CHAPTER THREE

Three decades of radiotherapy advancements for pediatric ependymoma

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Abstract

Over the past 30 years, advancements in radiotherapy have transformed the treatment of pediatric ependymoma, improving tumor control and reducing treatment-related complications. Early protocols, such as RT1 and ACNS0121, demonstrated the efficacy of immediate post-operative radiotherapy, particularly for children as young as 12 months, setting benchmarks for modern treatment strategies. The introduction of conformal photon therapy revolutionized tumor targeting by minimizing radiation exposure to surrounding normal tissues, while proton therapy has emerged as the preferred modality in developed countries due to its superior normal tissue-sparing properties. Despite these advances, long-term comparative data between photon and proton therapy remains limited.

Critical factors in radiotherapy planning include tumor location, patient age, molecular features, and the potential for neuraxis dissemination. Advances in imaging, such as high-resolution MRI and emerging molecular staging techniques, have enhanced precision in treatment planning and risk stratification. However, challenges persist for patients with residual or recurrent disease. Reirradiation has emerged as a promising option for relapse, demonstrating high rates of tumor control and low risks of complications when combined with timely surgical intervention and multidisciplinary care.

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This chapter highlights the importance of leveraging data from three separate clinical trials to refine treatment strategies and address cognitive outcomes, which have been identified as a major area of clinical importance and research. Future trials are expected to explore molecular risk stratification and the integration of systemic therapies alongside radiotherapy to optimize outcomes, ensuring continued progress in the care of children with ependymoma.

1. Radiotherapy

Advances in radiotherapy have been transformative in the treatment of childhood ependymoma over the past 30 years, marking a significant turning point in clinical care. Before this era, the role of radiation therapy was poorly defined, particularly for children under the age of three, where the prevalence of ependymoma is notably high. At that time, radiation therapy was rarely considered for this age group, and there was considerable uncertainty regarding optimal dosing and treatment volumes.

The introduction of conformal radiation therapy using photons revolutionized the approach to treatment. This technique was designed to precisely conform the prescription dose to the targeted tumor volume while minimizing exposure to critical intra- and extra-axial normal tissues. The goal was to reduce treatment-related complications, improve the overall toxicity profile, and enhance the therapeutic index. These

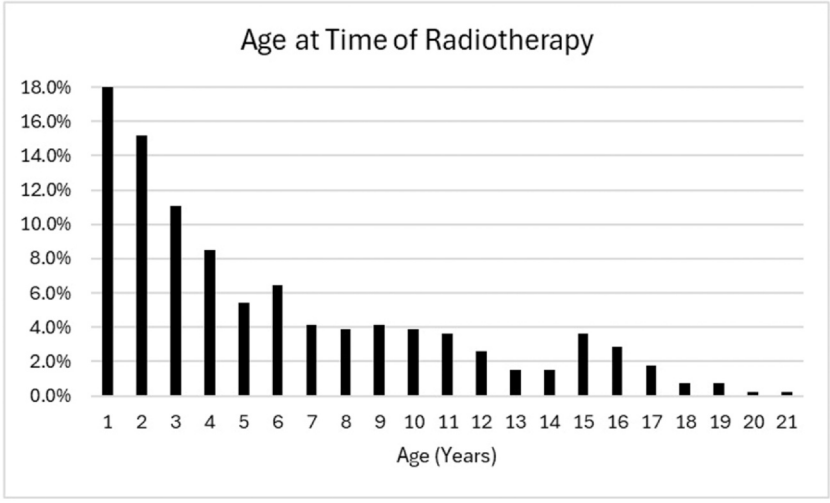

Fig. 1 Age distribution of children treated with radiotherapy on ACNS0831.

advancements have significantly improved outcomes and have provided a clearer framework for the use of radiotherapy in young children.

In this chapter, we will explore the history and context of these developments, highlighting the clinical and technical progress in radiotherapy that has brought us to the current state-of-the-art practices. These innovations continue to shape the future of pediatric ependymoma treatment, offering hope for improved survival and quality of life for affected children (Fig. 1).

2. The radiation oncologist's perspective

From the perspective of a radiation oncologist, childhood ependymoma is recognized as a locally aggressive tumor where the role of surgery and the extent of resection are critical to achieving optimal outcomes. Another key factor influencing treatment is the tumor's location, which significantly impacts radiation treatment planning and delivery. Tumor location affects normal tissue dose constraints, the risk of pre-existing and post-treatment complications, and expected tumor control. These considerations highlight the importance of a multidisciplinary approach to ensure effective and safe treatment.

The majority of children diagnosed with ependymoma present with tumors in the infratentorial compartment, often accompanied by symptoms of obstructive hydrocephalus. These tumors frequently involve critical structures such as the brainstem, cerebellum, or cranial nerves, leading to post-surgical complications due to the tumor's proximity to and interaction with normal tissues during gross-total resection. Even without accounting for surgical injury, infratentorial ependymomas pose unique challenges in radiation treatment planning. Radiation oncologists must carefully balance the goal of tumor control with minimizing radiation exposure to sensitive structures like the brainstem, cochleae, and, in rare cases, the hypothalamic-pituitary axis when tumors extend superiorly along the intracranial incisura or into the supratentorial compartment. Fortunately, such complex scenarios are rare in developed countries, allowing for more streamlined treatment approaches in most cases (Fig. 2).

For tumors arising in the supratentorial compartment, the diversity of tumor locations adds complexity to radiation treatment planning and increases the risk of complications. Tumors in lower-risk areas, such as the posterior frontal, parietal, or occipital regions, are generally easier to

