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Short Hypofractionated Radiotherapy in Palliation of Pediatric Malignancies: Outcomes and Toxicities

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Abstract

Purpose—Treatment strategies in palliation of pediatric cancer remain a significant challenge. In this study, we aimed to assess efficacy and safety of a short course of hypofractionated RT for metastatic, or recurrent childhood tumors.

Methods and Materials—A total of 104 lesions in 62 pediatric patients with metastatic or recurrent cancer were treated with a short hypofractionation schedule (>1 but ≤5 fractions; 3 Gy per fraction) between 2007 and 2017 in our institution. Primary endpoint was local control (LC). Other endpoints included treatment response, overall survival (OS), progression-free survival (PFS), and toxicity. Toxicities were assessed using the Common Terminology Criteria for Adverse Events v.4.0.

Results—The most common histologies were neuroblastoma - 50 (48.1%), osteosarcoma - 17 (16.4%), and Ewing sarcoma - 13 (12.5%). A median total dose of 24 Gy was delivered in a median of 5 fractions. Out of 104 lesions, 26 (25.0%) were treated with SBRT, 24 (23.1%) – IMRT, 48 (46.2%) – 2D or 3D-CRT. Complete/partial response was observed in 63 (60.6%) lesions, stable disease - in 34 (32.7%). At a median follow-up of 8.7 months, there were 21 (20.2%) local failures. The 1- and 2-year LC rates were 74% and 68%, respectively. LC was better for tumors without prior irradiation 83% vs 57% with prior RT (p=0.004). LC rates did not differ between RT techniques, or total BED10 (≤30 vs >30 Gy). At the time of analysis, 38 (61.3%) deaths were recorded. The 1-year PFS and OS rates were 31% and 44%, respectively. Incidence of any grade ≥3 toxicity was 6.7% (7 of 104). There were no grade 5 events.

Conclusions.—Short hypofractionation scheme yields effective disease control and treatment response with favorable side effect profile. Select pediatric patients with symptomatic metastases or recurrent disease can be considered for a short course of palliative RT.

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Summary

This study analyzed outcomes in 62 pediatric patients who were treated with a total of 104 courses of short hypofractionated radiotherapy to the sites of recurrent or metastatic disease.

Hypofractionation to a median cumulative biologically effective dose (BED10) of 43 Gy produced robust short-term local control and resulted in favorable treatment response and toxicities.

Nevertheless, survival outcomes remained dismal. Large-scale prospective studies are required to identify optimal dose schemes for palliation of incurable childhood tumors.

Introduction

Palliation of pediatric malignancies is a challenging task for clinicians managing this unique patient population. While surgery is often associated with significant morbidity and extended recovery time, systemic therapy and prolonged courses of radiotherapy (RT) can lead to increased outpatient visits and prolonged hospital stays. In this context, palliative measures aimed at delivering treatment within a short period of time with minimal toxicity should be prioritized. One such strategy could be a delivery of a shorter hypofractionated course of radiation.

The use of hypofractionation regimens in the management of metastases has been well described in adult population.^{1–7} The utility of such an approach in pediatrics is poorly defined. This may in part be explained by a well-founded concern for increased late toxicities and paucity of randomized data on palliative RT for metastatic childhood tumors. At the same time, there is substantial evidence suggesting both favorable local control at metastatic sites and acceptable side effect profile with the use of conventional fractionation in pediatric cancers.^{8–12} However, longer multi-week courses of palliative RT may have a deleterious impact on the quality of life of these often-debilitated patients and increase both psychosocial and economic burden on child's caregivers.

Understanding efficacy and safety of shorter hypofractionation schemes is critical to improving pediatric palliative care. Currently, valid clinical data on this important topic are limited. Very few studies have addressed the question of hypofractionation for metastatic or recurrent pediatric malignancies^{13–15}. Some Children's Oncology Group (COG) clinical trials for Ewing sarcoma and rhabdomyosarcoma are currently investigating the role of intensified treatment approaches, such as stereotactic body radiation therapy (SBRT), for bone metastases. However, the results of these studies are not going to be available for a few years. In such a context, we performed a retrospective analysis characterizing outcomes after a short course (>1 but ≤ 5 fractions) of hypofractionated RT for metastatic, or recurrent pediatric malignancies.

