with EU-RHAB chemotherapy and craniospinal irradiation. The pilot DECRYPT BABYBRAIN trial (NCT06942039) evaluates a radiation-sparing approach built on a high-dose chemotherapy backbone with maintenance chemotherapy and serial intrathecal chemotherapy, and includes a dedicated maintenance arm for low-risk AT/RT.

5.3 | Embryonal Tumors With Multilayered Rosettes

Embryonal tumors with multilayered rosettes (ETMR) are rare but highly aggressive embryonal CNS neoplasms that predominantly affect children under 3 years of age [79, 80]. While ETMRs exhibit heterogeneous anatomical distribution, the majority arise in supratentorial regions (approximately 70%), with the remaining 30% occurring infratentorially; spinal involvement is exceedingly uncommon [81, 82]. These tumors are characterized by rapid growth and aggressive clinical behavior, often progressing despite treatment. Surgical management is particularly challenging due to the young age of patients and the diffuse, infiltrative nature of ETMR, making GTR difficult without incurring significant morbidity [79, 80, 83]. Nonetheless, retrospective analyses suggest improved OS with maximal resection, high-dose chemotherapy, and RT [81].

5.3.1 | Pathologic and Molecular Features

ETMR is defined by distinctive histopathologic and molecular features. Histologically, these tumors exhibit multilayered or pseudostratified rosettes interspersed with extensive neuropil-rich areas [5, 80]. From a molecular standpoint, amplification of the C19MC oncogenic miRNA cluster on chromosome 19q13.42 represents a defining hallmark, observed in approximately 90% of cases [79, 84, 85]. In the rare cases without C19MC amplification, DICER1 germline mutations or other microRNA pathway aberrations are often identified [84]. Biallelic mutations of *DICER1*, a critical gene in miRNA processing, occur in roughly 5% of patients [86]. ETMRs also exhibit low single-nucleotide variants (SNVs), but high genomic instability driven by abnormal R-loop structures, which provides the therapeutic rationale for using topoisomerase and PARP inhibitors to target these R-loops [86]. ETMRs consistently overexpress LIN28A, an RNA-binding protein detectable by IHC, although its expression is not entirely specific [87]. Diagnosis is typically confirmed through a combination of methylation profiling and NGS, which reliably identifies C19MC amplification or DICER1 alterations. Methylation has allowed us to differentiate ETMR from other tumors previously grouped under "CNS-PNET," including CNS NB-FOXR2. This is important as CNS NB-FOXR2 has significantly better outcomes with current therapies compared to ETMRs [88].

5.3.2 | Current Treatment Landscape

At present, there are no standardized treatment algorithms for ETMR, and therapeutic strategies largely aim to delay or avoid RT due to the profound neurocognitive sequelae in this very young population [80]. Most current protocols borrow from historical approaches in CNS PNET, incorporating intensive systemic chemotherapy with or without intrathecal therapy (Table 4) [89, 90]. The P-HIT trial, which included 30 ETMR patients, reported a 5-year OS of 47% with induction chemotherapy (carboplatin/etoposide) followed by high-dose chemotherapy and stem cell rescue, markedly superior to the approximately 8% survival reported in historical cohorts [90]. Additional regimens, such as COG ACNS0334 and DFCI protocols, adapted from AT/RT

TABLE 4 | Embryonal tumor with multilayered rosettes.

Study/Protocol	Treatment approach	5-year OS	Key findings
P-HIT	Induction chemotherapy (carboplatin/etoposide) followed by high-dose chemotherapy with autologous stem-cell rescue	47%	Markedly improved survival compared with historical cohorts (~8%); included ~30 patients with molecularly confirmed ETMR
Historical cohorts (Korshunov et al. [82])	Intensive systemic chemotherapy ± intrathecal therapy	~8%	Very poor outcomes with conventional chemotherapy alone; high rates of early relapse and progression
COG ACNS0334	Intensive multi-agent chemotherapy with high-dose methotrexate-based induction (adapted embryonal tumor regimen)	Limited data available	ETMR patients included in small numbers; outcomes not reported separately; long-term efficacy remains undefined
DFCI AT/RT-based regimen	Surgical resection + anthracycline-based chemotherapy ± intrathecal therapy ± radiotherapy	Limited data available	Applied to selected ETMR cases; heterogeneous use of radiotherapy; no ETMR-specific survival estimates published
Retrospective analysis (Mayr et al. [91])	Heterogeneous multimodal regimens with or without radiotherapy	Not reported	Among 26 long-term survivors (>3 years), all but two received radiotherapy, suggesting a potential association with durable disease control

Abbreviations: AT/RT, atypical teratoid/rhabdoid tumor; COG, Children's Oncology Group; ETMR, embryonal tumor with multilayered rosettes; OS, overall survival.

treatment frameworks, have been utilized. There were 14 patients with ETMR enrolled on ACNS0334. The addition of methotrexate did not improve EFS in this cohort (20% 5-year EFS in those who received methotrexate vs. 33.3% in those who did not) [43].

