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Review

Precision based approach to tailoring radiotherapy in the multidisciplinary management of pediatric central nervous system tumors

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ABSTRACT

Modern day survivorship from childhood malignancies is estimated to be over 80%. However, central nervous system tumors remain the leading cause of cancer mortality in children and is the most common solid tumor in this population. Improved survivorship is, in part, a result of improved multidisciplinary care, often with a combination of surgery, radiation therapy, and systemic therapy. With improved survival, long term effects of treatment and quality of life impacts have been recognized and pose a challenge to maximize the therapeutic ratio of treatment. It has been increasingly more apparent that precise risk stratification, such as with the inclusion of molecular classification, is instrumental in efforts to tailor radiotherapy for appropriate treatment, generally towards de-intensification for this vulnerable patient population. In addition, advances in radiotherapy techniques have allowed greater conformality and accuracy of treatment for those who do require radiotherapy for tumor control. Ongoing efforts to tailor radiotherapy, including de-escalation, omission, or intensification of radiotherapy, continue to improve as increasing insight into tumor heterogeneity is recognized, coupled with advances in precision medicine employing novel molecularly-targeted therapeutics.

1. Introduction

Survival rates from childhood malignancies have seen considerable improvement. Historically, fewer than half the children diagnosed with cancer survived; though in the past few decades, death rates have declined, and the 5-year overall survival (OS) in the modern day is estimated to be >80%.[1–3] Notably, outcomes vary by the type of malignancy. Pediatric central nervous system (CNS) tumors are the second most common malignancy after leukemia, and the most common solid tumor in this population, accounting for about a quarter of pediatric tumors.[4] In addition, they are now the leading cause of cancer mortality in children. Treatment of pediatric CNS malignancies requires multidisciplinary care, often utilizing multimodality treatment with a combination of surgery, radiation therapy, and chemotherapy to improve cancer specific survival.

Radiation therapy plays a critical role in the management of many pediatric tumors. While low grade gliomas (LGG) can often be managed by surgery alone, in the setting of an unresectable disease due to high risk location, subtotal resection (STR) or recurrent disease, radiotherapy offers local control benefits.[5] Outcomes from surgery alone in the management of CNS tumors including high grade gliomas

(HGG), medulloblastoma, ependymoma, and craniopharyngioma were not satisfactory, and thus, required additional adjuvant treatment. Adjuvant radiotherapy demonstrated improved local control as well as a strategy to treat tumors in high-risk locations.[6–8] In the treatment of germ cell tumors, radiotherapy and chemotherapy are the mainstay of treatment with the addition of surgical considerations for non-germinomatous germ cell tumors (NGGCT).[9] Radiotherapy also often plays an important role in the treatment of recurrent or progressive CNS tumors.

While multimodality therapy has been integral to improving cancer specific outcomes, the management of pediatric malignancies remains a challenge to maximize the therapeutic ratio by also limiting toxicities. In particular, radiation related late toxicities are of concern in this population. It is well documented that CNS directed radiotherapy in children have long term implications, with great concerns regarding debilitating neurocognitive deficits and endocrinopathies.[10] In addition, there are surgical risks to resection and chemotherapies can also contribute to CNS toxicity and leukoncephalopathies.[11] Thus, the balance between cancer control and minimizing treatment related toxicity must be consistently re-evaluated and requires appropriate risk stratification. Advances in radiotherapy techniques has offered dosimetric advantages

to reduce toxicity and enable physicians to further tailor radiotherapy to the patient.

Historically, risk stratification has largely centered upon histopathologic grading, age, and extent of resection.[12] Nonetheless, there remains notable heterogeneity in treatment response and clinical outcomes within these subgroups. Advances in molecular classification has helped further stratify distinct subgroups with varying prognoses. This is helping to redefine modern treatment paradigms in a more tailored manner to avoid overtreatment of those with excellent prognoses while devising strategies to improve outcomes for those with poor prognoses.

Here, we discuss the role of radiotherapy in the multimodality management of pediatric tumors and how advances in risk stratification can further tailor radiotherapy for patients with a precision-based approach in the modern era.

