CLINICAL PRACTICE RECOMMENDATIONS

Rare CNS embryonal and sarcomatous tumours and Astroblastoma, *MN1*-altered

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Please note, that it is highly recommended to register patients within the CNS-InterREST registry (**Inter**national Registry for Patients with **R**are CNS-**E**mbryonal and **S**arcomatous **T**umours**)**

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1 Background and included tumour entities

The classification of rare embryonal and sarcomatous tumours of the CNS has undergone extensive changes in the past years following constantly improving insights into their underlying molecular biology. In the fifth edition of the WHO classification of tumours of the CNS (WHO CNS5) published in 2021, the diagnostic criteria of existing entities have been refined and several new tumour types have been incorporated either as definite or as provisional entities [1].

Many of the tumours, which can now be assigned to a specific type within the spectrum of rare CNS embryonal tumours and CNS mesenchymal, non-meningothelial tumours, have previously received a diagnosis of “primitive neuroectodermal tumour (PNET)”. This term was introduced to classify tumours based on their morphological appearance as small-cell, malignant CNS tumours [2,3]. The respective tumours were delineated as supratentorial PNET (stPNET) in the 2000 WHO classification [4] and as CNS PNET in the 2007 WHO classification of CNS tumours [5]. Molecular analyses of histologically diagnosed CNS PNETs revealed that other tumour types including high-grade gliomas (HGG), ependymomas, atypical teratoid rhabdoid tumours (ATRT), and medulloblastomas have been misdiagnosed as CNS PNETs. These analyses helped to refine existing entities and delineate new entities e.g. embryonal tumour with multilayered rosettes (ETMR), each with distinct molecular aberrations and clinical behaviour [6,7]. Hence, in 2016 in the updated 4th edition of WHO classification of CNS tumours the term CNS PNET has become obsolete and was replaced by CNS embryonal tumour, NOS [1,7,8].

The 2021 WHO CNS5 classification lists ETMR, CNS neuroblastoma, *FOXR2*-activated (CNS NB-*FOXR2*), CNS tumours with *BCOR* internal tandem duplication (CNS *BCOR* ITD), and CNS embryonal tumour NEC / NOS as separate entities in the group of other CNS embryonal tumours. For CNS *BCOR* ITD it remains unclear if the tumours are of neuroepithelial or mesenchymal origin. Within the mesenchymal tumours of uncertain differentiation, *CIC*-rearranged sarcoma, and primary intracranial sarcoma, *DICER1*-mutant are newly introduced [1] and are discussed within this document. Of note, (intracranial) Ewing sarcoma is also classified as mesenchymal tumour of uncertain differentiation. However, it is not included in this document, as clinical recommendations are in the responsibility of the respective Ewing sarcoma working groups.

Due to the changes in classification, the high heterogeneity within the group and resulting lack of entity-specific clinical data, these tumours represent a major challenge to both diagnosis and clinical management. The treatment of the resulting specific rare CNS embryonal tumour entities is still mainly based on historic CNS PNET treatment concepts. Although widely used, these concepts cannot be considered “standard” for the specific rare CNS embryonal tumours. Likewise, no treatment standard exists for the newly delineated mesenchymal CNS tumour entities with specific molecular alterations.

Not all tumours derived from the morphological spectrum of CNS embryonal tumours can be assigned to a specific molecularly defined tumour-entity yet, and the delineation of further rare entities is anticipated.

Within the cohort of historic CNS PNET re-evaluated by DNA methylation profiling, a small distinct group of tumours characterized by *MN1* fusions was delineated [7]. Additional cases with matching methylation profiles had various other histological features and the group was thus originally termed high-grade neuroepithelial tumours with *MN1* alteration (HGNET-*MN1*). In the meantime, it has been shown that most of these tumours with a respective *MN1* fusion present as astroblastoma on morphology, and the group has thus been renamed into astroblastoma, *MN1*-altered, in the 2021 WHO CNS5 classification [1]. There is so far no WHO grade assigned and the impact of morphological features on clinical behaviour of this entity is not yet known. Consequently, this entity has only provisionally been included in the here described group of tumours. It will need to be decided in the future if astroblastoma, *MN1*-altered may be assigned to the SIOP-E low-grade or high-grade glioma working group.

This document is intended as a guideline for diagnosis and treatment of rare CNS embryonal and sarcomatous tumours and astroblastoma, *MN1*-altered.

These include:

Rare CNS embryonal tumours:

- **Embryonal tumours with multilayered rosettes (ETMR)**
- **CNS neuroblastoma, *FOXR2*-activated**
- **CNS tumour with *BCOR* internal tandem duplication**
- **CNS embryonal tumour, NEC/NOS**

CNS sarcomatous tumours:

- ***CIC*-rearranged sarcoma**
- **Primary intracranial sarcoma, *DICER1*-mutant**

Astroblastoma, *MN1*-altered

Importantly, the actual classification represents the current status of knowledge and will be prone to continuous changes in the coming years.

1.1 General aspects of the neuropathological diagnosis of rare CNS-embryonal tumours, rare sarcomatous CNS tumours and Astroblastoma, *MN1*-altered

Whereas in previous CNS WHO classifications the diagnosis of rare CNS-embryonal, sarcomatous or astroblastoma tumours relied on morphological characteristics, these tumours are now defined in WHO CNS5 by a combination of morphological and molecular markers. Essential and desirable diagnostic criteria which should be applied for the diagnosis, are provided for each tumour type [1].

For the diagnostic work-up of these tumours, ideally various molecular techniques should be accessible in addition to standard (immunohistochemical) staining. Depending on the type of tumour, the molecular characteristics can be analysed using a combination of DNA methylation profiling (EPIC array and classification by the Heidelberg brain tumour classifier

(www.molecularneuropathology.org)), FISH, NGS or Sanger sequencing. In unusual cases additional whole genome or RNA sequencing may be necessary.

If molecular analyses are not available or could not be successfully performed, a provisional diagnosis of embryonal, sarcomatous, or astroblastoma tumour, NOS (not otherwise specified) should be provided and 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. Splitting of the tumour tissue and referral to several centres should be avoided as this might result in unnecessary repetitive investigations and preclude further high-end molecular analyses due to lack of tumour tissue.

In cases where molecular analyses were successfully performed but the results do not lead to an established WHO CNS5 diagnosis, a NEC (not elsewhere classified) diagnosis is appropriate. Yet, the available tissue of such cases and the molecular data should still be referred to specialized centres and/or a central biobank as this helps to recognize and define new, rare tumour types.

It should be kept in mind that this field is moving rapidly and new molecular alterations will be described in the future.

2 Rare CNS embryonal tumours

2.1 Staging of rare CNS-embryonal tumours

Cerebral and spinal MRI according to the SIOP-E Imaging Guidelines[9] at the time of diagnosis is mandatory in all patients. If clinical condition of the patient allows, spinal MRI should be performed before surgery to prevent diagnostic uncertainties due to postoperative changes.

Patients should undergo early post-operative MRI assessment of the extent of resection. “Early postoperative MRI” is defined as MRI performed less than 72 hours after surgery (best 24 - 48 hours), and it needs to be obtained according to the above-mentioned guidelines and comparable to the preoperative MRI.

Post-operative lumbar puncture should be performed to assess for metastatic spread where it is safe to do so. This is generally undertaken at day 14 post-surgery or beyond. If tumour cells are present in CSF from a lumbar puncture performed within 14 days of surgery, the lumbar puncture should be repeated on day 15 or later after surgery.

