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Original Article

Clinical practice and outcomes of palliative radiation therapy in pediatric oncology patients: An international comparison of experiences from two distinct countries and health care systems

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ABSTRACT

Background and purpose: This study describes clinical outcomes of palliative radiation therapy (RT) for children treated in distinct health-care environments—the US where there is advanced integration of palliative resources and Brazil, a country in the process of developing provisions for pediatric palliative care.
Methods and materials: Palliative RT cases of pediatric oncology patients aged ≤21-years from 2010 to 2016 in two Brazil-based and one US-based (Johns Hopkins Hospital, JHH) academic centers were reviewed in this study.
Results: Eighty-eight pediatric patients were treated to 131 lesions with palliative RT. Forty-nine patients from the JHH cohort comprised 84 cases and 39 patients from the Brazil cohort comprised 46 cases. The most common indication for palliative RT was pain (55% overall, 39% Brazil, 63% JHH). Sixty-seven percent of patients experienced a complete (CR) or partial response (PR) to palliative RT, 12% reported stable symptoms (SS), and 22% reported progressive symptoms (PS). The median survival from the end of palliative RT was 3.6 months (95% confidence interval (CI), 2.3–4.8 months). When treated with palliative RT for pain, 83% of patients experience CR/PR, facilitating reduction or discontinuation of opiates in 46% of these patients.
Conclusion: Despite different practices, the clinical results using palliative RT for pediatric patients treated in two unique healthcare environments demonstrated it is an effective tool for pediatric oncology patients across systems.
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By estimates from the World Health Association (WHO) Health Statistics and Informatics Department, there are over 83,000 children with cancer around the world who have palliative care needs at the end of life each year, and 80% of these children are in significant pain [1]. Through the Worldwide Palliative Care Alliance (WPCA) assessments, only 11 countries (6%) have integration of pediatric palliative care. These include Australia, Belgium, Canada, Germany, Israel, Italy, New Zealand, Poland, South Africa, United Kingdom, and the United States of America. Nineteen countries (10%) provide limited services with patchy funding and few hospice services. Thirty-six countries (19%), including Brazil, are in the process of developing provisions for pediatric hospice-palliative care. The remaining vast majority, 126 countries (66%), have no known pediatric palliative care activity, and there is a disproportionately higher rate of children in need of palliative care for cancer at the end of life in many of the countries lacking pediatric palliative care provisions. Although well integrated in certain health systems, for other regions of the world, palliative care is still in its infancy [1–3].

All of these challenges to the access of pediatric palliative care are magnified when considering the palliative treatment of children using radiation therapy (RT). Although there are clear indications for palliative RT, including pain, cord compression,

Abbreviations: RT, radiotherapy; CNS, central nervous system; Sx, symptoms; Post-op, post-operative; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; AP/PA, anterior-posterior-posterior-anterior; SBRT, stereotactic body radiation therapy; Fx, fractions; A&P, abdomen/pelvis; H&N, head and neck; SRS, stereotactic radiosurgery; CR, complete response; PR, partial response; SS, stable symptoms; PS, progressive symptoms.

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intracranial symptoms, respiratory distress, obstructive symptoms, and superior vena cava syndrome, data are sparse for the use of palliative RT in children with cancer. There is little consensus regarding its application in the pediatric population given few reports including toxicity and lack of prospectively collected data in children to guide dose and fractionation. Current practices are based on extrapolation from the adult palliative RT literature, with few reports supporting the efficacy of the palliative RT in pediatrics [4–12].

Our group previously reported a survey of practice patterns of pediatric palliative RT across an international research consortium [13]. Recognizing the significant diversity of the use and administration of palliative RT across six international institutions, we pursued a follow-up study to further understand the differences in clinical indications, toxicity, and outcomes for children treated with palliative RT between two cohorts of patients from the United States and Brazil. This focused study aims to evaluate and compare the clinical outcomes of palliative RT for children between the US where there is advanced integration of palliative resources and Brazil, a country in the process of developing provisions for pediatric palliative care.