2. Role of radiotherapy and how it can be tailored based on risk stratification in the multidisciplinary care of pediatric brain tumors

2.1. Management of pediatric LGG

LGGs are the most common CNS tumor in children, accounting for about 30%–40% of CNS tumors.[13,14] These are a heterogenous group of tumors with various histologies that can occur anywhere in the CNS.[15] The mainstay of treatment is surgical resection, which can be curative after gross total resection.[16,17] Extent of resection has been shown to be one of the most significant prognostic factors; thus, risk stratification has traditionally been focused on extent of resection and comprised of three main groups, including gross total resection (GTR), STR, or biopsy only. For those who do not undergo a GTR, 5-year progression free survival (PFS) rates of 45%–65% are noted.[18] This PFS rate was also impacted by tumor location and histology.

As a significant portion of patients can have a long period of stable disease, the role and timing of adjuvant therapy is discussed in a more nuanced manner, considering factors such as age, severity of symptoms, and risks associated with progression. Radiotherapy is considered in the case of subtotal resection or for recurrent/progressive disease and plays an important role in local control, achieving >87% 5-year disease control.[5] Radiotherapy also plays an important role in the treatment of optic pathway LGG as early radiotherapy intervention preserves visual acuity.[19]

However, to reduce potential long term radiation related toxicity, radiotherapy is often deferred, especially for young children, opting for observation alone.[20] Furthermore, children with LGG may be at higher risk for deficits in cognitive and adaptive functioning even with surgical resection alone. In addition, age has been shown to be a significant factor in cognitive decline after radiotherapy and those under 5 years old have had the largest decline in cognitive function and vasculopathy.[5,21] Thus, reduction in compounding risk factors for neurotoxicity is ideal. Radiotherapy is also often deferred in those with neurofibromatosis type 1 (NF1), as they may be subject to an increased risk of radiation related secondary malignancy.[22]

For those with unresectable LGG or progressive/recurrent disease, chemotherapy has often been pursued, especially in younger children or those with NF1, to delay initiation of radiotherapy, achieving about 35%–50% PFS at 5 years.[23,24] Still, many patients will eventually require radiotherapy. As delaying radiotherapy may come at a risk of reduced PFS and reduced visual acuity in optic pathway LGG, optimal management should be discussed in a multidisciplinary fashion.[19,25]

A molecularly defined subgroup of pediatric LGGs harboring the BRAF V600E mutation, especially in combination with CDKN2A deletion, has been identified as a high-risk subgroup that is an independent predictor of poorer outcomes. About half of BRAF V600E mutated LGGs will progress at 5 years. In addition, these tumors have demonstrated a worse response to both radiotherapy and chemotherapy, with a 5-year PFS of 42% and 30%, respectively.[26] As such, the potential for molecularly targeted therapy is being explored.

The discovery that the tumorigenesis of pediatric LGGs frequently stems from activation of the RAS/MAPK pathway has opened the realm of targeted agents in the treatment of pediatric LGGs.[26–28] Mechanisms to activate the RAS/MAPK pathway include upstream targets of *RAS*, *BRAF*, and *MEK* genes, which offers potential targets for treatment. BRAF inhibitors have been used in other BRAF V600E cancers with good efficacy such as in the treatment of melanoma; thus, there may be a role in its treatment of LGG. Thus far, there exists few case reports suggesting good response to these targeted agents in pediatric LGGs.[31–33] Phase I/II trials using targeted agents such as MEK inhibitors, including trametinib, selumetinib, and cobimetinib, and BRAF inhibitors, including dabrafenib and vemurafenib, for progressive or recurrent tumors are evaluating safety and efficacy of these agents.[29–34] In addition, there are ongoing phase III clinical trials comparing standard chemotherapy agents to MEK inhibitor, selumetinib, for the management of untreated, unresectable LGG. This will evaluate the efficacy as well as the side effect profile of these therapies including effect on neurocognitive function, motor function, vision, and quality of life.[35] Results of these studies can help guide future investigation for optimal management in these patients, including the role and timing of radiotherapy.

As discussed, many will require radiotherapy in their course of treatment; thus, the optimal timing and technique of radiotherapy continues to be of interest. More precise radiotherapy, including conformal radiotherapy, stereotactic radiotherapy, and proton radiotherapy, provides additional methods to reduce the potential side effects of radiotherapy while maximizing local control.[5,36–38]

2.2. Management of HGG

Pediatric high-grade gliomas comprise about 10%–20% of pediatric brain tumors and often carry a poor prognosis.[39] Surgical resection is the standard upfront management, as extent of resection has been demonstrated to be an important prognostic factor, followed by adjuvant radiotherapy to optimize local control, and consideration of chemotherapy, similar to management in the adult population.[40–42] However, HGG in eloquent locations, such as brainstem gliomas, present a challenge due to morbidity of surgery. In these cases, management relies on radiotherapy and consideration chemotherapy.[43]

