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Rare embryonal and sarcomatous central nervous system tumours: State-of-the art and future directions

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ABSTRACT

The introduction of molecular methods into the diagnostics of central nervous system (CNS) tumours and the subsequent deciphering of their molecular heterogeneity has resulted in a significant impact on paediatric neurooncology. Particularly in the field of rare embryonal and sarcomatous CNS tumours, novel tumour types have been delineated and introduced in the recent 5th edition of the WHO classification of CNS tumours. The rarity and novelty of these tumour types result in diagnostic and therapeutic challenges. Apart from distinct histopathological and molecular features, these tumour types exhibit characteristic clinical properties and require different therapeutic approaches for optimal patient management. However, based on the limited availability of clinical data, current therapeutic recommendations have to be based on data from small, predominantly retrospective patient cohorts. Within this article, we provide guidance for diagnostic work-up and clinical management of rare CNS embryonal tumours ('embryonal tumour with multi-layered rosettes', ETMR; 'CNS neuroblastoma, *FOXR2*-activated', CNS NB-*FOXR2*; 'CNS tumour with *BCOR*-ITD, CNS *BCOR*-ITD) and rare CNS sarcomatous tumours ('primary intracranial sarcoma, *DICER1*-mutant', CNS *DICER1*; '*CIC*-rearranged sarcoma', CNS *CIC*). By emphasizing the significant consequences on patient management in paediatric CNS tumours, we want to encourage wide implementation of comprehensive molecular diagnostics and stress the importance for joint international efforts to further collect and study these rare tumour types.

1. Introduction

The classification of embryonal and sarcomatous central nervous system (CNS) tumours is a constantly evolving field and has experienced extensive restructuring in the past decade. This rapid process is mainly driven by the implementation of molecular biomarkers into the classification system. In the recent 5th edition of the WHO classification of CNS tumours, diagnostic criteria have been refined and several new tumour types have been included in the categories of rare CNS embryonal tumours and CNS mesenchymal tumours of uncertain

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differentiation (Louis et al., 2021). Many of these tumours were previously diagnosed as "primitive neuroectodermal tumour" (PNET), a descriptive diagnosis that was based on the morphological appearance as small-cell, malignant CNS tumours (Kleihues et al., 1993; Rorke et al., 1997). The entities supratentorial PNET and then CNS-PNET were introduced in the WHO classifications of CNS tumours in the years 2000 and 2007, respectively (Kleihues and Sobin, 2000; Louis et al., 2007). CNS-PNET comprised a heterogeneous group of tumours with descriptive morphological characteristics but lacking specific diagnostic criteria. The introduction of advanced and genome wide molecular diagnostics, especially DNA methylation profiling, unveiled the molecular heterogeneity of these tumours (Schwalbe et al., 2013; Sturm et al., 2016). Based on these analyses, most histologically diagnosed CNS-PNETs can nowadays be molecularly classified into known entities such as high-grade glioma (HGG), ependymoma, atypical teratoid rhabdoid tumor ATRT, medulloblastoma, or other rarer tumour types. Moreover, molecular analyses uncovered that embryonal tumours formerly described as different histologically defined entities like ependymoblastoma, embryonal tumours with abundant neuropil and true rosettes (ETANTR) or medulloepithelioma, are all molecularly highly similar and are now considered to be histological variants of the same entity termed 'embryonal tumour with multilayered rosettes' (ETMR) (Korshunov et al., 2014; Louis et al., 2016; Spence et al., 2014). DNA methylation profiling also revealed several new molecularly defined entities among series of tumours with historic CNS-PNET diagnosis. These new tumour types, each defined by specific molecular alterations, a distinct methylation profile and specific clinical characteristics, also included tumours with histological diagnoses other than CNS-PNET. As such, they are not considered to be subtypes of CNS-PNET but rather distinct tumour types. Consequently, the histologically defined entity CNS-PNET was discarded in the 2016 version of the WHO classification of CNS tumours (Louis et al., 2016). The respective tumour types from this spectrum, that have been newly introduced in the 5th edition of the WHO classification of CNS tumours, include the embryonal tumour entities 'CNS neuroblastoma, *FOXR2*-activated' (CNS NB-*FOXR2*) and 'CNS tumour with *BCOR*-ITD (CNS *BCOR*-ITD). The tumour types 'primary intracranial sarcoma, *DICER1*-mutant' (CNS *DICER1*) and '*CIC*-rearranged sarcoma' (CNS *CIC*) are now listed in the group of mesenchymal tumours of uncertain differentiation, further expanding the landscape of CNS sarcomatous tumours (Louis et al., 2021). It has to be noted, that other novel tumour types with distinct molecular features such as gene fusions involving *PATZ1* (Alhalabi et al., 2021), *BCOR/BCORL1* (Pisapia et al., 2020; Tauziède-Espariat et al., 2020; Torre et al., 2019), or *PLAGL1* (Sievers et al., 2021) have recently been described and are not included in the 5th edition of the WHO classification of CNS tumours, yet. The classification of rare embryonal and sarcomatous CNS tumours is expected to undergo constant evolution and refinement in the coming years hopefully providing further improvement of diagnosis.

Despite these novel insights and specifications in molecular classification, both diagnosis and clinical management of patients with these newly defined tumour types represent major challenges. The lack of tumour type-specific clinical data emphasizes the urgent need for accelerated efforts to prospectively collect and analyse these cases based on international cooperation. To date, there are only limited data to guide therapeutic decisions for rare embryonal and sarcomatous CNS tumours. Existing treatment strategies are mainly based on reports of single cases, small series and limited cohorts of patients, who were treated heterogeneously and were retrospectively reclassified by molecular analyses. However, the applied treatment strategies do not address the diverse biological and clinical nature of the different rare CNS embryonal tumour types. The available clinical data do not suffice when deciding the "optimal" treatment, but solely allow identification of tumour types, where previous therapeutic regimens were of benefit. Consequently, the treatment choices for patients with one of the newly defined rare embryonal or sarcomatous CNS tumour types are based on limited clinical experience.

Within this review, we summarize the diagnostic approach and clinical management that results from the introduction of the novel types of rare embryonal and sarcomatous CNS tumours with the 5th edition of the WHO classification of CNS tumours. The article is based on the European Standard of Clinical Practice (ESCP) recommendation, which has been prepared by the authors on behalf of the European Society for Paediatric Oncology (SIOPE) brain tumour group and is available at https://paedcan.ern-net.eu/the-escp-project/.

