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REVIEW

Stereotactic Radiation Therapy in Children and Young Adults: Can We Apply Adult Treatment Paradigms?

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The use of stereotactic radiation therapy (RT) in the treatment of children and young adults with malignancies and benign conditions has been increasing. However, the evidence guiding stereotactic RT in this population is in a nascent phase compared with adult-derived data. In this critical review, the authors discuss some of the adult evidence behind stereotactic body RT and stereotactic radiosurgery and how it can be applied to children with cancer. An overview of pediatric-specific evidence and guidelines for stereotactic body RT and stereotactic radiosurgery is discussed, including indications, treatment approaches, outcomes, and future directions for research.

Introduction

The discovery of the oligometastatic state in cancer has allowed patients with disseminated malignancy to be treated with curative intent by delivering local control therapy to all sites of the disease.[1] However, children with cancer commonly have malignant histologies that have systemic micrometastatic disease even when apparently localized on staging. Treatment typically requires intensive chemotherapy in combination with surgery or radiation therapy (RT) for local control; examples include Ewing sarcoma or rhabdomyosarcoma.[2] This contrasts with adult patients with some types of carcinoma who may be cured with local control therapy alone.[3] Also, unlike adults with carcinoma, many common childhood malignancies such as Wilms tumor, neuroblastoma, Ewing sarcoma, and rhabdomyosarcoma require standard therapy that often includes local treatment to all the initially involved sites of metastases when feasible and not excessively morbid, even if they have responded to chemotherapy. Although metastasectomy has long been known as an effective therapy for selected children with cancer, such as individuals with lung metastases from osteosarcoma,[4] the broad application of ablative local therapies, such as stereotactic body RT (SBRT), for other types of metastatic pediatric cancers has lagged behind that of adult cancers, with comparatively less prospective data

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available.[5] Due to concerns about the late effects of RT in children, the field of pediatric oncology has historically relied much more on chemotherapy and surgery, with relative avoidance of RT in pediatric patients compared with adult patients, contributing to the relative scarcity of available prospective data on RT and novel radiation techniques in pediatric patients.

There are many potential clinical and dosimetric advantages of SBRT for younger patients, including less disruption from systemic therapy, quicker recovery post-RT, a sharper dose fall-off sparing normal tissues, and an increased biologically effective dose (BED), which may overcome radioresistant histologies. In the brain, stereotactic RT is commonly termed stereotactic radiosurgery (SRS). In low- and middle-income countries, a short course of stereotactic RT may also reduce linear accelerator utilization, improve treatment adherence, and reduce patient costs in regions with a high burden of pediatric cancer and limited access to RT.[6] Pediatric cancer is unique in that metastatic sites for radiosensitive histologies can also be treated with conventionally fractionated courses of RT, including Wilms' tumor,[7] neuroblastoma,[8] rhabdomyosarcoma,[9,10] and some radiosensitive bone sarcomas (Ewing sarcoma).[11] However, as discussed above, stereotactic RT has potential uses and advantages over conventional fractionated RT for children and young adults with metastatic disease, locally recurrent disease, oligometastatic disease, and consolidation of metastatic disease when combined with systemic therapy.

In this critical review, an overview of adult literature on stereotactic RT is provided, with a focus on how one can apply this data to children. We then discuss available prospective and retrospective evidence regarding stereotactic RT for extracranial and intracranial tumors in children and young adults, followed by a summary of future research directions.

How Can We Apply the Adult Literature?

SBRT, alternately termed stereotactic ablative radiation (SABR), describes the use of focused, highly conformal, hypofractionated RT to treat tumors locally using high doses of radiation with ablative intent.[12] SBRT is typically delivered over a treatment course of 5 or fewer fractions, paired with high-resolution imaging for target delineation and daily image guidance. The use of altered fractionation schemes with fraction sizes greater than 2 Gy per day has been classically frowned upon for young patients due to the radiobiological advantage of applying small daily fraction sizes for rapidly proliferating tumors ($\alpha/\beta \sim 10$) while minimizing long-term side effects in slow-responding normal tissues ($\alpha/\beta \sim 2$-3).[13,14] It is for this reason that fractionation for most pediatric cancers is set at 1.8 Gy per day or less, with RT for pediatric Hodgkin lymphoma at 1.5 Gy per day.[15] However, advances in radiation technology have permitted a reduction in normal tissue doses with modern, highly conformal planning, while emerging adult-derived evidence has supported SBRT as an effective treatment for metastatic disease.[16]

In adult patients, Palma et al[17] published a landmark phase 2 randomized controlled study (SABR-COMET, Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers) for individuals with a controlled primary tumor and up to 5 oligometastatic sites. Patients were randomized between the standard of care (where patients were treated for standard palliative indications to specific sites causing symptoms or at risk of an impending local problem with palliative RT, up to 30 Gy in 10 fractions) or SBRT to all sites of disease. With extended follow-up, patients who were treated with SBRT had superior progression-free survival (PFS) and overall survival.[18] Stereotactic RT delivered to patients in the setting of the study was cost-effective.[19] In a similar study conducted in patients with 5 or fewer oligoprogressive metastatic non-small cell lung cancer or breast cancer, SBRT to metastatic sites demonstrated a PFS benefit for non-small cell lung cancer but not breast cancer.[20] These studies have sparked interest in whether an oligometastatic state could exist in children,[21] which tumor types could have an oligometastatic state present, and whether SBRT can be used to effectively treat or potentially cure children with oligometastatic cancer.[22]