The Chang staging system is used to categorise the metastatic status [10]:

M0: No evidence of gross subarachnoid or hematogenous metastasis
M1: Microscopic tumour cells found in cerebrospinal fluid
M2: Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3: Gross nodular seeding in spinal subarachnoid space
M4: Metastasis outside the cerebrospinal axis.

In patients with known tumour predisposition syndromes, staging should include screening for other associated tumour entities.

2.2 Treatment of CNS-embryonal tumours

Treatment strategies for CNS-embryonal tumours differ with regard to the specific diagnosis and are further specified below.

Treatment generally includes a surgical resection with the aim of maximal safe resection. Postoperative treatment may include irradiation either as craniospinal irradiation with boost to the tumour bed and metastases, or focal irradiation, which are both combined with multiagent chemotherapy regimen. Selection of the postoperative treatment depends on factors such as diagnosis, age, metastatic and residual tumour status, as well as local and national practice.

Available evidence for selection of specific treatment strategies for the here described rare CNS-embryonal tumours is generally limited and is mostly based on retrospective cohort studies on heterogeneously treated patients. Due to the rarity and novelty of the entities, there are no prospective data available.

The following information is provided on the nature of and general treatment principles for individual tumour entities, all of which are rare. Treatment should be guided by the principles of management in paediatric neuro-oncology, the available evidence albeit limited, by national approaches to therapy, and by individual patient factors.

Advice on the management of individual patients and the details of various regimens can generally be provided by national experts.

In addition, advice can be provided by members of the SIOP-Europe rare embryonal and sarcomatous Tumour Group (see title page).

2.3 Embryonal tumour with multilayered rosettes (ETMR):

2.3.1 Introduction

ETMR is a highly aggressive, CNS WHO grade 4 tumour, mainly occurring in early childhood. It is molecularly characterized by high level amplification of the large microRNA cluster *C19MC*. Amplification of *C19MC* was first recognized within a sub-group of CNS PNETs with poor survival [11]. Increasing insights into the molecular biology of paediatric brain tumours led to the finding that this hallmark molecular alteration is characteristic for a specific clinicopathological entity of embryonal rosette-forming neuroepithelial tumours that can morphologically present as embryonal tumour with abundant neuropil and true rosettes (ETANTR) [12], as well as ependymoblastoma (EBL) [13] and medulloepithelioma (MEPL) [14], two long established morphologically defined sub-entities of CNS PNET [15]. As a consequence, the term ETMR was introduced for this distinct group of tumours in the 2016 WHO classification of CNS tumours [8]. Amplification of *C19MC* in ETMR is often accompanied by fusion of this locus to the *TTYH1* gene and is present in approximately 90% of ETMR [16–19]. In *C19MC*-negative ETMR, amplification of another microRNA cluster (*MIR17HG*) and bi-allelic mutations of *DICER1*, a gene encoding a critical protein within the microRNA processing machinery, have been

identified [20]. Importantly, most *DICER1*-mutant ETMRs arise on the basis of a *DICER1* mutation within the germline, a cancer predisposition condition termed *DICER1* predisposition syndrome [16,20,21].

2.3.2 Neuropathological diagnosis

ETMR is defined as an embryonal CNS tumour displaying three different morphological patterns: ETANTR, EBL or MEPL. Molecularly these tumours are, irrespective of their morphology, highly similar and characterized either by a *C19MC* alteration or in rare cases by bi-allelic *DICER1* mutations.

Essential diagnostic criteria: histopathological presence of one of the three typical morphological patterns and either *C19MC* alteration or a *DICER1* mutation and for unresolved lesions a DNA methylation profile aligned with ETMR.

Recommended diagnostic work-up:
In the majority of cases the typical morphological patterns are recognizable on HE sections and immunohistochemical LIN28A expression complements the diagnosis. In small samples without characteristic morphological features, immunohistochemical LIN28A expression may guide the diagnosis. However, LIN28A expression is not specific and may be observed in other tumour types e.g. ATRTs or malignant gliomas necessitating an exclusion of these tumours. *C19MC* amplification can be detected by FISH with commercially available probes (e.g. C19MC/TPM4, Cytotest®, CT-PAC033), SNP (single nucleotide polymorphism)-array-based techniques or DNA methylation array based copy number plots generated by the Heidelberg brain tumour classifier (www.molecularneuropathology.org) as part of DNA methylation data analysis. Some cases have only a small cluster of *C19MC* gained or amplified cells, which may not be detected by the copy number plots generated from the methylation arrays, but can be detected by FISH. Cases without *C19MC* amplification should be screened for *DICER1* mutations and if present genetic counselling should be recommended. In rare cases negative for *C19MC* amplification and *DICER1* mutation, identification of *MIR17HG* amplifications may help in defining the correct diagnosis.

2.3.3 Clinical features and available evidence on treatment

Most children diagnosed with ETMR are younger than 3 years of age (median 2.5 years, range approx. 0.5–8 years) and gender ratio has been reported to be almost balanced [15,16,22,23].

The most common localisation of ETMR is the supratentorial region, and 30%-40% arise in the infratentorial region, including cerebellar and pontine origin, while spinal ETMRs are rare [15,16,24,25]. In general, ETMRs present as large, heterogeneous, but well demarcated lesions on MRI, frequently exhibiting cystic components and intratumoural haemorrhage, which may also lead to an acute presentation [26]. Metastases at initial presentation are reported for 15–25% of patients with both macroscopic intracranial or spinal leptomeningeal spread and microscopic spread to the CSF reported [22–25,27].

Clinical features that have been associated with an inferior outcome are brainstem localization and metastatic disease at diagnosis [22,25]. Most of reported patients with brainstem localization of an ETMR died shortly after diagnosis [22–24,27,28]. Rarely, longer survival of patients with

brainstem ETMR have been reported with limited follow-up time after subtotal or gross total resection, while molecular confirmation of diagnosis was not available for all these cases [29,30]. In contrast, supratentorial tumour location has been identified as a positive prognostic factor in one retrospective study (34% versus 20% 5-year OS) [22]. Of the patients with metastatic spread at presentation, there are only single patients reported that have survived within the reported observation time, and presence of metastases has been associated with inferior prognosis [22,23,25].

Upon tumour progression both local and less commonly distant CNS metastases occur and in rare cases, extra-CNS relapses have been described [15,31]. Within the available retrospective studies, there was no prognostic impact detected for the histological presentation as either ETANTR, EBL, or MEP [15,24,27].

The overall prognosis of ETMR is poor, and most tumours progress during the first year after diagnosis with frequent progressions or relapses on-treatment. Reported overall survival rates are approximately 25% in retrospective cohorts with heterogenous treatments and up to 66 % in patients that were treated within or according to former trials for young children with embryonal tumours with an intensified treatment approach including gross total resection, high-dose chemotherapy and irradiation [15,22–25,27]. Further long-term survivors of over 5 years have been described as individual cases or in small series [32,33]. Most of the tumour progressions occur early, including in patients still on treatment [22,23,25], while only a few patients could be salvaged in the face of progression. Late relapses seem to be rare [23].

No entity-specific treatment has so far been prospectively evaluated for ETMR. Most described patients have been treated according to diverse medulloblastoma or CNS PNET studies or according to other high-risk infant CNS tumour or ATRT-protocols.

Available data suggest a positive prognostic role for resection status. Complete resection has been identified as a positive prognostic factor in two retrospective series [24,25]. However, postoperative resection status did not impact on outcome in two other studies [22,23] which may be explained by a high rate of re-resections after onset of treatment in the latter series. In focused analyses of long-term survivors, most but not all patients underwent gross total resection within their treatment course [32,34,35].