2. Diagnostics in the molecular era

The relevance of integrated histopathological and molecular diagnostics for CNS tumours was elucidated within the last decade, leading to introduction within the 2016 WHO classification of CNS tumours (Louis et al., 2014, 2016). Next to focussed molecular diagnostics, DNA methylation profiling has emerged as a valuable and robust method to classify CNS tumours based on their epigenetic signature (Capper et al., 2018). This is of particular importance when classifying the rare and heterogeneous tumour types within the spectrum of embryonal and sarcomatous tumours. Depending on the type of tumour, the characteristic molecular features can be analysed by a combination of DNA methylation profiling, fluorescence *in-situ* hybridisation (FISH), next-generation sequencing (NGS), or Sanger sequencing. For selected cases, whole genome sequencing (WGS) or RNA sequencing are useful additional molecular analyses to identify rare or novel genomic alterations. The essential and desirable diagnostic criteria for the respective entities, as outlined in the 5th edition of the WHO classification of CNS tumours are summarized in Table 1 (Louis et al., 2021). Fig. 1 summarizes molecular, diagnostic, demographic, and clinical parameters of the respective entities.

3. Histopathological and molecular characteristics of rare CNS embryonal tumour types

3.1. ETMR

ETMR is a WHO grade 4 tumour type, which is mainly characterized by amplification of the microRNA cluster on chromosome 19 termed *C19*MC, present in approximately 90% of all cases (Lambo et al., 2020). Amplification of *C19*MC was first described within a subset of CNS-PNETs with poor survival (Li et al., 2009). Improving insights in the molecular biology of paediatric brain tumours led to the finding that this hallmark alteration is characteristic for a specific clinicopathologic entity of embryonal rosette-forming tumours. These tumours can morphologically present as embryonal tumour with abundant neuropil and true rosettes (ETANTR) (Eberhart et al., 2000), ependymoblastoma (EBL) (Rubinstein, 1970), or medulloepithelioma (MEPL) (Molloy et al., 1996), with the latter two being long established morphologically defined sub-entities of CNS-PNET. ETMR was introduced as a unifying term in the 2016 WHO classification of CNS tumours (Korshunov et al., 2014; Louis et al., 2016). In most cases, amplification of the *C19*MC locus is linked to fusion to the *TTYH1* gene (Kleinman et al., 2014; Lambo et al., 2020). The *C19*MC-negative ETMR (~10%) are in part characterized by amplification of another microRNA cluster on chromosome 17 (MIR17HG), present in around 1% of all cases, or bi-allelic mutations in *DICER1*, a gene encoding a critical protein within the microRNA processing machinery, present in around 5% of all cases (Lambo et al., 2019). The latter predominantly arise in the context of DICER1 syndrome (Lambo et al., 2019, 2020; Uro-Coste et al., 2019). With respect to the diagnostic work-up, the typical morphological patterns are usually recognizable on Hematoxylin-Eosin (HE) sections and immunohistochemical LIN28A expression complements the diagnosis (Fig. 2, A-C). In small samples without characteristic morphological features, immunohistochemical LIN28A expression may guide the diagnosis. However, LIN28A expression is not specific and may be

Table 1
Essential diagnostic criteria and recommended work up for rare embryonal and sarcomatous tumours according to the 2021 WHO Classification of Tumours of the Central Nervous System.

Tumour type	Essential diagnostic criteria	Recommended diagnostic-work up
Rare CNS embryonal tumours:		
Embryonal tumour with multilayered rosettes	CNS embryonal tumour with morphological and immunohistochemical features of one of the three ETMR patterns: embryonal tumour with abundant neuropil and true rosettes, ependymoblastoma or medulloepithelioma and *C19*MC, *MIR17HG* or *DICER1* alteration	• Lin28A immunohistochemistry • *C19*MC amplification: FISH, SNP, copy number plots of DNA methylation data • *C19*MC non altered: sequencing for *DICER1* mutation • *DICER1* mutation present: recommendation for genetic counselling and germline testing
CNS neuroblastoma, FOXR2-activated	Embryonal tumour with foci of neuroblastic or neuronal differentiation and activation of *FOXR2* by structural rearrangements and gene fusion. For unresolved lesions a DNA methylation profile aligned with CNS neuroblastoma, *FOXR2* activated confirms the diagnosis.	• Expression of OLIG2, synaptophysin, predominantly vimentin negative • Ancillary IHC: SOX10 and ANKRD55 • Exclusion of high-grade glioma • DNA methylation or RNA sequencing
CNS tumour with BCOR internal tandem duplication	Malignant primary CNS tumour with a predominantly solid growth pattern, uniform oval or spindle-shaped cells with round to oval nuclei, and a dense capillary network and molecularly an internal tandem duplication in exon 15 of BCOR needs to be present. For unresolved lesions a DNA methylation profile aligned with CNS tumour with BCOR internal tandem duplication confirms the diagnosis.	• Strong widespread nuclear BCOR expression • May express focally OLIG2 but are generally negative for GFAP and synaptophysin • PCR-ITD, Sanger sequencing • DNA methylation
CNS embryonal tumour, NEC	An embryonal tumour originating in the CNS and absence of criteria qualifying for the diagnosis of a more specific type of embryonal CNS tumour are required.	• Exclusion of other embryonal tumour types, sarcomas and malignant gliomas
CNS embryonal tumour, NOS	A CNS tumour with embryonal morphology and incomplete or failed molecular diagnostics	• Referral to a national/international reference centre
Rare CNS sarcomatous tumours:		
CIC-rearranged sarcoma	A sarcoma with a predominant round cell phenotype, mild nuclear pleomorphism, epithelioid and/or spindle cell components, variably myxoid stroma, variable CD99, and frequent ETV4 and WT1 expression and a *CIC*-fusion	• Evidence of a *CIC* gene fusion • CD99, ETV4 or WT1 expression • DNA methylation
Primary intracranial sarcoma, DICER1-mutant	A primary intracranial sarcoma, *DICER1*-mutant, is composed of spindled or pleomorphic tumour cells typically displaying eosinophilic cytoplasmic globules, immunohistochemical evidence of myogenic differentiation, and occasionally foci of chondroid differentiation.	• DICER1 mutation • DNA methylation • Recommendation for genetic counselling and germline testing

observed in other tumour types e.g. ATRTs or malignant gliomas necessitating an exclusion of these tumours. The characteristic amplification of *C19*MC can be detected either by FISH or based on copy number analyses from SNP-array, DNA methylation array, or WGS. Some cases have only a small cluster of *C19*MC gained or amplified cells, which may not be detected by genome wide copy number analyses but can be detected by FISH. Cases without *C19*MC amplification should be screened for *DICER1* mutations and if present, genetic counselling is recommended. In rare cases which are negative for *C19*MC amplification and *DICER1* mutation, identification of *MIR17HG* amplifications may help in defining the correct diagnosis.