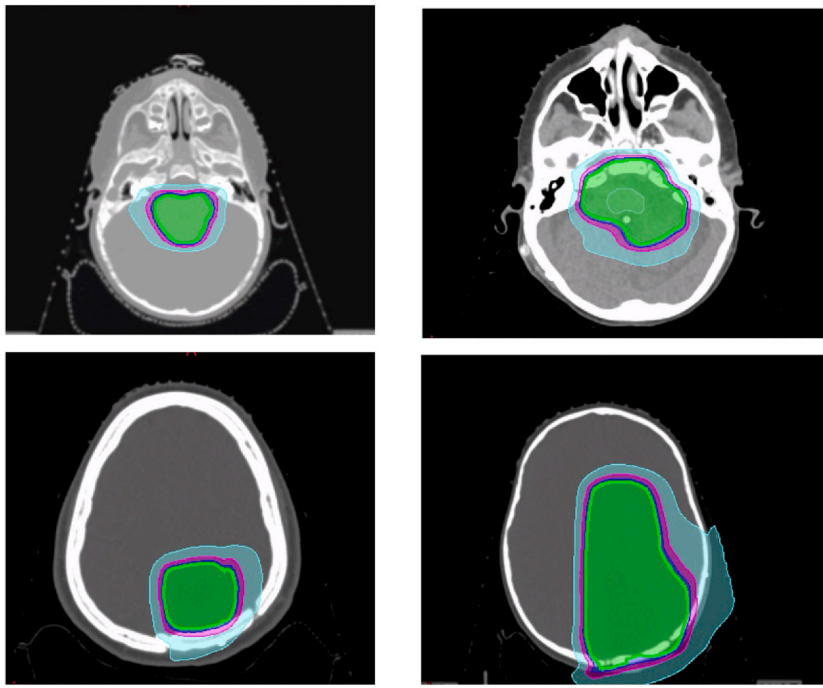

Fig. 2 Limited (left) and advanced cases (right) of infratentorial (upper) and supratentorial (lower) ependymoma.

approach and treat. However, tumors located in higher-risk areas, such as the frontal lobe, temporal lobe, or central regions, present greater challenges. These locations require careful consideration to spare critical structures like the hypothalamic-pituitary unit, optic nerves and chiasm, orbital structures, or the infratentorial fossa and associated hearing apparatus. Each case demands a tailored approach to maximize tumor control while minimizing risks to normal tissues (Fig. 3).

Overall, advances in surgical techniques and radiotherapy planning have significantly improved the ability to manage childhood ependymoma effectively. By leveraging modern imaging and treatment technologies, radiation oncologists continue to refine strategies that optimize outcomes while minimizing treatment-related complications, bringing hope to affected children and their families.

Another critical factor considered by radiation oncologists during radiation treatment planning is the extent of tumor involvement and the potential for neuraxis dissemination. While ependymoma has a known

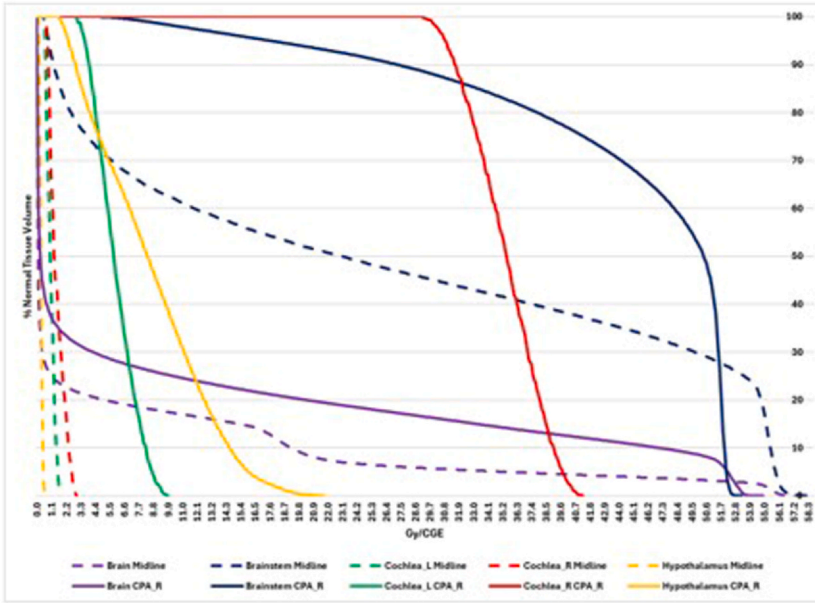

Fig. 3 Dosimetry comparison midline vs. right cerebellopontine angle tumor location.

propensity for spreading along the neuraxis, this occurrence is relatively rare at the time of initial presentation for children diagnosed in developed countries. However, when dissemination is not detected early in the radiation treatment planning process, it can compromise the ability to provide comprehensive care and limit the chances of achieving a cure. Historically, uncertainty surrounding the prevalence of metastatic disease at diagnosis led to the routine use of craniospinal irradiation in cooperative group studies and other series involving childhood ependymoma. While intended to address potential dissemination, this approach resulted in significant and unnecessary morbidity without improving disease control (Evans, Anderson, Lefkowitz-Boudreaux, & Finlay, 1996). These outcomes contributed to the perception of radiotherapy as a morbid treatment, without fully distinguishing between the effects of focal and craniospinal treatment volumes (Fig. 4).

Fortunately, advances in diagnostic imaging, particularly high-resolution MRI of the brain and spine, combined with expert evaluation of cerebrospinal fluid (CSF) cytology, have significantly reduced the anticipated incidence of neuraxis dissemination at diagnosis. Emerging technologies, such as the assessment of cell-free DNA in CSF (Afflerbach et al.,

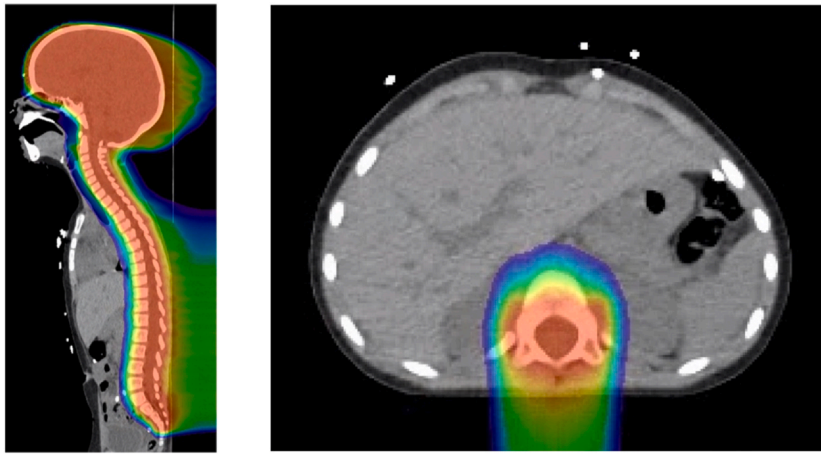

Fig. 4 Example of craniospinal irradiation for metastatic ependymoma.

2024), hold great promise for revolutionizing the staging process for ependymoma. These innovations may shift staging from traditional clinical risk classification to a more sophisticated molecular risk classification that integrates tumor and CSF analysis. As refined markers of metastatic dissemination are validated, they are likely to introduce new challenges and opportunities for improving risk stratification and radiation treatment planning.

