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Radiotherapy for Primary Pediatric Central Nervous System Malignancies: Current Treatment Paradigms and Future Directions

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Short title: Radiotherapy for Pediatric Central Nervous System Malignancies

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Abstract

Background: Central nervous system tumors are the most common solid tumors in childhood. Treatment paradigms for pediatric central nervous system malignancies depend on elements including tumor histology, age of patient, and stage of disease. Radiotherapy is an important modality of treatment for many pediatric central nervous system malignancies.

Summary: While radiation contributes to excellent overall survival rates for many patients, radiation also carries significant risks of long-term side effects including neurocognitive decline, hearing loss, growth impairment, neuroendocrine dysfunction, strokes, and secondary malignancies. In recent decades, clinical trials have demonstrated that with better imaging and staging along with more sophisticated radiation planning and treatment set-up verification, smaller treatment volumes can be utilized without decrement in survival. Furthermore, the development of intensity-modulated radiotherapy and proton-beam radiotherapy has greatly improved conformality of radiation.

Key Messages: Recent changes in radiation treatment paradigms have decreased risks of short- and long-term toxicity for common histologies and in different age groups. Future studies will continue to develop novel radiation regimens to improve outcomes in aggressive central nervous system tumors, integrate molecular subtypes to tailor radiation treatment, and decrease radiation-associated toxicity for long-term survivors.

Introduction

With over 2,750 cases per year in the United States, central nervous system (CNS) tumors comprise a heterogeneous group of tumors with diverse histologies [1]. For many pediatric CNS tumors, such as ependymoma and medulloblastoma, progress in multimodal therapy has led to dramatic improvements in survival over the last five decades [1, 2, 3]. On the other hand, there remain pediatric CNS malignancies, such as pediatric high-grade gliomas (pHGGs) or diffuse midline gliomas (DMGs), for which survival remains poor despite intensive multimodal therapy [4].

Radiation therapy is a critical component of multimodality treatment of many pediatric CNS tumors [2, 3, 4, 5, 6, 7, 8]. The radiation field and dose are defined primarily based on histology and staging for curative intent [9, 10]. In the setting of recurrence, radiation can also play an important role in prolonging survival and palliating symptoms. CNS radiation carries acute or short-term side effects; most of them will resolve after completion of radiation, but some, such as brain or brainstem necrosis, can carry significant morbidity [11, 12]. Moreover, radiation increases the risk of significant long-term toxicities, including neurocognitive decline, hearing loss, endocrine dysfunction, growth effects, vascular complications, and secondary malignancies [11, 13, 14, 15, 16, 17].

Thus, delivering optimal radiation doses while limiting doses to organs at risk is a priority for pediatric patients with CNS malignancies. In the last three decades, there have been considerable advancements in radiation treatment delivery and planning, including intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and proton-beam radiotherapy, that may achieve better therapeutic ratios (*i.e.,* difference between tumor control and normal tissue toxicity) when compared to 3-dimentional conformal radiotherapy (3DCRT) [18]. We herein review modern radiotherapy considerations for CNS tumors in pediatric patients and discuss the latest evidence-based treatment paradigms for the most common pediatric CNS tumors.

Modalities of radiation treatment

Photon radiotherapy

For many decades, pediatric patients were treated with conventional planning or 2D radiotherapy, where x-ray films were used to define radiation fields, leading to significant dose to normal structures. With the introduction of CT-based radiation planning, 3D conformal techniques allowed for improved planning target volume (PTV) delineation. By using shaped radiation fields from different directions, organs at risk were better spared compared to 2D radiotherapy without loss of tumor control [19]. In recent decades, intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) have been increasingly used. IMRT and VMAT deliver radiation that is modulated using multi-leaf collimators (MLC) in static or dynamic arrangements [18]. These plans are generated using inverse planning, in which radiation prescription dose, PTV coverage, and dose constraints for organs at risk are specified upfront, and these treatment objectives are optimized. IMRT and VMAT allow for a more conformal dose distribution to the PTV and lower doses to adjacent organs at risk; however, treatment planning requires more time and more normal tissue will receive lower doses of radiation [20, 21]. Retrospective studies have found less hearing loss after IMRT/VMAT compared to conventional or 3D conformal radiotherapy [22], while other side effects, such as hematologic toxicity or neurocognitive decline, do not appear significantly different between IMRT/VMAT and 3D conformal radiotherapy [23, 24].