3.2. CNS NB-FOXR2

CNS neuroblastoma was included in previous editions of the WHO classification of CNS tumours as a morphologically defined entity, but CNS NB-*FOXR2* was first described by Sturm et al. (2016) as a distinct tumour type morphologically resembling CNS neuroblastoma. These tumours are characterized by chromosomal rearrangements (enhancer hijacking) that lead to increased expression of the transcription factor forkhead box R2 (*FOXR2*) gene (Sturm et al., 2016). Further studies have revealed that almost all of these tumours exhibit a chromosomal gain of 1q and some additional copy number alterations including 3p and 6q loss as well as 17q gain (Holsten et al., 2021; Korshunov et al., 2021; von Hoff et al., 2021). The diagnosis of CNS NB-*FOXR2* requires 1) histopathological confirmation of an embryonal tumour with foci of neuroblastic or neuronal differentiation and 2) activation of *FOXR2* by structural rearrangement and gene fusion. Extensive molecular testing is mandatory for the diagnosis of CNS NB-*FOXR2*. This may either be focussed on the identification of the *FOXR2* alteration e.g. by RNA sequencing, or by demonstration of the typical DNA methylation profile. Immunohistochemically, OLIG2 and synaptophysin expression is typically seen, whereas vimentin is usually absent (Fig. 2, D-F). As additional markers SOX10 and ANKRD55 have been described to support the diagnosis (Korshunov et al., 2021).

3.3. CNS BCOR-ITD

Another molecularly defined tumour type harbouring distinct alterations of the BCL6 Corepressor (*BCOR*) gene was also first described in the above mentioned molecular profiling study of "CNS PNETs" (Sturm et al., 2016). These tumours are characterized by an internal tandem duplication (ITD) in exon 15 within the c-terminal region of *BCOR*, a polycomb repressor complex component. Therefore, these tumours are named CNS *BCOR*-ITD in the 5th edition of the WHO classification of CNS tumours (Louis et al., 2021; Sturm et al., 2016). Interestingly, the same alteration was found in clear cell sarcomas of the kidney as well as soft-tissue sarcomas which also predominantly arise in young children (Wong et al., 2018). It has to be noted that alterations of the *BCOR* gene, other than *BCOR*-ITD, are also found in other tumour types including high-grade glioma or SHH medulloblastoma, but this does not qualify these tumours to be diagnosed as CNS *BCOR*-ITD (Mackay et al., 2017; Northcott et al., 2017). With respect to diagnostics, CNS *BCOR*-ITD present with a solid growth pattern, uniform oval or spindle-shaped cells with round to oval nuclei, a dense capillary network, and focal pseudorosette formation (Fig. 2, G). Importantly, *BCOR*-ITD are frequently misdiagnosed as gliomas, ependymomas, or other embryonal entities as they might show glioma-like fibrillarity but also rather undifferentiated tumour cells. OLIG2 may be focally expressed but GFAP and synaptophysin are predominantly negative. Immunohistochemical detection of strong nuclear BCOR overexpression is a highly suggestive but not entirely specific biomarker (Fig. 2, H) (Haberler et al., 2019; Łastowska et al., 2020; Mardi et al., 2021; Yoshida et al., 2018). Therefore, molecular confirmation of the internal tandem duplication in exon 15 of *BCOR* by PCR (Kenny et al., 2016), targeted sequencing, or NGS approach or

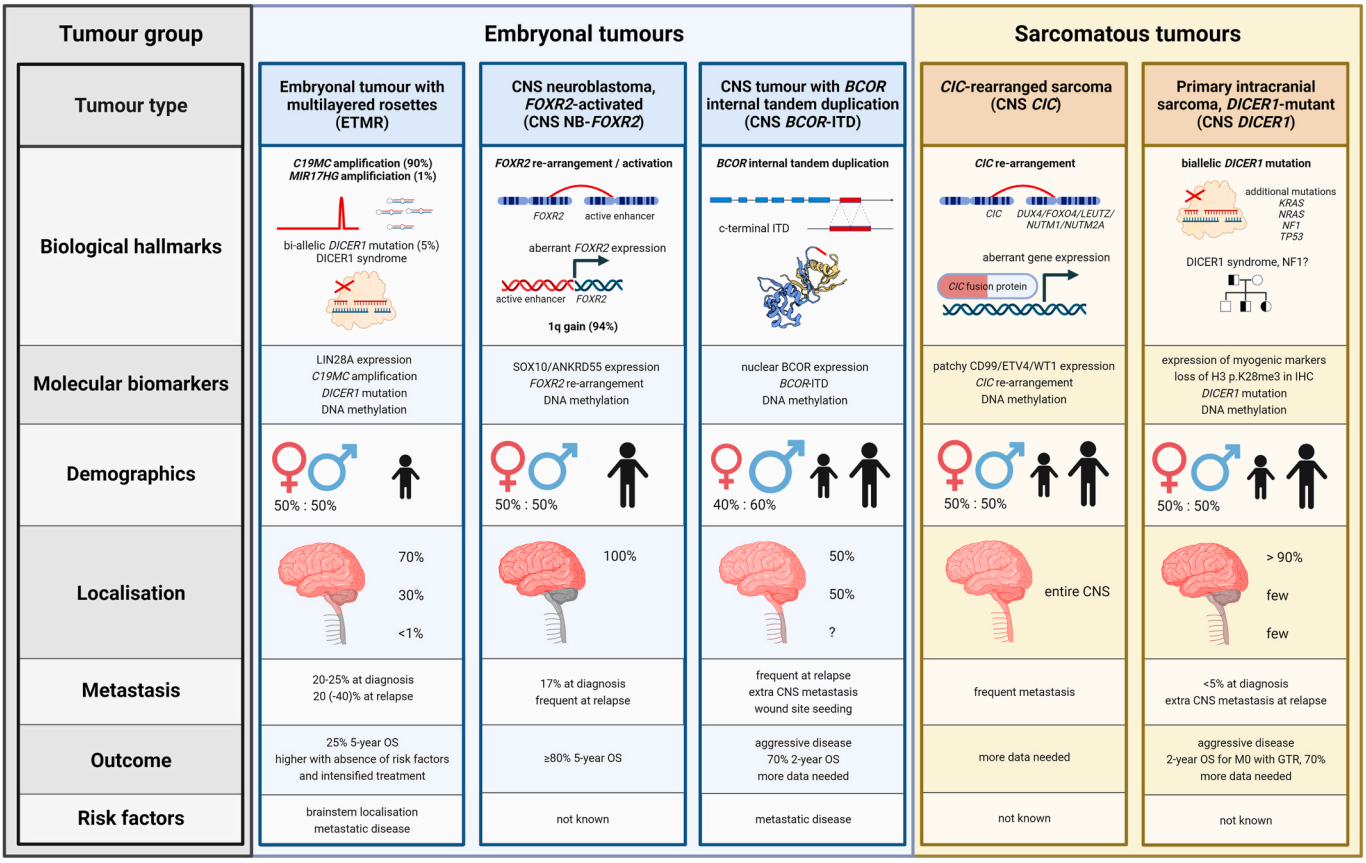

Fig. 1. Summary of rare embryonal and sarcomatous CNS tumour types
Molecular, diagnostic, demographic and clinical parameters are summarized. Created with BioRender.com.

alternatively, presence of a respective DNA methylation profile is required for diagnosis (Louis et al., 2021).

