

Original Article

ESTRO-SIOPE guideline: Clinical management of radiotherapy in atypical teratoid/rhabdoid tumors (AT/RTs)



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ARTICLE INFO

Keywords:

Atypical teratoid rhabdoid tumor
Radiotherapy
Brain tumor
Children

ABSTRACT

Background and purpose: Treatment of patients with atypical teratoid/rhabdoid (AT/RT) is challenging, especially when very young (below the age of three years). Radiotherapy (RT) is part of a complex trimodality therapy. The purpose of this guideline is to provide appropriate recommendations for RT in the clinical management of patients not enrolled in clinical trials.

Materials and methods: Nine European experts were nominated to form a European Society for Radiotherapy and Oncology (ESTRO) guideline committee. A systematic literature search was conducted in PubMed/MEDLINE and Web of Science. They discussed and analyzed the evidence concerning the role of RT in the clinical management of AT/RT.

Results: Recommendations on diagnostic imaging, therapeutic principles, RT considerations regarding timing, dose, techniques, target volume definitions, dose constraints of radiation-sensitive organs at risk, concomitant chemotherapy, and follow-up were considered. Treating children with AT/RT within the framework of prospective trials or prospective registries is of utmost importance.

Conclusion: The present guideline summarizes the evidence and clinical-based recommendations for RT in patients with AT/RT. Prospective clinical trials and international, large registries evaluating modern treatment approaches will contribute to a better understanding of the best treatment for these children in future.

Atypical teratoid/rhabdoid tumors (AT/RT) are tumors of the central nervous system (CNS) most commonly diagnosed in very young children [1–5], with most (70–80 %) tumors found in children under three years of age [6,7]. The German Childhood Cancer Registry reported that the median age at diagnoses was 18 months [8]. These rare embryonal tumors are locally aggressive and one of the most malignant CNS tumors. Also, they spread throughout the CNS by cerebrospinal fluid (CSF). Up to

one-third of the patients have disseminated disease in the brain or spinal canal or both at diagnosis [9,10]. AT/RT are characterized by alterations of SWItch/sucrose nonfermentable related, matrix associated, actin dependent regulator of chromatin, subfamily B (SMARCB1) gene or less frequently of SMARCA4 [11,12], and cover three distinct molecular subgroups (tyrosinase (TYR), myelocytomasis oncogene (MYC), sonic hedgehog (SHH)) [13]. Diagnosis at very young age, anatomically

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<https://doi.org/10.1016/j.radonc.2024.110227>

Received 8 March 2024; Accepted 10 March 2024

Available online 14 March 2024

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challenging sites and complex treatment approaches make clinical management of patients with AT/RT challenging. These tumors are usually treated with surgery, radiotherapy (RT), and chemotherapy (CTx). Clinical results come from small series reporting the children's outcome treated according to various multimodality regimes. Despite a multimodality therapeutic approach, AT/RT are associated, however with a poor prognosis. The mean survival time ranges from 6 to 18 months [1,9,14]. The North American AT/RT registry has reported one of the largest cohorts consisting of 42 children. All children received post-operative CTx, 31 % received RT, 38 % intrathecal CTx, and 31 % stem-cell rescue. The median event-free survival (EFS) and overall survival (OS) were 10.0 and 16.8 months, respectively [15]. In a recently published large retrospective study, 47 children were treated between 1999 and 2014 in Taiwan [4]. Older age (≥ 3 years), supra-tentorial site, and treatment with CTx, RT, or both were significantly associated with a better survival. Molecular profiling was not done in both these studies. A prospective US study reporting the results of the 'Head Start (HS) I/II' trials, assessing the role of induction CTx, with or without high-dose methotrexate, and consolidation with autologous hematopoietic progenitor cell rescue reported an EFS of 6 and 12 months for HS I and II, respectively [16]. These earlier studies highlight the overall poor outcome of these patients regardless of therapeutic strategies. However, modern diagnostic techniques and therapy strategies may have contributed to improvements in clinical outcomes. The prospective ACNS0333 study with 65 patients illustrated the dramatic progress of treatment concepts over the last decades. EFS in patients < 36 months of age were significantly improved with the modern treatment concept approaches compared with historical treatment approaches which did not include applying RT for all patients or methotrexate and high-dose CTx [17]. The European Registry for rhabdoid tumors (EU-RHAB) recommended combination CTx therapy with neurosurgery and conventional, intraventricular, and high-dose CTx with stem-cell rescue or RT [18]. Different prognostic factors, such as complete remission, TYR subgroup, age, and RT have been described [19,20]. The EU-RHAB revealed that high-dose CTx did not show any advantage over conventional CTx, while RT (on univariate analysis) had a significant impact [19]. A recently published analysis of a large group of patients of EU-RHAB and its precursors ($n = 186$) confirmed RT as a prognostic factor for outcome [21]. The current multinational trial SIOPE ATRT01 (EudraCT 2018-003335-29) evaluates the non-inferiority of three courses of high-dose CTx compared to focal RT as consolidation therapy [22].

Today's imaging techniques improve diagnostic findings and target delineation. Modern RT offers a variety of innovative conformal techniques that significantly spare normal tissues. However, homogenous approaches for patients not enrolled in clinical trials are missing. The purpose of this guideline is to provide recommendations on the clinical management of RT in patients with AT/RT. It includes a European consensus on diagnostic imaging, therapeutic principles, RT considerations regarding timing, dose concepts, techniques, target volume definitions, dose constraints of radiation-sensitive organs at risk (OAR), concomitant CTx, and follow-up care. It defines the current hands-on approach for radiation oncologists treating patients affected by AT/RT.

Methods & materials

The guideline committee of the European Society for Radiotherapy and Oncology (ESTRO) nominated nine experts to develop a joint guideline of the ESTRO and the SIOPE (European Society of Paediatric Oncology) regarding clinical management of radiotherapy in AT/RT. The authors were European clinical and scientific experts in pediatric radiation oncology, being members of the ESTRO ($n = 8$), SIOPE ($n = 7$), the Paediatric Radiation Oncology Society (PROS; $n = 7$), and the SIOP Brain Tumor Group (SIOP BTG; $n = 5$). A systematic literature search was conducted during November 2021 using PubMed/MEDLINE for articles and Web of Science for meeting abstracts. Medical Subjects

Headings (MeSH) terms and free text words were used. The search included keywords for the term "AT/RT in children" and the intervention "radiotherapy" combined with further specific RT terms ("organs at Risk", "delineation", "contouring", "margin", "dose constraints", "tolerance dose", "radiation tolerance", "target volume", "gross tumor volume", "clinical target volume", "planning target volume", "timing"). The full search strategy is displayed in Suppl. 1. In PubMed, filters were not used. In Web of Science, the search was limited to only meeting abstracts since 2015. In a title screening, results were selected if papers contained data on AT/RT, and English texts were available. The search detected 260 and 42 results in PubMed and Web of Science, respectively. After the screening, 195 papers and 42 meeting abstracts were available. The bibliography was supplemented by existing guidelines as well as recommendations on target delineation and dose constraints for pediatric brain tumors. Additionally, available AT/RT protocols containing RT applications were used. High-quality systematic reviews, meta-analyses, randomized controlled trials, and cohort studies were used to ensure evidence-based statements.

