Review Article | Palliative Medicine and Palliative Care for Incurable Cancer

Little patients, big impacts: a narrative review of palliative and emergent radiotherapy for pediatric cancers

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Background and Objective: The use of radiotherapy (RT) in the palliative and emergent settings for pediatric cancers is an under-utilized resource. Our objective was to provide an evidence-based review of the data to increase awareness of the benefit for this population along with providing guidance on pediatric specific treatment considerations for palliative care physicians, pediatric oncologists, and radiation oncologists.

Methods: A narrative review was performed querying PubMed, MEDLINE, ClinicalTrials.gov databases, and supplemented with review articles, survey studies, current and recent clinical trials. When limited data existed, well-designed retrospective and prospective studies in the adult setting were evaluated and expert opinion was provided from pediatric oncologists.

Key Content and Findings: Pediatric specific treatment considerations include the use of anesthesia, impact of treatment on the developing child, and logistical challenges of RT. Treatment modality and dose selection are driven by histology and symptomatic site of pain, where we discuss detailed recommendations for hematologic, central nervous system, and solid tumors. For palliative RT, an underlying principle of searching for the lowest effective dose to balance response rate with minimal acute and late treatment related morbidity and logistical hardships is of paramount importance when caring for a pediatric patient. Lastly, we outline how to effectively communicate this option to patients and their caregivers.

Conclusions: Palliative RT can be of valuable benefit in most settings for patients with pediatric cancer. There is an unmet need for prospective data to inform on dose-fractionation along with patient and caregiver reported outcomes.

Keywords: Radiotherapy (RT); palliative care; palliative medicine; pediatric; cancer

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Introduction

The primary principle of palliative radiotherapy (RT) is that radiation should improve the overall quality of life of children whose life span is shortened by their disease, where less invasive methods of symptom relief are not sufficient. However, for the pediatric patient population, there remains an information gap and underutilization of RT in the palliative setting.

RT practice patterns in a multi-institutional series demonstrated only a minority (11%) of pediatric cancer patients were treated with a palliative intent. Importantly, the range of utilization of palliative RT across different institutions was 1–28% suggestive of significant institutional variability. The physicians surveyed conveyed concerns that toxicity and logistics (travel, time away from home, financial, etc.) were frequently and/or sometimes a barrier for receiving palliative RT treatment (1). In short, for palliative RT to be successful, the benefits and risks have to be broadly defined to be patient-centered, rather than narrowly-focused on tumor symptom relief.

We seek to provide a comprehensive resource for providers to illuminate the evidence supporting RT for pediatric cancers in the palliative and emergent setting with a goal to break down the barriers for use, including how to communicate with patients and their families about this potentially healing tool. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-505/rc).

Methods

Table 1 summarizes the search strategy performed to identify relevant articles on the use of RT in the palliative and emergent setting for pediatric patients [age ≤21 years old (yo)]. Articles were analyzed for relevance, histology specific information including dose and fractionation, and quality of data. There were no prospective studies identified on the use of RT in the palliative setting for pediatric patients. These articles were supplemented with additional current and recent clinical trials, review papers, and survey studies. In areas that lacked pediatric specific data, well-designed retrospective and prospective studies in the adult setting were evaluated. When limited data existed, expert opinions from pediatric oncologists and radiation oncologists were provided.

Principles of palliative RT

External beam RT delivers treatment non-invasively over the course of minutes while the patient lies on a treatment table in a reproducible position (2). Treatments are typically delivered in daily treatments called fractions (3).

RT in the curative setting is typically delivered in conventional fractionation (1.8–2 Gy per treatment delivered over 4–6 weeks on average) to allow for late-responding normal tissues to repair, while higher dose per fraction (hypofractionated) regimens with >2 Gy per day are often used in the palliative setting (3-5). Hypofractionated regimens deliver dose over a shorter duration of time, resulting in a higher biological effectiveness while reducing the number of patient visits (6).

Advancements in RT have led to more conformal radiation with techniques such as intensity-modulated RT (IMRT) (highly modulated form of X-ray treatment) or proton therapy (7,8). However, these treatment techniques can take days to a week or two to plan) and, in the case of protons, are only available in relatively few centers.

Palliative RT must be timely. For patients with rapidly progressing symptoms, that may mean starting radiation within a day. Therefore, 3-dimensional conformation (X-ray) RT (3D-CRT) or electron RT is often the best choice for patients with urgent needs. For patients with slowly progressing disease without escalating symptoms, or in patients with a lesion being treated that appears threatening to but not yet reducing quality of life, radiation can be started in several days to weeks. For patients with less acute and have more refractory histologies, stereotactic radiosurgery or stereotactic body RT (SBRT) may be an option (9,10).

Pediatric specific treatment considerations

The logistics and burden of receiving RT are often greater in children than in adults. Most children's hospitals are not attached to RT centers, necessitating transportation for urgent or emergent radiation needs. Considerations include medical stability for transport and appropriate staffing should the patient have a medical emergency while undergoing treatment. In cases of high acuity patients, the patient may be accompanied by nurse or physician staff to ensure appropriate pediatric specialty care. Pediatric patients are often treated with general anesthesia for each daily fraction to optimize a reproducible daily set up, and

Table 1 The search strategy summary

Items	Specification
Date of search	March 15, 2022 to July 15, 2023
Databases and other sources searched	PubMed, MEDLINE, ClinicalTrials.gov
Search terms used	Radiotherapy; palliative medicine; palliative care; pediatrics; radiosurgery; pediatric oncology; cancer; cancer pain
Timeframe	1970–2023
Inclusion criteria	English language; prospective and retrospective study type; survey studies; review articles
Selection process	Selection process was conducted independently with consensus upon peer review of manuscript text by all authors
Any additional considerations	Augmentation with current and recent clinical trials for pediatric caners

the medical oncologists or medical intensivists are key members of the team in assessing the safety of transporting a patient for treatment.