Available reports on ETMR patients point towards benefit for overall survival through more intensive treatment [22–25,32,34]. Treatment of the patients reported in the aforementioned retrospective studies was heterogenous. With regard to radiotherapy, both focal and craniospinal irradiation (CSI) have been applied and most reported long-term survivors have received irradiation [23,25,32,35].

The propensity of ETMR for metastatic spread may suggest a potential benefit of treatment with CSI. However, due to the young age of the patients, this cannot be applied regularly. The current available data on patients who were treated with local irradiation show comparable results to those receiving CSI [23,32,35]. Of note, few patients have been described that have survived longer than the observation time that have not received irradiation after gross total resection and high-dose chemotherapy have been described, while further predictive factors for identification of patients that may effectively be treated without irradiation are not yet known [22,25,32].

Regarding chemotherapy, superiority of an intensified chemotherapy treatment including high-dose chemotherapy over a conventional “infant-type” chemotherapy approach has been shown in two retrospective studies [22,25] and one older meta-analysis [36]. In a retrospective analysis of a heterogeneously treated cohort, response to chemotherapy was documented for 30% of ETMR patients [23]. Preclinical drug screening has identified topoisomerase inhibitors, anthracyclines, and dactinomycin as potentially effective agents [19,27,37,38]. This may indicate a possible benefit of ATRT regimen that in contrast to “CNS PNET” regimen include anthracyclines and dactinomycin. However, there are no comparative data so far. A small series of patients (n=4) treated with a modified IRS-III protocol has shown promising results, although patients have received multiple and heterogenous additive treatments [33]. Some investigators have explored the use of intrathecal therapy in addition to focal irradiation resulting in survival of over 5 years in individual cases [32].

Data on targeted or experimental treatments are rare. In the aforementioned preclinical drug screening, epigenetic modifying agents, mTOR inhibitors, bromodomain inhibitors and the GLI inhibitor arsenic trioxide showed some evidence of additional efficacy in mice [19,27,37,38]. A small series of patients (n=3) treated with targeted radioimmunotherapy using intraventricular ^{131}I-Omburtamab targeting B7-H3 has been reported, and may have a therapeutic benefit as a consolidation after chemotherapy and radiation therapy, with 2 treated patients remained disease-free after multiagent chemotherapy, local irradiation and ^{131}I-Omburtamab treatment [39]. Despite assumed recruitment of several patients with ETMR in molecular profiling trials for identification of potential treatment targets, only one report has been published so far on a patient effectively treated with dasatinib based on the PDGFR and SRC activity detected within the individual tumour [40]. Preclinical work for the set-up of a molecularly informed trial is ongoing [20].

2.3.4 Recommendations for treatment

ETMR are high-risk tumours. Therapy should be primarily based on national therapy guidelines. Members of the SIOP-Europe rare embryonal and sarcomatous tumour working group would be happy to provide advice (see title page).

Currently, there is no evaluated and agreed treatment standard. Therefore, general treatment principles are mentioned here rather than a specific treatment protocol.

General approach:

- A curative treatment approach should generally be undertaken.
- Patients with metastatic disease probably have a very poor prognosis, particularly if cranio-spinal irradiation is chosen not to be applied e.g. in very young children.
- Patients with brain stem involvement appear to have a worse prognosis than those with tumours outside this site; if this is due to poorer resection status or additional prognostic factors remains to be elucidated. As the role of residual tumour is unclear, the operative risk should well be weighed against the potential benefit of gross or near total resection in this localisation.

Resection:

Maximal safe resection is recommended as initial therapy.

- In the case of postoperative residual tumour, re-resection should be considered. Second surgery should - however - not delay the start of further therapy.
- As a proportion of ETMRs are chemoresponsive, the early start of chemotherapy treatment should be prioritised and an early MRI assessment undertaken. Second surgery should be then considered in order to obtain a gross total or near total resection.
- In cases of metastatic disease, the surgical strategy should be considered on an individual basis.
- Due to a high risk for early treatment-refractory progressions / relapses, any unnecessary treatment delay should be avoided, and early and frequent follow-up imaging is recommended.

Radiotherapy:

There is increasing evidence that radiotherapy is important to optimise the chance of cure.

- Thus, in general, following surgery treatment should consist of multi-agent chemotherapy together with either focal or craniospinal radiotherapy given early.
- The decision for the application of irradiation, the respective field (local versus CSI) and irradiation technique (photon versus proton) should be guided by age, staging and the size and location of the tumour.
- For young children (within the first 3 to 4 years of life) with non-metastatic disease, local irradiation to the tumour bed is recommended, while the limited evidence is acknowledged.
- For older children (> 3-4 years at diagnosis), the radiotherapy approach rests between CSI and focal radiotherapy with insufficient evidence for clear recommendations. The radiotherapy approach (CSI vs. focal) should be thus determined on an individual factors and national considerations.
- Irradiation should be performed early in the treatment course. If high-dose chemotherapy is planned, this should precede the irradiation and should not be given afterwards, due to a high risk for toxicity.
- It is appreciated that for some patients, dependent on very young age, site and extent of tumour and other factors, there may be a wish to avoid treatment with (focal) radiotherapy. However, there are only very few long-term survivors reported that have been treated with a radiation-free approach. As prerequisite for a radiotherapy avoiding approach with curative intent for very young children, gross total resection should be achieved, and conventional and high-dose chemotherapy applied.
- In case of residual tumour, a re-resection should be evaluated before onset of irradiation.

Chemotherapy:

In some regimens/guidelines (e.g. UK CCLG approach), conventional chemotherapy is followed by myeloablative chemotherapy prior to either focal or craniospinal radiotherapy.

- Possible chemotherapy regimens used in the treatment of ETMR include:
  - Regimens used for ATRT e.g. modified IRSIII [33], EuRhab [41]
  - Regimen evaluated for rare CNS-embryonal tumours: P-HIT [22], SJMB03 [42]
  - Regimen evaluated for young children with high-risk CNS tumours: Head Start, ACNS0334
- There are no comparative data available yet
- Some investigators have explored the use of intraventricular/intrathecal chemotherapy although, at present, there is no evidence that this is beneficial. In general, administration of intraventricular/intrathecal chemotherapy following irradiation should be carefully considered taking into account potential toxicities and clinical status of the patient.

Tumour predisposition

Upon detection of somatic *DICER1* alterations in the tumour, genetic counselling and germline investigation is highly recommended to determine if *DICER1* syndrome is present.

Staging and follow up should take tumour predisposition into consideration and affected patients and family members should be included into a cancer predisposition surveillance program for early detection of associated other malignancies [43].

2.4 CNS neuroblastoma, *FOXR2-activated*

2.4.1 Introduction

CNS neuroblastoma was previously included in the WHO classification of CNS tumours as a morphologically defined entity. In the study by Sturm et al. 2016, a distinct group of tumours was delineated by DNA methylation profiling that is characterised by chromosomal rearrangements leading to increased expression of the forkhead box R2 (*FOXR2*) gene [7]. *FOXR2* has been described to play a role in tumourigenesis and proliferation in several tumours, and the functional role for induction of CNS-embryonal tumours has been confirmed [44]. Due to the morphological resemblance of a subset of the *FOXR2*-activated CNS-embryonal tumours to the previously described CNS neuroblastoma, the entity was named CNS neuroblastoma, *FOXR2*-activated (CNS NB-*FOXR2*) [1]. Nearly all tumours show a gain of 1q beside other copy number variations such as 3p loss, 16q loss, and 17q gain [23,45,46]. The entity has been introduced as a molecularly defined entity within the 2021 edition of WHO classification of CNS tumours [1].