The development of this guideline was based on the ESTRO Guideline Committee procedure policy [23]. The recommendations are a consensus of the authors developed in four quarterly discussion processes and a final voting online survey. They are based on the evidence and experts' perspectives of currently accepted treatment approaches for patients with AT/RT. Respective recommendations are summarized and highlighted in the text. This guideline passed a mandatory ESTRO internal review.

Diagnosis, staging, radiology & molecular findings

The imaging appearance of AT/RT could be heterogeneous, but several features arise a suspicion of diagnosis and point to specific molecular subtypes. Imaging should be done according to the protocol of the SIOPE Brain Tumour Imaging Group to ensure a high standard and image quality [24]. It is strongly recommended to involve reference pathologists and radiologists for accurate diagnosis, staging, and molecular subtyping.

Diagnostic imaging

AT/RT are predominately located in the supratentorial or infratentorial brain, but can also affect the spinal cord. Supratentorially, they may be centred in basal ganglia, white matter, and cortex. Intraventricular locations are also possible. In the posterior fossa, two locations are classical: the cerebellopontine angle, or centred in the quadrigeminal cistern, which may extend supratentorially through the tentorial incisure. Often large on the discovery, AT/RT harbors irregular but well-limited contours, possibly perilesional edema, frequent calcifications or hemorrhage. They may present with bony erosion [25]. AT/RT display heterogeneous hypo-intensity on T1-weighted images, and heterogeneous hyper-intensity on T2-weighted images. Contrast enhancement is present most of the time. Central cystic necrosis is suggestive of the diagnosis, and peripheral cysts are possible. AT/RT can also present with calcification. Diffusion is highly restricted in AT/RTs and is a strong clue for diagnosis. On multimodal imaging, arterial spin labeling (ASL) perfusion is very high, except in SHH AT/RT of the quadrigeminal cistern. Spectroscopy shows elevated peak lactate, lipid and choline, very low N-acetylaspartate (NAA) and low myoinositol peaks.

Taken together, an aggressive neoplasm in a child below 18 months of age with certain criteria, such as necrosis, hemorrhage and calcification should always raise the suspicion of an AT/RT.

Staging imaging

Staging work-up will result in classifying the tumor in either localized, or metastatic; with or without post-operative residual tumor and

ESTRO recommendations on clinical management of RT in AT/RT Diagnosis.

- In cranial tumors, diagnostic imaging requires brain MRI with T1-weighted images (without and with contrast enhancement), T2 weighted images, FLAIR and diffusion weighted images.
- In addition, complete staging (spinal MRI and CSF cytology) is mandatory to verify.
 - localized or metastatic disease.
 - with or without post-operative residual tumor.
- In spinal primary tumor, regular spinal and cranial MRI is required.
- Involvement of reference pathologists, reference radiologists, and human geneticists is highly recommended.
- Early postoperative MRI of the tumor region within 72 h post-surgery is needed.
- Regular re-staging examinations during therapy course are recommended.

/or presence of synchronous rhabdoid tumor(s). Early postoperative MRI of the tumor region within 72 h post-surgery is needed. Apart from craniospinal MRI, whole body MRI is recommended for complete staging. At the time of diagnosis, spinal dissemination is already noted in 20–30 % [9,10]. Detection of leptomeningeal metastases in the entire dural sac using MRI should be based mainly on sagittal T1-weighted sequences with contrast enhancement. If there are lesions within the spine suspicious of tumor/metastases, axial gradient echo T1-weighted (2D or 3D) should be performed over the region of interest. In case of doubt, additional high resolution T2-weighted sequences and diffusion-weighted imaging with apparent diffusion coefficient (DWI with ADC) can be helpful. CSF cytology adds to the accuracy of diagnosis of spread and will be performed after spinal MRI. It is recommended to regularly perform re-staging examinations during the therapy course.

Pathology and molecular biology

Analyses of pathological and molecular characteristics is highly recommended for diagnosis. Since WHO classification 2016 [26], inactivation of SMARCB1 gene (95 %) or SMARCA4 (5 %) with corresponding loss of nuclear protein product integrase interactor (INI)-1 is a requisite for AT/RT diagnosis. The molecular subgroups TYR-, SHH- and MYC-AT/RT based on different tumor DNA methylation and transcriptome findings and are associated with distinct molecular mechanisms driving oncogenesis.

Table 1

Overview of clinical protocols for the treatment of AT/RT.

Acronym	Sponsor	Title	Registration number	Status	Activated	Publications
ACNS0333	Children's Oncology Group	Combination Chemotherapy, Radiation Therapy, and an Autologous Peripheral Blood Stem Cell Transplant in Treating Young Patients With Atypical Teratoid/Rhabdoid Tumor of the Central Nervous System	NCT00653068	Active, not recruiting	2008	[17]
SJMB03	St. Jude Children's Research Hospital	Treatment of Patients With Newly Diagnosed Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumor, or Atypical Teratoid Rhabdoid	NCT00085202	Active, not recruiting	2003	[7]
02-294 DFCI	Dana-Farber Cancer Institute	A Phase II Study of Intrathecal and Systemic Chemotherapy With Radiation Therapy for Children With Central Nervous System Atypical Teratoid/Rhabdoid Tumor (AT/RT) Tumor	NCT00084838	Completed	2003	[48]
SJYC07	St. Jude Children's Research Hospital	Risk-Adapted Therapy for Young Children With Embryonal Brain Tumors, Choroid Plexus Carcinoma, High Grade Glioma or Ependymoma	NCT00602667	Active, not recruiting	2007	[7]
SJATRT	St. Jude Children's Research Hospital	Phase 2 Study of Alisertib as a Single Agent in Recurrent or Progressive Central Nervous System (CNS) Atypical Teratoid Rhabdoid Tumors (AT/RT) and Extra-CNS Malignant Rhabdoid Tumors (MRT) and in Combination Therapy in Newly Diagnosed AT/RT	NCT02114229	Recruiting	2014	
SIOPE ATRT01	German Paediatric Oncology Group	An international prospective umbrella trial for children with atypical teratoid/rhabdoid tumours (ATRT) A randomized phase III study evaluating the non-inferiority of three courses of high-dose chemotherapy (HDCT) compared to focal radiotherapy as consolidation therapy	EudraCT 2018-003335-29	Recruiting	2022	
EU-RHAB		European Rhabdoid Registry		Open	2005	[19,20,21,47]

Molecular / radiologic correlations

Indicator of tumor molecular subtypes is tumor location: TYR-AT/RTs most commonly arise in the cerebellopontine angle, being exophytic from the middle cerebellar peduncle or the cerebellar hemispheres; SHH-ATRTs have two classical locations: either in the posterior fossa in the quadrigeminal cistern (SHH-2) and the supra-tentorial area (SHH-1), or in the basal ganglia (with tumors often extending far beyond); MYC-ATRTs in the posterior fossa are extra-axial (internal auditory canal, jugular foramen, cranial nerves), while in the supra-tentorial brain they are typically cortical. Intraventricular tumors are also possible, found in all subgroups.