Materials and Methods

Patient Selection and Radiation Treatment

Approval by our Institutional Review Board was obtained prior to initiating the study. A total of 104 lesions in 62 patients aged ≤ 18 years with metastatic or recurrent disease were treated with a short hypofractionated palliative RT between 2007 and 2017 in our institution.

A short hypofractionated regimen was defined as a delivery of >1 but ≤ 5 fractions using 3 Gy per fraction once daily. Only fully completed courses of prescribed RT were included for analysis. Radiation was delivered using intensity-modulated RT (IMRT), stereotactic body radiotherapy (SBRT), proton beam RT, three-dimensional conformal RT (3D-CRT), or two-dimensional RT (2D RT). General anesthesia was administered for children who were unable to lie steady for the duration of treatment either due to young age, or debilitating symptoms.

For each course of radiation, extracted data included patient's age, gender, race, Lansky Performance Score (LPS), tumor histology, anatomic location, bony vs non-bony site of the lesion, metastatic vs recurrent setting, RT technique, dose per fraction, total dose, and treatment schedule. Data on indication for treatment (symptom palliation vs asymptomatic radiographic progression of metastatic or recurrent disease) were also collected. In order to account for variations in RT regimens, we converted radiation doses to a total biologically effective dose with α/β of 3 (BED3), and total biologically effective dose with α/β of 10 (BED10). Dose data on those sites that had been previously irradiated were also obtained, and respective total BED3 and BED10 of prior RT courses were calculated.¹⁶

Study Endpoints and Statistical Analysis

Primary study endpoint was local control (LC) which was evaluated retrospectively using follow-up imaging studies. Local failure was defined as a tumor relapse within the radiation target volume at any point after treatment completion. Secondary endpoints included treatment response, overall survival (OS), progression-free survival (PFS), and toxicity. Treatment response was determined mainly radiographically. Treatment response was assessed clinically only in scenarios where post-treatment imaging was not performed. Complete response (CR) was defined as no evidence of residual tumor on post-RT imaging studies, or a complete resolution of symptoms after the treatment. Partial response (PR) was defined as any decrease in tumor size or extent on post-RT imaging, or any improvement of symptoms. Stable disease (SD) was defined as no change in tumor size, or extent, or patient's symptomatology. All other post-RT radiographic and clinical findings were deemed progression of disease (PD). Furthermore, pertinent symptom response data were evaluated. Complete symptom response was defined as a complete resolution of a symptom as reported by a patient, a parent, or a guardian. Partial symptom response was defined as a significant partial improvement in a symptom. No response was defined as a failure to achieve a complete or partial symptom response. Toxicities were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

Survival intervals were calculated from the date of the last RT treatment to the date of last contact or first occurrence of the event of interest. Local control and survival estimates with corresponding 95% confidence intervals (CIs) were measured for the study endpoints using the Kaplan-Meier method. The log-rank test was utilized to compare distributions of LC stratified by various clinical and treatment-related factors. Hypothesis testing was two-sided and conducted at the 5% level of significance. All statistical analyses were performed using StataIC version 14 (StataCorp LP, College Station, Texas).

Results

Clinical and radiation characteristics

Baseline patient and clinical characteristics are summarized in Table 1. The median age was 12 years (range, 3–18 years). Median LPS prior to initiating RT was 80 (range, 40–100). The most common histologies of the irradiated lesions were neuroblastoma (NB) – 50 (48.1%), osteosarcoma – 17 (16.4%), and Ewing sarcoma (ES) – 13 (12.5%). The majority of tumors constituted bony lesions – 75 (72.1%), or represented a metastatic disease – 91 (87.5%). Short hypofractionated RT was most commonly used for the lesions of the axial skeleton – 42 (40.4%), followed by the lesions of the appendicular bone – 27 (26.0%), and CNS tumors – 18 (17.3%). Symptom palliation was an indication for RT in 80 (76.9%) cases, whereas asymptomatic radiographic progression of metastatic or recurrent disease – in 24 (23.1%) cases. The most commonly treated symptoms were bone pain – 61 (76.3%), pain due to soft tissue mass – 7 (8.7%), and neurologic symptoms due to brain mass – 7 (8.7%) (Supplemental Table 1). Concurrent chemotherapy was delivered during 16 (15.4%) courses of RT. A total of 46 (74.2%) patients received systemic therapy after completion of RT.