2.4.2 Neuropathological diagnosis

Definition: CNS neuroblastoma, *FOXR2*-activated, is an embryonal neoplasm exhibiting varying degrees of neuroblastic and/or neuronal differentiation, including foci of ganglion cells (ganglioneuroblastoma) and neuropil-rich stroma and undifferentiated embryonal tumours at the ends of the spectrum. It is characterized by activation of the transcription factor *FOXR2* by genomic structural rearrangements.

Essential diagnostic criteria are: an embryonal tumour with foci of neuroblastic or neuronal differentiation and the activation of *FOXR2* by structural rearrangement and gene fusion. For unresolved lesions a DNA methylation profile aligned with CNS neuroblastoma, *FOXR2* activated confirms the diagnosis.

Diagnostic work-up:
Immunohistochemically, CNS neuroblastoma, *FOXR2*-activated frequently express Olig2, synatophysin and are predominantly vimentin negative. Combined expression of SOX10 and ANKRD55 have been described as diagnostic [45]. In poorly differentiated tumours, diffuse paediatric-type high-grade glioma H3-wildtype and IDH-wildtype is an important differential diagnosis and needs to be excluded. 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.

2.4.3 Clinical features and available evidence on treatment

CNS NB-*FOXR2* tumours arise in young children (median age 5-8 years, range 2-16 years, across different reports), while age at presentation is usually older than for patients with ETMR [23,45]. The gender ratio appears to be balanced [23,45]. To date, only supratentorial CNS NB-*FOXR2* tumours have been reported [7,45,47]. In one study, CNS metastases were present in 17% of cases [23].

Most of the so far reported patients with CNS NB-*FOXR2* have received treatment according to diverse CNS PNET protocols. Retrospective analyses suggest that this group of tumours exhibit a good overall prognosis with 5-year overall survival rates of >= 80% [23,45]. However, both local and distant relapses occur and progression-free survival rates have been reported as 60-80% [23,45,46]. Data on the prognostic impact of staging at presentation are limited. Importantly, of the few reported patients with metastatic disease there were several survivors, justifying a curative treatment approach in case of metastatic presentation [23,47]. Evidence on the prognostic relevance of postoperative residual tumour is limited, with one retrospective study showing that it has no impact on survival [23].

Current data suggests that the best survival rates were achieved after treatment with upfront CSI combined with chemotherapy according to former CNS PNET studies [23,45]. In one retrospective pooled study, the frequency of distant relapses was higher in patients who had received a local irradiation. In this study, objective response rates of 60–70% were observed following chemotherapy and HDCT treatment and effective use of salvage radiotherapy for RT-naïve patients has been described [23]. This suggests that young patients with CNS NB-*FOXR2* who cannot be treated with CSI may profit from a radiotherapy-omitting regimen, and the use of local irradiation may rather be avoided.

Overall, numbers of reported patients are so far very low, leading to a risk of disparate results in future cohorts and underlining the necessity for prospective registration and documentation of treatment and outcome for patients with CNS NB-*FOXR2* until a prospective trial is available.

2.4.4 Recommendations for treatment

CNS NB-*FOXR2* are tumours with expected moderate to good overall survival. Therapy should be primarily based on national therapy guidelines. Members of the SIOP-Europe rare embryonal and sarcomatous tumour working group would be happy to provide advice (see title page).

The following general therapeutic approaches are based on retrospective data. There is no prospectively evaluated treatment regimen available.

Resection:

Maximal safe resection is recommended as initial therapy.

- In the case of postoperative residual tumour, re-resection should be considered. Second surgery should, however, not generally delay the start of further therapy.
- As CNS NB-*FOXR2* are expected to be chemoresponsive, upfront chemotherapy treatment may be used in case of postoperative residual tumour, and an early MRI assessment undertaken. Second surgery should then be considered in order to obtain a gross total or near total resection (see below).

In cases of metastatic disease, the surgical strategy should be considered on an individual basis.

For patients aged above 3-4 years at diagnosis and stage M0 R0:

- Upfront treatment with CSI is recommended, with a medulloblastoma standard-risk dose of 23.4 Gy CSI and boost to the tumour bed.
- Subsequent treatment with a medulloblastoma-like maintenance regimen is recommended.
    - After irradiation, a maintenance treatment analogous to the maintenance regimen within the SIOP MB 5 protocol could be considered (8 courses BABABABA), with toxicity surveillance and dose reductions analogous to the protocol.
    - Alternative maintenance regimens include the “Packer-Regimen” (as evaluated in CCG-9892, HIT-91, and PNET-4), ACNS 0332, and others.
- Some national groups may wish to treat CNS NB-*FOXR2* using regimens designed for high-risk medulloblastoma e.g. SJMB03.

For patients with localized, unresectable postoperative residual tumour, aged above 3-4 years at diagnosis:

- Upfront chemotherapy may be used with subsequent re-evaluation of surgery.
- A reasonable option would be upfront treatment with 2 courses of carboplatin / etoposide (as used in the SIOP HR-MB protocol) although other embryonal CNS tumour protocols may be used.
- Second surgical opinion is recommended.
- Further treatment should include irradiation with CSI and maintenance chemotherapy treatment as described for stage M0R0 patients.

For patients with metastatic disease, aged above 3-4 years at diagnosis:

Patients with metastatic CNS NB-*FOXR2* may have a moderate prognosis, if treated sufficiently (see above).

- Treatment according to a protocol for high-risk medulloblastoma or CNS PNET with increased (high-risk) CSI dose is recommended, e.g. ACNS 0332 [48], St Jude MB03 or MB12, HIT-2000 [49].
- Upfront chemotherapy may be used with subsequent re-evaluation of re-surgery.

For young patients aged below 3-4 years at diagnosis:

- Combination chemotherapy regimen +/- re-resection + high-dose chemotherapy is recommended. If complete remission (CR) is achieved by these measures, omission of irradiation is recommended.
- Possible treatment regimens with the intention of omission of irradiation are:
  - Regimen evaluated for rare CNS-embryonal tumours: P-HIT [22]
  - Regimen evaluated for young children, high-risk, CNS tumours: e.g. Head Start, ACNS 0334

2.5 CNS tumour with *BCOR* internal tandem duplication (ITD)

2.5.1 Introduction

Another novel high-grade neuroepithelial tumour was originally named high-grade neuroepithelial tumour with *BCOR* alteration (HGNET-*BCOR*). In WHO CNS5 the diagnosis was specified as CNS tumour with *BCOR* internal tandem duplication (CNS *BCOR*-ITD). These tumours are characterized by a distinct DNA methylation profile and harbour specific genetic alterations within the *BCOR* gene [1,7]. Interestingly, the eponymous ITD within the c-terminal domain of the BCOR protein, was previously also detected in clear cell sarcomas of the kidney as well as soft tissue sarcoma [7,50,51].
In the abovementioned first study by Sturm et al. based on methylation analysis additional epigenetically similar cases have been identified – however - harbouring other aberrations within the *BCOR* gene including point mutations or deletions all of which are not diagnostic CNS *BCOR* ITD and would at present be subsumed under the term of embryonal tumour, NEC [7]. Moreover, recent reports have identified potentially related tumours harbouring gene fusions involving either *BCOR* or *BCORL1* and either *EP300* or *CREBBP* as fusion partners [52–54]. However, these tumours were partly rather described morphologically as gliomas (high grade gliomas as well as low grade gliomas) and to date it is not clear in how far these tumours differ with respect to clinical presentation and outcome [53,54].