While daily anesthesia use is necessary in many cases to minimize intra-fraction motion, this increases the potential short- and long-term toxicities associated with RT (11-13). It is emotionally and logistically difficult for patients and their parents, requiring patients to be fasting, or nil per os (NPO) prior to treatment and necessitating longer time in the center. The NPO times can also make it more difficult for patients to maintain nutrition.

Princess Margaret Cancer Centre (Toronto, Canada) has published on the frequency of anesthesia use in pediatric patient for RT. General anesthesia was used in 90% of patients under 3 yo, 28% in patients age 3–6 yo, 1% in patients age 7–11 yo, and <1% in patients ≥12 yo. The threshold at which they transition from the majority of patients needing anesthesia to proceeding without is 4 yo (56.6% for 3 yo, 29.8% for 4 yo) (14). Anesthesia use is higher for each age group at institutions treating a lower volume of pediatric patients, likely due to a lack of awareness of strategies that may be implemented to avoid anesthesia use (15). Strategies may include working with a child-life specialist (16,17), distraction using video technology (18), use of additional educational materials to acclimate the patient to the treatment experience, giving the child a mask to practice with at home prior to simulation and treatment, or allowing comfort objects like a favorite stuffed animal on the treatment table with the patient.

Sometime palliative radiation is delivered in urgent situations where curative therapy is possible. For example, a patient's disease presentation may include spinal cord compression (SCC) or acute vision loss. In cases such as these, care must be taken with target delineation and treatment planning to minimize long term toxicities of RT. Radiation to growth plates prior to maturation can lead to hypoplasia and asymmetries with significant functional implications as the child develops. Rao *et al.* present a concise summary with an anatomic road map of growth plates and clinical correlates of radiation-induced growth toxicity (19). Other outcomes of RT in infancy or childhood may include but are not limited to fertility loss, breast hypoplasia, congestive heart failure, pulmonary disease, diabetes mellitus, hypothyroidism, neurocognitive deficits, or secondary malignancies (20-27).

Palliative RT for pediatric leukemia and lymphoma

Leukemia and lymphomas are the most common malignancies in children, accounting for approximately 40% of all pediatric cancers. The primary treatment is chemotherapy, which addresses systemic disease while sparing the potential late effects associated with RT. However, RT continues to play an important role in conditioning for hematopoietic stem cell transplantation, and certain consolidative and palliative scenarios for leukemias and lymphomas, particularly as high-risk, relapsed, and refractory diseases are still very radiosensitive entities (28). In the palliative setting, a multidisciplinary approach to care is crucial in safe and effective management as RT can play an important role in preserving function and relieving symptoms (*Table 2*).

Indications for palliative RT for leukemias and lymphomas

Superior vena cava syndrome (SVCS)

SVCS refers to a structural compression of the superior

Table 2 Suggested palliative radiotherapy doses for pediatric leukemia and lymphoma

Indication	Histology	Dose and fraction	Expected response
Superior vena cava syndrome	Any	20 Gy in 5	>80% symptomatic relief
		30 Gy in 10	
Ophthalmic manifestations	Any	18–24 Gy in 10–12	>85% stabilization/improvement
Cranial nerve palsy	Any	10–12 Gy in 5–6 if treating base of skull alone	80–85% stabilization/improvement
		24 Gy in 12 for whole brain	80–95% stabilization/improvement
Spinal cord compression	Indolent lymphoma	4 Gy in 2	>80% at least partial response
	Leukemia	24 Gy in 12	~95% symptomatic relief and local control
	High grade non-Hodgkin lymphoma	30 Gy in 10	>90% stabilization/improvement
Leukemia cutis	Any	18–26 Gy in 10–13	50–90% initial complete response rate
Symptomatic splenomegaly	Leukemia	5–10 Gy in 5–10	80–90% pain response/reduction in spleen size/ cell count improvement
	Non-Hodgkin lymphoma	20 Gy in 10 or higher	80–90% reduction in spleen size, local control

Provider discretion is permitted for dose-fractionation variations based on comprehensive patient evaluation and goals of care.

vena cava causing outflow obstruction and constellation of symptoms including headache, facial swelling, and dyspnea. The majority of malignancy related SVCS is caused by lung cancer in adults, and is rare among children with leukemias and lymphomas (29). The primary therapy for SVCS secondary to hematologic malignancy is often systemic therapy (30). However, in urgent cases such as airway compromise, combination of corticosteroid with stenting or RT could be considered. While direct robust comparison is lacking, stenting may provide faster venous patency resulting in more immediate and prolonged symptom relief compared to RT (31-33). When RT is indicated with palliative intent, 20 Gy in 5 fractions or 30 Gy in 10 fractions may bring effective symptomatic relief more than 80% of the cases (30,34). For children with lymphomas requiring RT for SVCS and having curative potential, treatment with 1.5–2 Gy per day may be prudent to avoid compromising future RT planning.