Germline alterations

Germline alterations (rhabdoid tumor predisposition syndrome) are reported in 10–35 % of patients with AT/RT and correlate with young age at diagnosis (<12 months), and development of synchronous tumors as well as more aggressive clinical course and poorer prognosis compared to sporadic rhabdoid tumors [27]. Therefore, blood or tissue analyses concerning germline alterations is recommended to assess individual risk profile.

ESTRO recommendations on clinical management of RT in AT/RT Therapeutic principles.

- Decision on treatment approach should be done after discussion in a multidisciplinary tumor board.
- Treatment should be age- and risk-adapted.
- In principle, three modalities (surgery, CTx, and RT) can be offered. However, the role of RT has to be discussed according to patient's age.
- In case of residual disease at time of RT, resectability should be re-evaluated.
- Care should be performed in specialized clinics (incl. children's clinic and anesthesia team).
- Enrolment of patients in clinical trials and international registries is strongly recommended.

Therapeutic principles

Treatment of AT/RT is very challenging due to the low incidence of disease and complexity of care. Therefore, the therapeutic approach should be discussed and decided within a multidisciplinary team of specialists (pediatric oncologists, surgeons, pathologists, radiologists, radiation oncologists, and clinical nurse specialists). The care is preferably centralized in experienced, specialized pediatric oncology clinics including referrals networks. To ensure high-quality approach, treatment within prospective trials or international registries is highly encouraged. The standard of care should be applied, if there is not an open trial or registry or the respective inclusion criteria are not met. So far, different treatment strategies are used. Table 1 lists previous and current treatment protocols containing RT in AT/RT.

Current treatment approach in AT/RT should be trimodal (surgery, CTx, and RT). Besides age and molecular subtype, maximum safe resection is the most important prognostic factor. For some patients multiple surgeries are needed. CTx is usually administered as multi-drug treatment, partly intrathecal. Some approaches use high-dose CTx with methotrexate combined with stem-cell rescue. The use of RT remains controversial. For risk- and age-adjusted intensive therapy, RT should be considered and discussed individually in all cases. However, some multimodality treatment studies including high-dose CTx with stem-cell transplantation have shown that patients can survive even when not having received RT [16,28,29].

Treatment and care of AT/RT is complex, not at least because of the patients' very young age. Besides the three modalities (surgery, CTx, and RT), additional applications and surgical interventions (ventriculoperitoneal shunt, Omay/Rickham reservoir) may be required. An affiliated children's clinic is needed for administration of concomitant CTx and treating possibly serious complications during RT (e.g. shunt infections, neutropenia, high-grade mucositis requiring pain medication, and need for enteral feeding). Furthermore, sedation is required for imaging and RT when affected children are too young to cooperate. This procedure enables accurate treatment delivery of RT. Preferably, it is to be performed by an experienced anesthesiological team specialized in pediatric/infant anesthesia. General anesthesia with deep sedation is obtained. Frequent sedation is usually well-tolerated [30–32]. The need of anesthesia during RT treatment preparations or performance, might be not only a question of age of the child under 5–7 years, but for older children as well. Agitation, anxiety, and compliance problems may affect older children as well, especially in the case of children with neurocognitive deficits when they are away from their parents. Hence, anesthesia may be unavoidable in such cases. Additional behavioral therapy may be useful to help children to cooperate during RT and neuroimaging.

Timing and sequencing of radiotherapy within multimodality treatment strategy

The best time for introducing RT in the treatment of AT/RT is under study. Historically, for patients < 36 months old, schedules of intensive CTx including autologous stem-cell transplantation and avoidance of RT have been used. Although the available evidence shows early RT to be beneficial in the treatment of AT/RT, there is reluctance to irradiate very young children because of the neurocognitive and neuroendocrine implications in this age group. Most treatment protocols have attempted to either restrict the use of RT to salvage situations or to delay the treatment until the brain is more mature. Thus, RT is not offered in all protocols, and craniospinal irradiation (CSI) is offered only to children older than three years and to those with CNS dissemination at diagnosis. Focal RT seems to be more acceptable and can also be offered to younger children (below 12 months of age), if considered appropriate, e.g. in palliative settings. Several studies have shown that multimodality therapy including surgery, intensive multidrug systemic treatment and RT yield a better survival [1,33–38] than if RT is omitted from the primary treatment. This has also been shown in infants [39]. Early RT soon after surgery seems to be beneficial [40–42] because local recurrences often occur already during induction CTx [20,43–45]. A current pooled analysis reviewing 501 patients (53.1 % treated with RT) highlights the potential benefit of adjuvant RT despite the potential risk of toxicities in younger children (median age 2.2 years) [37]. The 1-, 3-, and 5-year OS rates were 78.8 % 51.0 %, and 43.7 % with RT compared to 32.2 %, 18.6 %, and 15.9 % without RT, respectively. RT was an independent prognostic factor for OS (hazard ratio (HR) 0.295, $p < 0.001$) [37]. A reasonable strategy to avoid part of neurotoxicity in very young children is to perform focal irradiation after surgery and induction CTx, as published by Reddy et al [17]. In this COG's trial conducted to examine the efficacy and safety of intensive post-operative CTx and focal irradiation [17], focal irradiation was scheduled at the end of consolidation treatment in the younger patients group (<6 months in infratentorial M0, < 12 months in supratentorial M0) and after induction CTx and before consolidation CTx in M0 patients older than this age. In this analysis, timing of radiation (post-induction vs. post-consolidation) did not affect survival (4-year OS rate 49 % vs. 48 %) and RT was better tolerated in the group of focal irradiation after the consolidation CTx, than in the cohort receiving early RT after induction CTx. They reported two deaths attributed to CNS necrosis (at 49 and 494 days after completion of protocol therapy) in the last mentioned group [17].

The European strategy is to give RT as early as possible, after surgery for patients older than 18 months, or after induction CTx for patients

ESTRO recommendations on clinical management of RT in AT/RT Timing of radiotherapy.

- In children above the age of 3 years (≥ 36 months) RT is part of first-line multimodality treatment.
- For non-metastatic disease, focal RT is recommended for children older than 12–18 months.
- Age- and risk-adapted RT can be applied even in children younger than 12–18 months after multidisciplinary tumor board discussion.

ESTRO recommendations on clinical management of RT in AT/RT Dose and volume concept.