Materials and methods

Patient identification

All pediatric patients 21 years or younger treated with radiation therapy from January 2010 to December 2016 at 3 institutions with dedicated pediatric expertise, 2 centers in Brazil (Grupo de Apoio ao Adolescente e à Criança com Câncer and Centro Infantil Boldrini) and 1 in the United States (Johns Hopkins), were retrospectively reviewed.

Clinical data

Palliative intent was defined as treatment with the goal to improve symptoms or to prevent impending symptoms such as in the case of intracranial or spine involvement. Each participating institution independently gathered clinical data including cancer diagnosis, gender, age, indication for palliative RT, treatment response, toxicity, and survival data for pediatric patients they had treated with palliative RT.

Radiation protocol

The immobilization, use of anesthesia, RT technique, and RT dose and fractionation were at the discretion of the treating radiation oncologist, considering each specific clinical scenario.

Statistical analysis

Each palliative RT course was analyzed separately with respect to toxicity and clinical response and reported using descriptive statistics. The Chi-Square test was used to assess for differences between expected and observed frequencies between cohorts. The Kaplan–Meier and log-rank tests were used to assess for differences in time to events. A p-value of <0.05 was considered significant in this analysis, which was performed using SPSS version 20.0 software (SPSS, Chicago, IL, USA).

Results

Eighty-eight pediatric patients received palliative RT, of which 49 were treated in the US and 39 in Brazil (Table 1). Nineteen percent of patients were <5 years of age overall (28% Brazil, 12% JHH). Only 2 of the 71 patients ≥5 years of age required anesthesia during palliative RT administration; however, 15 of the 17 patients <5 years of age were treated with anesthesia. Patients with osteosarcoma and neuroblastoma comprised a large proportion of the Brazil cohort, while palliative RT for lymphoma and leukemia was more common at JHH.

Table 1
Baseline clinical characteristic of pediatric patients necessitating palliative radiation therapy.

	All (N = 88)	JHH (N = 49)	Brazil (N = 39)
Age at time of RT			
<5 years	17 (19%)	6 (12%)	11 (28%)
≥5 years	71 (81%)	43 (85%)	28 (72%)
Anesthesia use			
Yes	17 (19%)	4 (8%)	13 (33%)
<5 years	15 (88%)	4 (100%)	11 (85%)
≥5 years	2 (12%)	–	2 (15%)
Primary histology			
Embryonal brain*	4 (5%)	4 (8%)	–
Ependymoma	3 (3%)	–	3 (8%)
Neuroblastoma	13 (15%)	5 (10%)	8 (21%)
Glioma**	4 (5%)	2 (4%)	2 (5%)
Wilms	1 (1%)	–	1 (3%)
Rhabdomyosarcoma	15 (17%)	9 (18%)	6 (15%)
Ewing Sarcoma	8 (9%)	4 (8%)	4 (10%)
Osteosarcoma	13 (15%)	4 (8%)	9 (23%)
Lymphoma/leukemia	14 (16%)	14 (28%)	–
Other CNS	1 (1%)	1 (2%)	–
Other soft tissue	4 (5%)	2 (4%)	2 (5%)
Other bone	1 (1%)	1 (2%)	–
Other	7 (8%)	3 (6%)	4 (10%)

Abbreviations: RT, radiation therapy; CNS, central nervous system.
* Includes Medulloblastoma, PNET, ATRT.
** Includes low- and high-grade glioma.

Patients at JHH were commonly treated with palliative RT to more than one site, with 84 palliative RT cases in 49 patients with an average of 1.7 sites per patient. More than one palliative RT course was occasionally offered to patients in the Brazil cohort, with 46 palliative RT cases in 39 patients with an average of 1.2 sites per patient. More patients at JHH received treatment to the spine compared to the patients in the Brazil cohort (29% vs. 15%, respectively), while treatment for brain metastases was more common in the Brazil cohort (22% vs. 7%, respectively) (Table 2). There were similar rates of treatment to the non-spine bone and lung/chest wall, while treatment to the abdomen/pelvis, head and neck, extremity, and primary brain tumors was rare in both cohorts.