Ophthalmic manifestations and cranial palsies

Leukemias and lymphomas may present with ophthalmic manifestations, including eye pain, red eye, and vision loss, particularly since the orbit and the central nervous system (CNS) are potential sanctuary sites from chemotherapy (35). Although retina and posterior globe are the most common sites of ocular abnormality, any ocular structure including the anterior segment or optic nerve pathway can be involved (35). Discussion with the medical oncology team is paramount to evaluate if intrathecal systemic therapy such as high dose methotrexate is warranted as first line versus RT. If there is progression of ocular disease despite adequate CNS-directed systemic therapy, urgent radiation is indicated. Doses of 18–24 Gy in 1.6–2 Gy per fraction have resulted in greater than 85% disease control, although successful disease control with doses low as 8–12 Gy have been reported (36,37). Consultation with ophthalmology and pediatric oncology are required to determine the volume of radiation. At minimum, posterior globe and optic nerve of the affected eye and chiasm are required. However, contralateral posterior globe and optic nerve are often covered due to potential migration of disease or presence of subclinical disease (36). Depending on clinical scenario, the brain and the anterior structures of the eye may be covered as well.

In addition to the optic nerves, any other cranial nerve can be involved by leukemias or lymphomas (38). If cranial palsy is refractory to the appropriate systemic therapy, urgent RT is indicated. Historically, 24 Gy whole brain RT (WBRT) has been commonly used, with response rate of 80–95% (39,40). RT to the base of skull (BOS) alone to doses as low as 10–20 Gy have been used with response rate of 80–85% (38). However, WBRT may be associated with

more durable control of CNS disease and prevention of subsequent cranial nerve dysfunction compared to BOS RT alone (41). A lateral opposed parallel pair has the advantage of covering the structures of interest with short planning time, ease of setup, and minimal risk of geographic miss, but more conformal techniques such as IMRT for the whole brain or BOS may be considered to spare as much normal tissue as possible.

SCC

Non-Hodgkin lymphoma (NHL) is the most common histology associated with SCC in pediatric hematology (42,43). Management should involve establishment of diagnosis and initiation of appropriate systemic therapy, including steroids. In cases of refractory disease, RT is indicated to prevent neurological sequelae. Extrapolating from the adult literature, 4 Gy in 2 fractions for indolent lymphoma, 30 Gy in 10 for high-grade NHL, and 24 Gy in 12 for leukemia have been suggested (4,44,45). In contrast to non-hematological malignancy, surgery is not used often due to the chemo and radiosensitive nature of leukemias and lymphomas (46,47). However, surgical decompression may be an option after careful consideration of potential late effects of RT, prognosis, involved disease sites, and the ease of surgical access.

Leukemic infiltration of other organs

Skin is a relatively common site of leukemic infiltration outside of marrow, CNS, and testes. Leukemia cutis (LC) refers to infiltration of leukemic cells into the skin layers, which can cause pruritus, pain, and bleeding (48). In children, they commonly manifest with erythematous or violaceous nodules or papules in the head and lower extremities (48). As LC is often associated with marrow disease, the standard therapy is systemic therapy followed by bone marrow transplant (49). For symptomatic or bleeding lesions, palliative RT can be utilized at any stages of treatment to provide rapid relief of symptoms, although durable local control rate is less than 50% (49,50). Doses between 18–26 Gy in 1.8–2 Gy per fraction have been used, and there is no clear relationship between higher dose and disease response (49-51). Low energy electrons and bolus are typically used to cover the skin lesion adequately. Palliative total skin electron beam therapy (TSEBT) has been used for extensive symptomatic disease.

Splenic irradiation can be performed for symptomatic splenomegaly (i.e., pain, dyspnea, pancytopenia from sequestration, early satiety) in the setting of hematologic malignancy. Daily irradiation of 1 Gy to the whole spleen up to 5–10 Gy can provide significant pain relief or reduction in spleen size with a partial or complete response in 80–90% of patients (52). For NHL treated in the definitive or palliative setting, doses ≥20 Gy resulted in increased durability (median response 35 months *vs.* 4 months), suggesting consideration of a higher dose for splenic only disease or potentially patients with a limited metastatic burden (53).

Infiltration of other organs is less common. Cases ranging from bowel obstruction and perforation, acute kidney injury, and cardiac tamponade have been described in the literature (54-56). However, extra-CNS organ infiltration of leukemic cells is often asymptomatic and etiologies tend to be multifactorial (56). Supportive care, systemic therapy, and surgical corrections are the mainstays of treatment. Older case reports of heart failure due to cardiac infiltration of acute lymphoblastic leukemia treated with 20 Gy and gastrointestinal intussusception due to CLL infiltration treated with 22 Gy have been published (57,58).

For patients with low-grade disease, "Boom Boom" (2 Gy in 2 fractions) (59,60) and "Big Boom" (4 Gy in 1 fraction) (61) may result in significant relief for most patients with less durability compared to more protracted courses of treatment (60). These very low doses may not preclude the ability to deliver additional RT in the future.

Palliative RT for the CNS

RT is a key treatment for children with cancer who develop CNS pathology. Prior to the initiation of RT, patients should be evaluated for acute findings that need be treated primarily with non-RT approaches. Seizures, hydrocephalus, or focal neurologic deficits are common presenting symptoms. Patients with seizures should be evaluated for increased intracranial pressure; anti-epileptics should also be commenced (62). Patients with hydrocephalus should be evaluated by a neurosurgeon for potential cerebrospinal fluid (CSF) diversion with an extraventricular drain (EVD), endoscopic third ventriculostomy (ETV) or ventriculoperitoneal (VP) shunt. Patients with mass effect or symptomatic brain edema should be treated with dexamethasone prior to RT.

