STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR ATYPICAL TERATOID RHABDOID TUMOUR (ATRT)

This document has been developed by:

Dr. Esther van Mastrigt- van Sundert
Princess Maxima Center for Pediatric Oncology
Heidelberglaan 25, 3584 CS Utrecht, the Netherlands
Email: e.vanmastrigt-2@prinsesmaximacentrum.nl

Dr. Niels Franke
Princess Maxima Center for Pediatric Oncology
Heidelberglaan 25, 3584 CS Utrecht, the Netherlands
Email: n.e.franke@prinsesmaximacentrum.nl

Dr. Franck Bourdeaut
CLCC Institut Curie
26 rue d'Ulm, 75248 Paris Cedex 05, France
Email: franck.bourdeaut@curie.fr

Document version and date
V1.0 27-10-2022

DISCLAIMER:

These ESCP guidance documents were produced by the relevant tumour group or specialist committee as recommendations on current best practice. The ESCP guidance documents are not clinical trial protocols.

The interpretation and responsibility of the use of ESCP guidance documents lies fully with the user who retains full responsibility for the use of these guidance documents and his actions and (treatment) decisions based thereon, such as, but without limitation thereto: checking and prescribing certain doses, checking prescriptions, etc. A user should never base its decision solely on the content of these guidance documents and should always check any other relevant medical information that is available and make appropriate use of all relevant medical information.

These guidance documents have been made publicly available by SIOP Europe – the European Society of Paediatric Oncology and the European Reference Network for Paediatric Oncology (ERN PaedCan). It is the responsibility of the user who downloads these documents to make sure that:

- their use within the Paediatric Clinical Unit / Hospital is approved according to the local clinical governance procedures.
- appropriate document control measures are in place to ensure that the most up to date locally approved versions are considered.
- any anomalies or discrepancies within the documents are immediately brought to the attention of the relevant special interest group chair and the European Clinical Study Group who has developed the ESCP guidance document.

Every care has been taken whilst preparing these documents to ensure that they are free of errors. Nonetheless, SIOP Europe and ERN PaedCan cannot be held liable for possible errors or mistakes in these guidance documents, nor can SIOP Europe and ERN PaedCan be held liable for any kind of damage resulting out of the use of these guidance documents.

Table of contents

List of abbreviations

ACT	actinomycin D
ANC	absolute neutrophil count
ATRT	atypical teratoid rhabdoid tumour
CARBO	carboplatin
CIS	cisplatin
CNS	central nervous system
CPBTC	Canadian Paediatric Brain Tumour Consortium
CPG	clinical practice guidelines
CSA	craniospinal axis
CSF	cerebrospinal fluid
CSI	cranial spinal irradiation
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTV	clinical target volume
CYCLO	cyclophosphamide
DNA	deoxyribonucleic acid
DOXO	doxorubicin
DWI	diffusion weighted imaging
ETO	etoposide
ETMR	embryonal tumour with true rosettes
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GTR	gross total resection
GTV1	initial tumour before surgery/chemotherapy gross tumour volume 1
Gy	gray
HDCT	high dose chemotherapy
ICE	ifosfamide/ carboplatin/ etoposide
ICRU	International Commission on Radiation Units
IFOS	ifosfamide
IMRT	intensity-modulated radiotherapy
IT	intrathecal
LET	linear energy transfer
MRI	magnetic resonance imaging
MTX	methotrexate
MYC	myc oncogene
NCDB	National Cancer Database
OS	overall survival
PCP/PJP	pneumocystis carinii pneumonia/ pneumocystis jeroveci pneumoniae
PNET	primitive neuro-ectodermal tumours
PTV	planning target volume
RBE	relative biological effectiveness
RT	rhabdoid tumour
RT	radiotherapy
RTPS	rhabdoid tumour predisposition syndrome
SAD	source-to-axis distance
SEER	National Cancer Institute's Surveillance, Epidemiology, and End Results
SHH	Sonic hedgehog
SIOPE	SIOP Europe
TT	thiothepa
TYR	tyrosinase
VBL	vinblastine
VCA	vincristine/ cyclophosphamide/ actinomycin D
VCR	vincristine
VGHTPE	Taipei Veterans General Hospital
VMAT	volumetric modulated arc therapy

1. BACKGROUND AND RATIONALE

1.1. Background

Rhabdoid tumours (RT) are aggressive soft tissue tumours, and usually present below 3 years of age. Atypical teratoid/rhabdoid tumours (ATRT) arise in the central nervous system (CNS) and were first described in the 1980s and confirmed as an entity in 1996 (Biggs *et al.*, 1987; Rorke, Packer and Biegel, 1996). ATRT account for 0.3-0.6/100,000 births in the first year of life (Erdmann F, Kaatsch, P, Grabow, D, Spix, C. *German Childhood Cancer Registry - Annual Report 2019 (1980-2018)*. 2020) and 0.03/100,000 to 0.26/100,000 for children aged 5 to 9 years of age in the USA (PMID: **36196752**).. Still, it is the most common malignant CNS tumour in children below one year of age(Ostrom *et al.*, 2015).

ATRT occur both in supratentorial and infratentorial regions of the brain; infratentorial tumours are mostly found in the cerebellum and the cerebellopontine angle. Very rarely ATRT may also be found in the spine. Metastases via the cerebral spinal fluid (CSF) are common and are found in up to 20-30% of the cases at diagnosis (Tekautz *et al.*, 2005).

ATRT is a genetically relatively homogeneous disease. Most cases (> 95%) are characterized by bi-allelic loss-of-function mutations in *SMARCB1* in chromosome 22q11.2 (Versteege *et al.*, 1998; Biegel, 1999), and a small amount by loss-of-function mutations in *SMARCA4* instead located on chromosome 19p13.2 (Schneppenheim *et al.*, 2010). These genes encode for the BAF47 and BRG1 proteins, both members of the chromatin-remodelling SWI/SNF complex, which is important for structural and functional diversity during neurogenesis (Wilson and Roberts, 2011). Since these mutations result in a loss of the respective protein, loss of staining for either BAF47 or BRG1 by immunohistochemistry is used as a diagnostic tool to ensure the diagnosis of an ATRT. Importantly, about 25% of patients with ATRT demonstrate germline mutations in *SMARCB1* or *SMARCA4* and are at risk for developing other malignancies or second primary tumours, with synchronous occurrence.

Recently, based on DNA methylation profiling, ATRT have been molecularly divided in three groups, ATRT-tyrosinase (TYR), ATRT-sonic hedgehog (SHH), and ATRT-MYC (Johann *et al.*, 2016; Ho *et al.*, 2020). These subgroups are genetically, epigenetically, and clinically different (Ho *et al.*, 2020). Data of 143 uniformly treated patients from 13 countries involved with the EU-RHAB registry suggest that both age at diagnosis (<1 year vs ≥1year) and DNA methylation group (ATRT-TYR vs non-TYR) are independent predictors of overall survival (OS). Patients with an ATRT-TYR signature, age ≥1 year, had the best prognosis (5-year OS 71.5 ± 12.2%), while patients with a non-TYR signature and age <1 year had the worst prognosis (5-year OS 0%) (Frühwald *et al.*, 2020). Results from the COG, suggested a better prognosis for SHH than for MYC (Reddy *et al.*, 2020). This difference in prognosis in the SHH group between the two studies might be partly explained by the recently identified SHH-subgroups (Federico *et al.*, 2022). In this study a SHH subgroup was described (SHH-1B) with a favourable outcome. Altogether, currently, molecular subtypes do not influence the choice for treatment.

Overall survival rates have remained poor despite aggressive multimodal treatment approaches, combining surgery, radiotherapy and systemic and intraventricular chemotherapy. The young age of many patients and involvement of critical structures within the CNS limits the optimal use of this approach. For instance, gross total resection is difficult or even impossible in a large number of patients because of neurosurgical issues, and CSI is usually avoided in infants up to 36 months of age due to the risk of severe long-term neurocognitive and neuroendocrine sequelae (Squire, Chan and Marcus, 2007).