3.4. CNS embryonal tumours NEC/NOS

According to the 5th edition of the WHO classification of CNS tumours, tumours that morphologically present as CNS embryonal tumours, but lack further specific diagnostic criteria can be designated to one of the following diagnoses: CNS embryonal tumours, not elsewhere classifiable (CNS ET, NEC) cannot be assigned to one of the specific tumour entities despite full molecular work-up. This group likely comprises various very rare to date not well-characterized tumour types. Future studies including larger cohorts and in-depth characterization of molecular changes will help to resolve this group.

CNS embryonal tumours, not otherwise specified (CNS ET, NOS) are tumours, for which not all of the necessary diagnostic evaluations have or could not successfully be performed. These tumours may be classified as one of the specific types (as ETMR, CNS NB-*FOXR2*, CNS *BCOR*-ITD or other) upon further diagnostics, which should be initiated as soon as possible. It is strongly recommended to refer such cases (tumour tissue and available molecular data) to a national or international reference centre for further diagnostic work-up.

4. Histopathological and molecular characteristics of rare CNS sarcomatous tumour types

4.1. CNS CIC

CIC-rearranged sarcomas, primarily located within the CNS, were described in the series by Sturm et al. (2016) and in smaller case series (Bielle et al., 2014; Donahue et al., 2018; Łastowska et al., 2020; Yamada et al., 2020). This tumour type was introduced in the 2021 WHO classification of CNS tumours (Louis et al., 2021) and aligned with the diagnostic criteria of *CIC*-rearranged sarcoma occurring outside the CNS. Histopathologically, *CIC*-rearranged sarcoma located within the CNS present with similar features as its extra-CNS counterparts. They display diffuse sheets of undifferentiated, rather uniform round cells. Immunohistochemically patchy, CD99, ETV4 and WT1 expression guides towards the diagnosis (Fig. 2, J) (Antonescu et al., 2017). On the molecular level, these tumours are defined by fusions of *CIC* partnering with different genes including *DUX4*, *FOXO4*, *LEUTZ*, *NUTM1*, *or NUTM2A* (Bielle et al., 2014; Donahue et al., 2018; Helal et al., 2020; Hu et al., 2020; Sturm et al., 2016; Yamada et al., 2020). Of note, recently also *ATXN1*::*DUX4*, and *ATXN1*::*NUTM1* fusions have been described in primitive tumours of the CNS with high similarity to CNS *CIC* (Pratt et al., 2021; Siegfried et al., 2019). The impact of the different fusion partners on the diagnostic classification, biology, and clinical behaviour remains to be elucidated. Diagnosis must be confirmed by evidence of the structural *CIC* rearrangement, or by DNA methylation profile, aligning with this tumour type.

4.2. CNS DICER1

Primary intracranial sarcoma, *DICER1*-mutant, is another molecularly defined entity introduced in the 2021 WHO classification. These tumours are characterized by *DICER1* mutations, most often bi-allelic, which are frequently accompanied by additional somatic mutations (*NF1*, *FGFR4*, *NRAS*, *KRAS*, *EGFR*) (Diaz Coronado et al., 2021; Kamihara et al., 2020; Koelsche et al., 2018). Immunohistochemically these tumours present with spindled or pleomorphic tumour cells (Fig. 2, I)