A median total dose of 24 Gy (range, 15–40 Gy) was delivered to the analyzed sites in a median of 5 fractions (range, 3–5) (Table 2). Median dose per fraction was 5 Gy (range, 3–10 Gy). The three most common dose regimens were 20 Gy in 5 fractions – 35 (33.6%), 30 Gy in 5 fractions – 22 (21.1%), and 24 Gy in 3 fractions – 14 (13.5%). A total of 26 lesions (25.0%) were treated with SBRT, 24 (23.1%) – IMRT, and 48 (46.2%) – 2D or 3D-CRT. Short hypofractionated RT was delivered to 34 (32.7%) tumors that had been previously irradiated.

Local control

At a median follow-up of 8.7 months, there were 21 (20.2%) local failures out of 104 irradiated tumors. The LC rates at 1 and 2 years were 74% and 68%, respectively (Table 3). Kaplan-Meier curve for LC for the entire cohort is shown in Figure 1A. The 1-year LC rates were better for tumors with C/PR 86% vs 68% with SD ($p<0.00001$), and for tumors that had not been previously irradiated 83% vs 57% with prior RT ($p=0.004$) (Table 4). LC rates did not differ between RT techniques, or total BED10 (30 Gy vs >30 Gy). There was a trend toward improved 1-year LC with irradiation of ES 100% vs 82% NB vs 28% osteosarcomas ($p=0.09$). Additionally, a trend toward better 1-year LC was noted for bony vs non-bony sites, 81% vs 62% ($p=0.09$), and for metastatic vs recurrent lesions, 78% vs 55% ($p=0.08$).

Treatment response and survival

Complete/partial response (C/PR) was observed in 63 (60.6%) lesions, stable disease (SD) – in 34 (32.7%), and progression – in 7 (6.7%). Data describing symptom assessment after 80 (76.9%) courses of short hypofractionated RT are summarized in Supplemental Table 1. Overall response (complete, or partial) for all symptoms was documented in 51 (63.4%) cases. Complete and partial symptom response to palliative RT for bone pain were observed in 15 (24.6%) and 26 (42.6%) cases, respectively; for neurologic symptoms due to brain

mass – in 4 (57.1%) and 3 (42.9%) cases, respectively, and for pain due to soft tissue mass – in 1 (14.3%) and 1 (14.3%), respectively.

At the time of analysis, 38 (61.3%) deaths were recorded. The 1-year and 2-year PFS rates were 31% and 20%, respectively (Table 3). Median progression-free survival was 3.7 months. The 1-year and 2-year OS rates were 44% and 28%, respectively. Figures 1B and 1C depict Kaplan-Meier curves for PFS and OS for the entire cohort. Notably, two patients (3.2%) survived beyond 5 years of follow-up. One of the long-term survivors had a multi-year history of metastatic pheochromocytoma managed with numerous surgical resections and radiotherapy courses, whereas the other patient had a 10-year history of metastatic neuroblastoma managed with multi-modality approach.

Toxicity data

Acute and late radiation sequelae are summarized in Table 5. The incidence of any grade 3 toxicity was 6.7% (7 of 104), most of which (n=5) were grade 3. There were no grade 5 toxicities. Three of 7 toxicities were acute (< 60 days). One patient developed severe acute refractory vomiting and nausea with inability to tolerate PO intake requiring hospitalization and supportive therapy (i.e. intravenous fluid resuscitation and aggressive anti-emetic pharmacotherapy), with subsequent symptom resolution. Two patients developed acute moist desquamation of the irradiated skin which resolved with application of silver sulfadiazine cream shortly upon completion of RT. Two patients developed enteritis resulting in small bowel obstruction (SBO) requiring surgical resection >90 days post-treatment. Notably, both patients with SBO had received prior abdominal or pelvic RT before completing palliative hypofractionation regimen. Furthermore, no significant late radiation-related sequelae were reported for the two patients who survived 5 years posttreatment.