- Focal RT has to be applied in non-metastatic disease (age \geq 12–18 months).
- CSI should be considered only in metastatic disease (depending on age).
- Total recommended dose to primary site is 54 Gy (single dose 1.8 Gy). Dose reduction to 50.4 Gy can only be considered individually (e.g. in age below 36 months).
- The recommended CSI dose (for children $>$ 36 months) is 35.2–36.0 Gy with single doses of 1.6–1.8 Gy.
- Recommendation for CSI in children below 36 months of age should be only made after individual tumor board discussion. If required, the dose may be reduced to 23.4/24 Gy.
- Recommended total boost dose to persistent spinal and cranial metastasis is 45–50.4 Gy.

younger than 18 months [18]. Children below the age of 18 months should only be irradiated under particular circumstances depending on age, tumor localization, tumor extent, progression disease, and available RT technique. The current randomized study SIOPE ATRT01 provides the use of RT from the age of 12 months [46]; the strategy includes surgery, and induction CTx followed by consolidation therapy (high-dose CTx vs. RT).

Application of CSI varies depending on age. EU-RHAB recommended CSI in metastatic disease from age $>$ 18 months [18]. According to COG and SIOPE, CSI is applied in metastatic disease for children older than $>$ 36 months [17,46]. In contrast, St Jude Children's Research Hospital is using prophylactic CSI in non-metastatic disease from the age of 36 months [7,9]. To date, it is unclear whether CSI is indicated in non-metastatic disease, and therefore needs to be further investigated in future trials.

Dose and volume concept of radiotherapy

Historically, ATRT were treated like medulloblastoma. Due to the young age of patients and associated toxicity more risk adapted multimodality strategies has been pursued. The pattern of failure reported in different series displays local, distant, and combined events [2,17,47,48]. Some studies suggested that CSF spread is common at relapse [34,49]. Although, one study reported the benefit of preventive

CSI [50], another showed that therapeutic CSI for M + patients did not improve outcome [28]. Whether focal RT in non-metastatic disease is sufficient instead of CSI, remains still unclear. Most recurrences in children with localized disease are reported to be local [1] and German series indicated no impact of CSI on prognosis [21]. Therefore, the current recommendation is early focal RT in non-metastatic disease [51]. Early focal RT resulted in improved survival as compared to historical cohorts with 4-year OS of 43 % in the ACNS0333 trial [17,21,45,51].

The recommended dose to the primary site is 54 Gy in fractions of 1.8 Gy [17,18,52]. At a very young age (below 36 months), total dose may be reduced to 50.4 Gy [17,52]. In the case of macroscopic residual disease, a boost of 5.4 Gy in 3 fractions could be considered up to a cumulative dose of 59.4 Gy [18,46].

Children aged 36 months or older with leptomeningeal metastatic disease are treated with CSI to a dose of 35.2–36.0 Gy in 20–22 fractions, followed by a boost up to 54 Gy to the primary site and 45–50.4 Gy to the sites of persistent metastatic spinal and cranial disease [17,18,53]. For children aged 12 to 36 months with metastatic disease, there is still a debate as to whether CSI should be applied. The EU-RHAB protocol recommends 24 Gy in fractions of 1.6 Gy CSI for children aged up to 18 months with metastatic disease [18], the ACNS0333 recommends 23.4 Gy CSI in fractions of 1.8 Gy for children aged 12 to 36 months [17] and in the most recent SIOPE protocol no CSI is advised for patients below

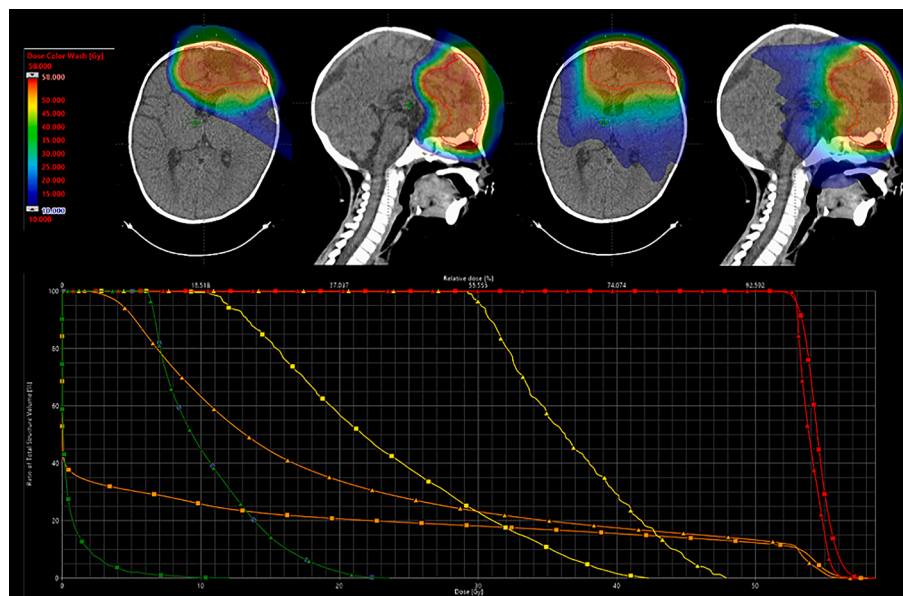


Fig. 1. Plan comparison for focal irradiation of a 1-year-old patient with localized supratentorial AT/RT. The upper panel shows the dose distribution in color-wash for doses 10—58 Gy (RBE). The axial and sagittal figure on the left side are from a 3 fields pencil beam scanning proton plan (PBS), the axial and sagittal figure on the right side are from a 3 arc volumetric modulated arc therapy photon plan (VMAT). In the lower panel the dose-volume-histogram for selected structures (green: left hippocampus, orange: whole brain, yellow: pituitary gland, red: clinical target volume), squares represent the proton plan and triangles the photon plan. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ESTRO recommendations on clinical management of RT in AT/RT Treatment techniques and modalities.

- Proton therapy is the preferred radiotherapy technique. Alternatively, highly conformal intensity/volumetric modulated techniques may be considered, if proton therapy is not available.
- Treatment in specialized RT centers within a multidisciplinary environment is strongly recommended.

36 months of age within first line therapy [46]. Individual decision to treat craniospinal axis in children below 36 months should be based on multidisciplinary tumor board recommendation and after discussion with parents and carers. It is highly recommended to treat patients with AT/RT either in trials or in international registries.

Radiotherapy treatment techniques

The choice of treatment modality (protons or photons) is a matter of debate [54]. Several authors suggest that proton beam therapy might be beneficial for this disease [14,20,34,36,37,52] as this treatment is highly conformal, has a lower integral dose and a better sparing of the normal brain than with traditional photon RT [14]. In the recently reported ACNS0333 trial, both photon and proton therapy were used. For both treatment modalities similar tumor control was reported. The risk of imaging changes and radiation necrosis was comparable for both types of RT [17]. Institutional outcome series have been reported for proton techniques [2,14,49,55]. To minimize the volume of irradiated brain, especially for young aged patients, it is recommended, if available, to preferably use proton therapy or highly conformal intensity/volumetric modulated radiation techniques. Beside the multidisciplinary framework, also inter-departmental collaboration is important, in which centers with high degree of expertise can offer assistance and review services. Fig. 1 shows a comparison between a photon and proton treatment plan for focal irradiation.