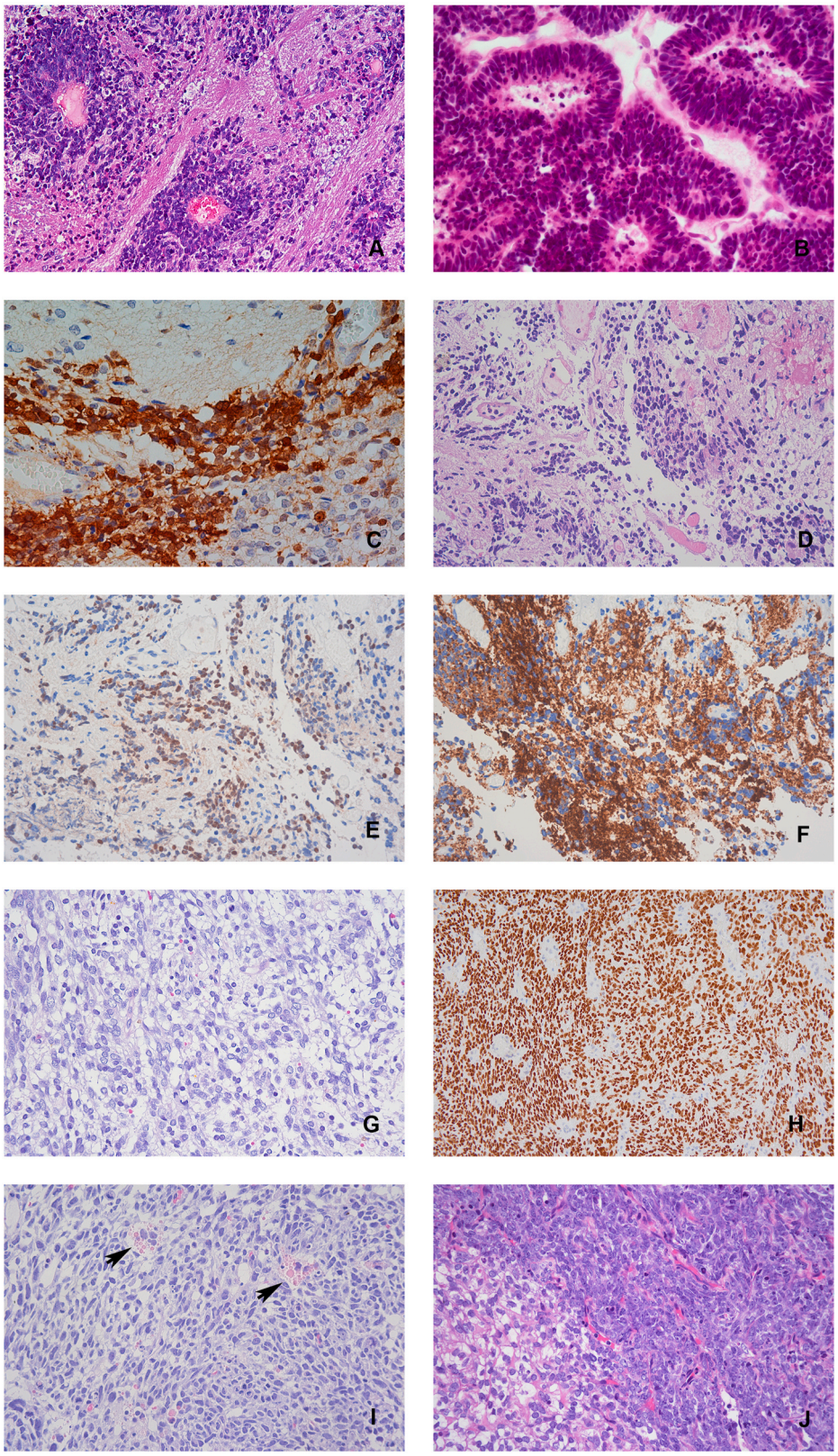

Fig. 2. Histopathological features of rare CNS embryonal and sarcomatous tumour types
A: ETMR with morphological features of ETANTR (A) and medulloepithelioma (B). Lin28A immunoreactivity in ETMR (C). CNS neuroblastoma, *FOXR2*-activated (D) displaying Olig2 (E) and synaptophysin (F) immunoreactivity. CNS tumour with *BCOR* internal tandem duplication (G) with characteristic immunhistochemical expression of BCOR protein (H). Primary intracranial sarcoma, *DICER1*-mutant (I) showing typical eosinophilic droplets (arrows). *CIC*-rearranged sarcoma (J).

frequently expressing myogenic markers and loss of H3 p.K28me3 (K27me3). The diagnosis must be confirmed by detection of the pathogenic mutation(s) in *DICER1* or by a DNA methylation profile aligning with this tumour type.

5. Imaging characteristics of rare CNS embryonal and sarcomatous CNS tumour types

To date, only few studies describing imaging characteristics of these tumours are available and it is currently not possible to distinguish

between entities based on magnetic resonance imaging (MRI) (Cardoen et al., 2022; Dangouloff-Ros et al., 2019; Ferris et al., 2020; Hu et al., 2020; Lee et al., 2019a; Tietze et al., 2022). While larger series (between 10 and 25 patients) only exist for embryonal tumour types (Cardoen et al., 2022; Dangouloff-Ros et al., 2019; Ferris et al., 2020; Tietze et al., 2022), the description of CNS CIC and CNS *DICER1* are currently based on only few cases (Hu et al., 2020; Lee et al., 2019a). CNS NB-*FOXR2*, CNS *BCOR*-ITD, and ETMR have in common that they are mostly large at diagnosis, well-circumscribed and usually T2-hyperintense compared to cortex, often associated with diffusion restriction. Of these tumours, the CNS NB-*FOXR2* appears to be the only one that is located exclusively supratentorially, whereas ETMR and CNS *BCOR*-ITD are found both supra- and infratentorially. They show mild to intermediate and heterogeneous enhancement, are many times characterized by large intralesional vessels, and are often hemorrhagic and/or calcified. The majority consists of both solid and non-solid, i.e. necrotic or cystic, parts and evoke no or only little to intermediate perifocal edema. The very few published cases with CNS *DICER1* and CNS *CIC* showed similar imaging characteristics of large supratentorial tumours, but the low number of cases does not allow substantive conclusion.

Selected images of an ETMR, CNS NB-*FOXR2*, CNS *BCOR*-ITD, CNS *DICER1* are shown in Fig. 3. It must, however, be underscored that especially in the case of CNS *DICER1* generally valid conclusions should not be drawn, as only few cases have been published so far. Larger series including neuroimaging are needed for these entities to better define characteristic neuroradiological features.

6. Clinical characteristics of rare CNS embryonal tumour types

Apart from their distinct molecular characteristics, distinct clinical features have been delineated by several international efforts. Clinical data is sparse so far and evidence on these entities is constantly evolving as the implementation of molecular diagnostics leads to an increased identification.

6.1. ETMR

The clinical characteristics of ETMR have been studied within various patient cohorts and study consortia. This tumour is most commonly diagnosed in very young children (median age 2.5 years at diagnosis, range 0.5–8 years) affecting both boys and girls (Juhnke et al., 2021; Khan et al., 2021; Korshunov et al., 2014; Lambo et al., 2020; von Hoff et al., 2021). ETMR most frequently arise in the supratentorial region, followed by infratentorial localization, whereas spinal ETMRs are rare (Horwitz et al., 2016; Khan et al., 2021; Korshunov et al., 2014; Lambo et al., 2020). ETMRs are generally well demarcated tumours, which present as heterogeneous and large lesions frequently also harbouring cystic or haemorrhagic components (Nowak et al., 2014). The latter may also result in acute presentation. In 15–25% of ETMR patients metastases are present at diagnosis being either solid, leptomeningeal spread or positive cerebrospinal fluid (CSF) cytology (Horwitz et al., 2016; Juhnke et al., 2021; Khan et al., 2021; Spence et al., 2014; von Hoff et al., 2021). The overall prognosis of patients is poor, a fact owing to early and frequent relapse already months after diagnosis. Only about one quarter of patients survive longer than 4–5 years (Khan et al., 2021; von Hoff et al., 2021). Inferior outcome has been shown to be related to brainstem location of the tumour and to metastatic disease at diagnosis (Friedrich et al., 2015; Horwitz et al., 2016; Juhnke et al., 2021; Khan et al., 2021; Spence et al., 2014; von Hoff et al., 2021). Metastatic spread is frequently observed during the course of disease and even extra-CNS metastases have been described (Korshunov et al., 2014; Shah et al., 2018). Importantly, the underlying histopathological pattern is not correlated to clinical outcome (Horwitz et al., 2016; Korshunov et al., 2014; Spence et al., 2014).

6.2. CNS NB-FOXR2

CNS NB-*FOXR2* have so far only been described in the supratentorial region. They predominantly arise in young school age children (reported median ages: 5–8 years, range 2–16 years across different reports) and are balanced across genders (Korshunov et al., 2021; Łastowska et al., 2020; Sturm et al., 2016; von Hoff et al., 2021). Based on partly overlapping retrospective case series, the overall prognosis of this tumour type appears favourable reaching over 80% 5-year overall survival rates (Korshunov et al., 2021; von Hoff et al., 2021). In 17% of patients, metastatic disease is present at diagnosis (von Hoff et al., 2021). Both local and distant relapses confer lower progression-free survival rates between 60 and 80% (Holsten et al., 2021; Korshunov et al., 2021; von Hoff et al., 2021). Due to limited data, estimations for prognostic parameters are difficult to identify. Prolonged survival has also been reported for patients with clinical high-risk criteria as postoperative residual tumour and metastatic disease, suggesting that a curative approach is possible also in these clinical settings (Łastowska et al., 2020; von Hoff et al., 2021). Comparison of outcome after local versus cranio-spinal irradiation in one retrospective cohort showed a higher frequency of distant relapses after local irradiation (von Hoff et al., 2021).