Timmerman created what is termed the "Timmerman Tables" in 2008, which provided adult oncologists with practical guidance on safe organ-at-risk (OAR) dosing in the setting of SBRT.[12] These OAR suggestions have since been updated[23]; there was also a global effort from the American Association of Physicists in Medicine to summarize data on the safe delivery of hypofractionated RT, termed HyTEC (high dose per fraction, hypofractionated treatment effects in the clinic), which provides oncologists with guidance on SBRT and SRS.[24] Careful adherence to dose guidance is required; adults receiving SBRT in the SABR-COMET study had a 29% incidence of grade ≥ 2 toxicity, with 3 deaths (out of 66 patients) at least possibly attributable to SBRT. Although the Pediatric Normal Tissue Effects in the Clinic effort was recently completed,[25] there are no corresponding OAR guidelines for hypofractionated RT in children. Thus, until such pediatric-specific data become available, using dose guidance derived from adult literature is a suitable, though imperfect, alternative.

Extracranial Stereotactic RT

Although adult studies are practice-changing and cement the role of SBRT for many individuals with metastatic cancer, their applicability to pediatric cancer is unclear and hypothesis-generating. Are children with oligometastatic cancer more analogous to adult patients with lung cancer who would derive survival benefits from ablative RT to metastatic sites? Or are they more similar to adults with breast cancer for whom the oligometastatic state may not exist[20]? In this section, we present data evaluating SBRT in children

with cancer, followed by a discussion about planning considerations specific to pediatric SBRT.

The safety and local efficacy of SBRT for children and young adults is supported by both prospective and retrospective data. Selected larger studies are summarized in Table 1. Studies of SBRT in children were evaluated in a comprehensive meta-analysis by Singh et al,[26] who evaluated 9 studies with 142 patients and 217 lesions treated. The most common lesion sites were spine or paraspinal (83 lesions), nonspinal bone (72 lesions), and lung (53 lesions), while the most common histologies were osteosarcoma (45 patients), Ewing sarcoma (43 patients), other soft tissue sarcoma (20 patients), and neuroblastoma (10 patients). Significantly, they found that every 10 Gy_{10} increase in BED (α/β = 10) was associated with a 5% improvement in local control at 2 years post-SBRT. Stereotactic RT to lung lesions is feasible[27]; an example is provided in Figure 1. Interestingly, in a bi-institutional series retrospective study,[28] soft tissue lesions treated with SBRT had poorer local control compared with bone metastases, which may be due to a need to respect the dose constraints of nearby visceral OARs. Among 47 patients who were symptomatic from their metastases, 62% had clinical improvement with SBRT.[28]

Pivotal data supporting SBRT in children and young adults with bone metastases from disseminated sarcoma were presented in a prospective, multi-institutional phase 2 study.[29] In this trial, 14 individuals were treated with 40 Gy in 5 fractions to 37 bone metastases. A key finding from this study was that patients who received SBRT at all sites of disease (which was termed "total consolidation") had superior PFS and overall survival compared with patients who had SBRT at some (but not all) sites of metastatic disease ("partial consolidation"). Limitations of this data include the small number of patients evaluated, consideration of only bony sites for SBRT (as soft tissue metastases were ineligible), and the comparison of total versus partial consolidation was a nonrandomized, unplanned, post hoc analysis.

Despite favorable local control probability among the studies presented in Table 1, the risk of distant progression was very high post-SBRT (l-year PFS less than 30%). Thus, it is unclear how many children have the possibility of a cure with SBRT, as may sometimes be seen in adults; for example, the 5-year PFS was 17% in SABR-COMET. This is likely due to a preponderance of pediatric cancers, such as Ewing sarcoma[30] and rhabdomyosarcoma,[31] that undergo micrometastatic spread during the course of the disease. For children treated with SBRT, even though the 1-year PFS is low, the 1-year OS was 75%,[26] emphasizing the importance of systemic therapy in controlling disease after distant recurrence post-SBRT. It is also important to remember that upfront therapy for pediatric cancers, in general, often includes very intensive systemic therapy, and patients who relapse after this therapy may have more biologically unfavorable disease compared with adult patients who receive less intensive systemic therapy than children.