Discussion

To the best of our knowledge, this is the largest to-date analysis of outcomes after short hypofractionated RT in palliation of pediatric malignancies. In this study, a high proportion of irradiated tumors constituted bone lesions and represented distant metastases and were neuroblastomas or bone sarcomas by histology and were treated with either SBRT or IMRT. The median total BED10 in the entire cohort was 43 Gy. The most common anatomic sites of irradiation were axial skeleton, appendicular bone, and CNS. In this context, a short hypofractionation regimen yielded effective local control and favorable treatment response. Toxicity profile was mainly acceptable, with only two CTCAE grade 4 and no grade 5 events. Select pediatric patients with recurrent or metastatic tumors can be considered for a short palliative course of RT (< 5 fractions). This may result in an invaluable shortening of overall treatment time without apparent compromise of clinical efficacy.

Local control outcomes observed in this cohort suggest that a short hypofractionation scheme could be an attractive alternative to longer courses of radiation in the context of incurable advanced childhood tumors. In fact, out of 104 irradiated lesions in the present cohort, 79.8% remained free of recurrence at a median follow-up of 8.7 months. Limited available data on local control after conventional fractionation in palliation of pediatric malignancies offers a useful comparison. For instance, Texas Children's Hospital analysis of

local therapy to metastases in stage IV rhabdomyosarcoma revealed a LC of 73% at a median follow-up of 2 years after irradiation of nonlung or nonbone marrow metastatic sites.¹² The majority of lesions in the above series received a total of 50.4 Gy in 28 fractions. Similarly, Kandula et al studied outcomes after irradiation of metastatic sites in patients with stage IV neuroblastoma and observed 23% local failures in 13 metastatic sites treated with at least 12 fractions of conventional RT to a median dose of 21.6 Gy.¹⁷ We must acknowledge that such comparisons of local control between hypofractionation and conventional schedules must be taken with caution considering heterogeneity of histologies, irradiated anatomic sites, and selection bias. At the same time, carrying out a large-scale randomized trial assessing the utility of different dose schemes in palliation of pediatric malignancies presents a substantial challenge.

In this study, nearly half of all treatment courses were delivered using SBRT or IMRT. Apart from the obvious benefit of improved normal tissue dosimetry, such modalities offer an additional potential advantage of dose escalation in the management of metastases or recurrences of radioresistant pediatric tumors. Nevertheless, in our analysis highly conformal approaches (i.e. SBRT/IMRT), or larger cumulative BED (>30 Gy) did not appear to convey improved LC. One should note, however, that osteosarcomas, for which such a benefit would be the most apparent, represented only a minority of cases in this cohort. Notably, the value of SBRT in palliation of pediatric tumors has been assessed in a Mayo Clinic retrospective analysis of outcomes after irradiation of metastatic or recurrent ES and osteosarcoma.¹³ Of 13 lesions treated with palliative intent to a median total SBRT dose of 40 Gy in 5 fractions, 10 (77%) were controlled until death or last follow-up. Irradiation of 8 (62%) lesions provided either complete or partial symptom relief, while no patients developed grade 3 or higher toxicities. Although the Mayo Clinic study had a short follow-up and a small sample size, it provides intriguing data on potential benefits of dose escalation with SBRT for metastatic or recurrent childhood tumors.

Identifying patients who may benefit the most from re-treatment of a previously irradiated metastatic site presents another challenging palliation task in pediatrics. In our analysis, a third of hypofractionated treatments represented a second course of irradiation. However, local control outcomes at the sites of prior RT were markedly worse than at the sites where hypofractionation was the first treatment course. Furthermore, higher doses of re-irradiation did not confer local control benefit; on the contrary, total BED₁₀ >40 Gy resulted in a dramatically inferior 1-year LC relative to total BED₁₀ ≤40 Gy. One may hypothesize that tumors progressing at the previously treated metastatic sites may contain radioresistant clones making it particularly challenging to achieve disease control. Furthermore, the value of re-irradiation may be histology and/or anatomic site dependent. In fact, few series investigating the question of re-irradiation in pediatric population suggest that recurrences in the CNS, specifically ependymomas and diffuse intrinsic pontine gliomas, represent a subset of childhood tumors that may derive a robust short-term therapeutic benefit with re-treatment.^{18–19}