Brain metastases

Brain metastases in children with cancer is rare, but can be a serious presentation of advanced or recurrent disease

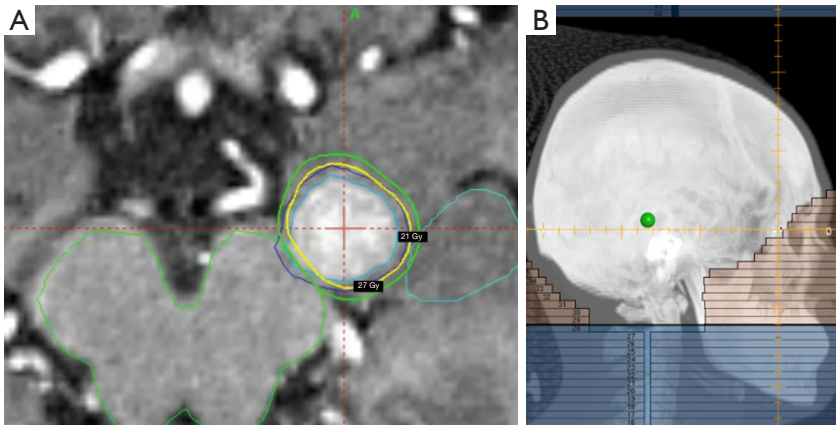

Figure 1 A 16-year-old male with metastatic osteosarcoma. The patient presented with headaches and seizures. Three intra-axial enhancing brain metastases were seen on contrast-enhanced brain MRI. All three lesions were treated with fractionated cobalt-60 stereotactic radiotherapy, 27 Gy in 3 fractions (prescribed to the 50% isodose line), using a relocatable frameless mask system. (A) SRS to the left temporal lesion is shown in the left panel. The thin cyan line represents the gross tumor volume. The dark blue line represents a 1 mm planning tumor volume. The 27 and 21 Gy isodose lines are shown in yellow and green, respectively. The brainstem and left hippocampus are delineated using thin green and teal lines, respectively. (B) The patient developed more than 12 new metastases on repeat MRI brain, 10 weeks after SRS. The patient subsequently received 20 Gy in 5 fractions whole brain radiotherapy, as shown. MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery.

(63-65). Management depends on whether patients have parenchymal brain metastases or leptomeningeal disease.

Parenchymal brain metastases

Children with a solitary brain metastasis typically follow an approach modelled on adult oncologic care, with initial neurosurgical resection (66), if safe, to achieve diagnostic confirmation and therapeutic relief of mass effect, followed by cavity radiosurgery (67). Children with multiple brain metastases should be evaluated for surgical removal of any symptomatic lesions (if needed), followed by radiosurgery (if small number of lesions) or WBRT (if numerous lesions) (*Figure 1*). The threshold number of metastases to define treatment with radiosurgery *vs.* WBRT is unclear in children; however, we have data to suggest treatment up to 15 brain metastases can be safe in adults, but the safety overall depends on the volume of lesions treated (68,69). Consideration of extracranial disease control should be taken into account when determining the role for radiosurgery *vs.* WBRT.

Leptomeningeal disease

Patients with isolated presentation of suspected leptomeningeal disease on magnetic resonance imaging (MRI) brain should have staging investigations completed, including MRI spine and CSF cytology for histologic confirmation, if possible and safe (i.e., no increased intracranial pressure). In children with known extracranial metastases, CSF cytology is not required. Children with intracranial leptomeningeal disease require WBRT with particular attention to include cranial nerve foramina in the skull base and coverage of the optic nerves. Dose prescriptions of 20 Gy in 5 fractions or 30 Gy in 10–12 fractions have been previously used (4).

Children with CNS metastases from rhabdomyosarcoma (70) or neuroblastoma (71,72) may benefit from craniospinal irradiation with conventional daily fractionation (1.8 Gy per day).

SCC

Patients with symptoms of SCC should be evaluated with contrast-enhanced MRI of the entire spine. Children with limited burden of disease outside the spinal column should be emergently referred for neurosurgical evaluation for decompressive surgery, followed by post-operative RT (73,74). Standard dose prescription in this setting is 20 Gy in 5 fractions or 30 Gy in 10 fractions (4).

In children who are not candidates for surgery, definitive RT with 20 Gy in 5 fractions or 30 Gy in 10 fractions

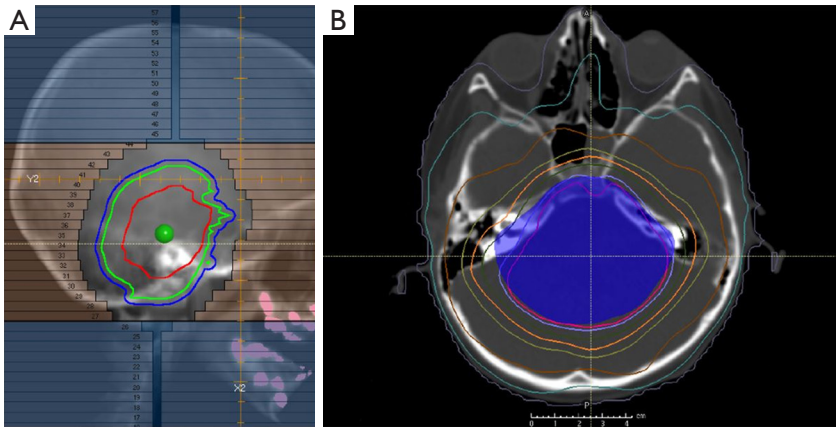

Figure 2 A 7-year-old patient with brainstem glioma who commenced RT emergently via lateral parallel opposed pair (A), followed by a VMAT plan (B). RT, radiotherapy; VMAT, volumetric-modulated arc therapy.

should be emergently commenced (4). The role of single-fraction RT for SCC has not been studied in children. Spine SBRT may be suitable for lesions that are not touching the spinal cord, but is contraindicated in the setting of a metastatic lesion causing SCC.