Stereotactic radiosurgery for the treatment of AT/RT either using a Gamma Knife, Cyberknife or linac-based radiosurgery approach can be considered as a boost for residual tumor after fractionated treatment or as a salvage therapy. Some experiences in radiosurgery for patients with AT/RT have been reported [56–58]. Spina et al. achieved a local control

rate of 66.7 % after radiosurgery, but 33.3 % of patients developed craniospinal tumor dissemination [56].

Target delineation, imaging, planning details, tolerance doses

Pre- and post-operative MRI according to SIOPE MRI guideline [24] (T1-weighted with contrast, T2-weighted and FLAIR sequences, and diffusion-weighted imaging) should be preferred for treatment planning. Co-registered MRI immediately before RT should be used for computed tomography scan (CT) planning. The target delineation should be based on co-registration of the planning CT and diagnostic MRI. Usually, a planning MRI and preoperative MRIs are used to properly identify the tumor bed and small residues. Contrast enhancement is not always present in the lesions. Tumor extensions through the skull base may be better visible on T2 sequences. This sequence can therefore be beneficial or a second plane with thin slices 2D T2 TSE.

In relation to the primary tumor location, the tumor bed should be delineated by including the parts of the brain that the tumor has been in contact with, by taking into consideration that a shift of these structures after surgery can have occurred. Any residual macroscopic tumor needs to be included into the tumor bed. In case of focal RT, the gross tumor volume (GTV) includes the tumor bed and any residual tumor. The pre-operative imaging defines the areas initially involved with disease. The clinical target volume (CTV) includes the GTV and is limited to the confines of the bony calvarium, falx and tentorium or extend up to but not beyond neuroanatomical structures. The CTV margin should be defined according to the protocol used. The recommended CTV margin to the reconstructed tumor bed is 10 mm and respective anatomical boundaries. It will be a matter of future trials if the margin can be further reduced to 5 mm similar to strategies for ependymoma.

Table 2
Recommendations on dose constraints.

Organ	Mean dose (Gy)	Max dose (D1%) (Gy)	Reference
Brainstem	54	59 (*-63)	[53]
Brainstem center (diameter 2–3 mm)	54	56	[53]
Spinal cord (below C1)	50.4	54	[53]
Optic nerve (left and right)	54	54 (*-56)	[53]
Chiasm	54	54 (*-56)	[53]
Cochlea (left and right)	30	45	[53]
Cochlea (left and right), if ototoxic chemotherapy	25	30	[53]
Lens (left and right)	5	7	[53]
Temporal lobe (left and right)	30 % Vol. < 25 Gy, 60 % Vol. < 20 Gy		[53]
Hippocampus (left and right)	30 % Vol. < 30 Gy, 60 % Vol. < 25 Gy		[53]
Thyroid	as low as possible	–	[53]
Pituitary	36	–	[53]
Vertebrae for CSI in growing children	Consider dose coverage of full vertebral bodies up to at least 20 Gy in growing children to best avoid significant growth asymmetry		[53]
Brain (necrosis)		58.8–59.8	[64]
Brain (neurocognition, methotrexate effect not included)	D _{100%} 18.1 Gy D _{50%} 22.2 Gy D _{20%} 29.1 Gy D _{10%} 35.7 Gy		[64]

*Only in high-risk scenarios individually according to risk profile and expected feasibility.

ESTRO recommendations on clinical management of RT in AT/RT.

Target delineation, imaging, planning details, and tolerance doses.

- For delineation, pre-and post-operative MRI according to SIOPE MRI guideline should be used.
- For focal RT, the GTV should include the tumor bed and residual tumor identified on the brain MRIs.
- For focal RT, the recommended CTV margin to the GTV is 10 mm, taking into account the anatomical boundaries.
- The PTV is defined as the CTV plus an additional margin depending on geometric precision of the technology applied both for CSI and focal RT by the institution.

ESTRO recommendations on clinical management of RT in AT/RT.

Quality assurance.

- High vulnerability of this particular patient cohort has to be considered and dose tolerances of OARs have to be respected according to the recommendations.
- High-quality of RT planning and application has to be assured, preferably by an external QA program, but as a minimal requirement by peer review process.

In case of CSI, the technology selected for CSI should ensure an optimal dose homogeneity within the entire spinal canal thecal sac = CTV). The whole brain CTV should include the entire frontal lobe and cribriform plate region. Measures to prevent asymmetric growth of the vertebral bodies should be taken into account [59]. The PTV is defined as the CTV plus an additional margin depending on geometric precision of the technology applied both for CSI and focal RT. Target volume delineation should be done according to the SIOPE brain tumor group consensus guideline [60].

The co-registered MRI is also beneficial for delineation of organs at risk (OAR). Published CT and MRI based atlas offer guidance, even if partly addressing adult patients [61–63]. Doses to OARs need to take the young age of the patient into consideration and are often lower than constraints usually applied for adults. The PENTEC group has recently published dose constraints for selected OARs in the pediatric population [64]. To prevent neurocognitive deficits the dose to the normal brain should be restricted as much as possible. Dose constraints recommendations are summarized in Table 2.

Quality assurance

Quality assurance is essential in order to obtain optimal treatment results and avoid unnecessary dose-burden to normal tissue [65,66]. In medulloblastoma, inadequate treatment planning showed a negative impact on tumor control and outcome, requiring quality control procedures for treatment planning before starting RT in prospective treatment protocols [65,67]. Quality control is based on extensive information before RT planning and typically covers the review of RT

treatment strategy, target delineation, dose planning, and reproducibility of the treatment. Recent data revealed that with the introduction of intensity modulated RT (IMRT), volumetric intensity modulated arc therapy (VMAT) and proton therapy integrating MRI, high rates of protocol deviations including identification and coverage of GTV and CTV as well as dose homogeneity within PTV and CTV were observed both in CSI and focal RT. Past evaluation criteria for quality control cannot be applied and need to be revised, including the assessment about their clinical relevance or acceptance, respectively [65,67]. If the patient is not included in a prospective clinical protocol, particular attention has to be directed to all treatment planning parameters and their possible pitfalls in AT/RT. A prospective, independent QA program, including a review of the RT treatment plan is recommended, at least in a peer review process. The QUARTET group has set up a RT quality assurance guideline for the ongoing SIOPE ATRT01 trial [46].