The indications for palliative RT are shown in Table 3. The most common indication for palliative RT across both cohorts was pain (55% overall, 39% Brazil, 63% JHH), followed by intracranial symptoms (12% overall, 20% Brazil, 7% JHH) and respiratory compromise/chest pain (12% overall, 15% Brazil, 10% JHH). Treatment for the prophylactic prevention of impending symptoms comprised 10% of cases at JHH and 2% (1 case) in the Brazil cohort.

The median time from symptom onset to palliative RT was 0.8 months (range, 0.0–10.9 months) across the entire cohort, with longer time to initiation of RT in the Brazil compared to the JHH cohort [1.9 months (range, 0.0–11 months) versus 0.7 months (range, 0.0–8.6 months), respectively] (p = 0.004). The RT technique used for palliative cases overall and separately in each cohort is shown in Table 4. Prescription dose and fractionation varied within and across the two cohorts. Prescribed and administered palliative RT dose/fractionations by treatment indication are listed in Supplementary Table 1. Seven patients (8%) of the JHH patients were treated with palliative RT using a stereotactic approach, however, stereotactic RT was not employed for palliative RT in the Brazil cohort. Twenty patients (15%) were unable to complete the prescribed course of RT, with a significantly higher percentage of

Table 2
Anatomic site necessitating pediatric palliative radiation therapy.

Institution	# of palliative RT cases	Percent of palliative RT cases by site								
		Non-spine bone	Spine	Brain (metastases)	A&P	H&N	Brain (primary)	Lung/Chest wall	Extremity (soft tissue)	Other
JHH	84	23 (27%)	24 (29%)	6 (7%)	6 (7%)	7 (8%)	2 (2%)	11 (13%)	3 (4%)	2 (2%)
Brazil	46	15 (33%)	7 (15%)	10 (22%)	2 (4%)	1 (2%)	3 (7%)	7 (15%)	–	1 (2%)
Total	130	38 (29%)	31 (24%)	16 (12%)	8 (6%)	8 (6%)	5 (4%)	18 (14%)	3 (2%)	3 (2%)

Abbreviations: RT, radiation therapy; A&P, abdomen/pelvis; H&N, head and neck.

Table 3
Indication for pediatric palliative radiation therapy.

Institution	# of palliative RT cases	Percent of palliative RT cases by indication*										
		Pain	Cord compression	Intracranial sx	Respiratory compromise/ chest pain	Bleeding	Liver distension	Bowel obstruction	Post-op spine	Post-op brain	Impending sx	Other
JHH	84	53 (63%)	6 (7%)	6 (7%)	8 (10%)	2 (3%)	–	1 (1%)	3 (4%)	2 (3%)	8 (10%)	4 (5%)
Brazil	46	18 (39%)	4 (9%)	9 (20%)	7 (15%)	3 (7%)	1 (2%)	–	1 (2%)	5 (11%)	1 (2%)	3 (7%)
Total	130	71 (55%)	10 (8%)	15 (12%)	15 (12%)	5 (4%)	1 (1%)	1 (1%)	4 (3%)	6 (5%)	9 (7%)	7 (5%)

Abbreviations: RT, radiation therapy; sx, symptoms; post-op, post-operative.
* Percentages may total >100% as each case may have had more than one indication.

Table 4
Palliative RT treatment characteristics.