Diffuse intrinsic pontine glioma (DIPG)

Children with DIPG present with acute or subacute onset of cranial neuropathy, ataxia and long-tract signs (75). Lesions typically have a classic radiologic appearance, with T2 hyperintense involvement of the brainstem (76). Neurosurgical consultation for consideration of biopsy may be considered, but is optional if the presentation has no atypical characteristics. If biopsy is undertaken, a histone 3 mutation is commonly found, leading to a pathologic diagnosis of diffuse midline glioma, H3 K27-altered (77).

RT should be commenced urgently, which results in symptomatic improvement in most patients (78). Standard RT prescription is 54 Gy in 30 fractions. An alternate prescription is 39 Gy in 13 fractions if a shorter course of therapy is desired (79-81). If an urgent conformal [IMRT/volumetric-modulated arc therapy (VMAT)] plan cannot be initiated rapidly, patients with progressing symptoms should receive the first few fractions using a 3DCRT plan until a conformal plan can be created (*Figure 2*).

Re-irradiation in the CNS

Clinical situations which may require emergent evaluation for re-irradiation to the CNS include patients with recurrent high-grade glioma (HGG) or DIPG (82,83). Patients should undergo neuroaxis staging (MR spine) to ensure no distant sites of recurrence (84). Children with recurrent HGG can safely receive a course of re-irradiation, which may be associated with improved progression-free survival and overall survival (85,86). Similarly, children with recurrent DIPG can undergo re-irradiation with improvement in symptoms (87) and may be associated with a survival benefit (88). While the optimal dose for re-irradiation is not well defined, with practice variation between institutions, 20 Gy in 10 fractions is a commonly used regimen (79,89).

Palliative RT for pediatric solid tumors

Many pediatric solid tumors are more sensitive to RT than many adult tumors. Yet, practice patterns for treating symptomatic disease in pediatric solid tumor patients vary widely between institutions and treatment centers and across diverse histologies with variable sensitivity to RT (1). Hence, we performed a histology-specific focused review of the literature about the utility of palliative and emergent RT for solid tumors with recommendations summarized in *Table 3*.

Neuroblastoma

Neuroblastoma is the most common extracranial tumor in children. Treatment routinely involves a multimodality approach given the high disease burden and metastatic potential associated with this pathology. Although RT is commonly used for consolidation in the treatment of high-risk neuroblastoma to the post-resection tumor bed and up

Table 3 Suggested palliative radiotherapy doses for pediatric solid tumors

Histology	Indication	Dose and fraction	Expected response
Neuroblastoma	All sites	20 Gy in 5	>80% symptomatic relief
	Vision loss	4.5 Gy in 3	N/A[†]
	Hepatomegaly	4.5 Gy in 3	N/A[†]
Osteosarcoma	All sites	36–45 Gy in 12–15	>75% response
	SBRT[‡]	40 Gy in 5	60% response rate
Ewing sarcoma	All sites	30 Gy in 10	84% symptomatic relief
	SBRT[‡]	30–40 Gy in 5	100% symptomatic relief
Rhabdomyosarcoma	All sites	30 Gy in 10	64% pain relief
	SBRT[‡]	30–35 Gy in 5	83% 1-year local control

Provider discretion is permitted for dose-fractionation variations based on comprehensive patient evaluation and goals of care. [†], N/A—often used as a bridge to systemic therapy in the newly diagnosed setting. Limited case numbers to provide expected response rate; [‡], for the properly selected patient (KPS >50–60%, size ≤5 cm, non-emergent). SBRT, stereotactic body radiotherapy; KPS, Karnofsky Performance Status; N/A, not available.

to five chemoimmunotherapy refractory metastatic sites, no clear clinical guidelines have established a radiation regimen for palliative treatment in metastatic disease.

Extrapolating from treatment in the upfront setting, excellent local control was demonstrated on ANBL0532 with 21.6 Gy with no additional improvement in local control seen with dose-escalation to 36 Gy in the setting of gross residual disease >1 cm^3, highlighting the radiosensitive nature of this disease (90-93). Moreover, dose reduction to 18 Gy for local control to the primary site may be sufficient and warrants validation on a multi-institutional trial (94). For metastatic sites, the strongest prognostic factor for local recurrence is persistence after induction chemotherapy, supporting the consolidative role of RT which results in LC >90% with doses of 21–24 Gy (90,91,93).