In addition, further improved patient immobilization techniques (either frame-based or frameless) have allowed for the development of stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) for pediatric CNS tumors. Using either a linear accelerator (LINAC) or GammaKnife (a radiosurgical system using multiple cobalt-60 gamma radiation sources), SRS or SRT allows for accurate delivery of high radiation dose (≥5 Gy) per fraction that is extremely conformal, thus leading to decreased dose to normal brain tissue. In addition to treating brain metastases from extracranial solid tumors, these techniques have been used for low-grade gliomas and various benign histologies as well as in the setting of boosting gross residual disease or treatment of recurrent tumors [25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35].

Electron radiotherapy

Electron radiotherapy is a form of external beam radiotherapy that can be used to treat superficial tumors. Electrons are negatively-charged particles and electron radiotherapy leads to rapid dose fall-off distally and thus spares deeper organs at risk. Although uncommonly used for treatment of pediatric CNS tumors, electron spinal fields can be considered for craniospinal irradiation (CSI) to limit dose to anterior organs at risk, such as esophagus, heart, and lungs [36, 37].

Proton radiotherapy

Another form of external beam radiotherapy, proton-beam radiotherapy takes advantage of physical and biological properties of the positively charged particle to allow for favorable dose distributions by having no exit dose, leading to reduced radiation doses to normal organs [18]. Proton radiotherapy conformality and delivery can be modulated by passive scatter and pencil
beam scanning (PBS) techniques with PBS providing more conformal doses by controlling dose delivery to proximal and distal edges [20]. While there are circumstances in which passive scatter may be beneficial, most centers are now using PBS [20]. Pediatric CNS tumors are frequently treated using proton-beam radiotherapy given these dosimetric advantages and studies suggest that proton-beam radiotherapy improves acute- and long-term toxicities, from neurocognitive decline to hearing loss, compared to photon radiotherapy [38, 39, 40, 41, 42]. While there is a theoretical benefit of proton-beam radiotherapy in decreasing the risk of secondary malignancies, real-world data have not yet found a significant difference albeit with relatively short follow-up [43, 44]. There is a small amount of neutron contamination from proton-beam radiotherapy [45, 46]. While it remains unclear whether this leads to clinically meaningful toxicities, some studies suggest that the neutron contamination from proton-beam radiotherapy may contribute to earlier onset of secondary malignant neoplasms or vasculopathy [45, 46]. In addition, there are studies that characterize the risk of brainstem injury after proton-beam radiotherapy, which in recent years, appears to be small with appropriate dose constraints [10, 12, 47, 48, 49]. It has been hypothesized that the physical properties of protons and in particular, the increased linear energy transfer and relative biological effectiveness at the end of range, may contribute to brainstem toxicity [12]. Thus, the most recent COG ependymoma protocol, ANCS0831, ultimately recommended two different dose constraints: 50% of the brainstem receiving ≤61 Gy or 52.4 Gy when using photons or protons, respectively (NCT01096368). Further research remains important to more fully characterize the benefits and potential of proton-beam radiotherapy compared with photon radiotherapy.

Because protons need to be generated by cyclotrons or synchrotrons, there are significant costs to building proton treatment centers, thus leading to a limited number of facilities within the United States and around the world [20, 50]. A recent study found that there are racial disparities in the use of proton radiotherapy for patients enrolled on Children's Oncology Group trials with black patients being less likely to receive proton-beam radiotherapy compared to non-Hispanic white patients [51]. Thus, future work remains important to improve access to proton-beam radiotherapy, particularly given the potential benefits for long-term survivors.

Brachytherapy

Brachytherapy is characterized by the use of sealed radiation sources to provide localized radiotherapy that often has favorable dosimetric profiles to neighboring normal tissues. Brachytherapy for pediatric CNS tumors remain uncommon, with the largest published cohorts in pediatric patients with low-grade gliomas [52, 53]. CNS brachytherapy leads to excellent long-term survival outcomes in pediatric low-grade gliomas and one study found that larger tumors (>15 cc) were more likely to recur after brachytherapy [52, 53]. In addition, CNS brachytherapy can also be considered as re-irradiation for tumor recurrence [54]. The most frequent sequelae after CNS brachytherapy for pediatric patients remains brain necrosis [55].