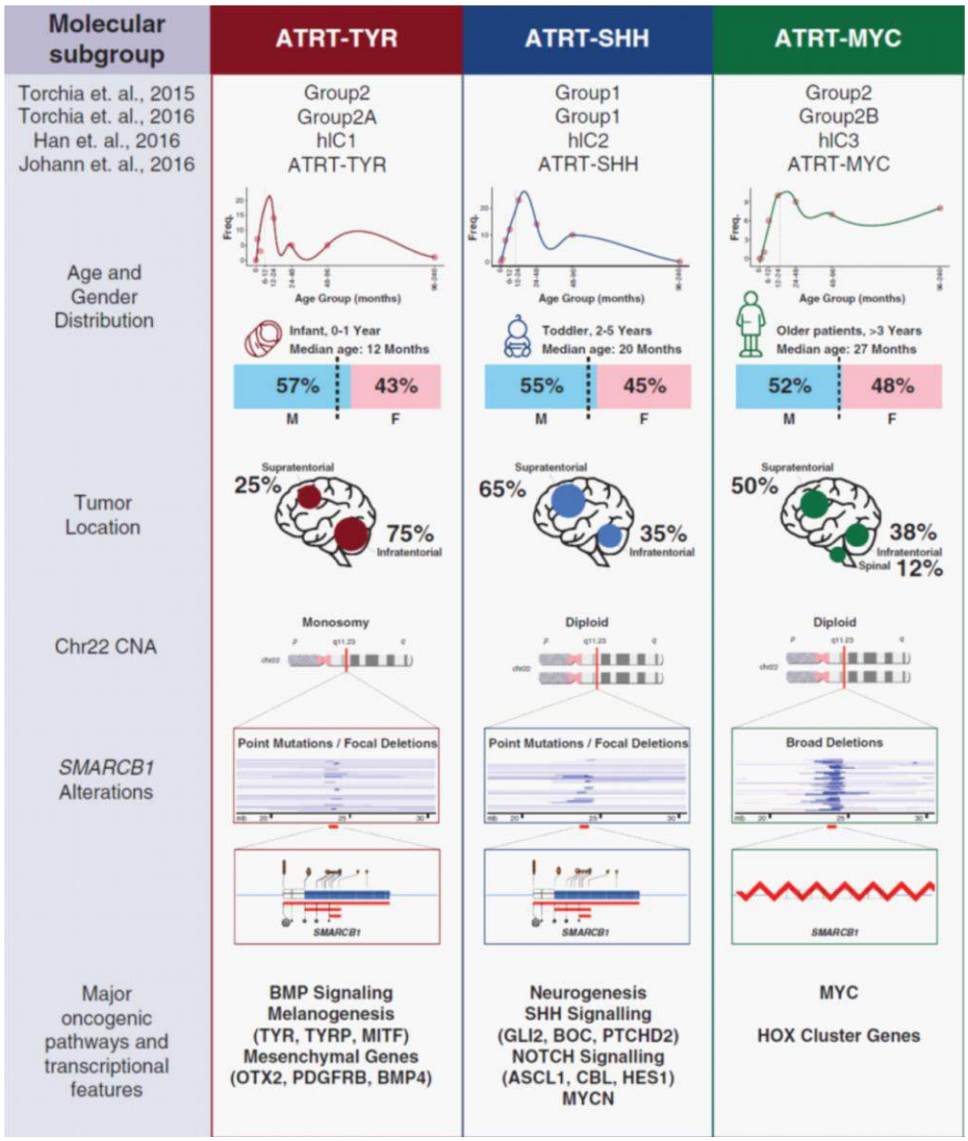

Figure 1 *Consensus overview of ATRT subgroups. Schema of salient clinical and molecular characteristics of ATRT subgroups, reprinted from Ho et al.(Ho et al., 2020).*

2. DIAGNOSTIC CRITERIA

This guideline applies to children (aged 0-18 years) diagnosed with ATRT, either localized or metastatic.

2.1. Laboratory investigations

Metastases via the CSF are detected in 20–30% at diagnosis (Buscariollo *et al.*, 2012). Therefore, all children should undergo screening for disseminated CNS disease, by CSF examination.

Recommendation:

- Post-surgical lumbar CSF sample should be obtained at day 10 to 14 post-surgery, to assess by cytology the metastatic status of the disease.

2.2. Imaging

ATRT may arise anywhere in the CNS and should be considered as a diagnosis when evaluating an aggressive-appearing intracranial tumour in an infant or young child. The appearance of ATRT on MRI appears to some extent similar to medulloblastoma, ependymoma, and other embryonal tumours such as ETMR. They usually present as a large heterogeneous mass with variable evidence of necrosis, haemorrhage and peritumoral oedema. Radiological features of ATRT are heterogeneous, with frequent presence of cystic and necrotic areas, calcifications, and haemorrhage. On MRI, T1 weighted images show hypo-intensity often with hyper-intense foci within the lesion, due to haemorrhagic components. Intra-tumoral haemorrhage is seen in about 50% of ATRT. On T2-weigthed images, the lesions are often heterogeneous: the solid components are iso- to hypo-intense on T2 weighted images, haemorrhagic and have hyperintense necrotic foci. Most ATRT enhance avidly with gadolinium and due to their dense cellularity, ATRT frequently demonstrate restricted diffusion (Poplack, 2015). Erosion of bone is a feature suggestive of ATRT (see Figure 2).

2.2.1. MRI imaging

The most important issue is comparability of the pre-operative, post-operative MRI examinations and subsequent follow up studies. The following protocol has been developped by the European SIOPE Brain Tumour Imaging Group and is based on consensus and evidence from earlier clinical trials. The protocol has evolved over the past few years and is being updated in response to changes in imaging practices. The protocol comprises a mandatory set of sequences which is a minimum requirement (Table 1) and additional sequences including multi-modal advance MR imaging which are recommended.

Table 1.1 Essential sequences for brain imaging

1.5 Tesla scanner

Sequence	Technique	Plane
T_1W	2D SE, TSE/FSE	Axial (along AC-PC axis)
T_2W	2D SE, TSE/FSE	Axial
FLAIR	2D TSE/FSE	Axial or coronal
T_1W + Contrast	2D SE, TSE/FSE	Axial, coronal and sagittal
DWI with ADC	2D EPI	Axial

SE: Spine Echo. FSE: Fast Spin Echo. TSE: Turbo Spin Echo. EPI: Echo Planar

3 Tesla scanner

Sequence	Technique	Plane
T_1W	3D gradient echo	Axial or sagittal
T_2W	2D SE, TSE/FSE	Axial
FLAIR	2D TSE/FSE	Axial or coronal
T_1W + Contrast	2D SE, TSE/FSE	Axial
T_1W + Contrast	3D gradient echo	Axial or sagittal
DWI with ADC	2D EPI	Axial

- *3D gradient echo (GRE) sequence is the inversion recovery GRE sequence (MPRAGE/ IR SPGR/Fast SPGR/ 3D TFE/3D FFE).*
- *2D sequences: Slice thickness≤ 4mm and slice gap ≤ 1mm (10 % of slice thickness is desirable). For very small lesions consider a slice thickness of 3 mm or less.*
- *3D sequence: Slice thickness ≤ 1mm with no slice gap. An isotropic voxel resolution of 1mm x 1 mm x 1 mm is desirable depending on scanner capability.*
- *Resolution parameters: Field of view – 23 mm (range 220-250 mm depending on head size); Matrix size - minimum 256 (512 is desirable for better resolution; 96- 128 for EPI sequences).*
- *Some centres perform T1 FLAIR, T1 inversion recovery (IR) or T1 gradient echo instead of T1 SE sequence due to its suboptimal quality on 3T scanners. This is acceptable as long as the diagnostic quality of the imaging is not compromised, and the same sequence is used consistently for the individual patient.*
- *There are increasing concerns of long-term gadolinium deposition and the use of macrocyclic gadolinium-based contrast agents is recommended as per recommendation of the European Medicines Agency.*

Table 1.2 Essential sequences for spine imaging

Sequence	Technique	Parameter	Plane
T_1W + Contrast	2D SE/ TSE	Slice thickness ≤3mm Slice gap <0.5mm	Sagittal whole spine (entire dural sac)
T_1W + Contrast	2D SE/TSE or 3D gradient	Slice thickness 4-5 mm No slice gap	Axial –suspicious areas*

* Physiological veins over the surface of the cord can be mistaken for nodules of dissemination and therefore axial slices without gaps (slice thickness should be 4 or 5 mm) are essential for all suspicious areas.