Retrospective studies in the palliative setting demonstrate similar efficacy with modest RT doses for local control and palliation. A French series by Caussa *et al.* evaluated the impact of dose-response for palliative RT among 34 patients (69 metastatic sites) with metastatic high-risk neuroblastoma with overall response rate measured by a composite endpoint of pain relief or >25% reduction in tumor volume (95). Soft tissue metastases treated to a median dose of 20 Gy (range, 8–36 Gy) appeared to be the most responsive with 84.2% response rate, which increased to 100% when doses ≥15 Gy were used. Bone (median dose 16.5 Gy) and CNS metastases (median dose 15 Gy) appeared to respond less (63.2% and 44%, respectively), with a trend toward improved response with higher doses ≥20 Gy (81.2% *vs.* 50%) for bone lesions. Similarly, Lazarev *et al.* reported 1-year local control of 82% in 50 patients with neuroblastoma treated with a short hypofractionated schedule of schedule of >1 but ≤5 fractions at ≥3 Gy; albeit median total dose of 24 Gy in 5 fractions was histology agnostic in this solid tumor cohort study raising the question of the dose received by the neuroblastoma patients specifically (96).

Recent protocols support the use of emergent RT at diagnosis to sites of life-threatening or functional-impairing disease, such as vision loss and hepatomegaly resulting in severe respiratory distress using low doses of 3 fractions at 1.5 Gy each (4.5 Gy total). For vision symptoms, evaluation by pediatric ophthalmology to correlate objective vision symptoms with imaging related findings can be critical as the physical exam in this often very young age group can be challenging. As per ANBL 1531, these sites do not require consolidation at time of RT for high-risk patients if these metastatic sites do not otherwise meet the criteria for requiring treatment.

While the prognosis remains poor in this setting, the meaningful benefit with modest doses required for palliation may outweigh the risk of long-term treatment related morbidity (26,27).

Osteosarcoma

Osteosarcomas are primary malignant tumors of the bone that are managed with systemic therapy and usually surgery

for local control. In pediatric patients with metastatic osteosarcoma, RT has been shown as an effective method of symptom control despite being radioresistant. In 1992, Lombardi *et al.* showed a complete or partial radiologic response in 81% of symptomatic lesions treated with a total dose of 36 Gy (3 weekly fractions of 6 Gy over 2 weeks) (97). Late toxicities observed included fibrosis, pathologic fracture, and perioperative wound infection. More recent data from Chen *et al.* in 2020 supported the use of higher dose to gain longer symptom relief with minimal toxicity (98). In this study, symptomatic improvement was seen in 75% of cases using the median equivalent dose in 2 Gy fractions (EQD2) of 40 Gy (range, 20–60.4 Gy) with a median number of fractions per course of 15 (98). Median time to symptom improvement was 15.5 days (range, 5–39 days) with median time to progression at 12.9 months. Similar outcomes of complete or partial responses in 61% of lesions treated has been demonstrated by Lazarev *et al.* (96).

In addition to conventional RT, SBRT has been used successfully for symptomatic control of osteosarcoma. In 2014, Brown *et al.* documented a 60% response rate for patients treated with symptomatic lesions at a median SBRT dose of 40 Gy in 5 fractions (range, 30–60 Gy in 1–10 fractions) (9). Similar response rates for osteosarcoma of 54% was demonstrated by Rahn and colleagues using a median dose per fraction and fractionation of 3 Gy and 10, respectively (i.e., 30 Gy in 10 fractions) (28). No Radiation Therapy Oncology Group (RTOG) grade 3 acute or late toxicities were observed (28).

Ewing sarcoma

Ewing sarcoma is an aggressive soft tissue tumor of adolescents and young adults, comprising approximately 5% of all soft tissue sarcomas with median age at diagnosis of 15 years (99). Ewing sarcoma and rhabdomyosarcoma are considered more chemotherapy and radiosensitive histologies compared to osteosarcoma and other soft tissue sarcomas.

In the upfront metastatic Ewing sarcoma setting, given long-term cure is possible, a local control strategy applied to primary and metastatic disease sites can prolong event-free survival (100). Effort for local control at week 13 of chemotherapy is recommended as well as metastatic site consolidation at the end of therapy (100,101). If metastatic sites are too numerous to treat, attention is focused on treatment refractory sites and/or sites that if progression were to occur could result in functional impairment.

If a patient presents with functional impairment, such as SCC, emergent initiation of steroids, systemic therapy and/or consideration of urgent RT is warranted since rapid response can be observed (102). If emergent RT is necessary at diagnosis, initiation of RT with conventional fractionation (1.8 Gy per day) with subsequent conversion to a definitive dose RT plan as a continuous course with the inclusion of chemotherapy is recommended for durable local control.

In Ewing sarcoma, the intent of RT for metastatic sites for palliation versus cure depends on multiple factors. In 2006, Koontz *et al.* described a 55% complete response rate and 29% partial response rate for pediatric patients (median age: 11.6 yo) undergoing palliative radiation for metastatic Ewing sarcoma using an average dose of 30 Gy (range, 4.5–68.5 Gy) (103). In the study previously discussed by Rahn *et al.* [2015], higher response rates (76%) were seen for pediatric patients treated with a median dose per fraction of 3 Gy (range, 1.5–20 Gy) over a median of 10 fraction (range, 1–28 fractions) (i.e., 30 Gy in 10 fractions) (28). Like osteosarcoma, the use of SBRT has shown considerable effectiveness in symptomatic relief with an acceptable side effect profile. Brown *et al.* showed a 100% response rate for symptomatic Ewing sarcoma metastases treated with a median SBRT dose of 40 Gy given in 5 fractions (range, 30–60 Gy in 1–10 fractions) (9).

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft-tissue sarcoma in the pediatric population with survival rates of those presenting with metastatic disease still poor at around 30% (104). A similar approach to Ewing sarcoma described in detail above is taken for metastatic rhabdomyosarcoma.