We were intrigued to find a remarkably favorable treatment response to the hypofractionation schemes in this patient cohort. Interestingly, progression of disease was noted only in 6.7% of cases, while a complete or a partial treatment response was observed

upon completion of the majority (60.6%) of treatment courses. These findings are consistent with the outcomes seen in the studies where longer courses of RT were infrequently utilized. In a French series investigating the role of palliative RT for metastatic neuroblastoma, Causa et al observed an overall response rate of 63.2% after irradiation of 38 bone metastases.²⁰ Longer irradiation courses (>5 fractions) were utilized in 44% of cases. In another analysis performed at University of California, San Diego (UCSD), Rahn et al investigated clinical outcomes after 83 courses of palliative RT for pediatric malignancies of various anatomic sites and histologies.¹⁵ In their study, Rahn and colleagues reported an overall response rate (partial or complete) for all sites at 72%. A slightly higher response rate in the UCSD study can be partially explained by differences in methodologies between our investigations: while we used predominantly radiographic findings to record treatment response, Rahn et al utilized symptom changes as a measuring parameter. Notably, in the UCSD analysis palliation was performed using a variety of dose regimens, ranging from 14 fractions of 2.5 Gy to 1 fraction of 8 Gy. These findings reiterate that while longer courses of RT may provide a robust clinical and/or radiographic treatment response in advanced pediatric cancers, shorter hypofractionation schemes represent an alternative with comparable efficacy.

While the most common indication for short hypofractionated RT in our study was symptom relief, asymptomatic radiographic progression of disease constituted a significant proportion of cases (a total of 23%). Such an observation suggests a potential preventative role of palliative hypofractionated RT in the setting of an incurable pediatric malignancy, as it may help prevent and/or delay the onset of debilitating morbidities. With regards to symptom palliation, the most common indication for treatment in our cohort was bone pain. Complete or partial relief was achieved in the majority of cases. Furthermore, neurologic symptoms due to brain mass resolved either completely or partially improved in all clinical scenarios in which short courses of RT were prescribed in the present cohort. These findings support the utility of hypofractionated RT as an effective technique to relieve debilitating bone pain and alleviate tumor-related neurologic disturbances in this unique patient population. Ultimately, given a short lifespan of children with metastatic cancer, more efforts of a treating physician should be focused on maximizing symptom control without incurring significant morbidity and/or prolonging overall treatment time.

Despite favorable short-term local control with palliative RT observed in our and other retrospective series, survival among children with advanced cancer remain poor. In the present cohort even though a majority of children received systemic therapy upon radiation completion, 2-year OS and PFS rates were dismal: 28% and 20%, respectively. Similar outcomes have been reported in studies where standard fractionation was used to treat metastatic sites.^{12, 15, 21} In an analysis of survival after conventional RT for metastatic ES in children, Paulino et al reported 2-year rates for OS and PFS at 30.3% and 23.3%.²¹ Rahn and colleagues observed a median survival of 6.5 months after palliative RT to the metastatic lesions in a cohort of 44 children with different primary malignancies.¹⁵ Similar to our study, the most common histologies in a Rahn et al analysis were ES, osteosarcoma, rhabdomyosarcoma, and NB. At a median follow-up of 6.5 months, only 23% of patient were alive, whereas in our cohort, 38.7% of children were alive at a median follow-up of 8.7 months. These findings highlight that, unfortunately, most pediatric patients with metastatic

stage will ultimately succumb to their disease. While eligible children should be strongly considered for enrollment on clinical trials, the care of patients with imminently poor prognosis should be focused on optimizing quality of child's life and decreasing treatment burden.