6.3. CNS BCOR-ITD

CNS tumours with *BCOR*-ITD have been predominantly reported in young children but may also be diagnosed in older children and young adults (reported median age 4 years, range 7 months–22 years) (De Lima et al., 2020; Sturm et al., 2016). Available knowledge is still based on small patient series showing that these tumours arise in both genders and across the entire CNS (De Lima et al., 2020; Ferris et al., 2020; Haberler et al., 2019; Kirkman et al., 2018; Łastowska et al., 2020; Paret et al., 2017; Yoshida et al., 2018). Importantly, CNS tumours with *BCOR*-ITD have a high propensity for CNS metastasis but in addition distant extracranial metastases, as well as continuous spread to extracranial tissues (e.g. wound site seeding) have been reported (De Lima et al., 2020; Kirkman et al., 2018; Paret et al., 2016). The aggressive behaviour is corroborated by the observed poor overall survival, which was approximately 70% after 2 years and 50% after 4 years in a pooled analysis of 24 published cases (De Lima et al., 2020).

6.4. CNS embryonal tumour, NEC/NOS

As CNS ET, NEC cannot be considered a uniform entity but rather a heterogeneous group of several rare types and no specific clinical behaviour can be assumed for tumours currently falling into this category. Within a retrospective cohort of clinically annotated patients with original “CNS-PNET” diagnosis, 22% of tumours could not be assigned to a specific diagnosis by DNA methylation analysis making it an important clinical challenge (von Hoff et al., 2021). Within this cohort, 5-year overall survival was 69% and progression-free survival was 54%. This moderate prognosis may likely be explained by the removal of cases with poor prognostic diagnoses from the cohort such as ETMR and high-grade glioma.

7. Clinical characteristics of rare CNS sarcomatous tumour types

7.1. CNS CIC

Within the spectrum of sarcomatous CNS tumours, clinical evidence on *CIC*-rearranged sarcoma is so far limited and tumours arise in all age groups (median age, 5,5 years; range, 0.5–64 years) (Bielle et al., 2014; Donahue et al., 2018; Hu et al., 2020; Ito et al., 2016; Łastowska et al., 2020; Sturm et al., 2016; Yamada et al., 2020). *CIC*-rearranged sarcoma have been described in all CNS compartments and the clinical course ranged from highly aggressive disease with less than 2 years survival to