Advances in molecular sequencing have identified distinct biologic subtypes of pediatric high-grade gliomas, including H3 mutation, IDH mutant, and H3/IDH wildtype and have further identified molecular alterations that may provide targets for therapy.[44,45] Though significant clinical benefit has yet to be demonstrated, molecular subgrouping will allow for more tailored treatment investigation in this aggressive tumor setting. Moreover, molecular interrogation of key signaling pathways promoting tumor progression are being identified and targeted in pediatric high grade gliomas. For example, the Pacific Pediatric Neuro Oncology Consortium (pnoc.us), has a number of active clinic trials for patients with newly diagnosed or relapsed high grade glioma testing novel therapies including immune checkpoint inhibitors, PARP inhibitors, RNA lipid vaccines, CD47 signal receptor protein-alpha axis inhibitors, and dopamine receptor D2 and D3 antagonists.

Additionally, infant HGG appears to have distinct clinical behaviors. Infant HGG have been found to commonly demonstrate fusions in NRTK.[45] NRTK plays an important role in oncogenesis; thus, NRTK inhibitor agents, such as larotrecinib, are undergoing clinical investigation.[46–49] Case reports have reported good response to larotrectinib with limited toxicity.[50] Thus, given the overall poor outcomes with current therapies and concerns for toxicities especially in infants, further exploration of targeted agents may help improve current therapeutic strategies. With the advances of radiotherapy technique to reduce toxicity and the potential for targeted therapy as an additional treatment option, the synergy and/or sequencing of these therapies will need to undergo investigation to optimize outcomes.

2.3. Management of medulloblastoma

Medulloblastomas are embryonal tumors typically arising in the cerebellum. Medulloblastoma is the most common high grade CNS malignancy in children, accounting for 20% of pediatric CNS tumors and 40% of posterior fossa tumors with a peak incidence in children 5–7 years old.[14,51] Medulloblastoma has a propensity to disseminate through the cerebrospinal fluid and result in distant relapse in about 30% of patients, leading to poor outcomes.[52] After surgery alone was demonstrated to be ineffective in the management of those with medulloblastoma, the necessity of adjuvant therapy after maximal safe resection with craniospinal radiotherapy and chemotherapy was established to improve OS.[6,53,54]

Traditionally, patients are treated with risk adapted therapy with risk stratification to either standard risk or high risk medulloblastoma based on clinical and treatment features including age, histopathologic subtype, metastatic status, and extent of resection. Those with standard risk included GTR or <1.5 cm^2 of residual disease, without metastatic disease, and with classic or desmoplastic histology, and they are typically treated with craniospinal irradiation (CSI) to 23.4 Gy with a posterior fossa (PF)/involved field (IF) boost to 54–55.8 Gy +/- vincristine followed by chemotherapy with a 5-year OS of ~80%.[55–57] High risk medulloblastoma included those with >1.5 cm^2 of residual disease post operatively, metastatic disease, or poor histology such as large cell or anaplastic, and they are typically treated with higher dose CSI to 36 Gy with a PF boost to 54–55.8 Gy with vincristine, followed by chemotherapy, resulting in a 5-year OS of ~60%.

SJMB03, a phase III clinical trial, molecularly classified medulloblastoma into four distant subgroups, WNT, SHH, group 3, and group 4, and demonstrated distinct PFS probabilities amongst these subgroups, thereby establishing a molecularly based risk stratification system.[58] In this trial, the WNT subgroup demonstrated the best PFS of 100% at 5 years, followed by group 4 subgroup with a 5-year PFS of 87.3%, SHH subgroup with a 5-year PFS of 77.5%, and group 3 subgroup with a 5-year PFS of 66.7%. These four distinct subgroups have been incorporated into the World Health Organization (WHO) classification of medulloblastoma.[59,60] Other genetic features continue to be help stratify patients into risk groups based on survival, including low risk, average risk, high risk, and very high-risk groups. For example, within these subgroups, those with *MYC* or *MYCN* amplification notably had worse outcomes.[61] Thus, *MYC* or *MYCN* amplification are excluded from average risk trials and are assigned to high-risk groups.