The present analysis reveals that in a well-selected group of patients short palliative hypofractionated schemes can be well tolerated. The exception in this cohort were two cases of radiation-induced enteritis resulting in SBO. Considering that both patients had received abdominopelvic irradiation, caution should be exercised when recommending palliation with hypofractionation schedule in a similar clinical context. Overall, toxicity outcomes in our analysis appear to compare well with those reported in the series where longer courses of palliative pediatric RT were utilized.^{8, 22–23} In a study of 76 palliative RT courses for pediatric malignancies of various anatomic sites and histologies, Mak and colleagues noted only two episodes of grade 3 and no grade 4–5 toxicities.²³ In their analysis, median number of RT fractions was 12 and median RT dose was 30 Gy, whereas in our study median number of fractions was 5 and median RT dose was 24 Gy. It is important to note that given heterogenous dose schemes and short follow-ups in the present and other series examining the utility of palliative RT, it is challenging to draw meaningful conclusions with regard to late toxicities. Therefore, special care should be taken when recommending hypofractionation for patients who are expected to live long enough to experience potentially significant late radiation sequelae.

Our analysis has several important shortcomings. First, given its retrospective nature and single-institution experience, the study is limited by a selection bias. Furthermore, some patients received RT to other sites of metastases using schemes longer than 5 fractions, hence, reported survival rates might have been overestimated. Additionally, variability of fractionation schedules used in this patient cohort also precludes us from making meaningful conclusions on the optimal dose regimen. Furthermore, we did not include data on the clinical outcomes after a single-fraction palliative RT for metastatic or recurrent disease. Given a lack of a significant LC benefit with BED10 30 vs >30 Gy in the present cohort, one may hypothesize that a single fraction of radiation may provide comparable palliative outcomes with regards to clinical efficacy and tolerability, and therefore further reduce treatment burden on a child and limit economic hardship on a child's family. Finally, the effect of concurrent systemic therapy on local control and/or toxicity profile with short hypofractionation is not clear from our data, as only 15% of patients received concomitant chemotherapy. Therefore, until there is better understanding of the value of concurrent chemotherapy with palliative short hypofractionated RT for pediatric malignancies, it might be prudent to delay initiation of systemic therapy until after completion of radiation.

Conclusions

In summary, short hypofractionated RT delivered over a course of 5 fractions or less can yield favorable local control and treatment response in a well-selected group of pediatric patients, without incurring significant treatment-related sequelae. This is not meant to ascertain that short hypofractionation regimen should be the sole radiation approach in the management of metastatic or recurrent pediatric malignancies. However, patients with

limited expected survival should be strongly considered for a shorter schedule. Decreasing overall treatment time is paramount to improving quality of life of this fragile patient population and reducing treatment burden on child's caregivers. Large-scale multi-institutional investigations are needed to identify optimal dose and fractionation in order to further improve local control and safety in this unique patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Kaplan-Meier Local Control and Survival Curves

A. Actuarial LC curve

B. Actuarial OS curve

C. Actuarial PFS curve

Table 1.

Patient and tumor characteristics

Characteristic	No. (%)
No. of patients/lesions	62/104
Age (years) (n=62)	
Median	12
Range	3–18
Sex	
Female	24 (38.7 %)
Male	38 (61.3 %)
Ethnicity	
White	37 (59.7 %)
Black	10 (16.1%)
Others	15 (24.2%)
Lansky Performance Score (LPS)	
Median	80
Range	40–100
Histology (by lesions)	
Neuroblastoma	50 (48.1%)
Osteosarcoma	17 (16.4%)
Ewing Sarcoma	13 (12.5%)
Rhabdomyosarcoma	4 (3.8%)
Wilms tumor	4 (3.8%)
GBM	4 (3.8%)
Other	12 (11.5%)
Disease	
Metastatic	91 (87.5%)
Recurrent	13 (12.5%)
Bony site	
No	29 (27.9%)
Yes	75 (72.1%)
Anatomic site	
CNS	18 (17.3%)
H&N	8 (7.7%)
Thorax/Abdomen/Pelvis	9 (8.6%)
Axial bone	42 (40.4%)
Appendicular bone	27 (26.0%)

Table 2.