In addition to tumor-specific factors, radiation oncologists must navigate a range of host clinical considerations, including patient age, preexisting morbidity, and emerging molecular features of the tumor, some of which have prospectively unvalidated prognostic significance (Donson et al., 2023). These variables inform critical decisions regarding the indications, rationale, potential side effects, and intent of treatment. They also influence the selection of radiotherapy parameters such as treatment volume, dose, fractionation, target volume margins, radiation modality, delivery methods, and daily treatment verification techniques. By integrating these diverse factors, radiation oncologists aim to optimize treatment outcomes while minimizing risks, ensuring a tailored and patient-centered approach to care (Table 1).

Conformal radiation therapy emerged in the 1990s as a transformative approach to safely escalate radiation doses to high-risk tumors while sparing normal tissues. Initially applied in adults with prostate cancer, head and neck cancer, lung cancer, and other challenging tumors, its potential to

Table 1 Target volume, margins, activation dates and cohort ages for selected clinical trials.

Trial	Activation date[a]	Target / margin (cm)[b]	Cohort age (years)
SFOP	1990–06	Posterior Fossa	0–5
HIT 2000	2011–01	2.0	0–21
St. Jude RT1	1997–06	1.0	1–21
AI EOP II	2002–06	1.0	3–20
COG ACNS0121	2003–08	1.0	1–21
St. Jud e SJYC07	2007–11	0.5	0–3
COG ACNS0831	2010–03	0.5	1–21
SIOP E P II	2015–06	0.5	1–21

[a]YYYY – MM format.
[b]Margin surrounding the post-operative tumor bed and residual tumor.

improve outcomes in pediatric patients was quickly recognized. For children with brain tumors, musculoskeletal tumors, and rare solid tumors unique to the young, conformal radiation therapy offered a safer and more effective treatment option (Merchant, 1997a).

3. North American experience

At St. Jude Children's Research Hospital, the RT1 protocol (Merchant, 1997b) activated in 1997, became the first ICRU-50-compliant clinical trial to use conformal radiation therapy in children with brain tumors. Designed to treat all histologic subtypes of localized (non-disseminated) tumors where craniospinal irradiation was not the standard of care, the protocol primarily addressed ependymoma, craniopharyngioma, and low-grade glioma. It also allowed children as young as 12 months to receive immediate post-operative radiotherapy—a critical need at the time, as cooperative group strategies to delay or avoid irradiation in very young children were associated with poor tumor control rates. The RT1 protocol quickly demonstrated improved tumor control rates and normal tissue sparing, which impressed surgeons and oncologists, encouraging more

aggressive surgeries and referrals for immediate post-operative radiotherapy in very young children (Merchant et al., 2004). This approach led to rapid accrual in the Children's Oncology Group ACNS0121 protocol (Merchant, 2003), which validated the RT1 results (Merchant et al., 2009) in a cooperative group setting (Merchant et al., 2019). This approach also led to reconsideration of lower age limits in other cooperative group clinical trials, that included radiotherapy. For example, the lower age limit for the use of radiotherapy was modified during the HIT 2000 study. Initially, radiotherapy was not administered to very young children. However, following a major amendment to the trial, the lower age limit for post-operative radiotherapy was reduced, allowing younger children to receive radiotherapy as part of their treatment strategy. This change aimed to improve outcomes in the younger patient population.

The RT1 (Merchant et al., 2009) and ACNS0121 (Merchant et al., 2019)protocols remain the benchmarks for ependymoma treatment, showcasing the best outcomes reported for children treated with extensive surgery and high-dose post-operative radiotherapy. These studies paved the way for further refinements in the COG ACNS0831 protocol (Smith, 2010), which introduced reduced clinical target volume margins (from 1 cm to 0.5 cm) and randomized between immediate post-operative radiotherapy alone and radiotherapy followed by maintenance chemotherapy. Although the final results, including patterns of tumor progression with reduced margins, are pending publication, the protocol represents an important step in optimizing treatment strategies.

Simultaneously, other significant North American studies have contributed to the field. The SJYC07 protocol (Upadhyaya et al., 2019), a multi-institutional collaborative study for very young children, investigated the use of chemotherapy prior to radiotherapy for various tumors, including ependymoma. While this approach did not improve tumor control rates, it provided valuable insights into the use of proton therapy, which did not significantly reduce the risk of selected complications. Additionally, the ongoing SIOP EP II protocol (Leblond et al., 2022), now nearing completion after 10 years, parallels the ACNS0831 protocol but introduces supplemental irradiation (4 Gy x 2) to residual tumors after conventional doses and fractionation based on results from the Italian Association of Pediatric Hematology and Oncology trial (Massimino et al., 2021). This unique approach may offer further refinements in managing measurable residual disease.

Nearly 30 years after the first patient was treated on RT1, long-term results from the early conformal treatment era are beginning to emerge. Howe et al. (Howe, Edmonston, Dirks, Boop, & Merchant, 2023), which analyzed a historic cohort with long-term follow-up of children under the age of 3 years, 90 % of whom had the PFA subtype and aggressive surgical resection (>80 % gross-total resection) and high-dose (>70 %, 59.4 Gy) immediate (>70 %) post-operative radiotherapy which contributed to their long-term outcomes.

4. European experience

The Société Française d'Oncologie Pédiatrique (SFOP), the French pediatric oncology cooperative group, has conducted major clinical trials for childhood intracranial ependymoma, including radiotherapy as part of treatment strategies. The SFOP Ependymoma Trial 1 (1990–1999) focused on evaluating the role of chemotherapy and radiotherapy in managing pediatric ependymoma, particularly in very young children (<3 years old). The trial aimed to delay radiotherapy by using chemotherapy first to reduce neurocognitive toxicity. Radiotherapy-free survival was 40 % at 2 years and 23 % at 4 years, and tumor control rates were suboptimal. Radiotherapy was reserved for salvage treatment in cases of relapse or progression and delivered using conventional fractionation (1.8 Gy/day, 5 days/week) up to a total dose of 50 Gy for posterior fossa tumors or 45 Gy for the spinal cord. Lateral beams encompassed the entire posterior fossa, while craniospinal irradiation (CSI) was reserved for proven distant metastases. Radiotherapy was deferred for a median of 15 months, allowing patients to avoid its potential side effects (Grill et al., 2001).