Toxicity, interaction with chemotherapy, and supportive therapy during radiotherapy

For maximal tumor control, the aim is to apply planned RT without interruptions and with concomitant CTx. Daily sedation has to be ensured, if necessary. However, acute toxicity in children with AT/RT receiving dose-intense CTx can occur, especially when receiving CSI. Main side-effect is bone marrow suppression, with changes in the blood count. Weight loss, nausea, vomiting, anorexia, discomfort, fatigue, and headache may occur. At the commencement of RT, an adequate blood count should be ensured, with a hemoglobin level of above 10 g/dl, neutrophils > 1.000 and platelets > 50.000. During RT (cranial/

ESTRO recommendations on clinical management of RT in AT/RT Toxicity with chemotherapy interaction.

- CTx need to be tailored in order to avoid interruptions of RT.
- Interdisciplinary care during RT is essential to manage side-effects and to modify therapy. Blood count should be adequate at the start of RT.
- Weekly assessment of weight and blood counts during RT are strongly recommended.
- No administration of:
 - Actinomycin D and Doxorubicin before (at least 2 weeks), during, and after (2–4 weeks) RT.
 - intrathecal and intraventricular CTx concomitant to RT.
 - concomitant i.v. CTx while CSI, but can be considered during focal RT.
- CTx dose reduction can be discussed with the pediatric oncologist.
- Best supportive care has to be offered according to side-effects (e.g. nausea, headache, etc.).

ESTRO recommendations on clinical management of RT in AT/RT Follow up and aftercare.

- Clinical and/or radiological follow up is to be performed by a multidisciplinary team.
- MRIs should be scheduled at least every 3–4 months for 2–3 years, thereafter bi-annually.
- Structured follow up protocol is recommended in order to monitor possible adverse events incl. health related quality of life.

craniospinal), weekly blood counts are necessary to monitor the risk of thrombocytopenia and anemia in order to substitute thrombocytes and erythrocytes if necessary; low number of neutrophils may increase the risk of infections, and may require antibiotics. During CSI, concurrent CTx must be avoided. After RT of the neuroaxis (while boosting the tumor bed) concomitant CTx may be considered [68]. Analyses of combined treatment strategies should be evaluated in future studies.

Interactions between RT and certain CTx agents can result in a high risk of toxicities, necessitating treatment interruptions. Therefore, precautions should be taken during concomitant CTx. Actinomycin D and Doxorubicin should be avoided at least two weeks before RT, during RT, and 2–4 weeks after RT. Furthermore, intrathecal and intraventricular CTx should not be given during and after RT. CTx doses during RT can be reduced depending on previous tolerance. If necessary, G-CSF should be given to avoid neutropenia. For patients with serious complications in pre-RT CTx, concomitant CTx should be avoided.

An additional side effect of CSI can be severe mucositis with swallowing problems and loss of weight. Weekly assessment of weight and dietetic advice are essential to avoid significant weight loss. Non-spicy and salt reduced soft or fluid nutrition can be helpful in case of minor symptoms. In case of increasing esophagitis and progressive weight loss, substitutions of calories or fluids may require a naso-gastric tube or intravenous nutrition. The substitution of fluids and calories has to be calculated according to the body weight of the patient. Anti-inflammatory and anti-fungal drugs and analgesics can reduce symptoms of esophagitis. Usually, the symptoms of acute esophagitis completely resolve 7–10 days after the completion of RT.

Headache, especially during the first days of treatment, and nausea (combined with or without vomiting) are often reported as acute side effects. Anti-emetics, often combined with dexamethasone, are recommended to reduce these symptoms. Dose of steroids have to be according to the age and weight of patients. The duration of corticosteroid treatment should be as short as possible. Anti-emetics can be given up to four times a day.

Follow up and aftercare (perspective of radiotherapy)

The overall prognosis of children with AT/RT is grim, but is improving with multi-modality treatments [69]. Long-term survival may be seen in selected children with possibly favourable DNA methylation and/or gene expression signatures (possibly toddlers with supratentorial tumors and ATRT-SHH subgroup [17,70]). Late (i.e. ≥ 36 months) recurrences, distant or local, have been observed in prospective [17] and retrospective [2,71,72] studies. Although successful salvage rates for those with recurring or progressing disease is low [73], survivors of AT/RT may benefit from clinical and/or radiological follow-up. Serial radiological imaging studies of the brain and spinal canal should be done every 3–4 months after the end of treatment, or earlier if clinically indicated, for 2–3 years, and at least bi-annually thereafter. Regarding imaging, the protocol of the SIOPE Brain Tumour Imaging Group the SIOPE study protocol should be respected during follow-up [24,53]. Clinical examinations should also be performed regularly in these growing survivors. Of note, these young children with AT/RT undergo intensive treatment, with a rate of treatment-related deaths up to 6–11.9 % [17,72], and may also be at risk for clinically relevant treatment-induced serious events. A structured follow-up protocol will

enable health professionals to monitor any such toxicity, not limited but including cognitive, motor, visual, and hearing impairment and propose appropriate therapies if appropriate. Of noteworthy, leukoencephalopathy was observed on follow-up imaging in a substantial number of patients who had treatment for brain tumors, particularly in those exposed to intrathecal methotrexate and had measurable decrements in measures of intelligence [74]. It is also advisable to assess the quality of life (QoL) using proxy-questionnaires in surviving children, as a substantial number of patients show some decrease in QoL scoring, especially in the social domain after therapy [2].

Limitations

Given the rarity of the disease, existing data is scarce. Small cohorts and mostly retrospective character of analyses limit the evidence level. Recognizing there are different approaches, this guideline summarizes evidence-based recommendations from established study protocols. Further recommendations arise from consensus of the attending experts based on clinical practice.

Conclusions

The present ESTRO guideline provides evidence and expert opinion-based recommendations of management of RT in patients with AT/RT. This aggressive and challenging disease demands complex treatment strategies. It occurs in very young children and is associated with a potentially high risk of treatment-related late toxicities. However, RT is an important element of the multimodality treatment approach. It is highly encouraged to treat children with ATRT within a multidisciplinary setting according to clinical trials or registries in highly specialized centers. Furthermore, prospective data collection and evaluation should be centralized. Prospective clinical trials and international, large registries evaluating modern treatment approaches would contribute to a better understanding of the optimal treatment approach for children with AT/RT. As several questions in the RT field remain open, it will be crucial to cover questions concerning RT within future multidisciplinary treatment studies.

CRedit authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We thank Sabine Frisch (West German Proton Therapy Center Essen, Germany) for conducting the literature search, and formal editing and revising the manuscript.

We acknowledge the comprehensive review of this guideline by Thankamma Ajithkumar, Michael Frühwald and Brigitte Bison. We sincerely appreciate their valuable comments and suggestions, which helped improving the quality of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2024.110227>.