A major advance in the field was the international, multi-institutional study, which represents one of the largest and most comprehensive analyses of ETMR to date [92]. This study included a molecularly confirmed cohort of children with ETMR and provided critical insights into prognostic factors, treatment patterns, and outcomes in the modern era. The authors demonstrated that OS remained poor, with 5-year OS rates below 50%, despite intensive multimodal therapy, underscoring the aggressive biology of ETMR and the limitations of chemotherapy-only approaches [92]. The study provided the strongest evidence to date supporting a survival benefit associated with RT in ETMR. Patients who received RT, either focal or CSI, had significantly improved survival than those who did not receive RT, even after adjustment for age and treatment intensity. These findings established RT as a key determinant of durable disease control in ETMR.

Multiple retrospective series also suggested a consistent survival advantage when RT is incorporated into therapy [91, 93]. In a systematic review of 228 published cases, Mayr et al. found that 26 patients survived beyond 3 years from diagnosis, and all but two had received RT [91]. These findings underscore the potential benefit of incorporating focal RT or CSI, despite associated risks.

Taken together, the ETMR literature converges on two points despite the absence of randomized data: high-dose chemotherapy improves survival over conventional chemotherapy alone (P-HIT), and radiotherapy whether focal or craniospinal is consistently associated with longer survival across the largest molecularly confirmed cohort and multiple retrospective series. The unresolved questions are the optimal timing and field of radiotherapy in children for whom its long-term toxicity is most severe, and whether any subgroup can be cured without it; the available evidence is almost entirely retrospective and subject to selection bias, as healthier patients are more likely to survive long enough to receive radiotherapy. As reflected in Table 4, cohorts are small, and treatment is heterogeneous, so survival estimates should be interpreted as broadly concordant in direction rather than directly comparable in magnitude.

5.3.3 | Future Directions

Prognosis for ETMR remains dismal, with most patients succumbing to disease within 2 years of diagnosis despite aggressive multimodal therapy. Given the rarity of ETMR and the consequent lack of randomized trials, future efforts aim to consolidate clinical experience through collaborative registry studies and prospective treatment protocols. PNOC031 (NCI-2025-01764) represents an important step toward establishing unified treatment guidelines. This protocol seeks to evaluate a multimodal approach incorporating systemic and intrathecal chemotherapy, with selective use of radiotherapy, while prospectively collecting clinical and tumor biology data to inform future therapeutic refinements. Beyond PNOC031, collaborative consortia such as CONNECT are working to enable prospective study of ETMR; across all of these efforts, the central obstacle remains the very small number of patients available for enrollment, which makes registry-based data sharing and international cooperation essential [94].

Emerging evidence suggests that early incorporation of focal radiotherapy may improve outcomes in ETMR [91]. This strategy

TABLE 5 | Pineoblastoma.

Study/Analysis	Population	Treatment approach	5-year OS/PFS	Key findings
HeadStart I–III	23 patients <6 years	Five cycles of induction chemotherapy followed by HDC-AuSCR	OS: 13%, PFS: 9.7%	Only 8 patients completed planned HDC; outcomes uniformly poor, indicating limited efficacy of HeadStart approaches for pineoblastoma
SIOP-E + HeadStart pooled	135 patients	Multimodal infant brain tumor protocols emphasizing chemotherapy and radiation avoidance	OS: ~12% (<4 years old)	Confirms extremely poor prognosis for pineoblastoma treated with radiation-sparing strategies
Meta-analysis (Mynarek et al. [103])	49 patients <3 years	Heterogeneous infant-type regimens	PFS: ~25%	Gross total resection and radiotherapy consistently associated with improved survival across studies
COG ARET0321	Extraocular retinoblastoma with CNS involvement	Intensive systemic chemotherapy ± radiotherapy	Not reported	Regimen inadequate for CNS embryonal tumors; outcomes for pineoblastoma not improved
COG ACNS0334	Pineoblastoma subset within high-risk embryonal brain tumors	Intensive induction chemotherapy with or without high-dose methotrexate, followed by consolidation ± HDC-AuSCR	Not separately reported for pineoblastoma	Phase III trial demonstrated event-free survival benefit of high-dose methotrexate in Group 3 medulloblastoma, but pineoblastoma-specific OS or PFS outcomes were not reported, limiting conclusions regarding efficacy for this subgroup