Current focus is now placed on molecular risk-directed therapy. The excellent prognosis of WNT medulloblastoma have encouraged current studies to explore the potential to de-escalate radiotherapy in this subgroup to spare neurocognitive toxicity of CSI, including ACNS1422 and FOR-WNT2 (Table 1).[62–64] However, radiotherapy appears to be a necessary component of management as an early phase 1 study for WNT medulloblastoma evaluating surgery followed by chemotherapy alone without radiotherapy was terminated early due to relapses.[65] SJMB12 and COG ACNS1422 are evaluating molecular risk-directed CSI and chemotherapy including reduced CSI dosing and lower dose chemotherapy for WNT medulloblastoma, while intensifying chemotherapy for other subgroups.[66]

2.4. Management of ependymoma

Ependymoma tumors can arise anywhere along the neuroaxis, most commonly intracranially and about two-thirds of cases occurring in the posterior fossa.[67] Most often, children around the age of 5 years are affected.

OS for ependymomas have been estimated at around 40%–64%, and these patients are at risk for late relapses.[67, 68] Maximal safe resection remains standard of care as extent of resection has been demonstrated to be an important prognostic factor, though a GTR can be challenging given the often close location to midbrain structures.[7] Given challenges

to achieving complete resection and concerns for local relapse, adjuvant radiotherapy has had an important role in improving local control.[7] Post operative radiotherapy has been demonstrated to significantly improved event free survival (EFS) of 77% at 7 years after STR and 88% after GTR.[69,70] Given these outcomes, there may be a role for radiotherapy avoidance, particularly after a GTR. To avoid radiation related cognitive effects in young children, multiple trials have evaluated the role of adjuvant chemotherapy to avoid or delay radiotherapy and to be used as salvage therapy, though outcomes have varied.[67,68] Results from ACNS0121 evaluating observation after GTR of classic supratentorial ependymoma found that a subset remained free of disease of 5 years.[71] Thus, ongoing investigation is needed to identify the subgroup of patients who may achieve good local control without radiotherapy. In addition, results of ACNS0121 evaluating the role of immediate post operative radiotherapy after GTR or near total resection in anaplastic histology showed improved EFS compared to historical outcomes after delayed radiotherapy, suggesting a retained role for postoperative radiotherapy.[71]

Molecular classification may provide more insight into the biological behavior of this heterogenous group of tumors. WHO grading has previously been based on histopathology alone, though its clinical utility has been limited given the heterogeneity in patient outcomes. Recent understanding of the molecular heterogeneity in this group of tumors has redefined WHO grading with improved prognostication.[60] Nine molecular subtypes of ependymomas are now recognized, 3 in each anatomical compartment (supratentorial, infratentorial, and spinal), which correlate better with distinct clinical outcomes. Among supratentorial ependymomas, the ZFTA fusion subtype may confer more aggressive biology compared to YAP fusion or subependymoma.[72,73] When evaluating posterior fossa ependymoma, PFB ependymoma are much less likely to recur or metastasize. After GTR, PFB ependymomas had improved 5-year PFS of 91% compared to 81% in PFA ependymomas, and results suggested adjuvant radiotherapy may not add significant additional benefit.[74] Currently, extent of resection has remained one of the most important prognostic factors. As molecularly based risk stratification becomes more refined, there is potential to use molecular features in combination with histology and extent of resection to re-evaluate those who may need adjuvant radiation and those who may fall into a lower-risk subgroup and consider deferring or omitting radiotherapy to avoid additional late toxicities.

2.5. Management of craniopharyngioma

Craniopharyngiomas are histologically benign suprasellar tumors that can nonetheless cause significant morbidity due to local involvement. They typically have solid and cystic components and arise in children ages 5–10 years old. Two main subtypes include papillary and adamantinomatous, the latter of which is typically associated with pediatric craniopharymgioma and generally non-responsive to targeted therapy as they lack BRAF V600E mutations.[75] These tumors typically cause mass effect on important structures including the optic pathway, pituitary, and infundibulum. Thus, the mainstay of management has been surgical resection though there is a high reoccurrence rate of 20% despite GTR, and an even higher rate after STR.[76–78] GTR is difficult to achieve given the location of these tumors and can be associated with treatment related morbidity including diabetes insipidus, vision loss, and neurologic deficits.[79] An alternative treatment approach includes a STR followed by radiotherapy as radiotherapy has improved PFS though has not shown an OS benefit.[80,81] Salvage radiotherapy appears to be an effective option without any reduction in OS compared to early adjuvant radiotherapy; thus, the management strategy has often been favored to avoid neurocognitive and neuroendocrine deficits.[8,82,83]

Historically, systemic therapy has played a limited role in management as surgery and adjuvant or salvage radiation therapy have been the primary modes of therapy.[84] However, advancing research into the molecular pathogenesis of these tumors have elucidated potential

Table 1
Ongoing clinical trials for molecularly risk adapted radiotherapy in newly diagnosed medulloblastoma.