References

- Packer RJ, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop. *J Pediatr Hematol Oncol* 2002;24:337–42.
- Weber DC, et al. Tumor control and QoL outcomes of very young children with atypical teratoid/rhabdoid tumor treated with focal only chemo-radiation therapy using pencil beam scanning proton therapy. *J Neurooncol* 2015;121:389–97.
- Burger PC, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: a highly malignant tumor of infancy and childhood frequently mistaken for medulloblastoma: a pediatric oncology group study. *Am J Surg Pathol* 1998;22:1083–92.
- Liu YL, et al. Atypical teratoid/rhabdoid tumor in Taiwan: a Nationwide, population-based study. *Cancers (Basel)* 2022;14.
- Mousa A, et al. Atypical teratoid rhabdoid tumors (ATRT): King Faisal Specialist Hospital and Research Centre experience. *Int J Pediatr Adolesc Med* 2021;8:154–9.
- Lau CS, Mahendraraj K, Chamberlain RS. Atypical teratoid rhabdoid tumors: a population-based clinical outcomes study involving 174 patients from the surveillance, epidemiology, and end results database (1973–2010). *CancerManag Res* 2015;7:301–9.
- Upadhyaya SA, et al. Relevance of Molecular groups in children with newly diagnosed atypical teratoid rhabdoid tumor: results from prospective st. *Jude Multi-institutional Trials Clin Cancer Res* 2021;27:2879–89.
- Erdmann, F.K., P.; Grabow, D.; Spix, C. *German Childhood Cancer Registry - Annual Report 2019 (1980-2018)*. Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at University Medical Center of the Johannes Gutenberg University Mainz. 2020. https://www.kinderkrebsregister.de/typo3temp/secure_downloads/42507/0/1c5976c2ab8af5b6b388149df182582a4cd6a39/Buch_DKKR_Jahresbericht_2019_komplett.pdf (last accessed 05.01.2024).
- Tekautz TM, et al. Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. *J Clin Oncol* 2005;23:1491–9.
- Frühwald MC, et al. Age and DNA methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors. *Neuro Oncol* 2020;22:1006–17.
- Hasselblatt M, et al. High-resolution genomic analysis suggests the absence of recurrent genomic alterations other than SMARCB1 aberrations in atypical teratoid/rhabdoid tumors. *Genes, Chromosomes & Cancer* 2013;52:185–90.
- Hasselblatt M, et al. SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. *Acta Neuropathol* 2014;128:453–6.
- Johann PD, et al. Atypical teratoid/rhabdoid tumors are comprised of three epigenetic subgroups with distinct enhancer landscapes. *Cancer Cell* 2016;29:379–93.
- De Amorim Bernstein K, et al. Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors. *Int J Radiat Oncol Biol Phys* 2013;86:114–20.
- Hilden JM, et al. Central nervous system atypical teratoid/rhabdoid tumor: results of therapy in children enrolled in a registry. *J Clin Oncol* 2004;22:2877–84.
- Gardner SL, et al. Intensive induction chemotherapy followed by high dose chemotherapy with autologous hematopoietic progenitor cell rescue in young children newly diagnosed with central nervous system atypical teratoid rhabdoid tumors. *Pediatr Blood Cancer* 2008;51:235–40.
- Reddy AT, et al. Efficacy of high-dose chemotherapy and three-dimensional conformal radiation for atypical teratoid/rhabdoid tumor: a report from the children's oncology group trial ACN030333. *J Clin Oncol* 2020;38:1175–85.
- European Rhabdoid Registry - EU-RHAB. A multinational registry for rhabdoid tumors of any anatomical site, Version 5, 2016, available from: http://www.rhabdoid.de/fileadmin/Daten/Pdfs/EU-RHAB_Protokoll_Stand_08.12.2016.pdf (last accessed: 29.11.2022).
- Frühwald MC, et al. Age and DNA-methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors (ATRT). *Neuro Oncol* 2019.
- Bartelheim K, et al. Improved 6-year overall survival in AT/RT - results of the registry study rhabdoid 2007. *Cancer Medicine* 2016;5:1765–75.
- Frisch S, et al. Radiation therapy plays an important role in the treatment of atypical teratoid/rhabdoid tumors: analysis of the EU-RHAB cohorts and their precursors. *Int J Radiat Oncol Biol Phys* 2024.
- SIOPE ATRT01, 2019, available from: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-003335-29/DE> (last accessed: 28.12.2022).
- ESTRO. *Guidelines-Committee-policy_July-2022.pdf.aspx* (estro.org), 2022 (last accessed 27.02.2023).
- Avula S, et al. European Society for Paediatric Oncology (SIOPE) MRI guidelines for imaging patients with central nervous system tumours. *Childs Nerv Syst* 2021;37:2497–508.
- Warmuth-Metz M, et al. Bone involvement in atypical teratoid/rhabdoid tumors of the CNS. *AJNR Am J Neuroradiol* 2013;34:2039–42.
- Louis DN, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol* 2016;131:803–20.
- Nemes K, et al. Rhabdoid Tumor Predisposition Syndrome. Seattle: University of Washington; 1993.
- Yamasaki K, et al. Clinical characteristics, treatment, and survival outcome in pediatric patients with atypical teratoid/rhabdoid tumors: a retrospective study by the Japan children's cancer group. *J Neurosurg Pediatr* 2020;25:111–20.
- Lafay-Cousin L, et al. Central nervous system atypical teratoid rhabdoid tumours: the Canadian paediatric brain tumour consortium experience. *Eur J Cancer* 2012;48:353–9.
- Clerici CA, et al. Age-appropriate multidisciplinary approach to young children with cancer undergoing radiotherapy: the SIESTA procedure. *Pediatr Blood Cancer* 2021;68:e28650.
- Gårdling J, et al. Age-appropriate preparations for children with cancer undergoing radiotherapy: a feasibility study. *Journal of Child Health Care* 2017;21:370–80.
- Langemeyer V, et al. Evaluation of repeated sedation in children during proton beam radiotherapy: Experiences from a large monoinstitutional cohort. *International Journal of Radiation Oncology*Physics*Biolog* 2022;114:1069.
- Ishisaka E, et al. Neoadjuvant chemotherapy for atypical teratoid rhabdoid tumors (AT/RTs). *Childs Nerv Syst* 2020;36:721–7.
- Biswas A, et al. Atypical teratoid/rhabdoid tumors: challenges and search for solutions. *CancerManag Res* 2016;8:115–25.
- Underiner RM, et al. Meta-analysis of treatment modalities in metastatic atypical teratoid/rhabdoid tumors in children. *Pediatr Neurol* 2020;108:106–12.
- Squire SE, Chan MD, Marcus KJ. Atypical teratoid/rhabdoid tumor: the controversy behind radiation therapy. *J Neurooncol* 2007;81:97–111.
- Ma XJ, et al. Overall survival of Primary Intracranial atypical teratoid rhabdoid tumor following multimodal treatment: a pooled analysis of individual patient data. *Neurosurg Rev* 2020;43:281–92.
- Athale UH, et al. Childhood atypical teratoid rhabdoid tumor of the central nervous system: a meta-analysis of observational studies. *J Pediatr Hematol Oncol* 2009;31:651–63.
- Lu VM, et al. Age of diagnosis clinically differentiates atypical teratoid/rhabdoid tumors diagnosed below age of 3 years: a database study. *Childs Nerv Syst* 2021;37:1077–85.
- Ma Y, et al. Tandem high-dose chemotherapy without craniospinal irradiation in treatment of non-metastatic malignant brain tumors in very young children. *J Korean Med Sci* 2020;35:e405.
- Lee YE, et al. Repositioning disulfiram as a radiosensitizer against atypical teratoid/rhabdoid tumor. *Neuro Oncol* 2017;19:1079–87.
- Yang WC, et al. Effect of early radiotherapy initiation and high-dose chemotherapy on the prognosis of pediatric atypical teratoid rhabdoid tumors in different age groups. *J Neurooncol* 2020;147:619–31.
- Sung KW, et al. Tandem high-dose chemotherapy and autologous stem cell transplantation for atypical teratoid/rhabdoid tumor. *Cancer Research and Treatment* 2016;48:1408–19.
- Zaky W, et al. Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid/rhabdoid tumors: the head Start III experience. *Pediatr Blood Cancer* 2014;61:95–101.