Parameningeal rhabdomyosarcomas are at risk for leptomeningeal disease, and careful attention at initial diagnosis with adequate staging (e.g., MRI craniospinal axis and lumbar puncture) and consideration of restaging if a patient is presenting with failure-to-thrive and symptoms (e.g., nausea, neurologic symptoms) beyond what would be anticipated for the current known extent of disease (70). Treatment for leptomeningeal disease may benefit from consideration of craniospinal irradiation to a median dose of 36 Gy (range, 18–36 Gy) and/or WBRT to a median dose of 30 Gy (range, 6–41.4 Gy) with careful attention to prior areas of irradiation in regard to cumulative dose (70).

Compared to Ewing sarcoma, even more limited data exists regarding the optimal dose fractionation for the

palliative treatment of rhabdomyosarcoma in the pediatric population. As discussed previously, Rahn *et al.* for pediatric rhabdomyosarcoma patients a 64% response rate with a median dose-fraction regimen of 30 Gy in 10 fractions (28). Skamene and colleagues reported excellent (100%) local control for all 12 metastatic sites treated with definitive dose RT (41.4–50.4 Gy in 1.8 Gy fractions) with minimal treatment related toxicity (105).

Parsai *et al.* reported promising data in regard to the use of SBRT for pediatric, adolescent and young adult patients with sarcoma, including rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and other soft tissue sarcomas with excellent local control of 88.3% at 6 months, which was modestly reduced to 83% at 12 months for those surviving longer than 1 year (106). Importantly, the majority of local failures were in-field (60%), while the minority were marginal failures (40%), emphasizing the importance to study the most effective dose (for in-field failures) and ensuring adequate treatment volumes (for marginal failures).

Symptom management

A principle of palliative RT is to design a treatment plan to balance efficacy and durability of response with the intent of keeping risk of acute and late toxicities to a minimum. In many cases while the effects may be modest, these events may not be avoided entirely, and proactive symptom management may help reduce the impact (*Table 4*). The timeline of acute symptom development is often a gradual onset with the course of RT, peaking at the culmination or up to 1 week after treatment with gradual improvement with resolution of most effects seen by 4–6 weeks.

Radiation fatigue, akin to "participating in extracurricular activities" is best managed with gentle exercise and added rest.

Radiation dermatitis can result in folliculitis, dry skin, and/or red/peeling skin. This is typically managed with topical emollients twice a day, avoiding application 2 hours prior to treatment to minimize risk of intensification of radiation, and topical diphenhydramine (Benadryl) and/or hydrocortisone cream for pruritus.

Nausea is common, particularly with treatment fields near the brain, thorax, and gastrointestinal tract. As opposed to other acute effects of radiation, nausea can occur following the first treatment. Prophylactic use of 5-HT3 antagonists, such as ondansetron, dosed 1 hour prior to treatment is typically recommended. Lorazepam can mitigate nausea with an anxiety component, and for younger kids to minimize motion. A scopolamine patch can offer a non-sedating alternative. Olanzapine can help if there is an anorexia component. A short course of dexamethasone can be used in cases of refractory nausea.

Palliative radiation to the brain can cause additional acute effects like alopecia, somnolence, as well as headaches and swelling, which could lead to worsening or new neurological symptoms or seizures. Dexamethasone is useful to control these symptoms.

Esophagitis can be managed with dietary adjustments, such as avoiding dry, sharp, or acidic foods. For lower esophagitis or gastritis, a proton pump inhibitor (PPI) or antacids can offer significant relief. For proximal esophagitis or mucositis, a compounded lidocaine solution using a combination of 1:1:1 diphenhydramine, aluminum hydroxide and magnesium hydroxide suspension (Maalox), and viscous lidocaine offers symptomatic relief. If symptoms persist, care should be taken to rule out esophageal candidiasis.

Treatment fields involving the lower abdomen or pelvis can cause enteritis or cystitis. Acute diarrhea can be treated with dietary changes (constipation-promoting diet), along with loperamide as needed (assuming an infectious etiology, such as *Clostridium difficle* infection, is ruled out) (107). Urinary discomfort can be managed by dietary changes (reducing caffeine, acidity, carbonated beverages), and phenazopyridine (Pyridium).

Palliative radiation is often used to treat bony pain caused by disease, but treating these bony sites in the minority of cases can result in an inflammatory pain flare that can last hours to up to 7 days. This can be treated with analgesics such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) (if clinically safe to utilize) or a short pulse of steroids (96,108,109).

Communication with patients and families

High-quality communication is key to providing the best possible care for patients and their families. Patients and caregivers report greater prognostic understanding, increased confidence in their decisions, and improved quality of life when clinicians practice direct and compassionate communication about prognosis and anticipated symptoms (110-112). Children with cancer and their caregivers also want direct, honest, and empathic discussions with their clinicians, even when the information is difficult or distressing (113). Finally, patients and families

Table 4 Common acute side effects and suggested supportive care recommendations categorized by treatment site of radiotherapy