Radiation treatment considerations by histology

Medulloblastoma

Traditionally in North America, patients with medulloblastoma are risk-stratified by whether they have metastatic disease (in particular, CNS dissemination) or residual disease >1.5cm^2 [56]. For standard-risk medulloblastoma, patients receive CSI to 23.4 Gy with involved field boost to 54 Gy with weekly vincristine followed by adjuvant

chemotherapy, a treatment paradigm supported by a Phase III clinical trial [57]. Reduction of CSI dose from 36 Gy to 23.4 Gy without chemotherapy is not appropriate as a prospective randomized trial demonstrated an increased risk of early relapse [58]. For high-risk medulloblastoma, patients receive CSI to 36 Gy with whole posterior fossa boost to 54-55.8 Gy with concurrent chemotherapy (weekly vincristine with or without daily carboplatin) followed by adjuvant chemotherapy [59].

The most recent COG trial for standard-risk medulloblastoma demonstrated that involved-field boost was non-inferior to whole posterior fossa boost; however, 18 Gy CSI was inferior to 23.4 Gy CSI [3]. With further molecular classification, studies have found that WNT pathway-activated medulloblastoma carry a very favorable prognosis [56], thus ongoing prospective studies are exploring whether lower CSI dose (<23.4 Gy) is possible for patients with standard-risk WNT pathway-activated medulloblastoma (NCT02724579, NCT02066220, and NCT01878617). A recent clinical study found that omission of CSI is not appropriate for WNT-pathway activated medulloblastoma [60]. For high-risk medulloblastoma, an ongoing SIOP-HR-MB prospective study will examine the role of hyperfractionated accelerated radiotherapy with 39 Gy CSI and involved field boost to 59.8 Gy in twice daily 1.3 Gy fractions based on a Milan prospective study that showed a 5-year EFS of 70% with a hyperfractionated accelerated radiotherapy approach [61, 62]. In addition, the SIOP-HR-MB will study boosting the tumor bed alone (rather than the entire posterior fossa), with consideration of a boost to metastatic sites if there are ≤3 residual lesions after induction chemotherapy [61].

In recent years, proton-beam radiotherapy has become increasingly used for patients with medulloblastoma given the dosimetric advantages of decreased radiation doses to normal organs compared with photon radiotherapy. Studies have not found differences in relapse rates or overall survival between proton and photon radiotherapy [63]; however, a growing literature has found that proton-beam radiotherapy improves acute hematologic toxicity, neurocognitive outcomes, hearing loss, and endocrine dysfunction in patients with medulloblastoma [38, 39, 41, 42].

There are efforts to limit radiotherapy for young children given long-term side effects, especially devastating neurocognitive decline; however, overall survival of young children with medulloblastoma remains lacking [64, 65]. The current paradigm has been to utilize systemic therapy, intrathecal or high-dose methotrexate, and/or autologous stem cell transplantation to delay or omit upfront radiotherapy, achieving five-year overall survival rates of 70% or higher for patients with localized disease and about 50% for patients with disseminated disease [66, 67, 68]. There are considerations for the use of consolidative radiotherapy after systemic therapy or salvage radiotherapy at the time of recurrence [69, 70]. In the future, molecular analyses may help inform which specific subgroups of infant medulloblastoma may benefit from more intensive therapy [64, 71].