2.5.2 Neuropathological diagnosis

CNS tumour with *BCOR* ITD is a malignant CNS tumour characterized by a predominantly solid growth pattern, uniform oval or spindle-shaped cells with round to oval nuclei, a dense capillary network, focal pseudorosette formation, and an ITD in exon 15 of the *BCOR* gene.

Essential diagnostic criteria: histopathologically, a 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.

Diagnostic work-up

Histopathologically, these tumours frequently show some glioma-like fibrillarity but can be composed also of rather undifferentiated tumour cells eliciting the differential diagnosis of malignant glioma and other embryonal tumours. They may express focally OLIG2 but are generally negative for GFAP and synaptophysin. Immunohistochemically, strong nuclear BCOR expression guides towards the diagnosis [47,51,55,56]. Yet, it is not absolutely specific and may be encountered in other entities e.g. solitary fibrous tumours. A PCR assay [57], targeted sequencing, or NGS approach is required to confirm the *BCOR* ITD. Alternatively, a DNA methylation profile aligning with this tumour type is sufficient for classification. Importantly, *BCOR* mutations have also been reported in other CNS tumour entities such as SHH medulloblastoma and HGGs, which seem to play a role in the specific tumour biology but also do not qualify these tumours to be diagnosed as CNS tumour with *BCOR* ITD [58,59].

2.5.3 Clinical features and available evidence on treatment

Regarding the clinical nature of this disease, CNS tumours with *BCOR* ITD have been reported to arise predominantly in young children (median age 4 years, range 7 months – 22 years), but they may also arise in older children. Tumours may be localised across the entire CNS, also showing a propensity for CNS metastasis and even extracranial metastasis and direct invasion of surrounding tissues [47,51,55,60–63].

Based on the propensity for early disease progression or recurrence, these tumours are considered as having a highly aggressive biological and clinical nature which is corroborated by poor survival within the limited cases reported so far [7,60]. However, cases with longer overall survival of over 10 years has been reported in individual cases [47,64].

As these tumours are frequently histopathologically misdiagnosed as other tumour entities such as ependymoma, HGG or medulloblastoma, the case-based evidence on patient treatment is highly heterogeneous. Some patients seem to benefit from irradiation and long-term survivors have been reported [47,61,64]. However, there are also few long-term survivors after multiagent therapy without irradiation [47,61]. Numbers are very small, but it appears to be a trend for reduced relapse after use of upfront CSI [60]. In summary, the high aggressiveness of this tumour type and the molecular similarities to sarcoma types outside the CNS may justify aggressive treatment approaches based on sarcoma or “CNS PNET” regimens.

2.5.4 Recommendations for treatment

The recommendations below only refer to tumours with proven diagnosis of *BCOR* ITD. Please note that positive IHC-staining of BCOR is not sufficient to proceed to intensive treatment as for *BCOR* ITD.

Given the differing morphological presentation, the uncertainty of the current preliminary classification of the tumour as an embryonal tumour, and the presence of *BCOR* ITD in several peripheral sarcomas, it is in principle reasonable to treat with regimen analogous to either CNS embryonal or CNS sarcomatous tumours.

- Due to the highly aggressive nature of these tumours, a multimodal treatment approach is recommended, consisting of maximal safe resection, irradiation and chemotherapy.

Resection:

- Maximal safe resection is recommended.
- In case of relevant postoperative residual tumour, re-resection should be evaluated.

Radiotherapy:

- Due to the reported metastatic relapses, the authors would recommend treatment with CSI. However, there is so far no evidence for a survival benefit from CSI and local irradiation may be used as alternative both in conjunction with chemotherapy.
- A CSI dose of 23.4 Gy may be used for M0R0 patients, analogous to other CNS embryonal tumours, however there is no clear evidence for the adequate effectiveness of this dose and a higher dose (analogous to previous CNS PNET protocols) may be used for older patients.
- For young children (within the first 3–4 years of life) local irradiation may be used following chemotherapy (conventional +/- high-dose). In the case of non-metastatic, completely resected tumour, deferral of irradiation may be considered after application of conventional/high-dose chemotherapy.

Chemotherapy:

- For chemotherapy, high-risk protocols consisting of conventional, or conventional and high-dose chemotherapy, such as CNS PNET-, high-risk medulloblastoma-, or ATRT-protocol [41], or ICE [65] may be used.
- For very young children, the use of conventional and high-dose chemotherapy may be preferred in order to avoid craniospinal irradiation.
- If high-dose chemotherapy is used, this should precede irradiation and should not be given afterwards, due to a high risk of toxicity.
- Intraventricular chemotherapy may be used to treat leptomeningeal dissemination.

2.6 CNS embryonal tumour NEC / NOS

2.6.1 Introduction

Within the WHO CNS5, the designation of the diagnosis CNS embryonal tumour NOS / NEC is reserved for tumours that appear as CNS embryonal tumours, while a more specific diagnosis cannot be attributed [1]. This diagnosis is based on exclusion of other poorly differentiated neoplasms that share similar morphological and immunohistochemical appearance. Tumours with this diagnosis do not represent a specific entity, but likely represent a heterogenous group.

2.6.2 CNS embryonal tumour NEC

2.6.3.1 Neuropathological diagnosis

CNS embryonal tumour, NEC is a tumour arising in the CNS with embryonal morphology and immunophenotype where molecular analyses were successfully performed but the results do not lead to an established WHO CNS5 diagnosis. This tumour type probably comprises various very rare to date not well characterized tumour types. Future studies including larger tumour numbers and in-depth characterization of molecular changes will help refine this diagnosis.

Currently, essential as diagnostic criteria: 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. Molecular analyses were successfully performed but the results do not lead to an established WHO CNS5 diagnosis.

Diagnostic work-up:
Exclusion of other embryonal tumour types, sarcomas and malignant gliomas as described in section 1.1 Examples for this group of tumours would also include tumours that have no matching DNA methylation profile or tumours with specific genetic alterations not yet assigned to a specific WHO diagnosis.

2.6.3.2 Available evidence on treatment

For CNS embryonal tumour NEC, no uniform clinical behaviour can be assumed due to the unspecific nature and heterogeneity of this group of tumours. Likewise, there are no focused clinical data available. While previously most patients with (non-medulloblastoma, non-ATRT) CNS embryonal tumours have been treated according to CNS PNET studies, the course and outcome of treatment cannot be compared, as CNS embryonal tumours NEC represent only a small group of the patients included within the respective trials. By molecular reclassification, most of tumours previously diagnosed as CNS PNET were assigned to another known or newly delineated diagnoses [6,7,48]. In a retrospective cohort with clinically annotated patients with original CNS PNET diagnosis, 22% of the tumours could not be assigned to a specific diagnosis by DNA methylation analysis. These patients had a 5-year PFS and OS of 54% and 69%. This moderate prognosis is likely based on the clearance of the cohort from cases with poor prognostic diagnoses as ETMR and high-grade glioma.

Further deciphering of the heterogeneity of this cohort and characterisation of the respective rare entities will be key for clinical management.

2.6.3.3 Recommendations for treatment

- All diagnostic methods need to be applied before classification as CNS embryonal tumour NEC.
- No standard treatment can be recommended for patients with non-informative molecular diagnosis, as this group likely represents different rare tumour entities.

Likewise, no recommendation for irradiation can be given, while 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).