Abbreviations: CNS, central nervous system; COG, Children's Oncology Group; HDC-AuSCR, high-dose chemotherapy with autologous stem cell rescue; OS, overall survival; PFS, progression-free survival.

is currently being evaluated in the PNOC031 trial, which assesses induction chemotherapy followed by early focal RT in newly diagnosed, gross-totally resected, nonmetastatic ETMR, with 6-month progression-free survival as the primary endpoint. These findings may have important implications for future treatment paradigms.

5.4 | Pineoblastoma

Pineoblastoma (PB) is a rare, highly aggressive embryonal tumor of the pineal gland that primarily occurs in children [95, 96]. While these tumors originate within the pineal region, they often demonstrate suprasellar extension and can present with leptomeningeal dissemination. Recent integrative genomic analyses have revealed significant biological heterogeneity within pineoblastoma, delineating five distinct molecular subgroups: DICER1, DROSHA, KBTBD4, PB-MYC/FOXR2, and PB-RB1, the latter two being more common in infants and young children [97–99]. Germline predisposition plays a notable role, with germline *RB1* mutations conferring approximately a 5% lifetime risk of developing intracranial pineoblastoma [100, 101].

5.4.1 | Treatment Landscape and Clinical Outcomes

Due to the rarity of PB, no disease-specific prospective trials have been conducted (Table 5). Most available data are derived from infant brain tumor protocols such as the HeadStart I–III trials, which included 23 children with pineoblastoma under the age of 6 years [102]. Outcomes were dismal: only eight patients were able to complete five induction chemotherapy cycles followed by HDC-AuSCR, while the remainder succumbed to treatment toxicity or progressive disease. Five-year OS and PFS were 13% and 9.7%, respectively [102]. Similarly, pooled analyses from SIOP-Europe (SIOP-E) and HeadStart encompassing 135 pineoblastoma patients reported a 5-year OS of approximately 12% for those diagnosed before age 4 [103].

A meta-analysis of 49 patients under 3 years of age, treated across prior infant protocols, showed a 5-year PFS of approximately 25%, underscoring the uniformly poor prognosis despite multimodal therapy [95]. Factors associated with improved outcomes included GTR and the administration of RT, though these findings require validation in larger studies [95, 104]. Notably, younger age (<3 years), germline *RB1* mutations, and the presence of "trilateral" retinoblastoma (pineal involvement with bilateral ocular disease) were strongly associated with worse survival [105–108]. The COG ARET0321 study, which evaluated therapy for extraocular retinoblastoma including patients with CNS involvement, further highlighted the inadequacy of current regimens for this population [109].

The SJYC03 and SJYC07 protocols included patients with PB. Importantly, these studies further characterized PB using DNA methylation into four clinically relevant subgroups: PB-miRNA1, PB-miRNA2, PB-MYC/FOXR2, and PB-RB1. The

PB-MYC/FOXR2 and PB-RB1 subgroups were identified in younger children and had poor OS compared to the other subgroups despite intensive therapy [110].

ACNS0334 included nine patients with pineoblastoma; six with localized disease and three with metastatic disease. There was no statistically significant difference in the EFS or OS of those who received methotrexate compared to those who did not. However, interpretation is limited by a very small sample size [43]. To date, the incorporation of HDC-AuSCR has shown the maximum promise among radiation-sparing measures for this treatment group.

Across these pooled and meta-analytic datasets, the consistent message is that infant pineoblastoma carries a uniformly poor prognosis with radiation-sparing strategies, and that the two factors most reproducibly associated with improved survival—gross total resection and radiotherapy—are precisely the interventions hardest to deliver safely in this age group. There is emerging agreement that the molecular subgroups enriched in young children (PB-MYC/FOXR2 and PB-RB1) define the highest risk disease, but no consensus on how to translate this into therapy, and germline RB1-associated and trilateral disease remain especially refractory. Because every series is small, retrospective, and assembled from heterogeneous infant protocols rather than pineoblastoma-specific trials, the survival figures in Table 5 should be read as concordant evidence of poor outcome rather than as comparisons between defined regimens.