Treatment site	Acute side effects	Recommendations
Brain	Nausea	5-HT3 antagonist, scopolamine patch, lorazepam, olanzapine, or dexamethasone for refractory nausea
	Headache	Tylenol/NSAIDs, opioids, dexamethasone
	Seizures	Prophylactic antiepileptics, dexamethasone
	Swelling/somnolence	Dexamethasone
	Dermatitis	Emollients, topical steroids
Head & neck	Mucositis, esophagitis	Viscous lidocaine (as a compound: equal parts mixed 1:1:1-lidocaine, diphenhydramine/benadryl, aluminum hydroxide and magnesium hydroxide suspension/Maalox)
	Xerostomia	frequent sips of water, sodium bicarbonate rinses
	Dermatitis	Emollients, topical steroids
	Thrush	Nystatin, fluconazole
	Thickened secretions	Guaifenesin, papaya juice, meat tenderizer
	Otitis-media or externa	Antibiotic/steroid drops
	Dry eye	Artificial tears (daytime), eye ointment (nighttime)
Chest/thorax	Esophagitis	PPI or antacid, dietary adjustments
	Pericarditis	NSAIDs, or dexamethasone with taper
	Pneumonitis	Inhaled steroids for minimal symptoms, dexamethasone with taper for more severe
	Dermatitis	Emollients and topical steroids
Upper abdomen	Nausea	5-HT3 antagonists
	Anorexia	Cyproheptadine, dronabinol (Marinol)
	Gastritis	Carafate, antacids, PPIs
	Dermatitis	Emollients, topical steroids
Lower abdomen/pelvis	Cystitis	Phenazopyridine (Pyridium), dietary adjustments (low acidity, caffeine, spicy food, carbonated beverages)
	Enteritis	Loperamide
	Dermatitis	Emollients, topical steroids
Extremity/bone	Pain flare	Tylenol, NSAIDs, opioids, dexamethasone
	Dermatitis	Emollients, topical steroids
	Fracture	Pain medications or surgical stabilization

NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

who are part of such discussions report increased peace of mind and hopefulness, greater trust in their clinicians, and ultimately, less decisional regret (111,114). These outcomes are especially important when patient symptom burden may be high and/or likelihood of cure may be low.

And yet, communication in the setting of palliative and emergent RT for children with cancer can be challenging. Formal communication training for oncology clinicians is limited, leaving many clinicians underprepared to facilitate these complicated and emotionally challenging conversations. Indeed, the bulk of clinician communication training is focused on delivery of treatment options (i.e.,

"let's talk about the treatment option of RT") without the concurrent focus on that treatment's outcomes (i.e., "this treatment may alleviate some of your symptoms, and is not expected to cure your cancer"). Additionally, they may feel that by discussing "bad news" with patients and families, they are depriving them of a critical resource when they need it most: hope (115,116); nearly half of pediatric oncology clinicians equate these discussions with a "personal failure" (117). Perhaps for these reasons, a quarter of parents report unmet prognostic information needs regarding their child's cancer (118), most feel additional distress with their decision-making, and many regret missed opportunities to talk to their child and/or optimize their child's overall quality of life (112,116,119-121).

To bridge this gap, clinicians must model consistent, evidence-based communication strategies. Many of the core principles in adult oncology and palliative care communication science also apply to the care of children with cancer and their families. These include the primary roles for communication in this setting: to exchange information, to foster relationships, and to provide a forum for decision making (122). It is important to begin conversations related to goals of care early and revisit them often, to expect and validate emotion, and to elicit values and preferences to inform treatment decisions. There are also aspects of communication that are unique to pediatric oncology. For example, clinicians must navigate how to include children in these discussions in developmentally appropriate ways, accommodate individualized family dynamics, and balance caregiver and child autonomy in terms of decision making (123).

Pragmatic communication support guides for oncology providers exist (122), and ongoing research in the pediatric palliative care and oncology fields is helping to define key components of high-quality communication (124). Establishing a human connection through affection or remembering things important to patients and families can help build a framework of trust. Using NURSE statements to respond to patient and family emotion (Naming the apparent emotion, statements of Understanding or normalization of that emotion, paying Respect to parent roles and values, pledging Support of their child, family, and the shared decision-making process, and Exploring their thoughts, values, hopes and worries) can support the family and clinician through a difficult conversation (125). Families of children with advanced cancer have also identified inclusivity, humor, alliance, and feeling as if their clinician is partnering with them as facilitators of a therapeutic communication relationship (124).

Clinicians caring for children receiving palliative or emergent RT play a critical role in supporting decisions and clinical care at a time when such things have profound impacts on both immediate and long-term well-being of the entire family unit. Clinicians rely on patients and caregivers to disclose their most personal needs, hopes, and values; and they depend on the clinician to provide honest, empathetic, and complete information. This two-way partnership only works through thoughtful and skillful communication. When therapeutic relationships are built upon a foundation of strong communication, clinicians are more likely to be able to provide the kind of high-quality, compassionate, goal-concordant care that all patients deserve.

Conclusions

We have demonstrated the valuable benefit that palliative RT may have across all major pediatric tumor types along with the tools for how to empower the decision making of our patients and their families during this precious time. Advancements in the technology of RT continually allow for more rapid planning and increased precision and conformality in hope to widen the therapeutic threshold of maximizing efficacy and durability of response with reduced side effects. Yet, technological advancements alone are insufficient to best serve pediatric patients. Rather, there is a need to identify the lowest effective dose over the shortest length of time to reduce the logistical impact on quality of life and minimize risk of long-term effects. Coordination with the multi-disciplinary treatment team is critical to minimize delays in systemic therapy when employing palliative RT, and consideration of minimizing overlapping toxicities with systemic therapy and RT.

For pediatric patients, our literature review highlights the absence of prospective data for the use of palliative RT along with histology-specific data. There is an urgent need for prospective investigation of the value of palliative RT with involvement and careful attention to the patient and caregiver reported outcomes.

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