There is wide heterogeneity in the application of SBRT for children. The European Society of Paediatric Oncology did a survey of 20 pediatric centers in Europe.[32] A majority of centers (>65%) agreed that metastatic disease in children could be treated with curative intent. Half of the responding centers did not have a maximum number of metastatic lesions that would serve as a threshold between curative or palliative intent treatment. Among the groups using SBRT, no recommended dose fractionation was agreed upon; regimens ranged from 16 to 50 Gy over 1 to 7 fractions.[32] Guidelines from the National Pediatric Cancer Foundation propose SBRT with doses of 30 to 40 Gy in 5 fractions for bone or soft tissue Ewing sarcoma or rhabdomyosarcoma metastases less than 5 cm in size.[33]

Planning considerations for SBRT in children

For a pediatric radiation oncologist seeking direction about suitable SBRT dosing, one can take guidance from past and current prospective studies. A summary is provided in Table 2. Both Elledge et al[29] and the Children's Oncology Group (COG) studies[34-36] used a dose-painting technique, where the gross tumor volume (GTV) receives a higher dose

Table 1 Selected studies of extracranial stereotactic body radiation therapy in children and young adults

Study	Patients (lesions treated)	Study type	LC, %	PFS, %	OS, %	Comments
Singh et al[26]	142 (217)	Meta-analysis*	84 (1 y)	27 (1 y)	75 (1 y)	Higher BED is associated with better LC
Tinkle et al[28]	55 (107)	Retrospective, 2 institutions	75 (1 y)	18 (1 year)	61 (1 y)	Soft tissue lesions had worse local control
Parsai et al[5]	31 (88)	Retrospective, 1 institution	83 (1 y)	Not reported	73 (6 mo)	One high-grade GI toxicity
Elledge et al[29]	14 (37)	Prospective, 3 institutions	95 (6 mo)	29 (1 y)	84 (1 y)	SBRT to all sites of disease is associated with better PFS and OS

Abbreviations: BED = biologically effective dose; GI = gastrointestinal; LC = local control; OS = overall survival; PFS = progression-free survival; SBRT = stereotactic body radiation therapy.
* Includes studies within this table

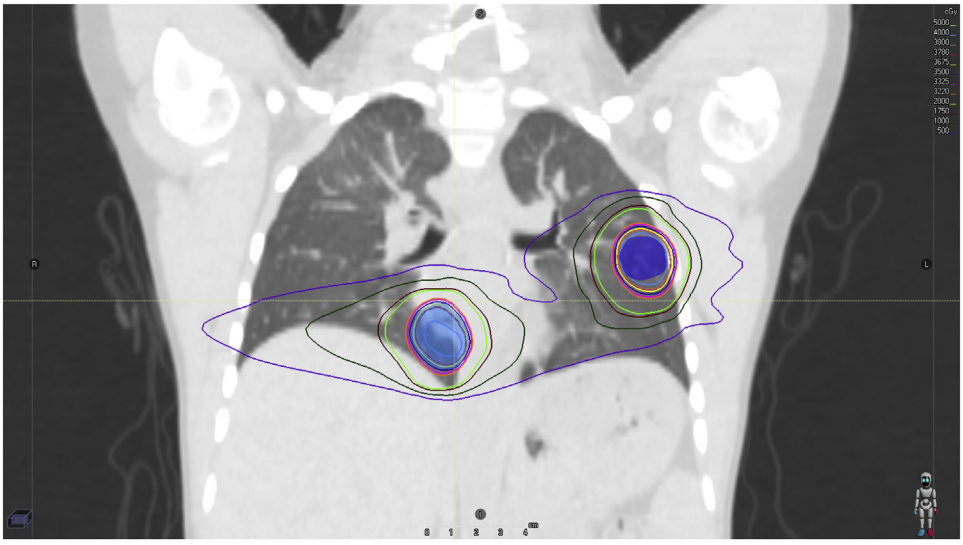

Fig. 1. A 9-year-old girl with lung metastases from embryonal sarcoma of the liver. The left-sided pulmonary lesion received 40 Gy in 5 fractions, while the right-sided lesion received 35 Gy in 5 fractions (due to proximity to central structures). Planning target volumes are shown in a blue color wash.

Table 2 Five-fraction stereotactic body radiation therapy prescription doses used in prior and ongoing prospective studies

Study	Histology	Treatment site	GTV	PTV
Elledge et al[28]	Any sarcoma	Bone metastasis ≤ 5 cm	40 Gy	30 Gy
AEWS1221[34]	Ewing sarcoma	Bone metastasis < 5 cm	40 Gy	35 Gy
ARST2031[35]	Rhabdomyosarcoma	Any site of metastasis ≤ 5 cm	35 Gy	30 Gy
AOST2032[36]	Osteosarcoma	Bone or lung metastasis < 5 cm	50 Gy	40 Gy

Abbreviations: GTV = gross tumor volume; PTV = planning target volume.

than the geometric planning target volume (PTV). In general, more radiosensitive tumor histologies (rhabdomyosarcoma) are recommended to receive lower doses, while radioresistant histologies (osteosarcoma) may benefit from higher doses. Data from one series suggest a significant local control advantage for radiosensitive sarcoma when treated with a BED (α/β = 3) ≥ 95 Gy.[37] Patients who have had prior 15 Gy whole lung RT to a planned region of pulmonary SBRT deserve special consideration; the COG studies decreased the prescription dose by 5 Gy to the lung metastasis GTV and PTV. For example, in a child with rhabdomyosarcoma and lung metastases not in radiologic complete response postchemotherapy, the patient would receive whole lung RT 15 Gy in 10 fractions, followed by 30 Gy in 5 fractions to the metastatic site GTV and 25 Gy in 5 fractions to the metastatic site PTV.