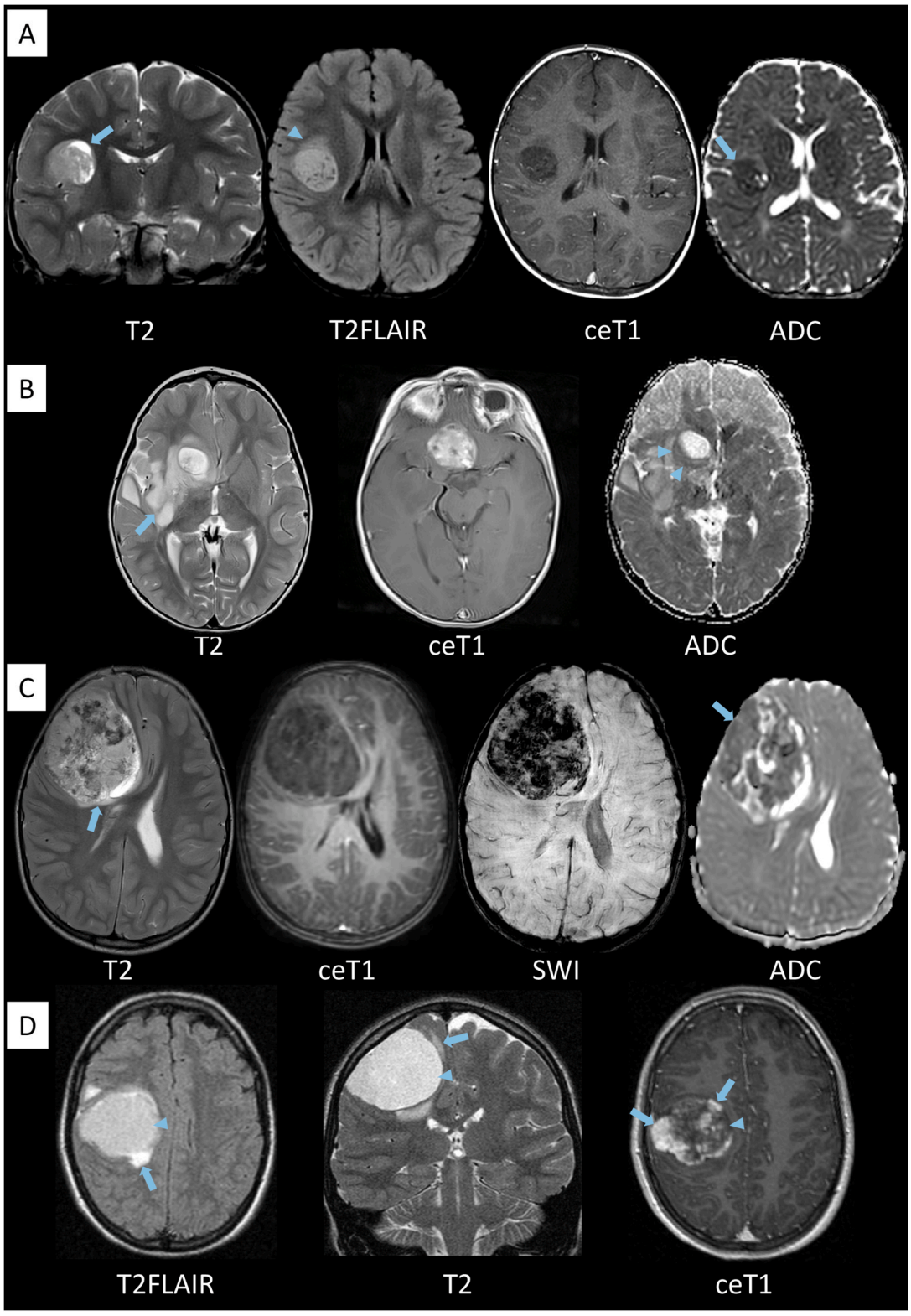

Fig. 3. Imaging characteristics of rare embryonal and sarcomatous tumour types
A: 2.5-year-old boy with an ETMR in the right frontal lobe. The tumour is T2 hyperintense compared to grey matter, contains non-solid regions presumably representing necrosis (light blue arrow on T2), shows subtle perifocal edema (arrowhead on T2FLAIR), no enhancement on contrast enhanced T1 (ceT1) and diffusion restriction (dark areas on the ADC map, light blue arrow). B: 2-year-old girl with a CNS NB-*FOXR2* in the left frontal lobe extending into the suprasellar region (not shown). Intermediate, relatively homogeneous enhancement and moderate perifocal enhancement is found (light blue arrows on T2). In this case, ADC values were not particularly decreased. C: 5-year-old boy with a CNS *BCOR*-ITD in the right frontal lobe that is mixed hyper- and hypointense on T2. The hypointensity is caused by extensive hemorrhages, better seen as signal losses on SWI. There is almost no enhancement on ceT1 and moderate diffusion restriction (light blue arrow on the ADC map). Mild perifocal edema is seen (light blue arrow on T2). D: 13-year-old girl with a CNS *DICER1* in the right fronto-parietal lobes: This tumour shows mild perifocal edema (light blue arrows on T2FLAIR and T2), central necrosis (arrowhead on T2FLAIR, T2 and ceT1) and inhomogeneous enhancement (light blue arrows on ceT1). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

long-term survivors (Bielle et al., 2014; Donahue et al., 2018; Hu et al., 2020; Ito et al., 2016; Łastowska et al., 2020; Le Loarer et al., 2019; Yamada et al., 2020).

7.2. CNS DICER1

Primary intracranial sarcoma, *DICER1*-mutant predominantly affects young children (median age 6 years; range, 2–17.5 years), but has also been described in the adult population with balanced gender distribution. Tumours seem to be most often localized in the supratentorial region but may also rarely occur in the cerebellum and spine (Diaz Coronado et al., 2021; Kamihara et al., 2020; Koelsche et al., 2018; Schweizer et al., 2022). Metastatic disease at the time of presentation seems to be rare, but both local, distant and even extra CNS relapses have been described (Diaz Coronado et al., 2021), with a "sarcomatous" metastatic pattern with pulmonary and bone lesions being the most common sites of metastasis outside of the CNS. Primary intracranial sarcoma, *DICER1* mutant may occur in the context of previous malignancies (Kamihara et al., 2020). If this is only in the context of *DICER1* syndrome or if other tumour predisposing syndromes such as Neurofibromatosis 1 may play a role remains to be elucidated (Lee et al., 2019b). Of note, an increased incidence of primary CNS sarcoma with *DICER1* alteration has been described in a Peruvian series, with no evidence of recurrent germline mutations in known cancer-related genes. This further highlights the possibility of so far unknown tumour predisposing syndromes involved in disease development (Diaz Coronado et al., 2021). As for other rare entities, clinical information is scarce but suggest a highly aggressive behaviour.

8. Implications for clinical management in the molecular era

For none of the here described tumour types prospectively evaluated therapeutic regimens exist. Hence, the current evidence is based on heterogeneous retrospective cohorts and case descriptions. Nevertheless, when considering the rare character of all of these diseases, the clinical decisions have to be based on currently available information, which is therefore summarized in the subsequent recommendations.

8.1. ETMR

Most extensive resection of ETMR has emerged as positive prognostic factor within two independent retrospective series (Horwitz et al., 2016; Khan et al., 2021). Moreover, most reports on survivors include patients after gross-total resection (Jaramillo et al., 2019; Khan et al., 2021; Mayr et al., 2020; von Hoff et al., 2021). In addition, these retrospective analyses point towards benefit of intensified multimodal therapeutic regimens (Horwitz et al., 2016; Juhnke et al., 2021; Khan et al., 2021; Mayr et al., 2020; Mozes et al., 2016; von Hoff et al., 2021). Due to the young age of ETMR patients, the decision on irradiation is often complex. Both, focal and craniospinal irradiation (CSI) have been applied and most reported survivors have received irradiation (Jaramillo et al., 2019; Khan et al., 2021; von Hoff et al., 2021). While the propensity for metastatic spread may propose a potential benefit of treatment with CSI, this cannot be applied for most patients due to the young age. Current available data on patients who were treated with local irradiation show similar results, while comparative data for focal irradiation versus CSI are lacking (Jaramillo et al., 2019; Mayr et al., 2020; von Hoff et al., 2021). In some cases, prolonged survival without irradiation has been reported following gross-total resection and high-dose chemotherapy but the underlying predictive factors remain unclear (Juhnke et al., 2021; Khan et al., 2021; Mayr et al., 2020). With respect to systemic therapies, intensified chemotherapy regimens including high-dose chemotherapy were associated with superior survival compared with less intensive therapy schemes (Alexiou et al., 2013; Juhnke et al., 2021; Khan et al., 2021). In recent published series, overall survival for patients with fully resected, non-brainstem, localized ETMR (n = 10 in Juhnke et al. and n = 14 Khan et al.) was up to 60% after treatment with high-dose chemotherapy and irradiation (Juhnke et al., 2021; Khan et al., 2021). A small series (5 patients) reported positive results for therapy with gross-total resection, focal irradiation, modified IRS-III protocol and various concomitant medications (Hanson et al., 2020). Some investigators have explored the use of intrathecal therapy in addition to focal irradiation with positive results in individual patients (Mayr et al., 2020). Preclinical studies have identified sensitivity of ETMR tumour models to topoisomerase inhibitors and several other agents, which need further preclinical verifications before evaluation in clinical trials (Kleinman et al., 2014; Lambo et al., 2019; Neumann et al., 2017; Schmidt et al., 2017; Spence et al., 2014).

8.2. CNS NB-FOXR2

For CNS NB-*FOXR2,* maximal safe resection is generally recommended for localized tumours. The favourable survival rates for patients, who were treated with upfront CSI in combination with subsequent maintenance chemotherapy suggest a respective treatment for patients, who are old enough to tolerate CSI (Korshunov et al., 2021; von Hoff et al., 2021). Based on current information, local irradiation cannot be recommended, as distant relapses were reported to be more frequent in patients having received only focal irradiation (von Hoff et al., 2021). This phenomenon has also been observed for medulloblastoma (Ashley et al., 2012; Mynarek et al., 2020). For young children not eligible for CSI, radiotherapy-omitting regimens and eventual use of salvage radiotherapy may therefore be used based on the currently limited evidence (von Hoff et al., 2021).