	All (N = 130)	JHH (N = 84)	Brazil (N = 46)
Median time from symptom onset to RT, months (range)	0.8 months (0.0–10.9 months)	0.7 months (0.0–8.6 months)	1.9 months (0.0–11.0) months
Median time from diagnosis to palliative RT, months (range)	22.0 months (0.2–158.4 months)	25.6 months (0.2–158.4 months)	21.1 months (0.6–110.7 months)
RT technique			
2-field	44 (34%)	38 (45%)	6 (13%)
3–4 field	44 (34%)	16 (19%)	28 (61%)
IMRT	23 (18%)	17 (20%)	6 (13%)
SBRT/SRS	7 (5%)	7 (8%)	-
Electrons	4 (3%)	4 (5%)	-
Rapid start 2-field or 3–4 field, then IMRT	6 (5%)	1 (1%)	5 (11%)
Rapid start 3-field, then IMRT	2 (2%)	1 (1%)	1 (2%)
RT prescription			
800 cGy × 1 fx	7 (5%)	5 (6%)	2 (4%)
400–600 cGy × 4–5 fx	19 (15%)	12 (14%)	7 (15%)
300 cGy × 10 fx	20 (15%)	18 (21%)	4 (9%)
250 cGy × 10–15 fx	8 (6%)	6 (7%)	2 (4%)
200 cGy × 10–12 fx	18 (14%)	17 (20%)	1 (2%)
150 cGy × 20–24 + fx	6 (5%)	–	6 (13%)
180–250 cGy × 15–20 fx	8 (6%)	–	7 (15%)
180–200 cGy × 20 + fx	12 (9%)	1 (1%)	11 (24%)
Other	32 (25%)	25 (30%)	6 (13%)
Failed to receive full palliative RT course	20 (15%)	5 (6%)	15 (33%)
Prior RT to site requiring palliation	19 (15%)	13 (15%)	6 (13%)
Median dose prior RT (range)	3960 cGy (800–5940 cGy)	3600 cGy (800–5940 cGy)	2750 cGy (800–5580 cGy)

Abbreviations: RT, radiation therapy; IMRT, intensity modulated radiation therapy, SRS/SBRT, stereotactic radiosurgery/stereotactic body radiation therapy; fx, fractions.

patients in the Brazil cohort compared to the JHH cohort stopping treatment early (33% vs. 6%, p = <0.001).

Fig. 1 depicts the symptom response rate to palliative RT overall and by cohort. Of the 130 patients included in this study, 102 (78%) had follow-up data available for review. Of these patients, 67% experienced a complete (CR) or partial response (PR) to palliative RT, with 81% of patients in the JHH cohort compared to 44% of patients in the Brazil cohort reporting CR/PR. Of the remaining patients, 12% reported stable symptoms (SS) and 22% reported progressive symptoms (PS).

Table 5 shows additional patient outcomes following palliative RT. Median time to symptom response from the end of palliative RT was 2.5 days (interquartile range (IQR), 0–20 days). The median survival from the end of palliative RT was 3.6 months (95% confidence interval (CI), 2.3–4.8 months). Of the 71 patients necessitating palliative RT due to pain, 63 (89%) had follow-up symptom response data available for review. Fifty-two of these 63 patients (83%) had improvement in their pain. Improvements in pain enabled 24 (46%) of these 52 patients to decrease or discontinue opiate use, including 23/39 (59%) in the JHH cohort and 1/13 (8%) in the Brazil cohort. Patients with a CR of their pain following palliative RT were more likely to have a shorter time from symptom onset to start of RT (median 0.7 months, 95%CI 0.5–1.0 months) than patients with a PR/no response (median 1.0 months, 95% CI 0.4–1.6 months, p = 0.015) and have a longer survival from end of palliative RT (median 17.1 months, 95% CI