Subsequently, SFOP institutions conducted a multicenter analysis of outcomes for 202 children with localized intracranial ependymoma treated between 2000 and 2013. Age, extent of resection, and tumor grade were identified as independent prognostic factors for overall survival (OS) and disease-free survival (DFS). Conventional fractionation (1.8 Gy/day, 5 days/week) was used, with doses of 54 Gy for children < 18 months and 59.4 Gy for older children or those with residual disease. The gross tumor volume (GTV) included residual tumor and/or the postoperative tumor bed, and the clinical target volume (CTV) was a 1 cm anatomically confined expansion of the GTV, reduced to 5 mm for the final fractions of the 59.4 Gy dose. The planning target volume (PTV) was a 0.3–0.5 cm

geometric expansion of the CTV. After 2009, the prescribed dose increased to 59.4 Gy, aligning with international recommendations (Ducassou et al., 2018).

The SIOP EP II study (Leblond, 2015)is an international clinical program aimed at improving outcomes for children, adolescents, and young adults (≤22 years) diagnosed with ependymoma. Stratum 1 (complete resection, no residual disease) evaluates the benefit of adjuvant chemotherapy (VEC-CDDP) versus observation following conformal radiotherapy (cRT). Stratum 2 (inoperable residual disease) investigates the addition of high-dose methotrexate (HD-MTX) to VEC chemotherapy, followed by conformal radiotherapy, using photons or protons, and an 8 Gy boost for persistent residual disease. Radiotherapy begins after surgery or chemotherapy, depending on patient stratification. The standard dose is 59.4 Gy, with a boost of 8 Gy for unresectable residual disease. Treatment volumes target the tumor bed and residual disease using a 0.5 cm clinical target volume margin, and conventional fractionation (1.8 Gy/day, 5 days/week) is employed.

The Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) conducted two major clinical trials focused on childhood intracranial ependymoma. The first AIEOP Ependymoma Trial, conducted prior to 2002, aimed to improve outcomes for children with completely resected classic WHO Grade II ependymoma and explored treatment strategies for patients with residual disease or anaplastic ependymoma. This trial established the framework for the subsequent study (Massimino et al., 2004). The second AIEOP Ependymoma Trial (2002–2014) stratified patients based on surgical resection status (NED vs. ED) and histological grade (WHO Grade II vs. III). It introduced tailored treatment regimens, including focal radiotherapy, chemotherapy, and second-look surgery for patients with residual disease. This trial aimed to improve survival outcomes, particularly for high-risk subgroups, and was the largest prospective trial on childhood ependymoma conducted by AIEOP (Massimino et al., 2016). Following these trials, the same institutions participated in the SIOP EP II study, which incorporated treatment strategies partly based on AIEOP's radiotherapy experience.

In the first AIEOP trial, radiotherapy timing was determined by surgical outcomes and patient age. For children with completely resected tumors, radiotherapy was administered immediately postoperatively as part of the adjuvant strategy to optimize local tumor control and improve survival, particularly for WHO Grade II tumors. For patients with residual disease, radiotherapy was delivered after second-look surgery or bridging

chemotherapy, emphasizing the reduction of residual tumor volume to enhance radiotherapy efficacy. Early initiation of radiotherapy within weeks after surgery was prioritized for most patients, aligning with standard practices to reduce the risk of tumor progression. This trial demonstrated the importance of tailoring radiotherapy timing based on surgical outcomes and patient-specific factors.

In the second AIEOP trial, children aged ≥ 3 years with completely resected tumors (NED) received focal radiotherapy using a 3D-conformal technique. For WHO Grade II tumors, radiotherapy was delivered at 1.8 Gy/day to a total dose of 59.4 Gy, while WHO Grade III tumors followed the same radiotherapy regimen, supplemented by 4 courses of VEC chemotherapy (vincristine, etoposide, cyclophosphamide) after radiotherapy completion. Younger children aged 1–3 years with Grade II tumors could receive 6 courses of VEC chemotherapy alone, avoiding radiotherapy based on local discretion.

Patients with residual disease (ED) underwent 1–4 courses of VEC chemotherapy to enable second-look surgery whenever possible. Radiotherapy followed at 1.8 Gy/day to a total dose of 59.4 Gy, with an additional 8-Gy boost delivered in 2 fractions (4 Gy each) to any measurable residual tumor identified on MRI. For children younger than 18 months, the total radiation dose was reduced to 54 Gy to minimize toxicity. Target volumes included the postoperative tumor bed with a 1 cm safety margin for the clinical target volume (CTV) and a 0.3–0.5 cm expansion for the planned target volume (PTV). For the boost, the CTV overlapped the residual tumor, with a 0.2–0.3 cm margin for the PTV. Special considerations limited spinal cord doses to 50 Gy and cervical spine doses to 54 Gy, where applicable. These radiotherapy protocols informed the regimen for residual disease in the SIOP EP II trial which was previously mentioned.

The HIT 2000 trial (Rutkowski, 2001) for pediatric intracranial ependymoma aimed to optimize treatment strategies by integrating advanced radiotherapy methods and combination chemotherapy regimens. Risk-adapted stratification was based on patient age, tumor grade (WHO grade II vs III), extent of resection, and metastatic status. For older children (≥4 years), hyperfractionated radiotherapy was combined with vincristine, cyclophosphamide, carboplatin, and etoposide for WHO grade III tumors. For younger children (<4 years), chemotherapy was prioritized to delay radiotherapy and reduce neurocognitive toxicity. Radiotherapy played a central role, tailored to patient age and tumor characteristics, with

hyperfractionated radiotherapy (68 Gy) for older children and conventional fractionated radiotherapy (54 Gy) for younger patients. Advanced planning techniques, such as 3D-conformal radiotherapy, ensured precision and minimized exposure to healthy tissues. The protocol influenced international trials, including the eventual SIOP EP II study.

In the HIT 2000 radiotherapy regimens, hyperfractionated radiotherapy was administered 2 × 1.0 Gy/day with intervals of 6–8 h, up to a total dose of 68 Gy to the postoperative tumor bed, including residual tumor, with a 2.0 cm safety margin. At 54 Gy, an MRI was performed to assess residual disease. If residual tumor is detected, the area was treated with a 5 mm margin up to 72 Gy. Persistent residual disease was treated with stereotactic single-session radiosurgery or surgery. Doses to critical structures, such as the brainstem or optic chiasm, were limited to 60 Gy, and the upper cervical spine below C1 is limited to 50 Gy. Conventional radiotherapy was delivered at 1.8 Gy/day, 5 days per week, up to a total dose of 54 Gy, targeting the postoperative tumor bed and residual tumor with a 2.0 cm safety margin. After completing radiotherapy, an MRI was performed to evaluate residual disease. Persistent residual tumor was treated with stereotactic single-session radiosurgery or surgery. Adjustments to the margins and doses were made to protect organs at risk, similar to the hyperfractionated regimen.