Ependymoma

Clinical trials have found that patients with intracranial ependymoma who receive adjuvant radiotherapy have excellent local control >70% and 5-year overall survival >80% for patients with gross total resection [2, 72]. For patients with localized ependymoma, involved field radiotherapy is used with a total dose of 54.0-59.4 Gy. For patients with disseminated disease, 36 Gy CSI is often used followed by involved field boost [73]. Patients with subtotal resection have poor outcomes after adjuvant radiotherapy (54.0-59.4 Gy) with 5-year EFS of 34-43% in recent prospective studies [2, 28, 72, 74]. A recent prospective clinical trial examined the role of stereotactic boost (8 Gy in 2 fractions) to gross residual disease after conventional radiotherapy and found that it was safe, achieving favorable 5-year PFS of 58.1% and OS of 68.7% [28]. The ongoing SIOP-EP-II will further characterize the safety and efficacy of a stereotactic boost (8 Gy in 2 fractions) to unresected ependymoma (NCT02265770). Proton radiotherapy has also been found to be safe and result in similar outcomes compared to photon radiotherapy [75, 76, 77]; however, long-term toxicities comparing the two modalities remain limited [78].

Some prospective studies have examined the role of adjuvant chemotherapy or observation for young patients after surgery; however, there remains a high recurrence risk without adjuvant radiotherapy [2, 79, 80]. Retrospective studies suggest that adjuvant radiotherapy leads to survival benefit even in children with ependymoma under the age of 3 years [81, 82]. While a prior study found that patients with supratentorial ependymoma had more favorable

outcomes without adjuvant radiotherapy compared to those with infratentorial ependymoma [79], results from COG ACNS0121 demonstrated that observation for patients with gross totally resected grade 2 supratentorial ependymoma, which portends excellent overall survival, led to 5-year EFS of 61.4% [2]. Nonetheless, these studies suggest that omission of post-operative radiation may be possible in a subset of children [2, 79, 80]; however, a better understanding of the biological landscape of ependymomas is warranted to refine the current risk stratification system [2].

High-Grade Gliomas

For pediatric patients with high-grade gliomas (HGGs), adjuvant radiotherapy is standard, with total doses of 54.0-59.4 Gy [4, 83]. For patients with DMG, including diffuse intrinsic pontine glioma (DIPG), conventional radiotherapy to 54 Gy in 30 fractions remains standard [84, 85]. Prior studies exploring radiation dose intensification and hyperfractionation showed no significant improvement in outcomes [86, 87, 88, 89]. Furthermore, many prospective studies have also explored the role of concurrent radiotherapy with various radiosensitizers or chemotherapeutic agents, but ultimately, none has shown significant improvement in outcomes [88, 89]. For DMG, studies have also explored the role of hypofractionated radiotherapy in an attempt to lessen treatment burden [88]. One prospective study failed to demonstrate non-inferiority for 39 Gy in 13 fractions when compared to 54 Gy in 30 fractions [84], while another matched cohort study found no differences in outcomes for patients receiving at least 50 Gy in 1.8-2.0 Gy per fraction compared to those receiving 39 Gy in 13 fractions or 44.8 Gy in 16 fractions [90].

Given that progression-free survival (PFS) and overall survival (OS) are exceedingly poor for progressive HGG, with median of 3.5 months and 5.6 months, respectively, recent studies have explored the role of re-irradiation for pediatric and young adult HGGs [91, 92, 93, 94]. While there is a variety of dose fractionation regimens, data suggest that re-irradiation is safe and can lead to median OS of 14 months [91, 92, 93, 94].

Intracranial germ cell tumors (GCTs)

After multimodal treatment, including radiotherapy, five-year OS rates are greater than 90% and 75% for pure germinomas and NGGCTs, respectively [5, 6, 8, 9, 95]. For localized pure germinomas, radiation options include CSI or chemotherapy followed by whole ventricular irradiation (WVI) with or without involved-field boost. A recent prospective clinical trial demonstrated that combined chemotherapy and reduced field focal radiotherapy had similar OS when compared with CSI [6]. Given that studies examining relapse patterns after chemotherapy and focal radiotherapy in localized pure germinomas have reported recurrences around the ventricular system [6, 96], WVI is the current standard of care instead of focal radiation alone [9].

For localized NGGCTs, the Children's Oncology Group (COG) trial ACNS0122 showed the best outcomes after chemotherapy followed by CSI, with five-year EFS and OS of 84% and 93%, respectively [95]. Currently, chemotherapy followed by response-adapted reduced field focal radiotherapy or WVI with or without involved field boost remains controversial in localized NGGCTs with conflicting data regarding increased relapse in the spine [97, 98]. An ongoing clinical trial COG ACNS2021 examines chemotherapy followed by response-adapted WVI and spinal canal irradiation for localized NGGCTs (NCT04684368). Meanwhile, 54 Gy focal RT (without WVI) was most recently investigated in the SIOP CNS GCT II following dose-intense chemotherapy with adequate local control [99]. For patients with metastatic intracranial GCTs, CSI followed by involved field boost remains standard [100].