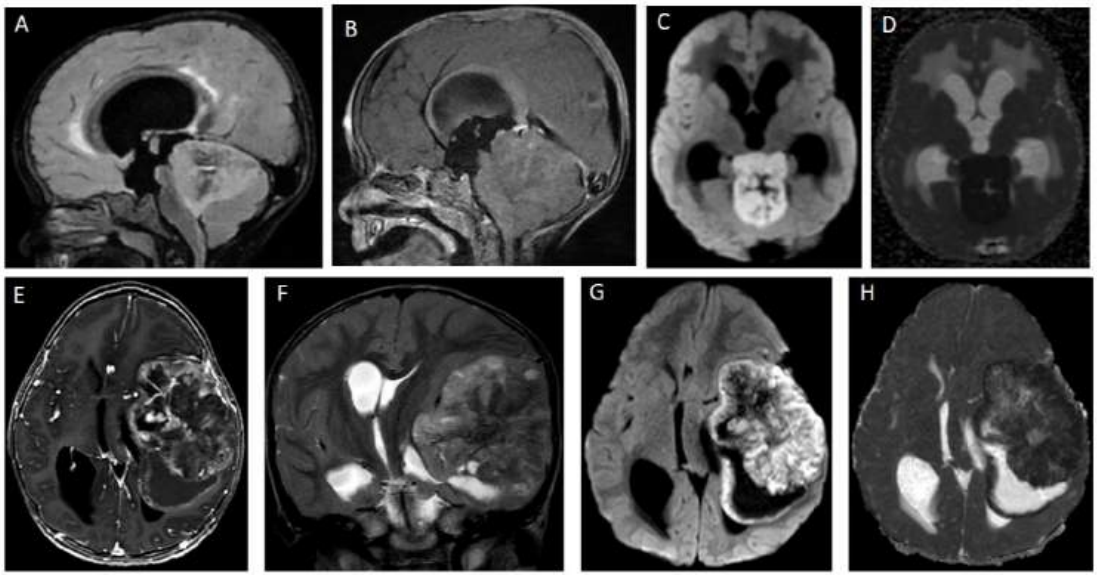

Figure 2 –*Typical MRI findings of ATRT*

Upper panel: typical localisation of ATRT from the ambiens cistern to the posterior fossa ATRT, hyper signal in FLAIR (A), low enhancement in T1 (B), hyper perfusion (C) and restricted diffusion (D);

Lower panel: supratentorial localisation of a solid and cystic ATRT, with heterogeneous enhancement in T1 (E), hyper signal in T2 (F), increased perfusion (G) and restricted diffusion (H).

Early postoperative imaging

The evaluation of early postoperative imaging for residual tumour is challenging. As very subtle residual tumours may not be visible on imaging, the presence of residual tumour should be made in consensus with the neurosurgical report. Optimal postoperative evaluation is made after 24 hours and before 48 hours following surgery. As non-specific intracranial enhancement is often seen 72 hours and later following surgery the postoperative MRI must be obtained within this time. A thin line of enhancement can be physiological or reactive on early postoperative MRI and a correlation with the non-contrast sequences for evidence of haemorrhage / tissue injury and detailed comparison with preoperative MRI may be required before considering the presence of residual tumour. The size of a possible residuum has to be measured in all three planes. A residuum is considered to be any area of persisting pathological signal and/or enhancement that is comparable with the appearance of the pre-operative tumour. DWI is helpful to differentiate residual tumour from any local surgical or ischemic injury, which may influence enhancement patterns and tumour evaluation on subsequent examinations. If image quality is inadequate or the appearance of the surgical cavity is difficult to interpret, repeated imaging in 2-4 weeks with additional sequences, better resolution parameters and additional planes may be necessary for further clarification.

When spinal MRI is performed post-operatively: non-specific subdural and intradural enhancement and possible intradural blood products and effusions may be identified on early post-operative imaging of the spine and must not be mistaken for meningeal dissemination. In case there is ongoing doubt or if intense subdural enhancement is seen, the spinal MRI should be repeated after 2 weeks for clarification.

2.3. Histopathology

Macroscopically, ATRT may resemble medulloblastoma, other embryonal tumours and even high-grade gliomas (Figure 3). ATRT is a malignant (WHO grade IV) embryonal tumour containing rhabdoid cells (Packer *et al.*, 2002). Rhabdoid cells are characterized by eosinophilic cytoplasm (Haas *et al.*, 1981). The cellular component can be variable and may consist of undifferentiated “small round blue cells,” with mesenchymal and epithelial components. These diagnostic cells may be grouped in nests close to areas composed of neuroectodermal, mesenchymal or epithelial tissue types. The presence of rhabdoid

cells and multi-lineage differentiation are unique to ATRT and help distinguish it from other embryonal tumours of the CNS. However, only about 10 to 15% of ATRT consist almost exclusively of rhabdoid cells. And in some cases the rhabdoid component can also be completely absent (Ellison, 2013; Sredni and Tomita, 2015; Louis *et al.*, 2016, 2021). Because of this morphological ambiguity; immunohistochemistry, cytogenetics and molecular findings are required to establish the diagnosis of ATRT. In the vast majority of rhabdoid tumours pathogenic mutations affect the SMARCB1 (INI1) tumour-suppressor gene. In rare cases, SMARCA4 is mutated instead (about 0,5-2% of ATRT). Since these mutations results in a loss of the respective protein, loss of staining for either SMARCB1 (also called INI1 or BAF47) or SMARCA4 (also called BRG1) by immunohistochemistry is used as a diagnostic tool to ensure the diagnosis of an ATRT (Holdhof *et al.*, 2021).

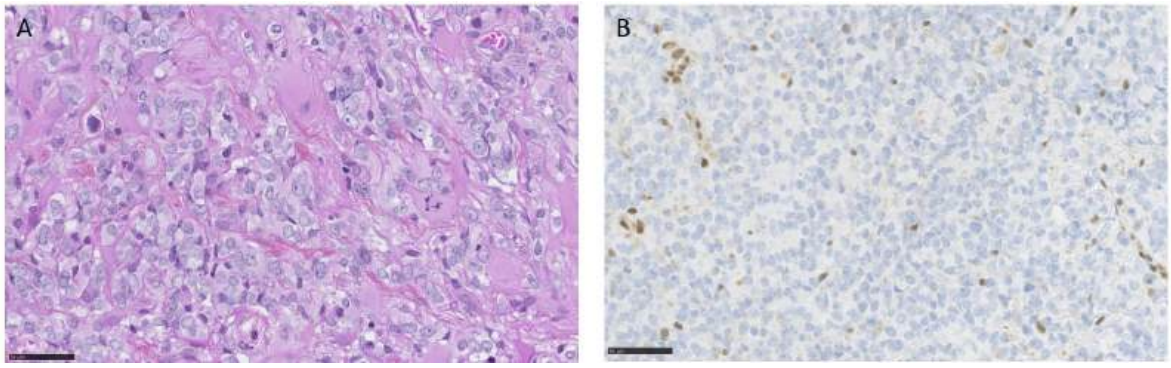

Figure 3 –Typical histopathology findings

A-Hematoxylin Eosin Safran staining showing un-cohesive cells with typical uncondensed chromatin, prominent nucleolus, and eosinophilic cytoplasm. B-immunostaining with BAF47 antibody showing a normal nuclear expression in stromal cells, and complete loss of expression in tumor cells.