Clinical trial	Clinical trial number	Study Phase	Patients enrolled/estimated	Study aim	Primary endpoint
COG ACNS 1422	NCT02724579	II	Target 45 patients with WNT medulloblastoma	Evaluating reduced dose CSI (CSI 18 Gy with tumor bed boost of 36 Gy, total 54 Gy) with reduced chemotherapy	PFS
SJMB 12	NCT01878617	II	Target 660 patients with medulloblastoma	–For WNT low risk, evaluating reduced dose CSI and reduced chemotherapy –For SHH, evaluating addition of vismodegib –For non WNT non SHH, evaluating addition of pemetrexed and gemcitabine	PFS
SIOP PNET5 MB	NCT02066220	II/III	Target 360 patients with medulloblastoma	–For standard risk, low-risk biologic profile, evaluating reduced dose CSI 18 Gy and reduced chemotherapy –For standard risk, average-risk biologic profile, evaluating CSI 23.4 Gy with modified intensity chemotherapy –For WNT high-risk, evaluating radiotherapy stratified by age and metastasis status, chemotherapy stratified by age –For SHH-TP53, evaluating radiotherapy stratified by age, metastasis status, and germline TP53 mutation and with reduced chemotherapy with doxorubicin, vincristine, high dose methotrexate, carboplatin, and intraventricular methotrexate	EFS
FORT-WNT2	NCT04474964	I	Target 30 patients with WNT medulloblastoma	Evaluating reduced dose CSI (CSI 18 Gy with tumor bed boost of 36 Gy, total 54 Gy) with chemotherapy	RFS, OS
Study assessing the feasibility of a surgery and chemotherapy-only inchildren with Wnt positive medulloblastoma	NCT02212574	I	Target 6 patients with WNT medulloblastoma.	Evaluating surgery and chemotherapy alone	PFS. Terminated early due to relapses.

Abbreviations: CSI, craniospinal irradiation; EFS, event free survival; PFS, progression free survival; OS, overall survival; RFS, relapse free survival.

targets for systemic therapy.[85] Adamantinomatous craniopharyngiomas have been found to have highly upregulated levels of IL-6, which can provide a potential target of therapy. The feasibility of tocilizumab, a monoclonal antibody against IL-6, is currently being explored.[86,87]

In addition, studies also revealed MAPK pathway alteration in adamantinomatous craniopharymgioma and MEK inhibition is beneficial in preclinical models of adamantinomatous craniopharymgioma.[88] Further, pathway PD-L1 is expressed in craniopharyngioma cyst lining, membranous PD-1 is expressed in neoplastic epithelial cells, and overall expression of PD-L1 is higher in craniopharymgioma when compared to other tumors and non-neoplastic brain.[89,90] Based on these results, the Pacific Pediatric Neuro-Oncology Consortium is exploring the combination of a checkpoint inhibitor with a pan-RAF inhibitor for these tumors.[91]

Overall, management of this tumor is challenging given the inherent morbidity of the mass and potential morbidity associated with various treatment options including aggressive surgery or radiotherapy. Effective treatments with lower toxicity profiles are needed. Improved radiotherapy technique with conformal radiotherapy and focal, targeted approaches, can limit the potential side effects of radiotherapy.[92] As these patients are expected to have a long OS, attention to quality of life outcomes is important.

2.6. Management of non germinomatous germ cell tumor

CNS germ cell tumors most commonly present in the pineal or suprasellar region in children ages 10–12 years old and divided into two major subgroups, germinomatous and nongerminomatous germ cell tumors (NGGCT).[93] NGGCT are less radiosensitive and have a worse prognosis with a 5-year OS of 20%–45%, though recent COG and SIOP trials have demonstrated improved OS ≥75% for localized NGGCT with multimodal therapy.[94]