Hyperfractionated radiotherapy, which delivers smaller doses twice daily, enabled dose escalation without increasing toxicity. This approach was popular at the time and also used by the AIEOP consortium. The goal was to improve local control by maximizing tumor cell kill while minimizing damage to surrounding normal tissues. Studies had demonstrated high progression-free survival rates in high-risk pediatric ependymoma patients with incomplete resection and WHO grade III tumors treated with hyperfractionated regimens up to 72 Gy. In north America, the POG-8532 (Kovnar, Kun, Burger, & Krischer, 1991) study showed promising progression-free survival in children with incompletely resected grade II tumors compared to conventional radiotherapy. These findings demonstrated the ability of hyperfractionated radiotherapy to optimize outcomes in challenging cases while maintaining a favorable toxicity profile. The final results of the HIT 2000 trial have not been published and are expected soon.

These studies highlight 3 decades of research and the essential role of radiotherapy in advancing pediatric ependymoma treatment, improving tumor control, reducing complications, and shaping the future of care for young patients.

5. Radiotherapy planning

Post-operative radiotherapy is the standard of care for children aged 12 months and older. For children under 12 months of age, the time required for post-operative recovery, referral for radiotherapy, staging, anesthesia evaluation, and treatment planning often allows these patients to reach the milestone age of 12 months before the initiation of treatment. In more recent COG protocols, timelines have been structured to provide sufficient recovery and preparation time, with 56 days allotted from surgery to enrollment and an additional 21 days from enrollment to the start of radiotherapy. This schedule ensures ample time for the patient to transition smoothly into the next phase of treatment.

Despite the well-established role of post-operative radiotherapy, each case should undergo multidisciplinary tumor board review and expert evaluation. Childhood brain tumors, including ependymoma, are rare, and the limited number of pediatric oncology centers worldwide means that few institutions or caregivers have extensive experience with all clinical scenarios. For radiation oncologists, having an unequivocal post-operative imaging report of the brain and spine is critical. Additionally, collaboration with the surgical team is essential to determine if second surgery or referral for resection by a highly experienced team is warranted in cases of incomplete resection or residual tumor. Whether residual tumor can be removed may depend on the experience of the surgical team and the quality of imaging, which may necessitate repeat imaging to inform treatment planning.

Once the decision to proceed with radiotherapy is made, the rationale and potential side effects must be explained thoroughly to the patient and family, with appropriate consent and assent obtained. Short-term side effects of radiotherapy are well-documented and may include nausea, vomiting, appetite loss, fatigue, hair loss, and mild skin reactions at the treatment site. Rare complications such as headaches, seizures, recrudescence of neurological symptoms, pancytopenia, or other overt symptoms are uncommon in patients with completely resected tumors and minimal post-operative complications. For children requiring daily anesthesia for treatment, risks such as irritability, insomnia, and other anesthesia-related effects, though generally rare, should also be discussed.

Long-term side effects are more concerning and require careful consideration. These may include impacts on cognition, endocrine function, hearing, vision, brain parenchyma (including white matter), brainstem function, growth and development of local bone and soft tissues, and the

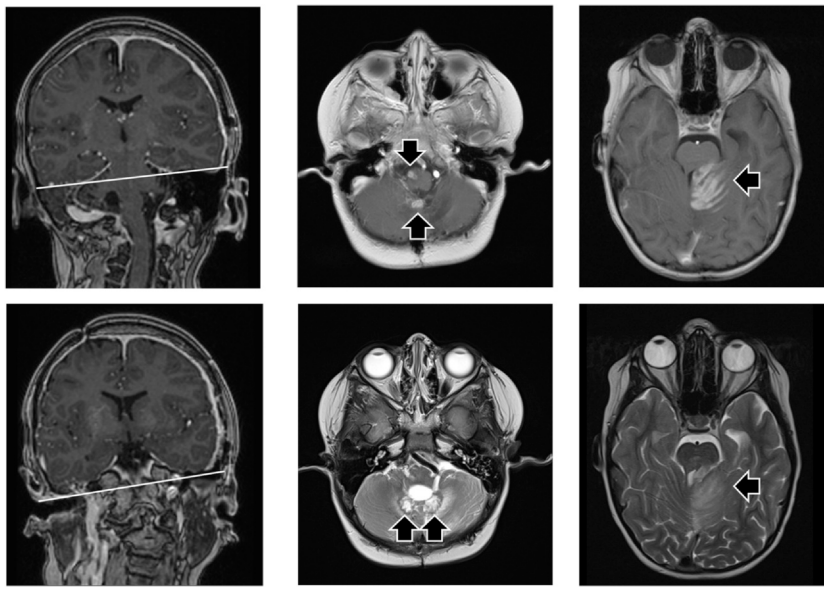

Fig. 5 Deformity (left), necrosis (middle), and secondary tumor (right) in children with ependymoma treated with radiotherapy.

risk of large vessel arteriopathy. While this list may seem extensive, the risks are relatively low, even for the youngest patients, as demonstrated by numerous publications. However, pre-existing conditions and additional treatments, such as chemotherapy, can enhance these risks.

The complications most concerning to radiation oncologists are radiation necrosis and secondary tumors. Although rare, these complications can have devastating or even fatal consequences, potentially reversing an otherwise favorable outcome. Careful planning, monitoring, and patient selection remain critical to mitigating these risks and ensuring the best possible outcomes for pediatric patients (Fig. 5).

Treatment planning for radiotherapy is a meticulous and highly customized process that begins with patient immobilization in the treatment position, followed by CT imaging to capture the brain and surrounding tissues. This imaging also accounts for areas that may be indirectly exposed to radiation through internal scatter, as well as the immobilization devices through which treatment beams may pass. The CT dataset provides a critical coordinate system for treatment planning, offering detailed information about tissue composition, including electron density, which is imported into treatment planning software to calculate radiation dose with precision.