2.6.3 CNS embryonal tumour NOS

2.6.2.1 Neuropathological diagnosis

CNS embryonal tumour, NOS is a tumour arising in the CNS with embryonal morphology and immunophenotype where molecular analyses have not yet or could not be successfully performed. As already mentioned, 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. Therefore, this diagnosis likely comprises the entities covered in the previous chapters and a subset of various very rare to date not well characterized tumour types (CNS embryonal tumour, NEC). Timely molecular analysis is priority for assignment of correct diagnosis and subsequent decision on necessary treatment.

Currently, essential as diagnostic criteria: an embryonal tumour originating in the CNS and absence of criteria qualifying for the diagnosis of a more specific type of embryonal CNS tumour, where molecular analyses have not yet or could not be successfully performed.

Diagnostic work-up:
Exclusion of other embryonal tumour types, sarcomas and malignant gliomas as described in section 1.1.

2.6.2.2 Available evidence on treatment

For CNS embryonal tumour NOS, timely molecular profiling is essential in order to refine diagnosis into established entities (e.g. ETMR, CNS NB-*FOXR2*, CNS *BCOR*-ITD, or other) and direct the patients to the respective treatment. For treatment recommendations, it is referred to the respective specific tumour chapters.

2.6.2.3 Recommendations for treatment

- In case of diagnosis of CNS embryonal tumour NOS, further diagnostic evaluations including referral to a national or international reference centre should be prioritised.
- In case of evidence of highly proliferative tumour morphologically presenting as CNS embryonal tumour, but pending molecular results (temporary classification as CNS embryonal tumour, NOS), use of chemotherapy may be discussed in order not to prolong start of treatment later than 28 (maximal 40 days) after surgery. A reasonable option would be upfront treatment with 2 courses of carboplatin / etoposide (as used in the SIOP HRMB protocol) although other embryonal CNS tumour protocols may be used.

3 CNS sarcomatous tumours

3.1 Staging of CNS sarcomatous tumours

Cerebral and spinal MRI according to the SIOP-E Imaging Guidelines [9] at the time of diagnosis is mandatory in all patients.

Patients should undergo early post-operative MRI assessment of the extent of resection. “Early postoperative MRI” is defined as MRI performed less than 72 hours after surgery (best 24 - 48 hours), it needs to be obtained according to guideline and comparable to the preoperative MRI.

Post-operative lumbar puncture should be performed to assess for metastatic spread where it is safe to do so. This is generally undertaken at day 14 post-surgery or beyond. If tumour cells are present in CSF from a lumbar puncture performed within 14 days of surgery, the lumbar puncture should be repeated on day 15 or later after surgery.

Comprehensive staging outside of the CNS is mandatory, as CNS sarcomatous tumours may present with metastasis outside of the CNS, but more importantly to confirm that the CNS lesion is the primary disease site and not a metastatic lesion from any extra-axial sarcomatous tumour.

Staging should therefore include at least chest X-ray and abdominal ultrasound. In addition, ultrasound of any clinical suspect lymph nodes is recommended.

Where available whole-body MRI as part of the staging at initial diagnosis is highly recommended.

In patients with suspected primary CNS sarcoma, *DICER1*-mutant, a chest CT at diagnosis should be performed to rule out the differential diagnosis of the CNS sarcomatous lesion being a metastasis of a pleuropulmonary blastoma [66]. Upon diagnosis of a primary CNS sarcoma with *DICER1* mutation, germline investigation to determine if DICER1 syndrome is present and subsequent genetic counselling is highly recommended as this has substantial impact on clinical management of the patients and families (please also refer to chapter 3.3.4 below).

The role of FDG PET-CT/MR in patients with CNS sarcomatous tumours remains to be elucidated and the expected diagnostic benefit has to be weighed against the additional radiation exposure. The use of screening with FDG PET is at the discretion of the treating physician.

The Chang staging system may be used to categorise the metastatic status in primary CNS sarcomatous tumours [10]:

M0: No evidence of gross subarachnoid or hematogenous metastasis
M1: Microscopic tumour cells found in cerebrospinal fluid
M2: Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3: Gross nodular seeding in spinal subarachnoid space
M4: Metastasis outside the cerebrospinal axis.

In case of extra-CNS metastasis further staging systems may be used to refine the clinical staging of the patient.

In patients with known tumour predisposition syndromes, staging should include screening for other associated tumour entities.

3.2 *CIC*-rearranged sarcoma

3.2.1 Introduction

CIC-rearranged sarcoma occurring within the CNS were first identified in a cohort of tumours with historic "CNS PNET" diagnosis within the above mentioned study of Sturm et al. and were later described in several single cases and smaller series [7,47,67–69]. Due to the similarities to extra-CNS sarcomatous tumours, they are classified as *CIC*-rearranged sarcomas of the CNS in the 2021 WHO classification of CNS tumours [1].

The majority of *CIC*-rearranged sarcomas present as malignant soft tissue tumours outside the CNS, with presence of a *CIC::DUX4* fusion in most cases [70,71]. On the contrary, many tumours reported so far within the CNS show *CIC::NUTM1* fusions [7,72]. Recently also *ATXN1::DUX4*, and *ATXN1::NUTM1* fusions have been described in primitive tumours of the CNS [73,74]. While *CIC*-rearranged sarcomas were initially termed "Ewing sarcoma family tumours" clear differences to Ewing Sarcoma have been shown [75–77], and *CIC*-rearranged sarcomas are not to be considered part of the Ewing Sarcoma family of tumours.

3.2.2 Neuropathological diagnosis

Definition: *CIC*-rearranged sarcoma occurring in the CNS is a high-grade poorly differentiated sarcoma defined by *CIC* fusion. The majority of these tumours are characterized by *CIC* rearrangements with *DUX4* as the fusion partner, but others have been identified (*FOXO4, LEUTZ, NUTM1, NUTM2A*) [67,68,74,78]. It remains to be elucidated whether these tumours represent one entity.

Histopathologically, this tumour displays similar features as its extra-CNS counterparts [71]. It is composed of diffuse sheets of undifferentiated round cells. Focal lobular arrangements, separated by thin fibrous septae and a minor spindle or epitheloid cell component are frequently present. The tumour cells are rather uniform but often display moderate nuclear pleomorphism. The cytoplasm is pale eosinophilic. Necrosis is common and mitotic activity is brisk. Myxoid changes may be present. Immunohistochemically, patchy CD99 as well as ETV4 and WT1 expression is present frequently.

Essential diagnostic criteria comprise evidence of a *CIC* gene fusion. The histology shows 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. A DNA methylation pattern matching with the methylation class *CIC*-rearranged sarcoma confirms the diagnosis.

Diagnostic work-up:
An undifferentiated small blue round cell tumour with sarcomatous features, and CD99, ETV4 or WT1 expression, should raise the suspicion of a *CIC*-rearranged sarcoma. Confirmation of the structural *CIC* rearrangement or a DNA methylation profile aligning with this tumour type is necessary.

3.2.3 Available evidence on treatment

The majority of *CIC*-rearranged sarcoma have been described in extra-CNS locations. They generally exhibit an aggressive course of disease with potential for recurrence and metastasis and are mostly treated with surgery and post-surgical chemotherapy and/or irradiation [71].

Relatively few cases of *CIC*-rearranged sarcoma originating from the cerebral as well as the spinal regions have been described so far, and no larger reported series exists [7,47,68,72–74,79]. Therapeutic strategies have mainly been based on treatment strategies for peripheral soft-tissue sarcomas and embryonal CNS tumours, consisting of various multiagent systemic therapies, surgery and irradiation [47,68]. In the published reports on CNS *CIC*-rearranged sarcoma, single patients were reported alive within first, or second remission. Among the surviving patients, most were irradiated upfront [47,67–69,72,78,79].