Historically, management has included chemotherapy followed by CSI, with 5-year EFS of 84%.[9] The use of chemotherapy alone with omission of radiotherapy appeared to be less effective; thus, emphasizing a role for radiotherapy, though the dose and volume remain a topic of investigation.[95] The possibility of a subgroup of patients who could receive de-escalated radiotherapy, in the setting of effective chemotherapy options, was investigated on ACNS1123. NGGCT on stratum 1 evaluated whole ventricle irradiation instead of CSI for those who had a complete response or partial response to induction chemotherapy and showed a 3-year PFS of 88%.[96,97] Second look surgery after induction chemotherapy was recommended but not required. This stratum closed early due to concerning pattern of recurrence, which all occurred in the spine, thus, raising concerns that additional therapy is needed to reduce the risk of spinal relapse. Current accruing trial, ACNS2021, will investigate outcomes of whole ventricle and spinal irradiation for those who respond to chemotherapy to reduce rates of spinal relapse in the treatment of localized NGGCT.[98] This trial will also investigate intensified chemotherapy followed by conventional radiotherapy for those who do not respond to induction chemotherapy.

2.7. Radiotherapy omission in young children

Radiotherapy plays an important role in the treatment of many pediatric tumors to optimize local control and improve OS as described. OS in young children under the age of 3 years have had the worse prognosis as management poses a significant challenge given the high neurotoxicity of CSI radiotherapy in this age group, including neurocognitive impairment and endocrinopathies with greater impact on longer term quality of life.[99] Multiple studies have identified young age as a risk factor for worse neurotoxicities.[100,101] However, some studies have suggested that reduced dose radiotherapy in young children has led to inferior outcomes.[102] Thus, optimizing multidisciplinary management of these tumors with the use of chemotherapy or surgical management

with attempts to defer radiotherapy in young children without compromising OS continues to be an evolving discussion.[103–105] As certain chemotherapy agents are also known to be neurotoxic, though thought to be less so than CSI, the optimal regimen to minimize toxicity remains an ongoing investigation.[106] Attempts to intensify chemotherapy to defer CSI for young children has been explored in various trials.

In a multi-institutional study, Baby POG, evaluating the role of postoperative chemotherapy for children under 36 months of age with malignant brain tumors, postoperative chemotherapy prevented disease progression to allow delay of radiotherapy for 1–2 years without compromising OS.[107,108]

In the Head Start I and II trials for non-metastatic medulloblastoma investigating intensified chemotherapy after maximal safe resection in those less than 3 years old, 52% of patients were able to defer CSI radiotherapy at 5-years; however, there were a few treatment related deaths.[109] Notably, those who had achieved a GTR appeared to do better than those with STR. Additionally, desmoplastic morphology appeared to do better than classical morphology.

HIT-2000-BIS4 trial evaluated systemic chemotherapy and intraventricular methotrexate to defer CSI in children <4 years old with medulloblastoma.[110] Later, patients were also risk stratified to receive focal radiotherapy; CSI was, instead, reserved as salvage therapy. In the group of desmoplastic medulloblastoma or extensive nodularity histology, the addition of intraventricular methotrexate improved 5-year PFS and OS rates to 93% and 100%, respectively, in comparison to rates seen in other chemotherapy alone trials. The group of classic medulloblastoma or large cell/anaplastic histology had a less favorable prognosis; however, the use of intraventricular methotrexate versus local radiotherapy did not show a difference in PFS or OS. Nine out of 11 children in this group with relapse went on the receive CSI.

From these trials, use of intensified chemotherapy appears to successfully lead to avoidance of irradiation in a portion of young children. Still, optimal chemotherapy regimen and toxicities of chemotherapy need to be closely evaluated. Identification of the subset of young patients in which radiotherapy may be deferred could benefit from further risk stratification such as by histology and extent of resection.

3. Toxicities of CNS directed radiotherapy in the pediatric population

Multidisciplinary management of pediatric cancers has led to improvements in OS and outcomes. Radiation therapy, though often a key component of therapy for optimal tumor control, is known to be a source of toxicity, most concerningly, late toxicity. As children are becoming long term survivors, the ability to minimize late toxicities is increasingly important.