In modern radiotherapy, treatment planning is further enhanced by the integration of MRI performed during the same appointment as the CT scan. The benefits of contemporaneous MRI cannot be overstated, as it provides superior soft tissue contrast and detailed anatomical information. For patients with infratentorial tumors, MRI must be performed in the treatment position to account for flexion or extension of the brainstem and spinal cord, as well as the presence of suboccipital fluid collections. For supratentorial tumors, while imaging in the treatment position is less critical due to the accuracy of registration methods, it is still essential to perform MRI close to the time of the CT scan. This ensures that any changes in the tumor bed, such as those caused by post-surgical shifts or subdural fluid collections, are accurately captured. Additional imaging during treatment may be warranted based on changes in normal tissue contours or brain shifts due to resolving hydrocephalus or reduced fluid collections, requiring careful clinical judgment.

The typical workflow for treatment planning includes the registration of pre-operative, post-operative, and treatment planning MR imaging to the treatment planning CT. This is followed by contouring the pre-operative tumor volume to serve as a guide for the extent of disease at diagnosis. Multisequence MRI is then utilized to delineate normal tissue volumes, the post-operative tumor bed, and any residual tumor, collectively defined as the gross tumor volume (GTV). In ependymoma protocols, the GTV refers to the post-operative tumor bed, emphasizing the importance of precise imaging and contouring.

To account for subclinical microscopic disease, the clinical target volume (CTV) is created by adding a margin to the GTV. Ependymoma is known to be microscopically invasive, necessitating careful margin design. Historically, conventional treatment applied a 2 cm margin projected onto planar film x-rays or portal images. With the advent of conformal radiation therapy, the margin was reduced to 1 cm in the RT1 protocol and later to 0.5 cm in the SJYC07 protocol, which was subsequently adopted in ACNS0831 and mirrored by SIOP EP II investigators. While the 0.5 cm margin has been widely applied, patterns of failure for SJYC07 and ACNS0831 have not been formally reviewed. Therefore, clinicians should exercise caution when adopting this margin, understanding the risks involved. It is reassuring to note that patients treated with the 1 cm margin in earlier protocols demonstrated a low risk of complications, providing a strong precedent for its effectiveness (Fig. 6).

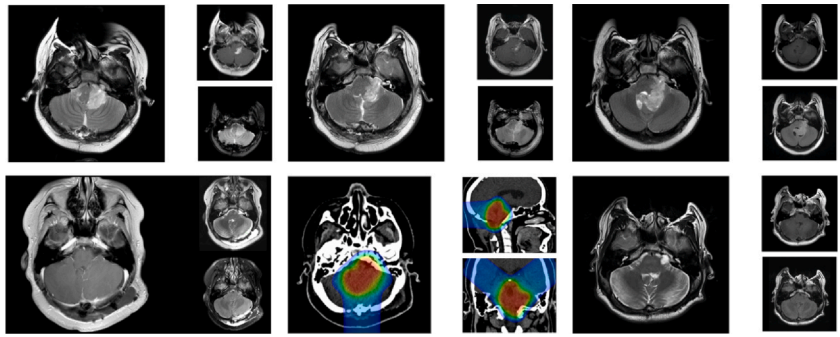

Fig. 6 Example of subtotal resection chemo second surgery and radiotherapy. Pre-operative imaging. Post-operative, Pre-chemotherapy imaging. Post- chemotherapy, Pre-operative imaging. Post-operative, Pre-irradiation imaging. Proton Beam Radiotherapy – 59.4CGE. Follow-up imaging – year 10 after diagnosis.

Overall, advances in imaging and treatment planning have significantly improved the precision and safety of radiotherapy for childhood ependymoma. By leveraging cutting-edge technology and evidence-based protocols, radiation oncologists continue to refine treatment strategies, ensuring optimal outcomes while minimizing risks.

In developed countries, most children with ependymoma are referred for proton therapy due to the patient's young age and the normal tissue-sparing properties of proton beams. Proton therapy is characterized by its sharp distal edge and rapid lateral fall-off, which minimizes radiation exposure to surrounding healthy tissues. The rationale is that the combination of young age at diagnosis, superior dosimetry characteristics, and a reasonable chance for cure with long life expectancy makes proton therapy the preferred treatment modality. While proton therapy offers advantages in selected cases, there is a lack of robust data to definitively support its superiority over photon therapy. Additionally, concerns have arisen regarding a potentially higher rate of necrosis associated with proton therapy compared to photon-based radiotherapy.

Head-to-head comparisons of proton and photon radiotherapy are currently unavailable, and most single- or multi-institution studies focus on equivalent tumor control rates, albeit with limited follow-up periods. Discussing the clinical and technical differences between photon and proton beams is beyond the scope of this chapter. However, long-term evidence from focal high-dose photon therapy using large clinical target volume margins suggests good-to-excellent disease control outcomes with

limited complications. Improved outcomes in recent years may be attributed to reduced target volume margins, advancements in imaging and targeting methods, reduced surgical morbidity, and enhancements in supportive care standards.

The future of radiotherapy for ependymoma hinges on the design of upcoming clinical trials. Without new insights from recently completed or soon-to-be-completed trials, radiotherapy remains a cornerstone of treatment, particularly as immediate post-operative therapy following gross total resection. Current evidence does not support removing radiotherapy from frontline treatment unless histologically low-grade ependymoma can be observed after microscopically complete resection without compromising overall survival. This remains a topic of ongoing debate. Additionally, molecular evidence suggesting the futility of radiotherapy or the superiority of experimental therapies could shift treatment paradigms. In such cases, concurrent radiotherapy combined with experimental agents may be considered, with radiation volumes – focal vs. craniospinal - tailored based on patient age and validated risks of distant tumor progression.

For patients with post-operative residual tumor, second surgery should be strongly considered and performed by experts prior to initiating radiotherapy. Whether chemotherapy prior to second surgery improves resection outcomes or simply provides a pause for the care team to coordinate efforts for a second surgical attempt remains unknown. However, evidence supports bridging first and second surgeries with a brief course of chemotherapy as a reasonable approach with low risk of complications.

6. Reirradiation

The standard treatment of surgery followed by post-operative radiotherapy achieves long-term tumor control for many patients; however, a significant proportion still experience relapse. Children with ependymoma are typically monitored closely, with follow-up schedules designed to ensure early detection of recurrence. During the first 2–3 years, patients are generally seen every 3–4 months, transitioning to semi-annual visits through year five, and annual follow-ups extending beyond 10 years. MRI studies of the brain are conducted at each follow-up, with spinal MR imaging performed annually through year 5 or 10, depending on institutional protocols and available resources. CSF cytology is usually performed at year one, if at all. This rigorous and detailed approach to follow-up

allows for the early identification of recurrent local or disseminated disease at its most treatable stage.