Recommendation:

Diagnostic recommendations follow the WHO 2021 classification (Louis *et al.*, 2021): An ATRT diagnosis is retained in a CNS embryonal tumour with a poly-immuno-phenotype, AND Loss of nuclear SMARCB1 or SMARCA4 expression in tumour cells OR (for unresolved lesions) a DNA methylation profile aligned with atypical teratoid/rhabdoid tumour.

Additionally, nuclear positivity of non-neoplastic cells serves as an important internal positive control. Its presence should be documented in the report. The following SMARCB1/INI1 and SMARCA4/BRG1 antibodies are proven to be specific and thus recommended for use by the individual national laboratories:

- SMARCB1/INI1: BAF47 mouse monoclonal antibody (BD Transduction Lab 612110), c-terminal antibody ab222519 (ABCAM), or clone 25/BAF47 (BD Biosciences)
- SMARCA4/BRG1: Brg1 rabbit antibody (Merck Millipore 07-478) or clone EPR3912 (Abcam)

2.3.1 Evaluation of germline alterations – rhabdoid tumour predisposition syndrome

RTs may present in a familial setting. Mutations of *SMARCB1* in the germline have been documented in 25–35% of patients with ATRT. Most of these patients are in general younger and exhibit more aggressive disease. We suggest that **all** patients who present with a RT should be tested for the presence of germline mutations in *SMARCB1* or *SMARCA4* to rule out rhabdoid tumour predisposition syndrome (RTPS). Patients who carry a germline mutation in *SMARCB1* have RTPS type 1 (OMIM #609322), whereas those with a germline mutation in *SMARCA4* have a RTPS type 2 (OMIM #613325). These mutations are inherited in an autosomal dominant manner, with a “second hit” by either a somatic mutation, or loss of heterozygosity within the tumour (Sredni and Tomita, 2015). Hence, germline carriers are not only at risk for developing other tumours, but also for developing second primary tumours, with synchronous occurrence. Around one third of patients with RTPS have multiple tumours, with bifocal manifestation most commonly in kidney and the CNS (Eaton *et al.*, 2011). Surveillance guidelines for *SMARCB1* germline mutations recommend thorough clinical investigation including neurological examination, MRI brain and abdominal ultrasound until the age of 5 years (Foulkes *et al.*, 2017; Frühwald *et al.*, 2021).

Recommendation:

Analyses of *SMARCB1* and *SMARCA4* germline alterations should be proposed to all patients, following the analysis of a tumour sample whenever possible. according to the mutations identified in the tumour.

2.4. Tumour staging

Tumour staging in regard to treatment is based on age at the time of diagnosis (< 12 months, 12-35 months and ≥ 36 months), and local versus metastatic disease. In order to diagnose metastatic disease, apart from craniospinal imaging it is necessary to perform CSF analysis around 14 days post surgically to detect metastasis in the spinal fluid. Since germline diagnostics are not readily available, it is important to exclude other primary tumour sites by means of imaging techniques (either whole body MRI in combination with abdominal ultrasound).

Recommendations:

- Perform CSF analysis 10-14 days post-surgical
- Search for extracranial tumour localisations by clinical examination and abdomen ultrasonography

3. TREATMENT DETAILS

Since ATRT are extremely rare and occur mainly in very young children, controlled prospective clinical trials are scarce and difficult to perform. However, since the original description of ATRT in the late 1990s, several studies have been performed in the build-up to the development of disease specific trials.

ATRT was first described as an intracranial rhabdoid tumour, which led to the basis of the first effective treatment protocol. This treatment according to the Intergroup Rhabdomyosarcoma Study IRS-III (arm for parameningeal primary tumours with intracranial extension) included resection followed by chemotherapy, radiotherapy and intrathecal chemotherapy which resulted in the first long term survivors (Olson *et al.*, 1995) and lead to the first prospective phase II trial (Chi *et al.*, 2009). In the following years, several treatment protocols were based on these strategies (e.g., Rhabdoid 2007 and EU-RHAB registry) while other groups used a more PNET-based approach. Table 2 summarizes the different cohorts described in the last decades. In the absence of a controlled randomized phase III trial, there is no firmly established standard of care, and several strategies may be considered as best practice options. Thus, the main recommendation is to enrol patients into available controlled clinical trials as long as there is one open at the time of diagnosis. In the absence of eligibility for a clinical trial, the following strategies can be considered as treatment options given their +/- equivalent results and taking into consideration the robustness of the data according to the number of patients reported.

Table 2. Overview of studies involving therapeutic strategies

	n	Conventional chemo drugs	nb of courses	High dose chemo	Intra-thecal intra-ventricular	Irradiation	PFS	OS	Level of evidence
DFCI PMID: 19064966 (2009)	20	Vincristine, Cisplatin, Cyclophosphamide, Etoposide, Temozolomide, Actinomycine D	17	none	Methotrexate, Cytarabine, Hydrocortisone	Focal for M0 After 2 courses	2 year 53%+/-13	2 year 70%+/-10	Level IV (cohort)
MUV PMID: 24402832 (2014)	9	Doxorubicin, Cyclophosphamide, Vincristine, Ifosfamide, Cisplatin, Etoposide, Methotrexate	3 (27 weeks)	Thiotepa Etoposide Carboplatin *1	Depocyte Etoposide	Focal for M0 At the end	5 year 100%	5 year 100%	Level IV (cohort)
EU-RHAB PMID: 31883020 (2020)	143	Vincristine, Actinomycin, Cyclophosphamide, Ifosfamide, Carboplatin, Etoposide.	12	Carboplatin-Thiotepa *1 (optional)	Before irradiation Methotrexate	Focal for M0 After 3 courses	5 year 34.7% +/-4.5	5 Year 30.5+/-4.5	Level V
ACNS0333 PMID: 32105509 (2020)	65	Methotrexate, Cisplatin, Cyclophosphamide, Etoposide	2	Carboplatin-Thiotepa *3	None	Focal for M0 After 2 courses		4 year 49%	Level IV (cohort)
SJMB03 Average risk (>3years) PMID: 33737307 (2021)	11	Cisplatin Cyclophosphamide, Vincristine	4	None	None	Craniospinal Upfront (23,4+54Gy)	5 year 72,7%+/-12,7	5 year 81,8%+/-11	Level IV (cohort)
SJMB03 High Risk (>3years) PMID: 33737307 (2021)	8	Cisplatin, Cyclophosphamide, Vincristine, Cyclophosphamide, Topotecan	4	None	None	Craniospinal Upfront (36-39 + 54Gy)	NA	5years 25%+/-12	Level IV (cohort)
SJYC07. intermediate Risk (<3 years) PMID: 33737307 (2021)	34	Methotrexate, Cisplatin, Cyclophosphamide, Vincristine	4	None	None	Upfront Focal	5 year 31,4%+/-9,2	5 year 43,9%+/-9,5	Level IV (cohort)

3.1. Surgery

As in other embryonal tumours, upfront surgery is the first important step in the treatment of ATRT. The prognostic role of the extent of resection is a matter of debate. While some studies showed an increased overall survival in patients where GTR was achieved (Chi *et al.*, 2009; Lafay-Cousin *et al.*, 2012; Bartelheim *et al.*, 2016; Yamasaki *et al.*, 2020) several other publications could not identify GTR as an independent prognostic factor (Tekautz *et al.*, 2005; von Hoff *et al.*, 2011; Buscariollo *et al.*, 2012; Schrey *et al.*, 2016; Frühwald *et al.*, 2020; Reddy *et al.*, 2020; Underiner *et al.*, 2020).

The extent of resection should be judged by the neurosurgeon applying the SIOPE recommendations (Gnekow, 1995). Classification of the extent of resection should therefore be a radio-diagnostic classification supported by the surgical report. Additionally, second look surgery to remove residual tumour when safely possible is advised.