5.4.2 | Future Directions

The persistently poor survival outcomes for infants with pineoblastoma underscore an urgent need for novel therapeutic strategies. Prospective studies must incorporate comprehensive molecular profiling to better define tumor biology and identify actionable targets for therapy. Future approaches may include risk-adapted strategies informed by molecular subgrouping, as well as evaluation of targeted therapies and radiation-sparing regimens for select low-risk subgroups. Additionally, dedicated efforts are needed to improve outcomes for patients with trilateral retinoblastoma harboring germline *RB1* mutations, who remain among the most challenging to treat.

6 | Emerging Embryonal CNS Tumor Entities

The fifth edition of the WHO CNS5 has integrated molecular diagnostics into the classification framework, refining prior entities and replacing outdated terminology such as PNET [5]. These updates have significantly enhanced diagnostic precision for infantile CNS embryonal tumors. However, continued prospective and retrospective studies are necessary to clarify the clinical behavior of previously misclassified tumors and improve understanding of these rare subtypes.

6.1 | CNS Neuroblastoma, FOXR2-Activated

One such recently defined entity is CNS neuroblastoma, FOXR2-activated, identified through DNA methylation profiling and characterized by FOXR2 alterations [111, 112]. These tumors typically occur in young children and adolescents, predominantly within the supratentorial compartment [113]. Although DNA methylation remains the diagnostic gold standard, emerging evidence suggests that FOXR2 activation may not be entirely specific to this tumor type, warranting further investigation into alternative oncogenic drivers [111].

6.2 | CNS Tumor With BCOR Internal Tandem Duplication

CNS tumors with BCOR internal tandem duplication (ITD) represent another newly described embryonal entity, defined by a recurrent BCOR exon 15 ITD [114–116]. These tumors primarily affect young children (median age: 4 years) and exhibit no strong predilection for infratentorial versus supratentorial localization, as observed in a review of 46 cases (20 supratentorial, 26 infratentorial) [115–117]. While activation of SHH and WNT signaling pathways has been documented, the clinical significance of these findings remains unclear [116].

6.3 | Cribriform Neuroepithelial Tumor

Cribriform neuroepithelial tumor (CRINET) is a rare embryonal tumor entity characterized by a cribriform growth pattern and *SMARCB1* loss [118–120]. Unlike AT/RT, CRINET demonstrates more favorable outcomes and is typically localized within the ventricular system [59, 121]. Patients often respond well to multimodal treatment regimens, distinguishing this entity from more aggressive embryonal tumors. Notably, tyrosinase expression and clustering of the DNA methylation profile of CRINET within the AT/RT-TYR subgroup link CRINET to this molecular subtype of AT/RT, suggesting that CRINET likely represents one end of a morphological and clinical spectrum rather than a completely distinct entity.

6.4 | CNS Embryonal Tumor, NOS/NEC

Finally, the category of CNS embryonal tumor, not otherwise specified (NOS) or not elsewhere classified (NEC) includes tumors with embryonal features that cannot be further classified due to insufficient molecular data [5, 122]. These tumors appear to have a supratentorial predilection, though definitive trends remain under investigation.

7 | Clinical Challenges and Future Perspectives

Currently, there are no dedicated clinical trials for these emerging embryonal tumor entities, primarily due to their rarity and the relatively recent adoption of molecularly defined nomenclature. Most patients diagnosed before age 3 have historically been managed with radiation-sparing regimens modeled after protocols for infant CNS PNET or medulloblastoma. As with the better-characterized entities, progress will depend on the international, registry-based collaboration discussed in the Conclusion section.

7.1 | Challenges in Management and Long-Term Sequelae

The treatment of infantile CNS embryonal tumors remains fraught with challenges, both in achieving disease control and in

TABLE 6 | Acute and long-term toxicities in infant embryonal CNS tumor therapy.