Patients enrolled in the RT1 protocol exemplify this proactive approach, receiving aggressive treatment strategies that included local surgery and metastasectomy when indicated, followed by a second course of radiotherapy. Early (Merchant, Boop, Kun, & Sanford, 2008) and subsequent (Tsang et al., 2018) reports of this approach revealed unexpectedly high rates of tumor control and a low risk of complications. Importantly, these studies demonstrated several key findings: craniospinal irradiation could cure patients with minimal-volume metastatic ependymoma; patients with locally recurrent ependymoma could successfully tolerate a second full-dose course of irradiation; combined local and distant failure was associated with the poorest overall survival; and reirradiation is a life-prolonging option for many patients.

The success of second-course irradiation relies heavily on timely surgical intervention and careful management at first relapse. The opportunity for reirradiation may be compromised if additional surgery is not pursued or if experimental agents are employed during initial relapse, allowing further disease progression. Similar to frontline treatment for ependymoma, the risk of recurrence remains high, emphasizing the need for future trials targeting recurrent disease. These trials are likely to incorporate concurrent systemic therapies alongside second-course irradiation to optimize outcomes and improve survival rates (Fig. 7).

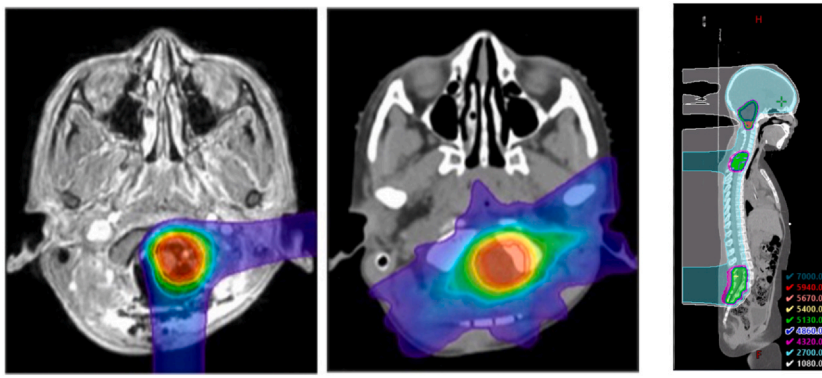

Fig. 7 Example of re-irradiation.

7. Summary

Over the past 30 years, advancements in radiotherapy have transformed the treatment of pediatric ependymoma, particularly through the adoption of conformal photon and proton beam therapies and their subsequent improvement. These innovations have enabled precise targeting of tumor volumes while minimizing radiation exposure to surrounding normal tissues, improving tumor control and reducing treatment-related complications. Early protocols, such as RT1 and ACNS0121, demonstrated the efficacy of immediate post-operative radiotherapy, especially for children as young as 12 months, and set benchmarks for modern treatment strategies. Subsequent protocols, including ACNS0831 and SIOP EP II, introduced refinements such as reduced clinical target volume margins and supplemental irradiation for residual tumors. Proton therapy has become the preferred modality in developed countries due to its superior normal tissue-sparing properties, though long-term evidence comparing it to photon therapy remains limited.

The chapter highlights critical considerations in radiotherapy planning, including tumor location, patient age, molecular features, and the potential for neuraxis dissemination. Advances in imaging, such as high-resolution MRI and emerging molecular staging techniques, have further enhanced precision in treatment planning and risk stratification. Despite improved outcomes, challenges remain, particularly for patients with residual or recurrent disease. Reirradiation has emerged as a viable option for relapse and requires timely intervention and multidisciplinary care. Future clinical trials are expected to explore clinical and molecular risk stratification (Junger et al., 2019; Ramaswamy et al., 2016), and concurrent systemic and targeted therapies alongside radiotherapy to optimize outcomes, ensuring continued progress in the care of children with ependymoma.

References

Afflerbach, A. K., Rohrandt, C., Brandl, B., Sonksen, M., Hench, J., Frank, S., ... Schuller, U. (2024). Classification of brain tumors by nanopore sequencing of cell-free DNA from cerebrospinal fluid. *Clinical Chemistry, 70*(1), 250–260. https://doi.org/10.1093/clinchem/hvad115.

Donson, A. M., Bertrand, K. C., Riemondy, K. A., Gao, D., Zhuang, Y., Sanford, B., ... Ritzmann, T. A. (2023). Significant increase of high-risk chromosome 1q gain and 6q loss at recurrence in posterior fossa group a ependymoma: A multicenter study. *Neuro-Oncology, 25*(10), 1854–1867. https://doi.org/10.1093/neuonc/noad096.

Ducassou, A., Padovani, L., Chaltiel, L., Bolle, S., Habrand, J. L., Claude, L., ... The French Society Of Children With, C. (2018). Pediatric localized intracranial ependymomas: A multicenter analysis of the societe francaise de lutte contre les cancers de

l'enfant (SFCE) from 2000 to 2013. *International Journal of Radiation Oncology, Biology, Physics, 102*(1), 166–173. https://doi.org/10.1016/j.ijrobp.2018.05.036.

Evans, A. E., Anderson, J. R., Lefkowitz-Boudreaux, I. B., & Finlay, J. L. (1996). Adjuvant chemotherapy of childhood posterior fossa ependymoma: Cranio-spinal irradiation with or without adjuvant CCNU, vincristine, and prednisone: A childrens cancer group study. *Medical and Pediatric Oncology, 27*(1), 8–14. https://doi.org/10.1002/(SICI)1096-911X(199607)27:1<8::AID-MPO3>3.0.CO;2-K.

Grill, J., Le Deley, M. C., Gambarelli, D., Raquin, M. A., Couanet, D., Pierre-Kahn, A., ... French Society Of Pediatric, O. (2001). Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: A multicenter trial of the French society of pediatric oncology. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 19*(5), 1288–1296. https://doi.org/10.1200/JCO.2001.19.5.1288.

Howe, G. N., Edmonston, D. Y., Dirks, G. C., Boop, F. A., & Merchant, T. E. (2023). Conformal radiation therapy for ependymoma at age </=3 years: A 25-year experience. *International Journal of Radiation Oncology, Biology, Physics, 116*(4), 869–877. https://doi.org/10.1016/j.ijrobp.2023.01.016.