Although the aforementioned Timmerman guidelines[23] or the American Association of Physicists in Medicine SBRT Task Group 101 report[38] can be a helpful starting point, it is unclear how normal tissue constraints should be modified for children or even if modifications are necessary. The initial series used a 10% reduction in normal tissue tolerance for patients less than 18 years of age or if concurrent chemotherapy was given[39]; other series have suggested that chemotherapy should be held for 2 weeks.[28] Multidisciplinary discussion and careful quality assurance are critical when considering SBRT for patients who have been heavily pretreated or who are receiving concurrent therapies.

There is no standard contouring approach for SBRT target volumes. Specifically, there are no clear guidelines regarding whether a clinical target volume (CTV) expansion is required, given the heterogeneity of the anatomic location of targets and the radiosensitivity of tumor types. For postchemotherapy bony targets, the COG approach can be considered in which the gross target volume equals the postchemotherapy volume plus the prechemotherapy bony abnormality, and the CTV is a 1 cm anatomically constrained volumetric expansion (NCT02306161). The international consensus guidelines for CTV among adults with nonspine bone metastases can be considered for intact bone metastases,[40] and the international guidelines for spine radiosurgery target volume delineation can also be considered for intact spine metastases.[41] However, target volumes for younger patients can be complex, and certain characteristics such as epidural disease, paraspinal disease, large target volumes, and soft tissue disease may put patients at higher risk for failure due to challenges with target delineation.[5,28] Using multiple imaging modalities such as

computed tomography, metabolic imaging (positron emission tomography), and magnetic resonance imaging is recommended when available; an example is provided in Figure 2. Radiation oncologists should take care to avoid epiphyseal growth plates in skeletally immature children if possible,[42] though compromise of tumor coverage should be avoided.

Intracranial Stereotactic RT

There is extensive published experience of intracranial SRS for benign/functional conditions and malignancies in adult patients since the invention of a dedicated cobalt-60 platform in the 1950s.[43] Radiosurgery was initially conceived to deliver RT with equivalent or improved efficacy and diminished toxicity compared with conventional, operative surgical management. Several technological platforms currently exist on which intracranial radiosurgery can be performed using both fixed-head frame and mask-based frameless techniques to deliver single or multifraction treatments.

Given the extensive evidence supporting the efficacy and safety of intracranial radiosurgery in adults, there has been increasing use of radiosurgery in the pediatric patient population for both benign and malignant conditions in the past few decades.[44] The potential indications, dosimetric advantages, and logistical convenience of intracranial radiosurgery