Recommendation:

- Although the data is conflicting, recommendation to aim for a complete resection in case of localised disease remains the accepted standard of care. Additionally, second look surgery to remove residual tumour when safely possible is advised.
- In patients with metastatic disease, safe resection of primary tumour
- Since ATRT is a rapidly dividing malignancy, subsequent therapy should be started as soon as clinically possible to prevent tumour regrowth.

3.2. Radiotherapy

Several studies have shown the efficacy of radiotherapy in the treatment of ATRT (Tekautz *et al.*, 2005; Chen *et al.*, 2006; Chi *et al.*, 2009; von Hoff *et al.*, 2011; Lafay-Cousin *et al.*, 2012; Slavc *et al.*, 2014; Bartelheim *et al.*, 2016; Frühwald *et al.*, 2020; Reddy *et al.*, 2020). Moreover, in retrospective cohort analyses, radiotherapy has been shown to be of prognostic relevance when used in a tri-modality approach (Schrey *et al.*, 2016; Fischer-Valuck *et al.*, 2017; Quinn *et al.*, 2019; Underiner *et al.*, 2020; Yang *et al.*, 2020). In addition, based on retrospective data, early radiotherapy has been suggested to be beneficial (Pai Panandiker *et al.*, 2012; Yang *et al.*, 2020).

Focal radiotherapy has proven to be likely sufficient in the context of the Dana Farber Cancer Institute protocol for localized diseases, (Chi *et al.*, 2009) thereby reserving craniospinal irradiation for metastatic disease; of note, this trial is characterized by a heavy burden of chemotherapy. In the contrary, recent results from the St Jude's trials SJMB07 suggested a benefit of upfront craniospinal irradiation even in M0 diseases, given that metastatic relapses were predominant (7/12 relapses) in children who completed focal irradiation (Upadhyaya *et al.*, 2021). Beside the craniospinal or focal field of irradiation, age in which radiotherapy is indicated differs per protocol. While the COG ACNS033 study age limits are 12 months for localized supratentorial ATRT and is 6 months for infratentorial tumours (Reddy *et al.*, 2020), the EU-RHAB registry group advised a limit of 18 months for all localizations (Frühwald *et al.*, 2020) changing to 12 months in the new randomized SIOPE ATRT01 study for infra-tentorial tumours and depending on the tumour volume (EU-RHAB, 2021). For CSI, the age limit is 36 months for full dose CSI (Reddy *et al.*, 2020; EU-RHAB, 2021) and a reduced dose is suggested for patients below the age of 36 months (Reddy *et al.*, 2020). In order to investigate a possible further reduction in the use of radiotherapy in young patients, the ATRT-01 trial is comparing focal radiotherapy with 3 courses of HDC in patients with M0 disease, age 12-36 months in a randomised setting (**Figure X**) (EU-RHAB, 2021).

Although proton therapy has been increasingly used as a treatment modality for ATRT (De Amorim Bernstein *et al.*, 2013; Suneja *et al.*, 2013; McGovern *et al.*, 2014; Tran *et al.*, 2020), no studies are performed comparing photon radiotherapy with protons. While it is to be expected that proton therapy will be superior in reducing long-term cognitive effects as seen in other paediatric brain tumours (Kahalley *et al.*, 2020; Child *et al.*, 2021), it must be noted that more standardized data are needed to fully comprehend the combination of intensive chemotherapy and high-dose proton therapy at very young age, in particular around the brain stem (Haas-Kogan *et al.*, 2018; Dell'Oro *et al.*, 2021).

Recommendation:

- In case of localized disease, and depending on the tumour location and volume, the use of focal radiotherapy is advised in children above the age of 12 to 18 months.

- Focal versus craniospinal irradiation for localized disease depends on the global treatment strategy chosen and age at diagnosis
- In case of metastatic disease, craniospinal radiotherapy is advised in children above the age of 36 months.

3.3. Conventional dose chemotherapy

As depicted in Table 2, various chemotherapy schemes have been used in the treatment of ATRT, most frequently using a rhabdoid backbone. In order to prevent tumour regrowth between chemotherapy courses, most of the schemes are dose dense. Since none of the schemes have been directly compared in a prospective trial setting and other treatment modalities varied between the studies, it is unclear which scheme should be preferred.

Alkylating agents (ifosfamide, cyclophosphamide), anthracycline (doxorubicin), vincristine, topoisomerase inhibitors (etoposide), platinum derived drugs (carboplatin, cisplatin), actinomycin-D, and methotrexate are the most commonly used drugs in conventional doses for the treatment of ATRT.

Recommendation:

- Most data are available on a dose-dense, rhabdoid-based conventional dose chemotherapy treatment scheme.
- Since ATRT is a rapidly dividing malignancy, treatment delays should be avoided if possible.

3.4. Intraventricular or intrathecal therapy

In a meta-analysis, intrathecal (IT) or intra-ventricular chemotherapy has been associated with an improved OS (Athale *et al.*, 2009; Underiner *et al.*, 2020), which was more pronounced with the use of multi agent versus single-agent chemotherapy. The preferred route of administration is via Ommaya/Rickham reservoir. Alternatively, administration through lumbar punctures can be performed with adapted dosing scheme (see paragraph 3.3.2). As a consequence, most trials in which irradiation is not used upfront include intraventricular or intra-thecal chemotherapy, at least until the beginning of radiation. Its use during or after irradiation is controversial because of possible neurological side effects; at least, intra-CSF methotrexate concomitant or following RT must be avoided to prevent acute neurological side effects.

Recommendation:

- Administration of intra-CSF (intra-thecal and/or intra-ventricular) chemotherapy until the start of radiotherapy or HDCT is advised in children not receiving radiotherapy upfront
- Ommaya or Rickham reservoirs may be considered for children with ATRT

3.5. High dose chemotherapy (HDCT)

HDCT has successfully been used in several treatment protocols (Benesch *et al.*, 2014; Cohen *et al.*, 2015; Bartelheim *et al.*, 2016; Reddy *et al.*, 2020; Yang *et al.*, 2020; Park *et al.*, 2021). In addition, a meta-analysis of Underiner er al. has shown that HDCT was independently associated with reduced risk of death in metastatic ATRT (Hazard ratio 0.21) (Underiner *et al.*, 2020). The pooled data analysis of Schrey et al. showed hazard ratios for HDCT resulting in a HR-RFS of 0.570 (0.357–0.910, p = 0.019), and HR-OS of 0.388 (0.214–0.704, p = 0.002) (Schrey *et al.*, 2016). This analysis included patients with localized disease as well as patients with metastatic disease.

HDCT is mostly given as an alternative for patients below the radiotherapy age limit in localized as well as in metastatic disease. In the age group between 12 and 36 months, radiotherapy is associated with a significant risk of severe late effects, notably neuro-cognitive decline, endocrine dysfunction, and short stature when craniospinal axis irradiation is considered (Squire, Chan and Marcus, 2007; Hasan *et al.*, 2011; Lafay-Cousin *et al.*, 2015). Whether the long-term benefits (e.g., avoidance of infertility, hypothyroidism, cardiac toxicity and pulmonary fibrosis) of highly focal radiotherapy will outweigh the risks of complications such as neurocognitive and endocrine late effects is a focus of the ATRT01 Trial.

Combining radiotherapy with HDCT in young patients with brain tumours resulted in worse neurocognitive outcomes (Szychot *et al.*, 2017).

Recommendation:

- HDCT with autologous stem cell rescue is advised in patients not eligible for radiotherapy.
- Combination of radiotherapy with HDCT in young children should be used very cautiously because of the neuro-cognitive long-term effects; it is advised to perform such treatment strategies in nationally recognized reference centres.

3.6. Multimodality treatment

Based on several recent studies, a dose intense multimodal regimen is considered as standard of care. Therefore, it is highly recommended that treatment takes place in a medical centre with a specialized paediatric (neuro-)oncology ward. While no comparative studies are available, no recommendation can be made on the basis of efficacy. Considering the rarity and the prognosis of the disease, including patients into study protocols is needed in order to improve the outcome. Inclusion in the SIOPe-ATRT-01 trial is recommended for eligible patients in participating countries.