Junger, S. T., Mynarek, M., Wohlers, I., Dorner, E., Muhlen, A. Z., Velez-Char, N., ... Pietsch, T. (2019). Improved risk-stratification for posterior fossa ependymoma of childhood considering clinical, histological and genetic features - a retrospective analysis of the HIT ependymoma trial cohort. *Acta Neuropathologica Communications,* 7(1), 181. https://doi.org/10.1186/s40478-019-0820-5.

Kovnar, E., Kun, L., Burger, P., & Krischer, J. (1991). Patterns of dissemination and recurrence in childhood ependymoma - preliminary-results of pediatric oncology group protocol=8532. *Annals of Neurology, 30*(3), 457 Retrieved from: ://WOS:A1991GF51400053.

Leblond, P. (2015). An international clinical program for the diagnosis and treatment of children with ependymoma (SIOP-EP-II) ClinicalTrials.gov ID NCT02265770. https://clinicaltrials.gov/study/NCT02265770.

Leblond, P., Massimino, M., English, M., Ritzmann, T. A., Gandola, L., Calaminus, G., ... Frappaz, D. (2022). Toward improved diagnosis accuracy and treatment of children, adolescents, and young adults with ependymoma: The international SIOP ependymoma II protocol. *Frontiers in Neurology, 13*, 887544. https://doi.org/10.3389/fneur.2022.887544.

Massimino, M., Barretta, F., Modena, P., Witt, H., Minasi, S., Pfister, S. M., ... Buttarelli, F. R. (2021). Second series by the Italian association of pediatric hematology and oncology of children and adolescents with intracranial ependymoma: An integrated molecular and clinical characterization with a long-term follow-up. *Neuro-Oncology, 23*(5), 848–857. https://doi.org/10.1093/neuonc/noaa257.

Massimino, M., Gandola, L., Giangaspero, F., Sandri, A., Valagussa, P., Perilongo, G., ... Group, A. P. N.-O. (2004). Hyperfractionated radiotherapy and chemotherapy for childhood ependymoma: Final results of the first prospective AIEOP (Associazione Italiana di Ematologia-Oncologia Pediatrica) study. *International Journal of Radiation Oncology, Biology, Physics, 58*(5), 1336–1345. https://doi.org/10.1016/j.ijrobp.2003.08.030.

Massimino, M., Miceli, R., Giangaspero, F., Boschetti, L., Modena, P., Antonelli, M., ... Gandola, L. (2016). Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma. *Neuro-Oncology, 18*(10), 1451–1460. https://doi.org/10.1093/neuonc/now108.

Merchant, T. E. (1997a). Conformal therapy for pediatric sarcomas. *Seminars in Radiation Oncology,* 7(3), 236–245. https://doi.org/10.1053/SRAO00700236.

Merchant, T.E. (1997b). A study for image-guided radiation therapy in pediatric brain tumors and side effects. ClinicalTrials.gov Identifier:NCT00187226. https://clinicaltrials.gov/study/NCT00187226?cond=NCT00187226&rank=1.

Merchant, T.E. (2003). Observation or radiation therapy and/or chemotherapy and second surgery in treating children who have undergone surgery for ependymoma. ClinicalTrials.gov identifier NCT00027846. https://clinicaltrials.gov/study/NCT00027846.

Merchant, T. E., Bendel, A. E., Sabin, N. D., Burger, P. C., Shaw, D. W., Chang, E., ... Ramaswamy, V. (2019). Conformal radiation therapy for pediatric ependymoma, chemotherapy for incompletely resected ependymoma, and observation for completely resected, supratentorial ependymoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 37*(12), 974–983. https://doi.org/10.1200/JCO.18.01765.

Merchant, T. E., Boop, F. A., Kun, L. E., & Sanford, R. A. (2008). A retrospective study of surgery and reirradiation for recurrent ependymoma. *International Journal of Radiation Oncology, Biology, Physics, 71*(1), 87–97. https://doi.org/10.1016/j.ijrobp.2007.09.037.

Merchant, T. E., Li, C., Xiong, X., Kun, L. E., Boop, F. A., & Sanford, R. A. (2009). Conformal radiotherapy after surgery for paediatric ependymoma: A prospective study. *The Lancet Oncology, 10*(3), 258–266 Retrieved from. https://www.ncbi.nlm.nih.gov/pubmed/19274783.

Merchant, T. E., Mulhern, R. K., Krasin, M. J., Kun, L. E., Williams, T., Li, C., ... Sanford, R. A. (2004). Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 22*(15), 3156–3162. https://doi.org/10.1200/JCO.2004.11.142.

Ramaswamy, V., Hielscher, T., Mack, S. C., Lassaletta, A., Lin, T., Pajtler, K. W., ... Taylor, M. D. (2016). Therapeutic impact of cytoreductive surgery and irradiation of posterior fossa ependymoma in the molecular era: A retrospective multicohort analysis. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 34*(21), 2468–2477. https://doi.org/10.1200/JCO.2015.65.7825.

Rutkowski, S. (2001). Radiation therapy and combination chemotherapy in treating young patients with medulloblastoma, supratentorial primitive neuroectodermal tumor, or ependymoma. ClinicalTrials.gov ID NCT00303810. https://clinicaltrials.gov/study/NCT00303810.

Smith, A. (2010). Maintenance chemotherapy or observation following induction chemotherapy and radiation therapy in treating patients with newly diagnosed ependymoma. ClinicalTrials.gov ID NCT01096368. https://clinicaltrials.gov/study/NCT01096368.

Tsang, D. S., Burghen, E., Klimo, P., Jr., Boop, F. A., Ellison, D. W., & Merchant, T. E. (2018). Outcomes after reirradiation for recurrent pediatric intracranial ependymoma. *International Journal of Radiation Oncology, Biology, Physics, 100*(2), 507–515. https://doi.org/10.1016/j.ijrobp.2017.10.002.

Upadhyaya, S. A., Robinson, G. W., Onar-Thomas, A., Orr, B. A., Billups, C. A., Bowers, D. C., ... Gajjar, A. (2019). Molecular grouping and outcomes of young children with newly diagnosed ependymoma treated on the multi-institutional SJYC07 trial. *Neuro-Oncology, 21*(10), 1319–1330. https://doi.org/10.1093/neuonc/noz069.