8.3. CNS BCOR-ITD

Regarding CNS *BCOR*-ITD currently available data on patient treatment is highly heterogeneous because the tumour entity is frequently misdiagnosed, based on the different morphologies these tumours may display. Overall, gross total resection appears to be a prerequisite for longer survival, and the majority of cases seem to benefit from irradiation and multiagent therapy (Bremer et al., 2020; Ferris et al., 2020; Łastowska et al., 2020). A potential benefit of CSI has been suggested by a retrospective case series (De Lima et al., 2020) and may further be justified by the observed propensity for distant relapses within the CNS. Based on the aggressive clinical behaviour and the molecular similarities to extra-CNS sarcoma types, intensive multimodal therapies seem to be justified for this tumour type, with use of chemotherapy regimen as evaluated for high-risk embryonal tumour types or sarcoma.

8.4. CNS embryonal tumour, NEC/NOS

No specific treatment can be recommended for CNS ET, NOS and exploitation of all necessary molecular diagnostics as well as referral for diagnostic review is recommended. However, in case of biologically highly aggressive tumours it should be noted, that the start of therapy (e.g. according to other high-risk embryonal tumours) should not be delayed. In case of diagnosis of CNS ET, NEC after application of all diagnostic methods, no standard treatment can be recommended. Of note, CSI should be reserved for older patients with clear evidence of an embryonal CNS tumour (i.e. exclusion of a rare high-grade glioma, glioneuronal tumour, or any low-grade tumour).

8.5. CNS CIC

So far, reported patients with *CIC*-rearranged sarcoma of the CNS have been treated with multimodal strategies following therapeutic recommendations for extra-CNS sarcomas or embryonal CNS tumours (Łastowska et al., 2020; Yamada et al., 2020). For some patients survival within the observation period has been reported and most of them were irradiated upfront (Bielle et al., 2014; Donahue et al., 2018; Hu et al.,

2020; Ito et al., 2016; Łastowska et al., 2020; Le Loarer et al., 2019; Yamada et al., 2020).

8.6. CNS DICER1

As primary CNS sarcoma with *DICER1* mutation may also morphologically closely resemble metastasis of other *DICER1* related tumours like pleuropulmonary blastoma (PPB), it is important to perform comprehensive staging outside of the CNS, to ascertain primary CNS tumour localization. A reliable conclusion on clinical behaviour is hampered by small numbers, different therapeutic approaches due to divergent historical diagnoses and short follow up. Preliminary data suggests an aggressive disease course. Patients seem to profit from complete tumour resection, an intensive multimodal treatment with protocols either adapted from embryonal brain tumour or sarcoma protocols and "sandwich" focal radiotherapy, but a standard treatment has as yet to be defined (Diaz Coronado et al., 2021; Kamihara et al., 2020; Koelsche et al., 2018; Schweizer et al., 2022). Still 70% overall survival rates have been described for non-metastatic patients with complete resection treated with radiochemotherapy (Diaz Coronado et al., 2021).

9. Future directions

Advancements of molecular diagnostics have significantly improved diagnostic accuracy for paediatric brain tumour in recent years. The molecular diagnostics now play a crucial role in clinical decision making, as exemplified by the integration of molecular stratification in the ongoing medulloblastoma trials. In the 5th edition of the WHO classification of CNS tumours, an integrative histopathological and molecular diagnosis, is introduced as diagnostic standard, and is now indispensable for optimal clinical patient management.

The here described, newly defined, rare embryonal and sarcomatous CNS tumour types have been diagnosed as diverse histopathological entities in the pre-molecular era (Sturm et al., 2016). Given the marked molecular and clinical differences between these tumour types, timely upfront state-of-the-art diagnostics with both histology and extensive molecular diagnostics is of particular importance for patients with these tumours. In this context, diagnostic delay represents a major challenge, as changes of the underlying diagnosis will likely impact therapeutic decisions, while the aggressiveness of the tumours necessitates early treatment start. To this end, it is indispensable to set-up expert centres and research networks to facilitate timely and comprehensive diagnostics, review processes and data collection. The timely availability of a precise and specific diagnosis is prerequisite for the appropriate selection of a treatment strategy for the individual patient and the potential relevance of diverse histopathological, molecular or clinical markers within the respective tumour types remain to be further defined. Only extensive international cooperation can provide us with sufficient data to increase our understanding on the tumour biology, the clinical behaviour and to identify prognostic markers. On this basis, efficient treatment strategies may be evaluated in future collaborative studies.

Within the heterogeneous group of CNS ET, NEC/NOS delineation of further rare entities with specific molecular and clinical features is expected, which will result in the ongoing dilemma, that therapeutic decisions need to be drawn before reliable clinical data are available. Especially for young patients, the balancing of expected toxicity and benefit in the absence of solid evidence is troublesome. Retrospective case descriptions and cohorts have shed some light onto to clinical nature of the so far delineated rareembryonal and sarcomatous CNS tumours, that may be used as orientation for therapeutic management (De Lima et al., 2020; Diaz Coronado et al., 2021; Khan et al., 2021; von Hoff et al., 2021).

All therapeutic assumptions on the limited available retrospective data need to be viewed as "preliminary" and require further evaluation in larger prospective series. The poor prognosis of many of those entities, combined with the small number of cases, emphasizes the urgent need for international joint efforts for these children.

In the future, additional levels of analyses e.g. proteomic data or liquid biopsies may aid in further delineation of the underlying biological characteristics, the resulting clinical behaviour and potential therapeutic interventions. Importantly, in-depth evaluations of tumour tissue and tumour models are essential to generate novel treatment hypotheses for evaluation within clinical trials.

Taken together, this underlines the need for international collaboration with prospective documentation of biological diagnosis, demographic and clinical data to enable informed treatment decisions and the development of future prospective studies.

10. Conclusion

The introduction of novel entities within the spectrum of rare embryonal and sarcomatous CNS tumours in the recent 5th edition of the WHO classification of CNS tumours is an essential prerequisite for more accurate therapeutic decisions for patients suffering from these rare entities. Based on retrospective patient series, first recommendations can be formulated for some of these entities. Set-up of international registries integrating biological and clinical data will be the key towards a more profound understanding of these tumours, monitoring of current treatment results, and delineation of therapeutic strategies that will prospectively be evaluated in future studies.

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Johannes Gojo: Conceptualization, Funding acquisition, Investigation, Writing – original draft. **Mimi Kjaersgaard:** Writing – review & editing, Investigation. **Barbara v. Zezschwitz:** Writing – review & editing, Investigation. **David Capper:** Writing – review & editing, Investigation. **Anna Tietze:** Investigation, Writing – original draft. **Marcel Kool:** Supervision, Investigation. **Christine Haberler:** Writing – review & editing, Investigation, Writing – original draft. **Barry Pizer:** Supervision, Writing – review & editing. **Katja v. Hoff:** Conceptualization, Supervision, Writing – review & editing.

Data availability

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