3.2.4 Recommendations for treatment

The current knowledge on tumour biology, response to different treatment modalities, and prognostic disease characteristics, is sparse. The knowledge and evidence on how to handle these paediatric patients is constantly gathered. Based on the lack of published evidence, involvement of an advisory group either on national or international level is recommended when deciding on treatment.

Therefore, general treatment principles are mentioned here rather than a specific treatment protocol.

Surgery

- Maximal safe resection is recommended. In case of relevant postoperative residual tumour, a re-resection should be evaluated.

Chemotherapy

- Different multiagent chemotherapy treatment protocols have been used in the published reports.
- With the very low grade of evidence, the choice of treatment protocol is subject to discussion. Due to the sarcomatous nature of the disease, multiagent chemotherapy protocols that include alkylating agents, anthracyclines, topoisomerases inhibitor and antimitotic drugs, may be chosen. Local and national guidelines should also be considered.
- Intraventricular therapy may be used, depending on individual choice of the treating physician.

Radiotherapy

- Due to the reported early metastatic relapses, treatment with CSI may be considered for older patients. However, as mentioned, there is no evidence for a survival benefit from CSI, and local irradiation may be used as alternative.
- There is not enough evidence to recommend a specific dose of CSI, this should be discussed locally and if appropriate with the advisory group.

3.3 Primary intracranial sarcoma, *DICER1*-mutant

3.3.1 Introduction

In the spectrum of CNS sarcomatous tumours a further molecularly defined entity has recently been described, the primary intracranial sarcoma, *DICER1*-mutant. These tumours show a heterogeneous histology with malignant spindle cell morphology, focal rhabdomyoblastic differentiation and pleuropulmonary blastoma-like embryonic “organoid” features; pleuropulmonary blastoma being the hallmark tumour of *DICER1* syndrome, a tumour predisposing syndrome being present in some, but not all *DICER1* associated CNS sarcoma patients [66,80].

In a major proportion of cases described so far, biallelic *DICER1* variants were identified with additional genomic alterations, most frequently MAPK pathway alteration (i.e. *KRAS*, *NRAS* and *NF1*) and *TP53* inactivation. Tumour mutational burden seems to be significantly higher in primary intracranial sarcoma, *DICER1*-mutant than in other *DICER1* associated tumour entities [66].

3.3.2 Neuropathological diagnosis

Definition: A primary intracranial sarcoma, *DICER1*-mutant is composed of spindled or pleomorphic tumour cells typically displaying eosinophilic cytoplasmic globules, immunophenotypic evidence of myogenic differentiation, and occasionally foci of chondroid differentiation. These tumours are genetically defined by mutations in the *DICER1* gene (either somatic or germline as part of *DICER1* syndrome) and frequently harbour additional alterations of the mitogen activated protein kinase pathway (e.g. in *KRAS*, *NF1*, *FGFR4*, *NRAS*, *EGFR*).

Essential diagnostic criteria: a primary intracranial sarcoma and pathogenic *DICER1* mutations or a DNA methylation profile aligning with this tumour type.

Recommended diagnostic work-up:
Immunohistochemically, these tumours frequently express myogenic markers. Loss of H3 p.K28me3 (K27me3) is a characteristic finding. A subset of the tumours show loss of ATRX and strong p53 expression, whereas GFAP, OLIG2, cytokeratins, EMA, S100, SOX10, and SOX2 are typically negative. Confirmation of the *DICER1* mutations is required. As *DICER1*-mutated tumours may arise in the context of DICER1-syndrome germline testing is recommended.

3.3.3 Clinical features and available evidence on treatment

Primary intracranial sarcoma, *DICER1*-mutant predominantly affects young children, but has also been described in the adult population. There doesn´t seem to be a gender preponderance. Almost all of the tumours described so far occur in the supratentorial region with the exception of two cases with a cerebellar tumour [80] and a congenital spinal tumour [81]. Primary intracranial sarcoma, *DICER1*-mutant may occur in the context of previous malignancies [66], 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 [82].

A reliable conclusion on clinical behaviour has been hampered by small numbers and short follow up but preliminary data suggests an aggressive disease course. Collection of histopathological, molecular and clinical data and correlation with response to therapy and outcome are urgently needed to improve management of this rare disease.

The few patients described with primary intracranial sarcoma, *DICER1*-mutant most often received surgery (generally aimed at gross total resection) and radiation, with chemotherapy applied in some instances [66,80,83].

In the first larger series described by Koelsche et al. most of these tumours were originally diagnosed as sarcoma NOS or embryonal rhabdomyosarcoma [80]. Detailed clinical and follow up data are lacking, but it can be assumed that if chemotherapy was applied, these patients were most often treated according to soft tissue sarcoma protocols. As this rare tumour entity is defined by the *DICER1* mutation and similarities to other primary *DICER1*-associated tumours could be highlighted, a small series of patients were treated by chemotherapy protocols that include similar agents as used in advanced pleuropulmonary blastoma (PPB) (including ifosfamide, doxorubicin, vincristine, and dactinomycin) [66].

Of note is, that there seems to be a much higher incidence of primary CNS sarcoma, *DICER1* mutant in the Peruvian population, lacking germline mutations of *DICER1*, *TP53* and *RAS* suggesting that so far unknown tumour predisposition syndromes may play a role [84]. In the large cohort of 70 patients described, PFS was highest in patients treated with upfront surgery followed by a sandwich of ICE chemotherapy (ifosfamide, carboplatin and etoposide) and focal radiotherapy [84].

The presence of Ras pathway gene activation in *DICER1*-associated lesions may suggest possible therapeutic avenues [66]. Therapies that target RAS activating pathways or RAS effector pathways (i.e. MAPK pathway inhibition) in these rare tumours should therefore be further investigated.

Given the lack of data for treatment of primary intracranial sarcoma, *DICER1*-mutated, available data on other malignant tumours associated to the DICER1 syndrome may be consulted: Evidence on treatment for PPB reveals a strong prognostic significance of complete tumour resection [85–89]. Chemotherapy is mandatory for any chance of cure in patients with solid Types II – III PPB. Different polychemotherapy regimens similar to those used in rhabdomyosarcoma have been used: IVA (ifosfamide, vincristine, actinomycin D, IVA with the

addition of doxorubicin (VAIA or IVADo) or with cyclophosphamide replacing ifosfamide [85,88,89]. The role of radiotherapy remains unclear in PPB.
The applicability of pleuropulmonary blastoma treatment standards for patients with primary intracranial sarcoma, *DICER1*-mutant remains to be elucidated.

3.3.4 Recommendations for treatment

General considerations

- After surgery, a “sandwich” protocol of chemotherapy and radiation may be chosen, with timing of radiation, field and dosage depending on tumour localization, age and general clinical condition of the patient.

Surgery

The impact of resection status on prognosis in these rare tumours remains to be elucidated.

- Maximal safe resection should be attempted.
- Re-resection should be considered in patients with relevant residual tumour before radiation.

Chemotherapy

- For chemotherapy, a soft tissue sarcoma protocol (i.e. CWS; IRS III) or ICE chemotherapy regimen may be used.
- As an alternative ATRT protocols, e.g. modified IRSIII [90] or EURhab [41] may be considered with the intention to use a CNS tumour protocol also including ”classical” sarcoma drugs with proven efficacy in the treatment of sarcomas outside of the CNS (i.e. vincristine, ifosfamide, dactinomycin)

Radiotherapy

Data are lacking to clearly guide decisions on dosage and radiation field.