Treatment modality	Acute toxicities	Long-term toxicities	Key notes (from trials/series)
Surgery	Blood loss, hemodynamic instability, infection, CSF leak	Neurologic deficits, posterior fossa syndrome, motor/cognitive impairment	Risk dependent on tumor location and extent of resection
Conventional chemotherapy	Myelosuppression, infections, mucositis, nephrotoxicity, ototoxicity	Hearing loss (cisplatin), infertility, growth impairment	Common across HeadStart, CCG, and COG protocols
HDC-AuSCR	Severe myelosuppression, sepsis, organ toxicity, treatment-related mortality (historically up to ~14%, now <5%)	Endocrine dysfunction, fertility impact, neurocognitive effects	Improved safety in modern protocols (HeadStart III/IV)
Intraventricular methotrexate	Chemical meningitis, leukoencephalopathy (often Grade 1–2)	White matter injury, potential neurocognitive effects	HIT-SKK: ~57% leukoencephalopathy, often mild
Focal radiotherapy	Fatigue, alopecia, acute neuroinflammation	Neurocognitive decline, endocrine dysfunction, vasculopathy	Risk increases with younger age
Craniospinal irradiation (CSI)	Myelosuppression, nausea, fatigue	Significant neurocognitive impairment, endocrine dysfunction, secondary malignancies	Major driver of long-term morbidity in infants
Proton therapy	Similar acute toxicity profile to photon RT	Reduced neurocognitive and endocrine toxicity (relative)	Dose sparing to normal tissue; growing standard in pediatrics

Abbreviations: CCG, Children's Cancer Group; CNS, central nervous system; COG, Children's Oncology Group; CSF, cerebrospinal fluid; HDC-AuSCR, high-dose chemotherapy with autologous stem cell rescue.

mitigating long-term sequelae (Table 6). The initial therapeutic objective is maximal safe surgical resection, as the extent of resection is strongly associated with improved outcomes [4, 14, 79, 123]. However, achieving GTR is frequently limited by the tumor's anatomic location and the risk of severe neurologic morbidity.

Adjuvant therapy typically involves intensive chemotherapy administered at high doses. While this approach improves survival, it carries substantial risks, including acute toxicities and long-term neurocognitive impairment [124–127]. RT, whether focal or CSI, often confers additional survival benefit, but is generally deferred in this age group because of its devastating long-term effects, including profound cognitive deficits and reduced functional independence [21, 126, 128].

Long-term follow-up studies underscore the severity of late effects as nearly all survivors exhibit some degree of neurologic impairment, encompassing developmental delays, motor deficits, and cognitive dysfunction [129–131]. These outcomes highlight the urgent need for therapies that balance efficacy with reduced toxicity. Advances in molecular profiling offer hope for biologically targeted strategies that may improve survival while minimizing the lifelong impact of treatment.

Disease monitoring traditionally relies on imaging, clinical evaluation, and cerebrospinal fluid (CSF) cytology, but novel approaches such as CSF-derived cell-free DNA (cfDNA) analysis offer promising noninvasive biomarkers for molecular residual disease detection and relapse prediction [132, 133]. Liquid biopsy approaches could enable real-time treatment adaptation, particularly for high-risk patients [132].

8 | Conclusion

Infant CNS embryonal tumors represent a rare yet highly aggressive subset of pediatric brain neoplasms, accounting for the majority of malignant tumors in this age group. While recent molecular insights have significantly enhanced our understanding of tumor biology and classification, therapeutic progress has lagged behind. Current management continues to rely heavily on maximal safe surgical resection and intensive chemotherapy, with RT often deferred or avoided due to the profound neurocognitive sequelae in very young patients.

Four themes recur across every entity discussed in this review and together define the contemporary challenges in this field. First, molecular profiling through DNA methylation classification and next-generation sequencing has become indispensable for accurate diagnosis and risk stratification, resolving entities previously grouped as CNS-PNET and identifying clinically actionable subgroups across medulloblastoma, AT/RT, ETMR, and pineoblastoma. Second, the neurocognitive, endocrine, and developmental toxicity of radiotherapy, and craniospinal irradiation in particular, remains the central constraint on treatment in this age group and the principal motivation for the radiation-sparing strategies that dominate current protocols. Third, the

TABLE 7 | Comparative summary of infant embryonal CNS tumor types.