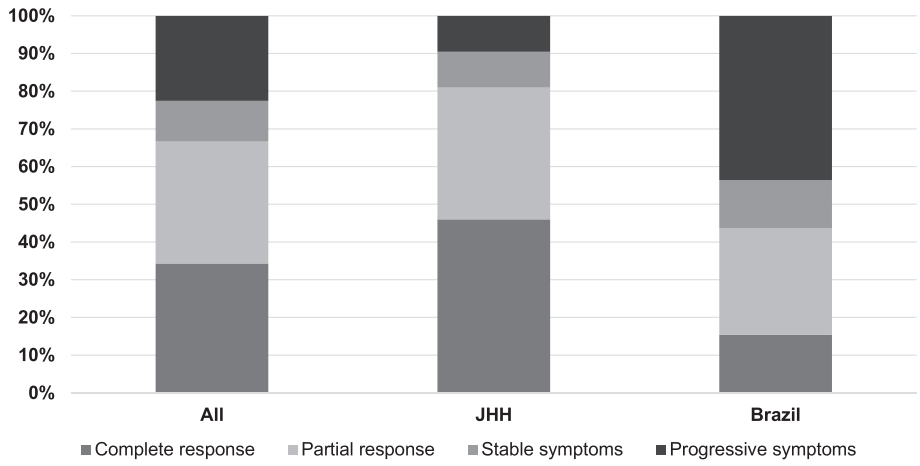

Fig. 1. Symptom response rates to palliative radiation therapy.

Table 5
Patient outcomes following palliative radiation therapy.

	All (N = 130)	JHH (N = 84)	Brazil (N = 46)
Median survival from end of palliative RT	3.6 months (95% CI, 2.3–4.8 months)	3.6 months (95% CI, 1.3–5.8 months)	3.8 months (95% CI, 2.3–4.8 months)
Symptom response rate (CR/PR)*	67%	81%	44%
Measure of symptom improvement**			
Decreased pain	52	39	13
Decreased opiate use	24	23	1
Improved function (breathing, neurological deficit, etc.)	23	18	5
Other	9	6	3
Median time to symptom improvement from end of palliative RT*	2.5 days (IQR, 0–20 days)	7 days (IQR, 0–20 days)	0 days (IQR, 0–1 days)
Grade 3+ toxicity***	5 (4%)	2 (2%)	3 (7%)

Abbreviations: RT, radiation therapy; CR, complete response; PR, partial response.
* Reported out of 102 patients of 130 with available symptom response follow-up data.
** Includes only patients with complete or partial response (n = 68). Patients may have measured improvements in more than 1 reported domain.
*** Grade ≥3 toxicities include: anorexia (large pelvic field RT), mucositis (head and neck RT), dermatitis (spine RT), rectal bleeding (pelvis RT), bradycardia (intracardiac mass RT).

0–35.7 months) than patients with a PR/no response (median 2.4 months, 95% CI 0.4–4.4, p = 0.001).

Radiotherapy toxicity data were available for 125 of the 131 patients (95%). 53 patients (42%) experienced a grade 1 or 2 toxicity. Grade 3 toxicity occurred in 4 patients, including 1 patient with radiation dermatitis after 20 Gy, 1 patient with rectal bleeding requiring argon laser treatment, 1 patient with mucositis leading to inability to take oral medications, and 1 patient with anorexia. One patient who was treated with palliative RT for an intracardiac mass developed grade 4 bradycardia while on treatment due to either tumor progression, radiation-induced tumor edema, or as a potential radiation-associated toxicity. There were no other grade 4 or higher toxicities attributed to RT.

Discussion

While palliative therapy is gaining recognition for its important role in the treatment of patients with chronic or terminal conditions, the support for its use varies across healthcare systems and countries [1–3]. Furthermore, the role of palliative RT is established for adults; however, its use, utility, and toxicities are less well characterized for pediatric patients. This series reviews the clinical indications, toxicity, and outcomes for children treated with palliative RT in 3 academic centers—one in the US with an established integration of palliative resources and two in Brazil where palliative care provisions are overall in the developing phase.