- At present there is no evidence to suggest routine use of CSI.
- In localized disease, focal irradiation may be used. In patients with significant residual tumour, consider a boost.
- Primary intracranial sarcoma, *DICER1*-mutant may metastasise outside of the CNS. Radiation therapy in patients with M4 disease should be discussed with the radiation oncologists on an individual basis.

Tumour predisposition

Staging and follow up should take tumour predisposition into consideration and affected patients and family members should be included into a cancer predisposition surveillance program for early detection of associated other malignancies [43].

4 Further rare CNS tumour entities

4.1 Astroblastoma, *MN1*-altered

4.1.1 Introduction

CNS tumours with *MN1::BEND2*/*CXXC5* fusion were first identified by large-scale analysis comprising mostly tumours diagnosed as astroblastomas on a histopathological basis [7]. Within the WHO CNS5 these tumours will be termed "Astroblastoma, *MN1*-altered". It has to be considered however, that also tumours presenting with other underlying histologic diagnoses may harbour these alterations and likewise not all tumours with histological features of astroblastoma harbour *MN1*-alterations [7,91–95]. Therefore, this novel entity is defined by the common molecular feature, a gene fusion involving the *MN1* gene and either *BEND2* or *CXXC5* as fusion partner [7,91,96]. More recently, cases of astroblastomas with *EWSR1::BEND2* gene fusions, clustering with *MN1*-altered astroblastomas by DNA methylation have been described further expanding the molecular landscape within this tumour entity [97,98]. Importantly, these gene-fusions are mutually exclusive with hallmark alterations defining other entities such as gliomas with *IDH1* or *BRAF* mutations or ependymomas with *ZFTA* (*RELA*) fusions. Of note, molecular analyses of astroblastoma cohorts have demonstrated that these include a significant proportion of other molecular entities, with "Astroblastoma, *MN1*-altered" only representing a subset of all tumours originally diagnosed as astroblastomas [94,95]. As former clinical analyses of astroblastoma patient cohorts did not account for molecular diagnoses they may not be representative for the entity "Astroblastoma, *MN1*-altered" [99].

4.1.2 Neuropathological diagnosis

Definition: Astroblastoma, *MN1*-altered is a rare well delineated glioma composed of cuboidal or elongated cells arranged in perivascular pseudorosettes with prominent perivascular sclerosis and *MN1* alterations. No WHO grade has been assigned.

Essential diagnostic criteria are: a glial neoplasm with astroblastic perivascular pseudorosettes and an *MN1* alteration and for unresolved lesions a DNA methylation profile of astroblastoma, *MN1*-altered. It has to be acknowledged that a proportion of tumours diagnosed as astroblastoma, *MN1*-altered by DNA methylation profile may not show clear histopathological features of astroblastoma. It has to be determined how these tumours relate to astroblastomas, *MN1*-altered.

Diagnostic work-up:
The characteristic morphological features are epitheloid cells which have a cuboidal, bipolar or spindle shape with a broad eosinophilic cytoplasm and are arranged in perivascular pseudorosettes, i.e. single or multiple cell layers around vessels. Areas with compact sheet-like growth pattern may be present. A typical finding is hyalinization of blood vessels and stroma, which may be prominent in some cases. The tumours are variable differentiated, whereas some are well differentiated with low proliferative activity, others are frankly anaplastic with increased mitotic activity, necrosis and microvascular proliferations.

Immunohistochemically, the tumour cells are positive for the glial markers GFAP and OLIG2. EMA is expressed in a cytoplasmic or membranous pattern, but some cases also show a dot-like staining, raising the differential diagnosis of an ependymoma.

Mutations of *IDH1* and *BRAF* or *ZFTA* (*RELA*) fusions are mutually exclusive with *MN1* alterations and rule out the diagnosis of an astroblastoma, *MN1*-altered.
Confirmation of the *MN1* fusion by FISH or RNA sequencing is required. It remains to be clarified whether tumours with other recently described fusions (e.g. *EWSR1::BEND2;* [97,98]) belong to this entity.

4.1.3 Staging of Astroblastoma, *MN1*-altered

Cerebral and spinal MRI according to the SIOP-E Imaging Guidelines [9] at the time of diagnosis is mandatory in all patients.

Patients should undergo early post-operative MRI assessment of the extent of resection. “Early postoperative MRI” is defined as MRI performed less than 72 hours after surgery (best 24 - 48 hours), it needs to be obtained according to guideline and comparable to the preoperative MRI.

As aggressive cases with metastasis have been described, spinal MRI is recommended for full staging.

Data on the relevance of CSF staging are currently lacking. Thus, routine lumbar puncture is currently not considered standard as general staging of this tumour type.

4.1.4 Clinical features and available evidence on treatment

Astroblastoma, *MN1*-altered arise in older children and adults (median age 13.5 years, 2-40) with a clear gender preponderance with more than 80% of these tumours arising in female patients [92]. Most tumours arise in the supratentorial region and are well-demarcated with both solid and cystic components [91,92,96].

Clinically, these tumours exhibit a high tendency towards recurrence as approximately two thirds of tumours recur (median PFS approx. 3 years). Tumours might even recur many years after initial diagnosis and multiple times [91,92,96]. While tumour recurrences are predominantly local, also metastatic recurrences have been described [91,92,96]. In contrast, overall survival appears to be more favourable (median OS 15 years), however up to 30% of patients ultimately succumb to their disease, generally after a long course of disease [92,96]. Interestingly, one study described a potential influence of the underlying histology pointing towards a more favourable prognosis for astroblastoma histology as compared to other primary diagnoses such as ependymoma or tumours originally diagnosed as “CNS PNET” in retrospective cohorts [92].

Within retrospective cohorts most patients have been treated with surgical resection and gross total resection appears to be possible in more than half of the cases [92,96]. Extent of resection is also potentially linked to an improved outcome [92]. To date, most patients have been treated with focal radiotherapy initially, few of them also receiving additional chemotherapy based on diverse regimens such as former “CNS PNET” regimens, or temozolomide [47,92,96]. Treatment of patients with metastatic disease also included CSI [96]. Interestingly, even patients without gross total resection may not experience tumour recurrence although subsequent treatment was not known for these cases [92]. In contrast, also irradiated tumours may still recur pointing towards a certain subgroup exhibiting higher aggressiveness [91,92].

Taken together astroblastomas, *MN1*-altered appear to have a high propensity towards local relapse, although a subset may be cured by tumour resection alone.

4.1.5 Recommendations for treatment

The recommendations below only refer to tumours with proven diagnosis of astroblastoma, *MN1*-altered:

Resection:

- Maximal safe resection is recommended as primary treatment element at initial diagnosis and for relapse.
- In case of relevant postoperative residual tumour, a re-resection should be evaluated

Chemotherapy:

- Chemotherapy treatment (e.g. TMZ-based such as Stupp [100]) may be used in the presence of additional potential high-risk markers (e.g. ambiguous histology, tumour anaplasia, initial metastasis) or at tumour recurrence.

Radiotherapy:

- For M0R0 patients, a surveillance strategy may be chosen depending on the clinical situation and on the presence of additional potential high-risk markers (e.g. ambiguous histology, tumour anaplasia)
- Focal RT for patients with residual or locally recurrent tumours may be considered.
- CSI may be used for metastatic patients, analogous to CNS embryonal tumours, while the dose should be individually discussed with the advisory board and radiotherapists.

5 References

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6 Appendix

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