Tumor type	Key molecular subgroups	Key biological features	Prognosis	Current treatment approach	Emerging targeted therapies
Medulloblastoma (MB)	WNT; SHH (SHH-I, SHH-II); Group 3; Group 4. Infants predominantly SHH (~50%–60%), then Group 3	SHH from granule neuron precursors; germline PTCH1/SUFU common in infants; Group 3 MYCN amplification/i17q adverse	Favorable for SHH DN/MBEN (5-year OS often >90% without CSI); poor for Group 3	Radiation-sparing intensive chemotherapy ± intraventricular MTX or HDC-AuSCR; CSI reserved for relapse/high risk	SMO inhibitors (vismodegib; limited by resistance and infant skeletal toxicity); oncolytic measles virus; CSF liquid biopsy for monitoring
Atypical teratoid/rhabdoid tumor (AT/RT)	AT/RT-TYR; AT/RT-SHH; AT/RT-MYC (DNA methylation subgroups)	Biallelic SMARCB1 inactivation (rarely SMARCA4); loss of SMARCB1/INI1 by IHC; up to ~55% germline (RTPS); TYR often infratentorial/favorable	Historically poor (5-year OS ~25%); improved with intensified multimodal therapy (ACNS0333 4-year OS 43%)	Intensive induction + HDC-AuSCR + intrathecal therapy + risk-adapted RT	EZH2 inhibition (tazemetostat); Aurora kinase inhibition (alisertib); checkpoint blockade; metronomic regimens (MEMMAT)
Embryonal tumor with multilayered rosettes (ETMR)	C19MC-amplified (~90%); DICER1-altered (rare); other miRNA pathway	Multilayered rosettes; LIN28A overexpression by IHC; R-loop-driven genomic instability; low SNV burden	Dismal (5-year OS <50% despite intensive therapy); most progress within 2 years	Intensive systemic chemotherapy ± intrathecal therapy + HDC-AuSCR; RT (focal/CSI) associated with longer survival	Topoisomerase and PARP inhibitors (targeting R-loops); prospective protocols (PNOC031); CONNECT consortium efforts
Pineoblastoma (PB)	DICER1; DROSHA; KBTBD4; PB-MYC/FOXR2; PB-RB1 (latter two enriched in young children)	Pineal region embryonal tumor; germline RB1 predisposition; trilateral retinoblastoma association	Poor in infants (5-year OS ~12%–13%; PFS ~25% in <3 years); PB-MYC/FOXR2 and PB-RB1 worst	Infant brain tumor protocols with intensive chemotherapy ± HDC-AuSCR; GTR and RT associated with better outcome	Molecularly informed risk-adapted strategies under development; targeted therapy investigational
Emerging entities (CNS NB-FOXR2; CNS tumor with BCOR ITD; CRINET; CNS embryonal tumor NOS/NEC)	Defined by DNA methylation: FOXR2 activation; BCOR exon 15 ITD; SMARCB1 loss (CRINET, within AT/RT-TYR spectrum)	Recently delineated from CNS-PNET; CNS NB-FOXR2 supratentorial with better outcomes; CRINET ventricular, favorable	Variable; CNS NB-FOXR2 and CRINET comparatively favorable; others uncertain	No dedicated trials; managed with radiation-sparing infant PNET/MB-modeled regimens	Molecular profiling to guide future biologically informed, registry-based approaches

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; CSI, craniospinal irradiation; HDC-AuSCR, high-dose chemotherapy with autologous stem cell rescue; NOS/NEC, not otherwise specified or not elsewhere classified; PFS, progression-free survival; SHH, sonic hedgehog.

biology that makes these tumors molecularly tractable has not yet translated into broadly improved outcomes, with effective molecularly guided and targeted therapies remaining largely investigational, and for several entities Group 3 medulloblastoma, ETMR, pineoblastoma, and metastatic AT/RT survival remains poor despite intensive multimodal therapy. Fourth, because each of these tumors is individually rare, meaningful progress depends on international collaboration: cooperative-group trials, consortium studies, and registry-based data sharing are essential to accrue adequate numbers, enable molecularly stratified trial

designs, and permit the cross-trial comparisons that this review has emphasized are currently complicated by heterogeneous patient selection, classification, and endpoints.

Future treatment paradigms must incorporate molecularly driven risk stratification and the integration of targeted and biologically informed therapies. Realizing this vision will require radiation-sparing, risk-adapted regimens delivered within collaborative, biologically annotated clinical trials and supported by emerging tools such as cerebrospinal fluid liquid biopsy for longitudinal disease monitoring. Such approaches hold promise not only for improving survival but also for reducing long-term morbidity, ultimately advancing the standard of care for this vulnerable patient population (Table 7).

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