One primary concern of CNS directed radiotherapy in children is the potential neurocognitive sequelae. Often consideration is made to balance neurologic morbidity from tumor itself and progression versus the impact of neurotoxicity from therapy. CNS directed radiotherapy can lead to a myriad of neurocognitive deficits in long term survivors, including decline in intelligence quotient (IQ), fine motor skills, verbal fluency, delayed attention, concentration deficits.[111–113] These children are more likely to require special education and continued assistance throughout life. The neurocognitive sequelae are likely due to multiple factors such as vascular insults and neuronal damage. Radiotherapy has been associated with reduction in cerebral white matter and may result in decline in intellectual development rate, thereby affecting their learning ability as compared to their peers.[111,112] Cortical thinning may be dose dependent and different parts of the cortex may be more susceptible.[114,115] In addition, cerebral microbleeds was found to be more frequent in children treated with cranial radiotherapy and could be a contributing factor to worse neurocognitive function.[116,117] In the Rad-Art study, cerebral microbleeds was found to occur in almost half of children treated with cranial radiotherapy 5 years post treatment and was associated with worse executive function and performed worse in delayed recall, verbal learning, attention, and working memory.[117] Those who received whole brain radiation were more likely to have cerebral microbleeds compared to those who received focal radiotherapy. In addition, those who received chemotherapy and anti-angiogenic agents were more likely to have cerebral microbleeds.

Another significant risk associated with intracranial radiotherapy is its impact on the hypothalamic pituitary axis (HPA), which can be especially concerning in young children who are still undergoing growth and development. Neuroendocrine function can be affected by surgery or chemotherapy alone as well. Irradiation of the HPA axis can lead to short statues, obesity, and alterations in pubertal development. With CSI, growth hormone and precocious puberty are often affected at lower doses of 18 Gy while other hormones affected by doses greater than 30–35 Gy.[118] Further, impact on neuroendocrine function demonstrates a dose-response relationship.[119,120]

Radiotherapy to the orbit and visual pathway can result in late complications such as cataracts, dry eye, glaucoma, and retinopathy.[121] Hearing impairment is less common from radiotherapy with the incidence of hearing loss low at doses less than 30 Gy, though the risk increases at higher doses in a dose dependent manner.[122] However, many patients will also receive chemotherapy, and platinum-based chemotherapy is known to be associated with ototoxicity.

Radiotherapy in the pediatric patient also harbors a late risk of neurovascular events. Evaluation of the Childhood Cancer Survivor Study estimated that children who had brain tumors treated with cranial irradiation were more likely to have a stroke compared to a sibling who did not receive cranial radiotherapy.[123,124] The stroke risk was also found to be dose dependent, such that mean radiation dose of >30 Gy was associated with increased risk of stroke. Further, the combination of radiotherapy and chemotherapy may also increase the risk of neurovascular event.

Radiotherapy to the spine can lead to musculoskeletal risks including increased risk of soft tissue hypoplasia, bone fracture, reduction in vertebral column height, and spine deformities.[125–127] Muscle hypoplasia has also been noted at doses >20 Gy, which may also contribute to scoliosis risk.[128] To reduce the risk of scoliosis from partial irradiation of the vertebral body, common practice is to irradiate the entire vertebral body.[129]

The risk of secondary malignancy is a rare late effect from therapy. As childhood cancer survival is improving, the incidence of secondary malignancy is estimated at about 9% of childhood CNS cancer survivors.[130] For long term survivors, secondary malignancy is one of the most common causes of death in adults.[131,132] Radiation therapy has been associated with increasing the risk of secondary malignancy, as has chemotherapy, though chemotherapy are more commonly associated with leukemias.[130,133] For radiotherapy, though most secondary malignancies occur within the prior radiotherapy field, distant organs are still at risk. Most common secondary tumors include meningiomas which account for about 70% of secondary tumors, while gliomas account for about 20%, and sarcomas account for <10%.[134]

In CNS radiotherapy, much heterogeneity exists with acute and late neurotoxicity experienced not encompassed by stratification by clinical characteristics such as tumor stage and treatment details such as dosing and technique. Genome wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) that can influence susceptibility to radiation related toxicity and radiosensitivity.[135] Radiation induced brain injury has been associated with genetic variants of CEP128 protein, which plays an important role in cell cycle progression.[136] Germline SNP on the peroxisome proliferator activated receptor gamma gene was associated with increased incidence of radiation induced leukoencephalopathy in a retrospective analysis.[137] GWAS can help tailor predictors of radiosensitivity or radiation induced toxicity to guide treatment and patient counseling.

4. Radiotherapy techniques

4.1. Proton beam radiotherapy

Photon based radiotherapy has seen major technologic advances from 3D fields to conformal techniques. These conformal techniques using arcs and modulation of multileaf collimators allow a greater degree of high dose sculpting to the target of interest. A tradeoff of this method is a greater volume of normal tissue that receives a low dose of radiotherapy. In addition, image guided radiotherapy allows for increased precision and accuracy of treatment.