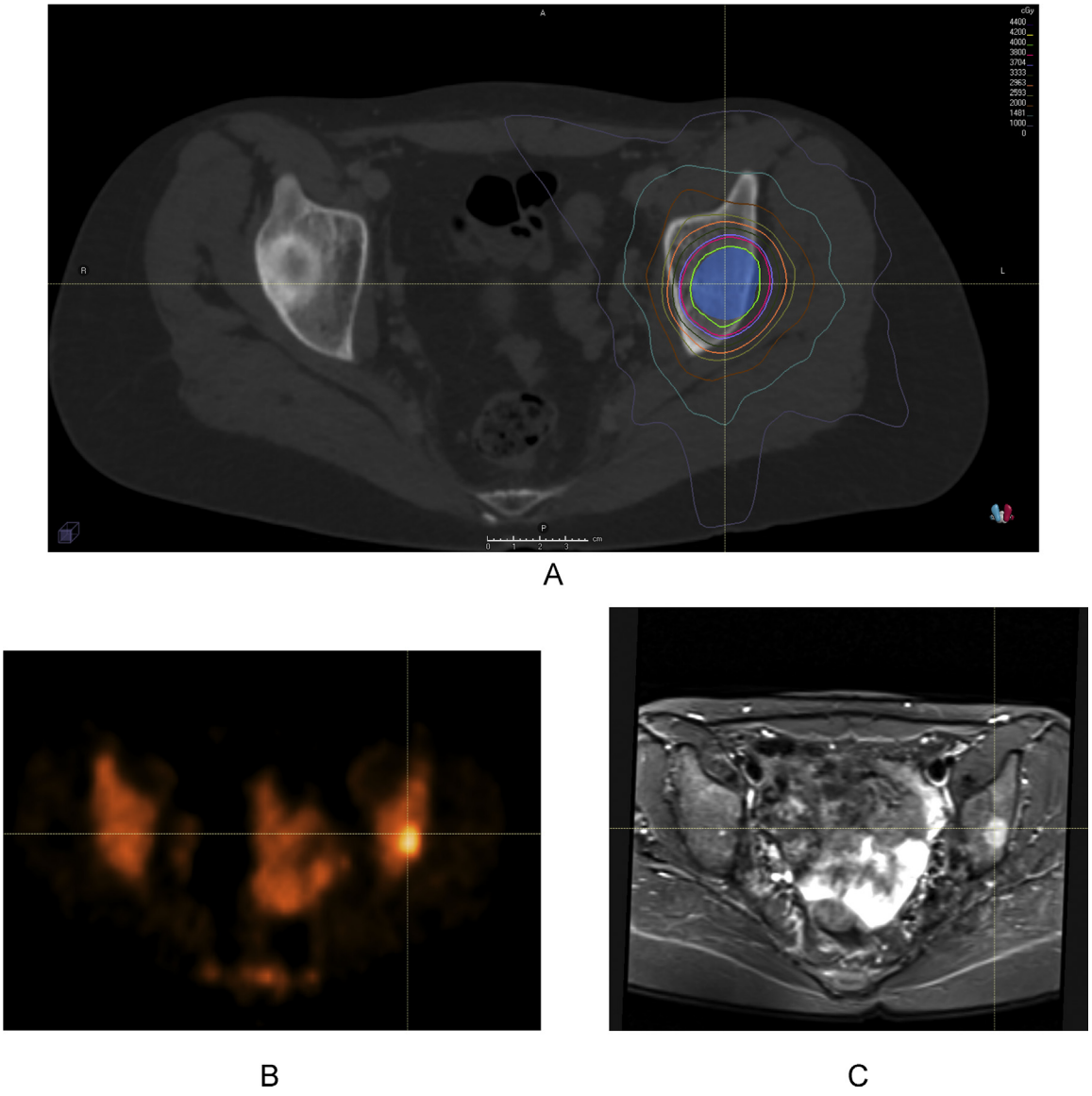

Fig. 2. (A) A 15-year-old girl with left acetabular bone metastasis from recurrent Ewing sarcoma. The lesion was prescribed 40 Gy in 5 fractions; the planning target volume is shown in blue color wash. Delineation of the metastasis was guided by fused (B) positron emission tomography and (C) Magnetic resonance imaging (short tau inversion recovery [STIR] sequence).

are particularly appealing for the pediatric patient population, given the desire to limit radiation field size and parenchymal brain dose. Limiting brain dose reduces risks of late toxicities such as neurocognitive[45,46] and neurohormonal impairment,[47] as well as secondary malignancy[48] in this vulnerable and developing patient population. The risk of a secondary neoplasm post radiosurgery is low, estimated at 0.045% over 10 years in adults,[49] though longer follow-up and pediatric-specific SRS risk data are needed.

Most studies in adults use single-fraction SRS, though radiosurgery over 3 to 5 fractions is being used more frequently for larger primary[50] and metastatic tumors[51] that are over 3 cm in maximal diameter. Similarly, most pediatric data are derived from studies that used single-fraction SRS.[44] Although the data are limited in the setting of younger patients, a recent meta-analysis of pediatric intracranial radiosurgery may help guide pediatric radiation oncologists regarding the suitable use of SRS in children and was used to inform the International Stereotactic Radiosurgery Society (ISRS) practice guidelines.[44] In this section, we will provide an overview of indications for radiosurgery in children, including malignant tumors, brain metastases, and benign intracranial lesions, along with histology-specific supporting literature, tumor control probabilities, and toxicities, where data are available.

Primary malignant brain tumors

Common pediatric primary intracranial malignant brain tumors include glioma, medulloblastoma, and ependymoma. Optimal initial treatment of these tumors requires a multidisciplinary approach and generally entails maximal safe resection of the tumor, followed by risk-stratified conventional RT and systemic therapy. Target volumes for conventional fractionated RT may include the tumor bed (ie, for glioma or localized ependymoma) or the entire craniospinal axis (for medulloblastoma). Treatments may be tailored based on patient age, disease staging, and molecular pathology.[52,53] Enrollment in clinical trials is encouraged.[2]

The role of SRS in the upfront management of primary brain tumors is not well studied in children. In the setting of initial wider-field RT (for example, craniospinal irradiation for high-risk medulloblastoma or whole ventricular RT for intracranial germ cell tumors), it is an open question whether a subsequent boost RT can be delivered with SRS rather than conventional fractionated RT. This would be analogous to applying SRS after whole-brain RT for brain metastases in adults[54] or delivering SRS to gross disease after initial wide-field RT for atypical meningioma.[55] However, prospective safety and efficacy data across different intracranial histologies are needed prior to applying SRS boosts in the upfront setting.