Recommendation:

- Inclusion in open clinical trials is highly encouraged; i.e., enrolling patients in the phase III SIOPE-ATRT-01.
- Alternatively, when participation in a clinical trial is not possible, several options can be discussed in a case/case or site/site manner: recommendations of the EU-RHAB registry, or treatment according to ACNS0333 (Reddy *et al.*, 2020), DFCI (Chi *et al.*, 2009) or SJMB03/SJYO7 (Upadhyaya *et al.*, 2021) protocols can be considered.

3.7. Treatment overview

Within Europe, SIOPE-ATRT-01 has recently started using an age adjusted treatment strategy (Figure 2). The protocol is based on the backbone used in the EU-RHAB registry, supplemented with a triple carboplatin and thiotepa high-dose chemotherapy consolidation (Figure 3) based on the CCG99703 (Finkelstein-Shechter *et al.*, 2010; Lafay-Cousin *et al.*, 2012; Cohen *et al.*, 2015; Guerra *et al.*, 2017) which are supported by the results of the ACNS0333 (Reddy *et al.*, 2020) and the ACNS0334 study (Aridgides *et al.*, 2019; Reddy *et al.*, 2020).

For patients with localized disease in the age group between 13 and 35 months, a randomization is introduced comparing focal radiotherapy with triple HDCT. This randomization aims to answer the question whether triple HDCT is non inferior to focal radiotherapy in terms of survival and side effects. The short and long-term toxicities of the 2 treatment modalities are assessed as secondary objectives (EU-RHAB, 2021).

For detailed treatment recommendations see SIOPE-ATRT-01 protocol, EU-RHAB registry guideline or corresponding alternative treatment protocol.

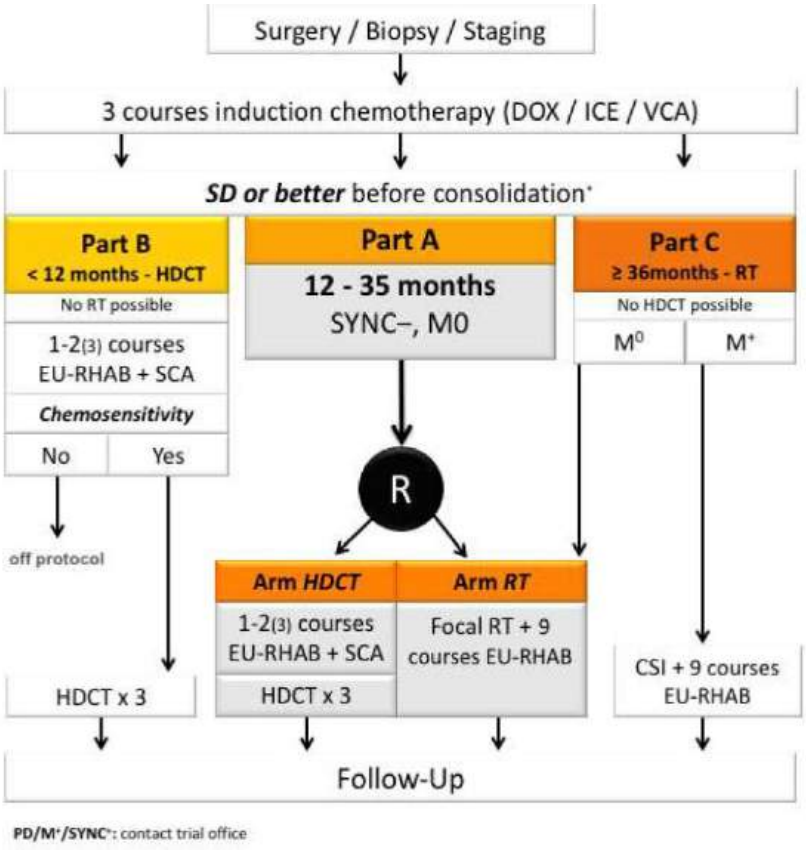

Figure 2. *Overview of age dependent treatment strategy of the SIOP-ATRT-01 study (EU-RHAB, 2021).* PD: progressive disease; M+: metastatic disease; SYNC: synchronous multifocal tumors

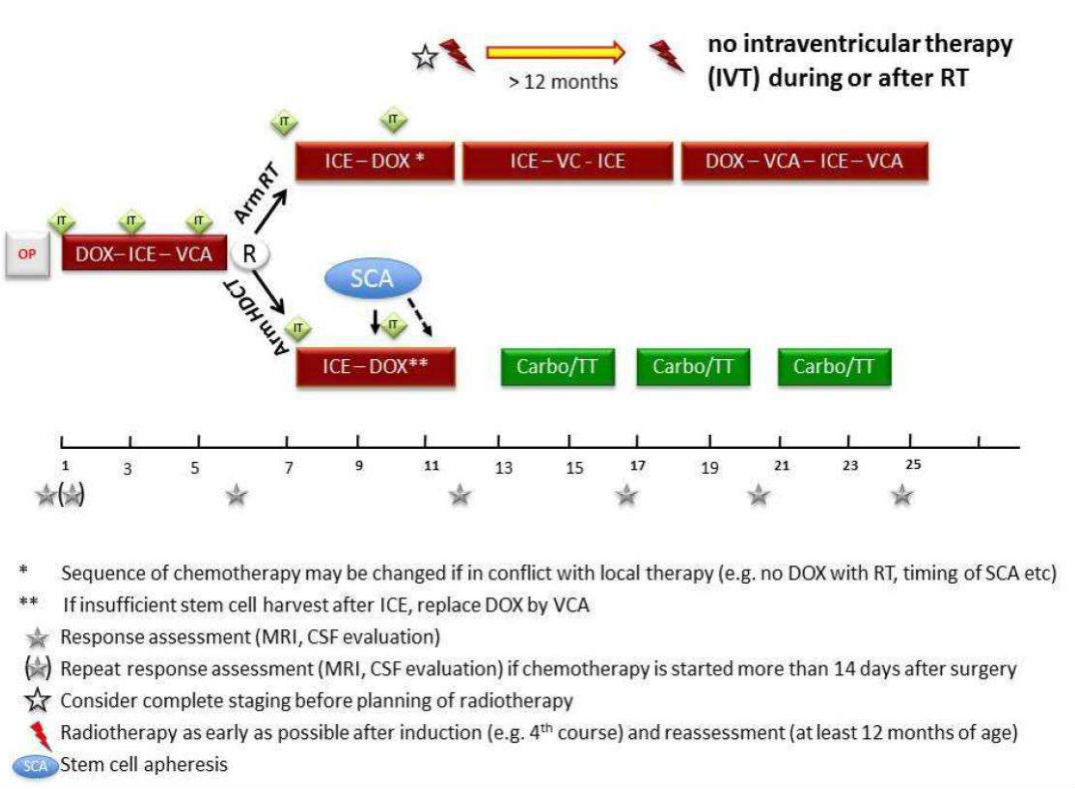

Figure 3. *Overview of detailed chemotherapy scheme of the randomization arm of the SIOP-ATRT-01 study (EU-RHAB, 2021).*

4. REFERENCE LIST

De Amorim Bernstein, K. *et al.* (2013) 'Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors', *International Journal of Radiation Oncology Biology Physics*. Elsevier Inc., 86(1), pp. 114–120. doi: 10.1016/j.ijrobp.2012.12.004.

Aridgides, P. D. *et al.* (2019) 'Outcomes after Radiation Therapy for Very Young Children with High-Risk Medulloblastoma or Supratentorial Primitive Neuroectodermal Tumor Treated on COG ACNS0334', *International Journal of Radiation Oncology, Biology, Physics*. Elsevier, 105(1), p. S109. doi: 10.1016/J.IJROBP.2019.06.602.