Proton beam radiotherapy presents another radiotherapy technique in attempt to decrease toxicities, primarily late toxicities. Advantages of the physical characteristics of proton radiation includes low entrance dose, such that most of the radiation dose is deposited at the target, and a sharp dose fall off, which eliminates exit dose radiation.[138] As such, proton radiotherapy can reduce dose to normal tissue. In pediatric patients, this may be particularly advantageous to minimize radiation dose to the normal brain and spine.[139,140] Currently, there is no randomized data to demonstrate reduced late toxicities with protons as compared to photons. However, there is some data to suggest improved cognitive outcomes with proton therapy showing that children who underwent proton therapy did not have a significant decline in IQ.[141] This longitudinal study found more favorable cognitive outcomes in almost all domains with proton radiotherapy compared to photon radiotherapy, aside from processing speed, which was impacted in both groups.[142] In the treatment of the spinal column, vertebral body sparing with proton radiotherapy reduced the rates of acute side effects including hematologic toxicities.[143] Vertebral body sparing also has the potential to reduce radiation dose to the growth plates, which may reduce risk for growth inhibition, without increasing risk of severe skeletal abnormalities.[144,145] There is retrospective data to suggest that vertebral body sparing may not increase risk of scoliosis compared to whole vertebral body irradiation at a median follow up at 19 month.[146] In this study, children <10 years old were treated with whole vertebral body irradiation, those >14 years old were treated with partial vertebral irradiation, in which clinical target volume (CTV) volume included the thecal sac alone but planning target volume (PTV) volume resulted in coverage of a portion of the posterior vertebral body, while those ages 10–14 were treated with either method after a nuanced discussion with family. Here, partial vertebral body coverage resulted in less growth suppression but similar spinal curvature compared to whole vertebral body coverage. There is currently an ongoing clinical trial assessing the feasibility of vertebral body sparing with proton radiotherapy for CSI, which will provide further insight into potential benefits of this treatment modality.[147] Proton radiotherapy remains an option for treatment of pediatric tumors with certain dosimetric advantages, and the risk benefit of proton therapy can be tailored based on patient and tumor characteristics.

4.2. Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is another radiotherapy technique that allows for rapid dose fall off, thereby allowing for dose escalation without harm to adjacent normal tissue. This is often considered for small volume areas nearby critical structures or in the re-irradiation setting to enable physicians to treat areas of recurrence to a therapeutic dose while minimizing normal tissue damage. SRS has been used in the treatment of residual or recurrent craniopharyngioma to avoid additional toxicity to the pituitary function and visual pathway with tumor control of about 66%–80%.[148–150] SRS has also been used in the treatment of ependymomas. Given the challenges achieving a GTR, and the risk of local recurrence, SRS boost after adjuvant external beam radiotherapy has been explored to improve local control. A small series of five children with unfavorable histology underwent SRS boost to improve local control and showed a durable control in four of the five children.[151] Another series with nine patients showed a 3-year relapse free survival of 56%.[152] In addition, SRS has been explored in the treatment of recurrent ependymoma in a few small, retrospective studies.[153] However, as distant failures are often seen, further improvements in the treatment of ependymoma is needed. SRS has been explored in other pediatric brain tumors as well for the treatment of residual or recurrent disease with about a 26% risk of radionecrosis with or without tumor requiring reoperation.[154] Prospective trials are needed to assess the risks and benefits of SRS, and the appropriate clinical scenario to benefit from SRS.

5. Conclusions

Radiotherapy plays an integral role in the multidisciplinary care of pediatric CNS tumors to optimize cancer outcomes. With increasing survival, balancing the toxicities of therapy is necessary to optimize quality of life for long term survivors as well. Advances in molecular classification and further risk stratification have been instrumental in advancing a precision based approached of treatment. As such, the role of radiotherapy, including, timing of radiotherapy, dose, target, and technique continues to evolve as therapeutic advances are made, such as with improvements in surgery, chemotherapy, and introduction of novel targeted agents. Precision based medicine will help redefine modern day treatment paradigms in the management of pediatric CNS tumors and further tailor patient counseling.

Declaration of competing interest

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Author contributions

C.P. was involved in writing the original draft, review, and editing. B.Q., S.M., and S.B. were involved in review and editing. S.B. conceptualized this work.

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