While SRS is not routinely employed as part of initial disease management, it is increasingly used in the recurrent or refractory setting.[5] This pattern of practice mirrors increases in SBRT[56] and SRS[57] in adult oncologic care. Most pediatric patients with these primary malignant tumors will have already received conventional fractionated RT. Even for patients who receive more limited field partial brain RT, treatment may include a significant volume of normal brain parenchyma, and nearby OARs, such as the brainstem, optic nerves, pituitary, or cochlea, may have already received radiation doses at conventionally accepted organ limits. As such, the technological ability to deliver highly conformal radiosurgery to recurrent disease provides potential therapeutic and dosimetric advantages in this pretreated patient population. The risk of toxicity related to radiosurgery depends on the preceding treatment and may be increased with specific concurrent or previous systemic therapies or prior conventional RT. Local control probabilities with the use of SRS in the recurrent setting have been reported for pediatric glioma (60%-100%), medulloblastoma (50%-70%),[58] and ependymoma (30%-90%).[59-62] Radiosurgery may also be used in the management of other less common primary malignant tumors, such as embryonal tumors with multilayered rosettes, atypical teratoid rhabdoid tumors, and primary intracranial germ cell tumors, primarily in the recurrent or refractory setting with persistent limited volume residual intracranial disease.

Murphy et al[44] performed a comprehensive meta-analysis of studies evaluating pediatric patients treated with SRS. They identified 68 studies, including 400 children treated with benign and malignant tumors and arteriovenous malformations (AVMs). They did not find any factors (age, sex, dose, tumor size, or previous treatment) associated with radiosurgery local control of these tumors, which may be related to small patient numbers.[44] The ISRS guidelines state that SRS may be considered at the time of recurrence, although data are limited. There is a theoretical concern that the large dose per fraction used in hypofractionated reirradiation may lead to increased toxicity (eg, radiation necrosis), though a Pediatric Normal Tissue Effects in the Clinic review of 17 studies (11 of which included patients reirradiated with single-fraction or hypofractionated SRS) did not find an association between fraction size of reirradiation and risk of necrosis.[63]

Brain metastases from extracranial tumors

In adults, the most common indication for radiosurgery is the treatment of brain metastases from extracranial primary tumors, such as melanoma, lung cancer, and breast cancer. The types and incidence of extracranial primary malignancies differ in children and include sarcomas, neuroblastoma, Wilms tumor, and extracranial germ cell tumors. As in adults, the use of radiosurgery in children with brain metastases can likewise be effectively employed with good local control outcomes.[61] In the absence of pediatric-specific dosing guidelines, adopting adult SRS doses for metastatic disease is reasonable.[64] However, children with brain metastases treated with SRS remain at high risk of subsequent distant failure.[65] Similar to the adult patient population, an

advantage of radiosurgery is minimal integral brain dose when treating a limited number of brain metastases. In addition, radiosurgery offers minimal disruptions to systemic therapy. Children with brain metastases often have an additional burden of extracranial disease that necessitates aggressive systemic therapy, which may not be able to be administered concurrently with an extended RT course due to synergistic toxicity concerns.

Benign intracranial lesions

Benign brain neoplasms in children may include craniopharyngioma, pituitary adenoma (pituitary neuroendocrine tumor), pilocytic astrocytoma, schwannoma, and meningioma, with the latter tumor type more common in patients with germline mutations such as neurofibromatosis. While benign, collectively, these tumors can incur significant morbidity due to locoregional mass effect and disruption of critical brain or cranial nerve function. These lesions are likewise optimally managed in an interdisciplinary manner, generally with surgery if possible, followed by RT upon recurrence. These lesions may be challenging to completely resect safely near critical brain structures (eg, optic nerves, brainstem, and hypothalamic-pituitary axis).[52,66,67] Moreover, these lesions may have periods of indolent growth with minimal symptoms, such that the risks of craniotomy or larger field conventional RT (photon- or proton-based) may favor periods of surveillance to minimize treatment-related morbidity and permit continued patient growth and development with sustained quality of life.[68] For example, adolescents with neurofibromatosis type 2 may benefit from initial observation to maintain hearing function as long as possible, with deferral of surgery or SRS.[69]

Radiosurgery may be used for patients with progressive benign brain neoplasms and is associated with high rates of local control and minimal treatment-related morbidity. Aggregated series report good 3- to 5-year rates of local control for craniopharyngioma (65%-90%),[70] pituitary adenoma (95%),[71,72] and meningioma (80%-90% for imaging-defined or grade 1 meningioma),[73,74] with the caveat that these tumors can span the spectrum from pediatric to adult patients; most reported series include mixed populations and longer-term local control data are needed for these benign, curable neoplasms. In the specific case of radiation-induced meningioma (such as from childhood leukemia treated with cranial irradiation), radiosurgery is also a suitable treatment with high long-term control probability and minimal toxicity; an example of SRS for a small radiation-induced meningioma is presented in Figure 3.[75] The ability to safely apply radiosurgery for benign tumors may be limited by proximity to the optic structures or large lesion size. In some cases, data from adult populations support fractionated radiosurgery over 3 to 5 fractions to permit safer delivery for tumors > 3 cm to minimize tumor edema and posttreatment radionecrosis.[50] However, very limited pediatric data are available on fractionated SRS for benign brain tumors in children.[44]