Radiation therapy characteristics (n=104)

Characteristic	No. (%)
RT technique	
SBRT	26 (25.0%)
IMRT	24 (23.1%)
2D/3D-CRT	48 (46.2%)
Electron RT	4 (3.9%)
Proton RT	2 (1.9%)
Total dose (Gy)	
Median	24
Range	15 – 40
Number of fractions	
Median	5
Range	3–5
Dose per fraction (Gy)	
Median	5
Range	3–10
Regimen (total Gy/number of fractions)	
24 Gy/3	14 (13.5%)
27 Gy/3	10 (9.6%)
30 Gy/3	2 (1.9%)
14.8 Gy/4	1 (1.0%)
16 Gy/4	1 (1.0%)
15 Gy/5	2 (1.9%)
20 Gy/5	35 (33.6%)
25 Gy/5	11 (10.6%)
30 Gy/5	23 (22.1%)
40 Gy/5	5 (4.8%)
Total BED3 (Gy)	
Median	88
Range	30–146
Total BED10 (Gy)	
Median	43
Range	20–72
Previously irradiated site	
No	70 (67.3%)
Yes	34 (32.7%)

Characteristic	No. (%)
Prior Total BED3 (Gy)	
Median	60
Range	27–260
Prior Total BED10 (Gy)	
Median	39
Range	21–120

Table 3.**Efficacy Outcomes** (Median follow-up 8.7 months (range, 1.4 – 39.0 months))

Variable	LC	PFS	OS
	(95% CI)	(95% CI)	(95% CI)
1-year	74% (0.62–0.83)	31% (0.22–0.41)	44% (0.34–0.54)
2-year	68% (0.54–0.79)	20% (0.11–0.31)	28% (0.19–0.38)
3-year	60% (0.38–0.76)	17% (0.08–0.28)	18% (0.09–0.29)

Abbreviations: LC – local control, PFS – progression-free survival, OS – overall survival, CI – Confidence Interval

Table 4.**The 1-year LC rates** (Median follow-up 8.7 months (range, 1.4 – 39.0 months))

Variable	1-year LC Rate (95% CI)	Log-rank <i>P</i>
Histology (by lesions)		
Neuroblastoma	82% (0.65–0.91)	0.09
Osteosarcoma	28% (0.01–0.69)	
Ewing Sarcoma	100%	
Other	61% (0.34–0.80)	
Disease		
Metastatic	78% (0.65–0.87)	0.08
Recurrent	55% (0.23–0.78)	
Bony site		
No	62% (0.37–0.79)	0.09
Yes	81% (0.68–0.90)	
Anatomic site		
CNS	63% (0.31–0.83)	0.53
H&N	100%	
Thorax/Abdomen/Pelvis	36% (0.01–0.78)	
Axial bone	80% (0.61–0.91)	
Appendicular bone	77% (0.50–0.91)	
RT technique		
SBRT	74% (0.51–0.88)	0.66
IMRT	78% (0.51–0.91)	
2D/3D-CRT	76% (0.55–0.88)	
Total BED10 (Gy)		
30	69% (0.45–0.84)	0.30
>30–72	77% (0.62–0.87)	
Previously irradiated site		
No	83% (0.68–0.92)	0.004
Yes	57% (0.33–0.75)	
Previous Total BED10 (Gy)		
40	72% (0.40–0.89)	0.007
>40	42% (0.12–0.70)	
Treatment Response		
Complete/Partial	86% (0.71–0.94)	<0.00001
Stable disease	68% (0.37–0.86)	
Progression of disease	-	

Table 5.**Toxicity Outcomes** (Median follow-up 8.7 months (range, 1.4 – 39.0 months))

Characteristic		Total No. (%)
CTCAE grade 3 toxicity (n=104)		
No		97 (93.3%)
Yes		7 (6.7%)
CTCAE grade 3 toxicity (n=7)		
3		5 (71.4%)
4		2 (28.6%)
5		0 (0%)
CTCAE grade 3 toxicity (n=7)		
Acute (≤ 60 days)		3 (42.9%)
Late (> 60 days)		4 (57.1%)
Type of CTCAE grade 3 toxicity	CTCAE grade	
Vomiting requiring hospitalization (acute)	3	1 (0.9%)
Moist desquamation (acute)	3	2 (1.9%)
Enteritis resulting in small bowel obstruction (late)	4	2 (1.9%)
Myositis (late)	3	1 (0.9%)
Peripheral sensory neuropathy (late)	3	1 (0.9%)