- [45] Pai Panandiker AS, et al. Sequencing of local therapy affects the pattern of treatment failure and survival in children with atypical teratoid rhabdoid tumors of the central nervous system. *Int J Radiat Oncol Biol Phys* 2012;82:1756–63.
- [46] Siope atrt01 quartet., Radiotherapy Quality Assurance Guidelines Version 11 2023. personal correspondence.
- [47] Benesch M, et al. Spinal cord atypical teratoid/rhabdoid tumors in children: clinical, genetic, and outcome characteristics in a representative european cohort. *Pediatr Blood Cancer* 2020;67:e28022.
- [48] Chi SN, et al. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. *J Clin Oncol* 2009;27:385–9.
- [49] McGovern SL, et al. Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhabdoid tumor of the central nervous system. *Int J Radiat Oncol Biol Phys* 2014;90:1143–52.
- [50] Yang WC, et al. Role of early and aggressive post-operative radiation therapy in improving outcome for pediatric central nervous system atypical teratoid/rhabdoid tumor. *Childs Nerv Syst* 2019;35:1013–20.
- [51] Fischer-Valuck BW, et al. 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* 2017;123:682–7.
- [52] McGovern SL, Grosshans D, Mahajan A. Embryonal brain tumors. *Cancer Journal* 2014;20:397–402.
- [53] SIOPE ATRT01 - An international prospective umbrella trial for children with atypical teratoid/rhabdoid tumours (ATRT) including A randomized phase III study evaluating the non-inferiority of three courses of high-dose chemotherapy (HDCT) compared to focal radiotherapy as consolidation therapy. Protocol Version 1.3.1, 2021, personal correspondence.
- [54] Seravalli E, et al. Dosimetric comparison of five different techniques for craniospinal irradiation across 15 european centers: analysis on behalf of the SIOPE-BTG (radiotherapy working group). *Acta Oncol* 2018;57:1240–9.
- [55] Jazmati D, et al. Feasibility of proton beam therapy for infants with brain tumours: Experiences from the prospective KiProReg registry study. *Clin Oncol (R Coll Radiol)* 2021.
- [56] Spina A, et al. Does stereotactic radiosurgery positively impact the local control of atypical teratoid rhabdoid tumors? *WORLDNeurosurg* 2017.
- [57] Ren YM, et al. Multimodal treatments combined with gamma knife surgery for primary atypical teratoid/rhabdoid tumor of the central nervous system: a single-institute experience of 18 patients. *Childs Nerv Syst* 2018;34:627–38.
- [58] Giller CA, et al. Robotically guided radiosurgery for children. *Pediatr Blood Cancer* 2005;45:304–10.
- [59] Hoeben BA, et al. Management of vertebral radiotherapy dose in paediatric patients with cancer: consensus recommendations from the SIOPE radiotherapy working group. *LancetOncol* 2019;20:e155–66.
- [60] Ajithkumar T, et al. SIOPE - brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy. *Radiother Oncol* 2018;128:192–7.
- [61] Eekers DBP, et al. Update of the EPTN atlas for CT- and MR-based contouring in neuro-oncology. *Radiother Oncol* 2021;160:259–65.
- [62] Eekers DB, et al. The EPTN consensus-based atlas for CT- and MR-based contouring in neuro-oncology. *Radiother Oncol* 2018;128:37–43.
- [63] Scoccianti S, et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. *Radiother Oncol* 2015;114:230–8.
- [64] Mahajan A, et al. Neurocognitive effects and necrosis in childhood cancer survivors treated with radiation therapy: a PENTEC comprehensive review. *Int J Radiat Oncol Biol Phys* 2021.
- [65] Dietzsch S, et al. Pretreatment central quality control for craniospinal irradiation in non-metastatic medulloblastoma : first experiences of the german radiotherapy quality control panel in the SIOPE PNET5 MB trial. *Strahlenther Onkol* 2021;197:674–82.
- [66] Kortmann RD, et al. HIT '91 (prospective, co-operative study for the treatment of malignant brain tumors in childhood): accuracy and acute toxicity of the irradiation of the craniospinal axis. results of the quality assurance program. *Strahlenther Onkol* 1999;175:162–9.
- [67] Dietzsch S, et al. Types of deviation and review criteria in pretreatment central quality control of tumor bed boost in medulloblastoma-an analysis of the german radiotherapy quality control panel in the SIOPE PNET5 MB trial. *Strahlenther Onkol* 2022;198:282–90.
- [68] *EU-RHAB, [Simultane Radiochemotherapie bei Patienten mit rhabdoiden Tumoren], 2015, personal correspondance to EU-RHAB group (14.10.2015).*
- [69] Reddy AT. Atypical teratoid/rhabdoid tumors of the central nervous system. *J Neurooncol* 2005;75:309–13.
- [70] Ho B, et al. Molecular subgrouping of atypical teratoid/rhabdoid tumors-a reinvestigation and current consensus. *Neuro Oncol* 2020;22:613–24.
- [71] Elsayad K, et al. Long-term survival following additive radiotherapy in patients with atypical teratoid rhabdoid tumors. *Strahlenther Onkol* 2016;192:569–81.
- [72] Park M, et al. Atypical teratoid/rhabdoid tumor of the central nervous system in children under the age of 3 Years. *Cancer Research and Treatment* 2021;53:378–88.
- [73] Wang CH, et al. Efficacy of temozolomide for recurrent embryonal brain tumors in children. *Childs Nerv Syst* 2009;25:535–41.
- [74] Rutkowski S, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. *N Engl J Med* 2005;352:978–86.