Pilocytic astrocytoma is a tumor type with a relatively long history of treatment with SRS. While the data mostly consist of single-institution retrospective reviews, multiple series report 10 to 15 years of follow-up with excellent local control.[76-78] Pilocytic astrocytoma can be cured with gross total resection alone. However, in the setting of recurrent or unresectable disease, patients are often treated with conventional RT, resulting in long-term PFS rates greater than 70%.[79,80] Reports of outcomes with SRS in pediatric patients with pilocytic astrocytoma show PFS of 77% to 96% at 10 to 12 years.[76-78] One study reported improved PFS after radiosurgery for pilocytic astrocytoma when patients treated are <18 years of age, have tumors smaller than 4.5 cm^3, and those without prior RT or chemotherapy.[78] However, it is important to point out that these data lack molecular annotation, which has opened up contemporary targeted therapies for pediatric low-grade glioma.[81] Conventional fractionated RT remains the more traditionally accepted treatment for pediatric low-grade glioma (including pilocytic astrocytoma) that is refractory to systemic therapy compared with radiosurgery. However, the ISRS practice guidelines suggest that SRS may be considered when fractionated RT is not indicated.[44] Considering the excellent local control and long-term survival of patients with this disease entity, better brain sparing with SRS may be important when weighing RT options.

AVMs are another indication of radiosurgery and may be congenital or sporadic. AVMs are associated with morbidity related to the risk of spontaneous or interventional-related hemorrhage.[82] The risk of spontaneous hemorrhage is particularly important in children, who have a long natural life expectancy and are at high risk of an eventual bleed over time (with a risk of bleeding of up to 4% per year, with one-quarter of bleeds fatal).[83] Radiosurgery, either administered in a single session[84] or in a staged fashion for larger lesions, can offer an alternative to invasive interventions such as endovascular embolization or surgical resection. SRS is an important treatment option, and sometimes the only feasible treatment option, for lesions that are large, deep, or in eloquent locations (Fig. 4).[85] Volume-staged SRS involves the treatment of different portions of a large AVM target over several months,[86] while dose-staged SRS treats the entire AVM with lower doses over a period of up to 4 years.[87] However, single-fraction treatment of the entire lesion is the most common approach for children with AVMs undergoing SRS.[44]

There are many studies evaluating radiosurgery for pediatric AVMs, with 49 reports with retrospective data.[44] Combined, the obliteration probability after SRS for children with AVM was 65% (95% CI, 60%-69%). The annual probability of brain hemorrhage post-SRS was 0.8% for intact lesions and 1.6% for previously ruptured AVMs.[88] A higher marginal dose[88] may be associated with superior AVM obliteration probability, though the SRS dose was likely inversely correlated with lesion size and, thus, confounds

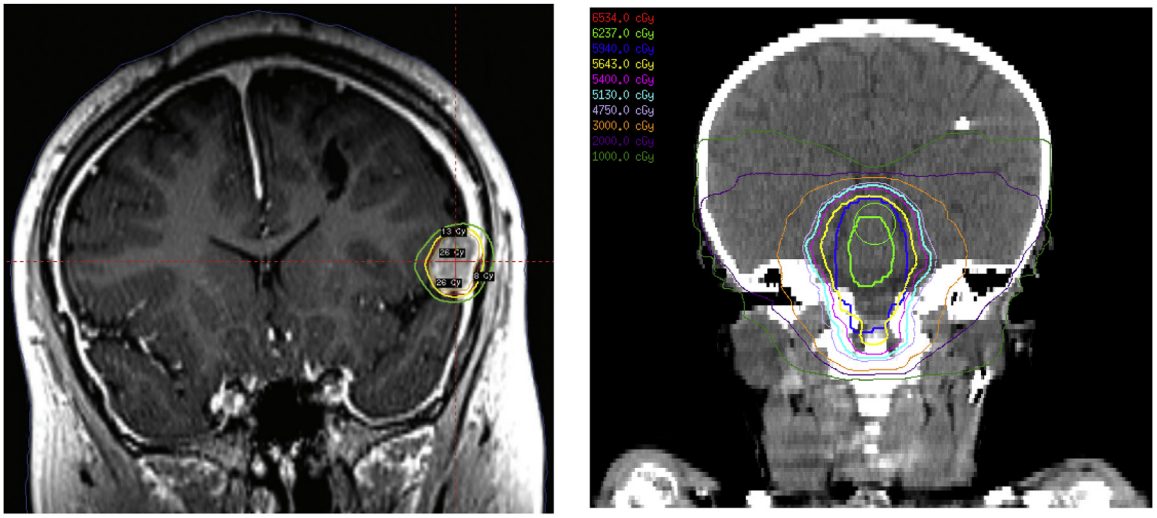

Fig. 3. (A) A 14-year-old girl was treated with single-fraction radiosurgery for an imaging-defined radiation-induced meningioma. Radiosurgery was delivered using a cobalt-60 platform with relocatable mask immobilization. Thirteen Gy was prescribed to the 50% isodose line. The orange line denotes the gross tumor volume, red denotes a 0.5 mm planning target volume expansion, yellow shows the 13 Gy isodose line, and green shows the 8 Gy isodose line. (B) This patient was previously treated with step-and-shoot intensity modulated radiation therapy for a recurrent choroid plexus papilloma in the fourth ventricle (59.4 Gy in 33 fractions) 11 years prior to radiosurgery. The region of the radiation-induced meningioma received between 10 and 20 Gy.