In recent years, proton-beam radiotherapy has been studied for treatment of intracranial GCT and found to be safe and effective with comparable disease control albeit with short follow-up [101, 102, 103]. Given the high cure rates and the superior dosimetric distributions of protons [102, 104], proton-beam radiotherapy may be able to improve long-term toxicity, but long-term studies remain needed.

Atypical teratoid rhabdoid tumor

Intracranial atypical teratoid rhabdoid tumors (ATRTs) are aggressive and patients have a 2-year PFS of 40-50% despite multimodal treatment, including surgical resection, intensive chemotherapy, radiotherapy, with or without autologous stem cell transplantation [7, 105]. Radiotherapy has been shown in retrospective studies to improve

outcomes for pediatric patients with ATRT [106, 107, 108]. Focal radiotherapy (50.4 – 54 Gy) can be considered for patients with localized disease, while CSI with involved field boost to a total dose of 50.4 – 54 Gy is recommended for patients with metastatic disease [7, 105]. For patients under the age of 3 years with metastatic disease, a lower CSI dose (23.4 Gy) can be considered if treated as per ACNS0333 while patients over the age of 3 years with metastatic disease generally receive 36 Gy CSI [105]. For patients under the age of 3 years, a total dose of 50.4 Gy can also be considered if treated as per ACNS0333 [105]. Focal proton radiotherapy for patients with localized disease results in similar outcomes to photon radiotherapy [109]. Prior data suggest that patients <3 years of age with ATRT have worse prognosis [108], potentially related to the omission of radiotherapy. A forthcoming randomized phase III clinical trial, SIOPE ATRT01, will investigate whether 3 cycles of high-dose chemotherapy are non-inferior to focal radiotherapy (54 – 59.4 Gy depending on extent of resection) as consolidation for patients between 1-3 years of age. All patients over the age of 3 years on SIOPE ATRT01 will continue to receive focal radiation for localized disease and CSI for disseminated disease.

Low-grade glioma and benign histologies

While radiotherapy was used frequently for low-grade gliomas (LGGs) and benign histologies, such as craniopharyngioma and meningiomas many decades ago, radiation is more frequently omitted now with better surgeries and systemic agent options [30, 110, 111, 112, 113, 114, 115, 116, 117, 118]. For low-grade gliomas, radiation is effective in improving symptoms, such as vision deficits, and can provide excellent local control [110, 111, 119, 120, 121]. A recent prospective study found that a clinical target volume expansion of 5mm was adequate, with five-year PFS of 71% and OS of 93% [119]. For pediatric patients with craniopharyngiomas, when gross total resection is not possible, adjuvant radiotherapy can provide excellent local control [114, 115, 116]. Proton-beam radiotherapy can also be considered for these etiologies with comparable outcomes [122, 123, 124, 125]. A recent study with a small cohort of 18 pediatric patients with LGGs showed no significant decline in neurocognitive function after proton radiotherapy [126].

Future Directions

In the coming decades, there are many exciting developments for the field of radiotherapy in the treatment of pediatric CNS tumors. There remain unanswered questions about the optimal dose- and fractionation-schemes along with radiation fields for different pediatric CNS tumors. There are ongoing investigations examining the role of dose de-escalation for standard-risk WNT pathway-activated medulloblastoma and decreasing the radiation field to WVI and spinal canal irradiation for localized NGGCTs (Table 1). These prospective studies will determine whether these treatments are effective and if so, will likely decrease long-term toxicities for these patients who have excellent prognoses. While radiation dose intensification and hyperfractionation did not improve outcomes in HGG [86, 87, 88, 89], the SIOP-HR-MB prospective randomized clinical trial will study whether hyperfractionated accelerated radiotherapy may benefit patients with high-risk medulloblastoma (Table 1).