Athale, U. H. *et al.* (2009) 'Childhood atypical teratoid rhabdoid tumor of the central nervous system: a meta-analysis of observational studies.', *Journal of pediatric hematology/oncology*, 31(9), pp. 651–63. doi: 10.1097/MPH.0b013e3181b258a9.

Bartelheim, K. *et al.* (2016) 'Improved 6-year overall survival in AT/RT - results of the registry study Rhabdoid 2007.', *Cancer medicine*, 5(8), pp. 1765–75. doi: 10.1002/cam4.741.

Benesch, M. *et al.* (2014) 'High-dose chemotherapy (HDCT) with auto-SCT in children with atypical teratoid/rhabdoid tumors (AT/RT): a report from the European Rhabdoid Registry (EU-RHAB).', *Bone marrow transplantation*, 49(3), pp. 370–5. doi: 10.1038/bmt.2013.208.

Biegel, J. A. (1999) 'Cytogenetics and molecular genetics of childhood brain tumors.', *Neuro-oncology*, 1(2), pp. 139–51. doi: 10.1093/neuonc/1.2.139.

Biggs, P. J. *et al.* (1987) 'Malignant rhabdoid tumor of the central nervous system.', *Human pathology*, 18(4), pp. 332–7. doi: 10.1016/s0046-8177(87)80161-2.

Buscariollo, D. L. *et al.* (2012) 'Survival outcomes in atypical teratoid rhabdoid tumor for patients undergoing radiotherapy in a Surveillance, Epidemiology, and End Results analysis', *Cancer*, 118(17), pp. 4212–4219. doi: 10.1002/cncr.27373.

Chen, Y. W. *et al.* (2006) 'Impact of radiotherapy for pediatric CNS atypical teratoid/rhabdoid tumor (single institute experience)', *International Journal of Radiation Oncology Biology Physics*, 64(4), pp. 1038–1043. doi: 10.1016/j.ijrobp.2005.10.001.

Chi, S. N. *et al.* (2009) 'Intensive multimodality Treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor', *Journal of Clinical Oncology*, 27(3), pp. 385–389. doi: 10.1200/JCO.2008.18.7724.

Child, A. E. *et al.* (2021) 'Long-term cognitive and academic outcomes among pediatric brain tumor survivors treated with proton versus photon radiotherapy', *Pediatric Blood and Cancer*, 68(9), pp. 1–12. doi: 10.1002/pbc.29125.

Cohen, B. H. *et al.* (2015) 'Pilot Study of Intensive Chemotherapy With Peripheral Hematopoietic Cell Support for Children Less Than 3 Years of Age With Malignant Brain Tumors, the CCG-99703 Phase I/II Study. A Report From the Children's Oncology Group', *Pediatric Neurology*. Elsevier Inc, 53(1), pp. 31–46. doi: 10.1016/j.pediatrneurol.2015.03.019.

Dell'Oro, M. *et al.* (2021) 'Normal tissue tolerance amongst paediatric brain tumour patients- current evidence in proton radiotherapy.', *Critical reviews in oncology/hematology*, 164, p. 103415. doi: 10.1016/j.critrevonc.2021.103415.

Eaton, K. W. *et al.* (2011) 'Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors.', *Pediatric blood & cancer*, 56(1), pp. 7–15. doi: 10.1002/pbc.22831.

Ellison, D. (2013) *Neuropathology : a reference text of CNS pathology*. Edinburgh; London: Mosby.

EU-RHAB (2021) *SIOPe ATRT01*. Available at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-003335-29/DE#A (Accessed: 3 October 2021).

Federico, A. *et al.* (2022) 'ATRT-SHH comprises three molecular subgroups with characteristic clinical and histopathological features and prognostic significance.', *Acta neuropathologica*. Springer Berlin Heidelberg, 143(6), pp. 697–711. doi: 10.1007/s00401-022-02424-5.

Finkelstein-Shechter, T. *et al.* (2010) 'Atypical teratoid or rhabdoid tumors: Improved outcome with high-dose chemotherapy', *Journal of Pediatric Hematology/Oncology*, 32(5), pp. e182–e186. doi: 10.1097/MPH.0b013e3181dce1a2.

Fischer-Valuck, B. W. *et al.* (2017) 'Assessment of the treatment approach and survival outcomes in a modern cohort of patients with atypical teratoid rhabdoid tumors using the National Cancer Database', *Cancer*, 123(4), pp. 682–687. doi: 10.1002/cncr.30405.

Foulkes, W. D. *et al.* (2017) 'Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome', *Clinical Cancer Research*, 23(12), pp. e62–e67. doi: 10.1158/1078-0432.CCR-17-0595.

Frühwald, M. C. *et al.* (2020) 'Age and DNA methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors.', *Neuro-oncology*, 22(7), pp. 1006–1017. doi: 10.1093/neuonc/noz244.

Frühwald, M. C. *et al.* (2021) 'Current recommendations for clinical surveillance and genetic testing in rhabdoid

tumor predisposition: a report from the SIOPE Host Genome Working Group', *Familial Cancer*. Springer Science and Business Media B.V., 10, pp. 1–12. doi: 10.1007/s10689-021-00229-1.

Gnekow, A. K. (1995) 'Recommendations of the Brain Tumor Subcommittee for the reporting of trials. SIOP Brain Tumor Subcommittee. International Society of Pediatric Oncology.', *Medical and pediatric oncology*, 24(2), pp. 104–8. doi: 10.1002/mpo.2950240209.

Guerra, J. A. *et al.* (2017) 'Marrow-ablative chemotherapy followed by tandem autologous hematopoietic cell transplantation in pediatric patients with malignant brain tumors', *Bone Marrow Transplantation*. Nature Publishing Group, 52(11), pp. 1543–1548. doi: 10.1038/bmt.2017.166.

Haas-Kogan, D. *et al.* (2018) 'National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury', *International Journal of Radiation Oncology Biology Physics*, 101(1), pp. 152–168. doi: 10.1016/j.ijrobp.2018.01.013.

Haas, J. E. *et al.* (1981) 'Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children.', *Human pathology*, 12(7), pp. 646–57. doi: 10.1016/s0046-8177(81)80050-0.

Hasan, A. *et al.* (2011) 'Treatment-related morbidity in atypical teratoid/rhabdoid tumor: Multifocal necrotizing leukoencephalopathy', *Pediatric Neurosurgery*, 47(1), pp. 7–14. doi: 10.1159/000323412.

Ho, B. *et al.* (2020) 'Molecular subgrouping of atypical teratoid/rhabdoid tumors—a reinvestigation and current consensus', *Neuro-Oncology*, 22(5), pp. 613–624. doi: 10.1093/neuonc/noz235.

von Hoff, K. *et al.* (2011) 'Frequency, risk-factors and survival of children with atypical teratoid rhabdoid tumors (AT/RT) of the CNS diagnosed between 1988 and 2004, and registered to the German HIT database.', *Pediatric blood & cancer*, 57(6), pp. 978–85. doi: 10.1002/pbc.23236.

Holdhof, D. *et al.* (2021) 'Atypical teratoid/rhabdoid tumors (ATRTs) with SMARCA4 mutation are molecularly distinct from SMARCB1-deficient cases.', *Acta neuropathologica*. Springer Berlin Heidelberg, 141(2), pp. 291–301. doi: 10.1007/s00401-020-02250-7.

Johann, P. D. *et al.* (2016) 'Atypical Teratoid/Rhabdoid Tumors Are Comprised of Three Epigenetic Subgroups with Distinct Enhancer Landscapes', *Cancer Cell*, 29(3), pp. 379–393. doi: 10.1016/j.ccell.2016.02.001.

Kahalley, L. S. *et al.* (2020) 'Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma', *Journal of Clinical Oncology*, 38(5), pp. 454–461. doi: 10.1200/JCO.19.01706.

Lafay-Cousin, L. *et al.* (2012) 'Central nervous system atypical teratoid rhabdoid tumours: The Canadian Paediatric Brain Tumour Consortium experience', *European Journal of Cancer*. Elsevier Ltd, 48(3), pp. 353–359. doi: 10.1016/j.ejca.2011.09.005.