the association with obliteration. Radiation-induced change (or edema) post-SRS was common, occurring as a radiologic finding in about one-quarter of patients, but was symptomatic only in 7.8%.[88] Posttreatment cyst formation was rare (2%).[89] After SRS, studies report less than a 3% risk of permanent neurologic deficits, with improved outcomes in patients with smaller targets.[88,90,91] Therefore, the ISRS guidelines recommend that radiosurgery should be considered a standard option for children with AVMs.[44]

Planning considerations for SRS in children

Radiosurgery for children may be delivered using a linear accelerator commissioned for SRS delivery or a dedicated radiosurgery platform. Using a platform that permits the use of a relocatable thermoplastic mask rather than an invasive Leksell frame is preferable for neoplastic indications to minimize the need for anesthesia,[92] concerns with frame fixation and pin penetration of a skeletally immature skull[61,93] and to maximize patient comfort. However, frame placement is preferred for radiosurgery treatments for benign AVMs to minimize the dose to normal brain tissues.[84]

There is no known pediatric data evaluating suitable GTV-to-PTV expansions for SRS in the setting of mask treatments. Extrapolation of adult data is reasonable, with a view to using smaller margins to minimize off-target dose. For example, adult data suggest that a PTV of 1 mm (radial) and 1.5 mm (superior and inferior) is suitable in the setting of a cobalt-60 radiosurgery platform with a real-time high-

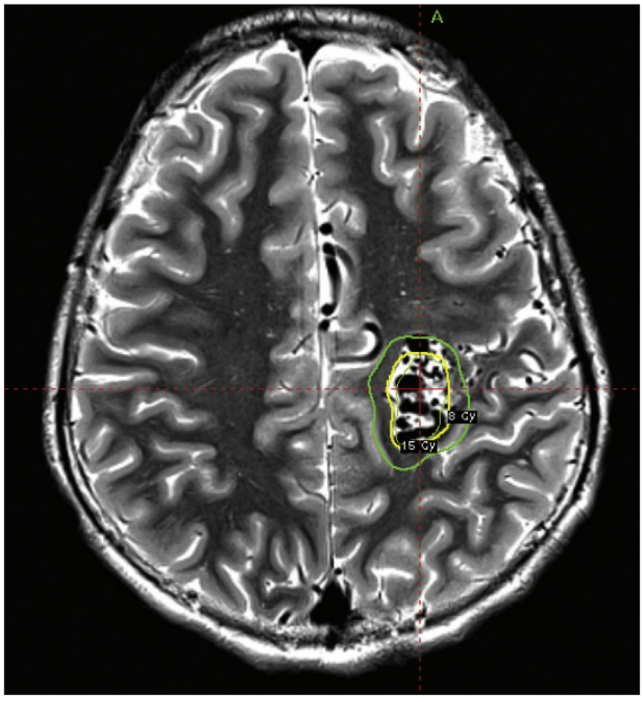

Fig. 4. A 13-year-old boy with a deep, left-sided arteriovenous malformation located near the motor cortex. This lesion was treated with frame immobilization on a cobalt-60 platform. The prescription was 15 Gy to the 50% isodose line (yellow line). The 8 Gy isodose line is shown in green.

definition motion management system.[94] Other institutions have used a smaller, uniform 1 mm PTV margin,[95] while additional data suggest that a geometric 0.5 mm PTV margin may be sufficient to maintain tumor coverage.[96] In the absence of data specific to children, careful image guidance, tight high-definition motion management settings, and the use of the smallest possible PTV (0.5 mm) in children undergoing awake SRS are reasonable (Fig. 3), depending on local equipment availability and institutional treatment protocols.

Single-fraction SRS doses for children depend on the specific histology and may range from 12 to 24 Gy for benign neoplasms,[44] 15 to 24 Gy for malignant lesions,[44] and 15 to 25 Gy for AVMs.[44,84,90]

Conclusions and Future Directions

Stereotactic RT is an established treatment for adults with extracranial metastases, brain metastases, and intracranial neoplasms. The evidence from adult-derived data can guide treatment for children, though high-quality data specific to pediatric patients remains limited. Thus, pediatric radiation oncologists are left to apply nonrandomized prospective studies, retrospective cohort data, or clinical practice guidelines and expert opinion to guide treatment. Nonetheless, the dosimetric advantages of stereotactic treatment techniques over conventional radiation are particularly appealing in the treatment of young patients, given the prevailing goals of maximizing tumor dose and minimizing acute and late toxicity. Future work should focus on (1) pooling data across multiple institutions to improve the generalizability of pediatric stereotactic RT data and (2) prospectively evaluating stereotactic RT and rigorously collecting data on local control, marginal recurrences, and distant failures. Leveraging prospective registries with digital RT data may provide an opportunity to evaluate SBRT and SRS in children treated in different institutions across diverse care settings.[97] We eagerly await SBRT-specific data from recently completed and ongoing COG studies and other international cooperative groups.

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