In recent years, there have been dramatic improvements in radiation techniques with IMRT/VMAT providing more conformal treatments while proton-beam radiotherapy has favorable dosimetric advantages. Thus, in recent years, studies have found that these techniques can improve toxicity profiles [22, 38, 39, 40, 41, 42]. While there are some concerns about neutron contamination from proton radiotherapy and increased low dose radiation from IMRT/VMAT, the clinical relevance of these concerns remains poorly understood. Future studies are needed to understand the benefits of these newer radiation techniques and in particular, additional comparative studies are needed. The newly-created Pediatric Proton/Photon Consortium Registry will help provide much-needed and important long-term toxicity information [127].

Although frequently used for recurrent CNS tumors, the use of SRS or SRT remains under-utilized for pediatric CNS malignancies [25, 35, 128]. Prospective studies are only recently starting to investigate the role of SRS or SRT in the upfront treatment of pediatric CNS tumors, such as supplemental radiation for sub-totally resected ependymoma [28]. Given the excellent conformality of SRS and SRT, further studies, such as SIOP-EP-II, are needed to understand whether these techniques can improve outcomes for pediatric CNS tumors (Table 1).

Conclusions

Over the last five decades, improvements in the treatment of many pediatric CNS tumors have led to increased survival and reduced long-term toxicity. Radiotherapy plays an important role in curing children with CNS malignancies; however, radiation carries significant risks of acute- and long-term toxicities. With improved technology, modern radiation techniques and fields have contributed significantly to these efforts of improving the therapeutic ratio. Future efforts continue to be needed to improve post-radiation toxicity for long-term survivors while developing novel radiation regimens to improve outcomes in aggressive CNS tumors that continue to carry a poor prognosis.

Conflict of Interest Statement

The authors do not have conflicts of interest to disclose

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Author Contributions:

Kevin Liu, Daphne Haas-Kogan, and Hesham Elhalawani performed the following:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
2. Drafting the work or revising it critically for important intellectual content
3. Final approval of the version to be published
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Specific additional individual cooperative effort contributions to study/manuscript design/execution/interpretation, in addition to all criteria above are listed as follows:

Kevin Liu: Conceptualization, data curation, creating tables, writing-original draft, and writing-review and editing. **Daphne Haas-Kogan**: Conceptualization, writing-original draft, and writing-review and editing. **Hesham Elhalawani**: Conceptualization, writing-original draft, and writing-review and editing.

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Table 1. Ongoing and forthcoming clinical trials with investigative questions regarding radiation dose/fractionation or radiation fields

Study Name (NCT # if applicable)	Cooperative Group/Institution	Phase	Tumor Histology	Treatment Arms/Strata with investigative questions regarding radiotherapy
ACNS1422 (NCT02724579)	COG	II	Newly Diagnosed WNT-Driven Medulloblastoma	18 Gy CSI with 36 Gy involved field boost (total dose of 54 Gy)
ACNS2021	COG	II	Newly diagnosed non-germinomatous germ cell tumors	Whole ventricular irradiation and spinal canal irradiation for patients with adequate response to induction chemotherapy
SIOP-EP-II (NCT02265770)	SIOP Europe	II/III	Newly Diagnosed Ependymoma	Stratum 2 for patients with residual disease after resection: 54-59.4 Gy conventionally fractionated conformal radiation followed by 8 Gy in 2 fractions stereotactic radiotherapy boost to residual disease
SIOP HR-MB (forthcoming)	SIOP Europe	III	Newly Diagnosed High-Risk Medulloblastoma	One randomized arm: 39 Gy CSI and involved field boost to 59.8 Gy in twice daily 1.3 Gy fractions
SIOP PNET 5 MB-SR (NCT02066220)	SIOP Europe	II/III	Newly Diagnosed Standard-Risk Medulloblastoma	Low-risk (WNT-driven medulloblastoma): 18 Gy CSI with 36 Gy involved field boost (total dose of 54 Gy)
SJMB12 (NCT01878617)	St. Jude's	II	Newly Diagnosed Medulloblastoma	Stratum W1 (low risk) for WNT-driven medulloblastoma: 15 Gy CSI with 36 Gy involved field boost (total dose of 51 Gy)