Dose and fractionation varied both between and within the JHH and Brazil cohort, highlighting the variety of regimens currently employed for palliative RT. This observation has also been noted in prior studies from our group [13] and others [14] and demonstrates the lack of consensus for optimal palliative management in pediatrics that stems from the complex social and medical considerations and the lack of prospective data to guide a standardized approach to palliative RT in pediatric patients. The safety and efficacy of a variety of dose and fractionation schedules are reported for palliative RT scenarios in adult patients including brain metastases [15–17], bone metastases [18–20], and spinal cord compression [21,22]. The randomized data in the adult population, and the consensus guidelines these data inform [23], have helped to inform the clinician how to balance the need for time-efficient and effective therapy with minimal toxicity and the appropriate level of durability based on the patient's clinical scenario. The practice of pediatric palliative RT is more heterogeneous than in the adult population, as only retrospective data exist describing the clinical experience of palliative RT in the pediatric population [4–7,9,10,13,14,24].

In the JHH cohort, palliative RT was delivered sooner after symptom onset (median 0.7 months vs. 1.9 months), more patients completed their full palliative RT course (94% vs. 67%), and CR/PR rate was higher (81% vs. 44%) than in the Brazil cohort. We also reported that patients with a CR to pain were more likely to have had prompt initiation of palliative RT. This may represent one contributing factor toward improved response rates in the JHH cohort. Varma et al. found that palliative RT for pediatric cancers was less

effective in the last 30 days of life compared to before the last 30 days of life (symptom response rates of 89% vs. 28%), partly due to widely disseminated disease and lower RT completion rates in the former group [12]. Considering the relatively poor prognosis for patients in our study, even small delays in initiation can lead patients to receive palliative RT within the final days of life or amidst progressive disease/other serious medical problems, thereby potentially rendering treatment less effective or clinically meaningful. This relationship between earlier timing of RT and improved outcomes has been suggested for a variety of adult cancers in the curative setting [25,26]. Overall, early initiation of palliative RT appears important.

As palliative care expands internationally for the pediatric population, it is important to consider potential barriers to timely initiation of RT. Logistical barriers include the availability of RT treatment resources, transportation, and anesthesia. Insurance or health agency authorization poses an additional barrier. Other, perhaps more addressable barriers include providers' reluctance to refer for RT and patient/family reluctance to proceed with RT due to perceived impact on quality of life (QoL) and fear of side effects [11,13]. Improved provider training on palliative care, in concert with development of guidelines for palliative RT in the pediatric population, is essential. Future prospective studies should also gather patient-reported QoL. Moreover, careful patient/family education of the timing of relief, few treatment fractions, and minimal risk of toxicities may help alleviate common concerns.

Strong opiates, particularly morphine, are commonly used for cancer-related pain in children, recommended by the WHO in the "second step" for moderate to severe pain [27]. In our study, we found that 46% of those with pain relief from palliative RT reduced their opiate usage, particularly those in the JHH cohort. The reduction in opiate use conferred by palliative RT may be desirable, as the former typically carries a greater risk of adverse effects. Monteiro et al. found that when morphine was used for cancer-related pain in children, side effects were present in 82/111 (74%) episodes. The most common side effects were constipation, drowsiness, itching, nausea, and vomiting [28]. Although severe side effects (eg, respiratory arrest) from opiates appear rare in children with cancer [28,29], the aforementioned low-grade toxicities may still significantly affect QoL.

Limitations of this study are primarily driven by its retrospective nature and the lack of participation of institutions from other countries and health systems beyond the academic US and Brazil-based institutions presented here. Heterogeneity within and between the two cohorts and patient numbers limits extensive comparisons. Additional data including experiences from other institutions across the world would be helpful to guide pointed recommendations to inform the practice of pediatric palliative RT across diverse health care systems. Furthermore, it is imperative that future prospective studies should include quality of life data, as these are arguably the most meaningful outcome in the palliative setting. For future integration of palliative RT in sectors currently lacking experience or support, it is imperative to develop and engage in randomized trials to guide palliative RT dose levels with dedicated follow-up efforts to assess response and toxicity.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.05.017.

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