Lafay-Cousin, L. *et al.* (2015) 'Neurocognitive evaluation of long term survivors of atypical teratoid rhabdoid tumors (ATRT): The Canadian registry experience.', *Pediatric blood & cancer*, 62(7), pp. 1265–9. doi: 10.1002/pbc.25441.

Louis, D. N. *et al.* (2016) 'The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary', *Acta Neuropathologica*. Springer Berlin Heidelberg, 131(6), pp. 803–820. doi: 10.1007/s00401-016-1545-1.

Louis, D. N. *et al.* (2021) 'The 2021 WHO Classification of Tumors of the Central Nervous System: a summary', *Neuro-Oncology*, 23(8), pp. 1231–1251. doi: 10.1093/neuonc/noab106.

McGovern, S. L. *et al.* (2014) 'Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhabdoid tumor of the central nervous system.', *International journal of radiation oncology, biology, physics*, 90(5), pp. 1143–52. doi: 10.1016/j.ijrobp.2014.08.354.

Olson, T. A. *et al.* (1995) 'Successful treatment of disseminated central nervous system malignant rhabdoid tumor', *Journal of Pediatric Hematology/Oncology*, pp. 71–75. doi: 10.1097/00043426-199502000-00013.

Ostrom, Q. T. *et al.* (2015) 'Alex's Lemonade Stand Foundation Infant and Childhood Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2007-2011.', *Neuro-oncology*, 16 Suppl 1, pp. x1–x36. doi: 10.1093/neuonc/nou327.

Packer, R. J. *et al.* (2002) 'Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop.', *Journal of pediatric hematology/oncology*, 24(5), pp. 337–42. doi: 10.1097/00043426-200206000-00004.

Pai Panandiker, A. S. *et al.* (2012) 'Sequencing of local therapy affects the pattern of treatment failure and survival in children with atypical teratoid rhabdoid tumors of the central nervous system.', *International journal of radiation oncology, biology, physics*, 82(5), pp. 1756–63. doi: 10.1016/j.ijrobp.2011.02.059.

Park, M. *et al.* (2021) 'Atypical Teratoid/Rhabdoid Tumor of the Central Nervous System in Children under the Age of 3 Years', *Cancer Research and Treatment*, 53(2), pp. 378–388. doi: 10.4143/CRT.2020.756.

Poplack, P. A. P. D. G. (2015) 'Principles and Practice of Pediatric Oncology', in *Principles and Practice of Pediatric Oncology*. 7th edn. Lippincott Williams And Wilkins, pp. 686–687. Available at: https://oncology.lwwhealthlibrary.com/book.aspx?bookid=1583.

Quinn, T. J. *et al.* (2019) 'Trimodality therapy for atypical teratoid/rhabdoid tumor is associated with improved

overall survival: A surveillance, epidemiology, and end results analysis.', *Pediatric blood & cancer*. John Wiley and Sons Inc., 66(12), p. e27969. doi: 10.1002/pbc.27969.

Reddy, A. T. *et al.* (2020) 'Efficacy of High-Dose Chemotherapy and Three-Dimensional Conformal Radiation for Atypical Teratoid/Rhabdoid Tumor: A Report From the Children's Oncology Group Trial ACNS0333.', *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. American Society of Clinical Oncology, 38(11), pp. 1175–1185. doi: 10.1200/JCO.19.01776.

Rorke, L. B., Packer, R. J. and Biegel, J. A. (1996) 'Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity.', *Journal of neurosurgery*, 85(1), pp. 56–65. doi: 10.3171/jns.1996.85.1.0056.

Schneppenheim, R. *et al.* (2010) 'Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome.', *American journal of human genetics*, 86(2), pp. 279–84. doi: 10.1016/j.ajhg.2010.01.013.

Schrey, D. *et al.* (2016) 'Multimodal therapy in children and adolescents with newly diagnosed atypical teratoid rhabdoid tumor: individual pooled data analysis and review of the literature.', *Journal of neuro-oncology*, 126(1), pp. 81–90. doi: 10.1007/s11060-015-1904-0.

Slavc, I. *et al.* (2014) 'Atypical teratoid rhabdoid tumor: improved long-term survival with an intensive multimodal therapy and delayed radiotherapy. The Medical University of Vienna Experience 1992-2012', *Cancer medicine*, 3(1), pp. 91–100. doi: 10.1002/cam4.161.

Squire, S. E., Chan, M. D. and Marcus, K. J. (2007) 'Atypical teratoid/rhabdoid tumor: The controversy behind radiation therapy', *Journal of Neuro-Oncology*, 81(1), pp. 97–111. doi: 10.1007/s11060-006-9196-z.

Sredni, S. T. and Tomita, T. (2015) 'Rhabdoid tumor predisposition syndrome.', *Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society*, 18(1), pp. 49–58. doi: 10.2350/14-07-1531-MISC.1.

Suneja, G. *et al.* (2013) 'Acute toxicity of proton beam radiation for pediatric central nervous system malignancies.', *Pediatric blood & cancer*, 60(9), pp. 1431–6. doi: 10.1002/pbc.24554.

Szychot, E. *et al.* (2017) 'Impact of induction chemotherapy, hyperfractionated accelerated radiotherapy and high-dose thiotepa on brain volume loss and functional status of children with primitive neuroectodermal tumour.', *Pediatric blood & cancer*, 64(11), pp. 1–8. doi: 10.1002/pbc.26619.

Tekautz, T. M. *et al.* (2005) 'Atypical teratoid/rhabdoid tumors (ATRT): Improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy', *Journal of Clinical Oncology*, 23(7), pp. 1491–1499. doi: 10.1200/JCO.2005.05.187.

Tran, S. *et al.* (2020) 'Clinical outcomes and quality of life in children and adolescents with primary brain tumors treated with pencil beam scanning proton therapy.', *Pediatric blood & cancer*, 67(12), p. e28465. doi: 10.1002/pbc.28465.

Tulla, M. *et al.* (2015) 'Incidence, Trends, and Survival of Children With Embryonal Tumors.', *Pediatrics*, 136(3), pp. e623-32. doi: 10.1542/peds.2015-0224.

Underiner, R. M. *et al.* (2020) 'Meta-Analysis of Treatment Modalities in Metastatic Atypical Teratoid/Rhabdoid Tumors in Children', *Pediatric Neurology*. Elsevier Inc., 108, pp. 106–112. doi: 10.1016/j.pediatrneurol.2020.03.003.

Upadhyaya, S. A. *et al.* (2021) 'Relevance of Molecular Groups in Children with Newly Diagnosed Atypical Teratoid Rhabdoid Tumor: Results from Prospective St. Jude Multi-Institutional Trials', *Clinical Cancer Research*. Clin Cancer Res, p. clincanres.4731.2020. doi: 10.1158/1078-0432.CCR-20-4731.

Versteege, I. *et al.* (1998) 'Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer.', *Nature*, 394(6689), pp. 203–6. doi: 10.1038/28212.

Wilson, B. G. and Roberts, C. W. M. (2011) 'SWI/SNF nucleosome remodellers and cancer.', *Nature reviews. Cancer*, 11(7), pp. 481–92. doi: 10.1038/nrc3068.

Yamasaki, K. *et al.* (2020) 'Clinical characteristics, treatment, and survival outcome in pediatric patients with atypical teratoid/rhabdoid tumors: A retrospective study by the Japan Children's Cancer Group', *Journal of Neurosurgery: Pediatrics*. American Association of Neurological Surgeons, 25(2), pp. 111–120. doi: 10.3171/2019.9.PEDS19367.

Yang, W. C. *et al.* (2020) 'Effect of early radiotherapy initiation and high-dose chemotherapy on the prognosis of pediatric atypical teratoid rhabdoid tumors in different age groups', *Journal of Neuro-Oncology*. Springer US, 147(3), pp. 619–631. doi: 10.1007/s11060-020-03456-1.