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Radiation for Bone Metastases in Ewing Sarcoma and Rhabdomyosarcoma

Dana L. Casey, BA¹, Leonard H. Wexler, MD², Paul A. Meyers, MD², Heather Magnan, MD², Alexander J. Chou, MD², and Suzanne L. Wolden, MD^{1,*}

¹Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

²Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York

Abstract

Background—The role, optimal dose, and efficacy of radiotherapy (RT) for the treatment of bone metastases in rhabdomyosarcoma (RMS) and Ewing sarcoma (ES) are unclear.

Procedure—All patients with ES or RMS who received RT for bone metastases with curative intent during frontline therapy at Memorial Sloan Kettering Cancer Center (MSKCC) between 1995 and 2013 were reviewed. Among the 30 patients (8 RMS and 22 ES), 49 bone metastases were irradiated.

Results—Median biologically effective dose (BED) was 42.4 Gy (range, 34.9–59.7) for RMS and 50.7 Gy (range, 31.3–65.8) for ES. Tumor recurrence occurred in six of 49 irradiated bone metastases. Cumulative incidence of local failure at a treated metastatic site was 6.6% at 1 year and 9.0% at 3 years. Dose, fractionation, and RT technique did not impact local control at an irradiated site. The presence of >5 bone metastases was associated with worse local control at an irradiated site ($P = 0.07$). The 3-year EFS was 33% in RMS and 16% in ES.

Conclusions—RT appears to be an effective modality of local control for bone metastases in ES and RMS. Local control at sites of metastatic bone irradiation is similar to local control at the primary site after definitive RT. Doses in the biologic range prescribed for the definitive treatment of primary disease should be used for metastatic sites of disease.

Keywords

Ewing sarcoma; radiation oncology; rhabdomyosarcoma

Introduction

Approximately 20% of patients with rhabdomyosarcoma (RMS) or Ewing sarcoma (ES) present with overt metastatic disease, most commonly involving the lungs, bone, and bone marrow [1–3]. In both metastatic RMS and ES, the presence of bone metastases portends a

*Correspondence to: Suzanne L. Wolden, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065, woldens@mskcc.org.

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particularly poor prognosis [4–6]. As part of the curative intent of treating stage IV disease, whole lung irradiation has been routinely employed in treating lung metastases [7–9]. A recent retrospective report from the EURO-E.W.I.N.G 99 trial recognized the importance of local treatment of extrapulmonary metastases in ES as well [10]. However, data regarding irradiation of bone metastases in RMS and ES is scarce, and the few retrospective reports contain a very small number of patients and do not assess prognostic features associated with local control [11,12]. Without a prospective trial evaluating the treatment of bone metastases in pediatric sarcoma, the indications for and optimal dose of radiation therapy (RT) in this setting are unclear. Varying treatment regimens are used on different protocols, at different institutions, and even within the same institution. The objective of this study was to evaluate the indications for, dose, and efficacy of RT for treatment of bone metastases in RMS and ES at a single cancer center.

Methods

Patients

This is a single-institution, retrospectively ascertained cohort of patients with RMS and ES treated with radiation therapy (RT) for bone metastases with a curative intent during frontline therapy between 1995 and 2013 at Memorial Sloan Kettering Cancer Center (MSKCC). Patients undergoing palliative treatment for bone metastases and patients undergoing treatment for relapse were excluded. We identified 30 patients, 22 with ES and eight with RMS, who received RT with curative intent to bone lesions other than the primary tumor site. Work-up for all patients consisted of a computed tomography (CT) scan or magnetic resonance imaging of the primary site, CT of the chest, and bone marrow aspirate and biopsy to evaluate for metastatic disease. Metastatic sites of bony involvement were imaged at diagnosis with radionuclide bone scans and/or [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET). The study was approved by the MSKCC Institutional Review Board/Privacy Board.

Treatment

Radiation—For treatment of the primary site, 20 patients received definitive RT, six underwent surgery and RT, and three underwent surgery alone. One patient had an unknown primary site and consequently did not receive any primary treatment. For treatment of bone metastases, all patients received definitive RT. Patients with 1–4 bone metastases typically received treatment to all sites of disease. Patients with 5 bone metastases received RT to a few select lesions due to concerns for bone marrow toxicity if five or more bones were to receive RT. In these cases, bones chosen for RT were bones with residual disease post-induction chemotherapy, bones with continued uptake on bone scan or persistent FDG activity on PET, and/or weight-bearing bones. The biologically effective dose (BED) was calculated to allow for comparisons between differences in fractionation schedules, using an α/β ratio of 10 [13]. Three patients received total body irradiation (TBI) after bone RT; the TBI course was included in the BED calculations in all three patients because of the short (<1 month) time interval between bone irradiation and TBI.

Chemotherapy—All patients but one with ES were treated on or according to institutional or Children's Oncology Group (COG) protocols consisting of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide. The other patient was additionally treated with actinomycin D. Six of eight patients with RMS were treated on the high-risk arm of an MSKCC phase II pilot protocol IRB #03-099, consisting of irinotecan, carboplatin, cyclophosphamide, doxorubicin, ifosfamide, etoposide, and vincristine. One patient with RMS was treated on COG ARST0431, and one patient was treated with vincristine, ifosfamide, and etoposide.

Statistical Methods and Design

Event-free survival (EFS) was calculated as the time from initiation of treatment to the first event. Events were defined as local and/or distant failure or progression or death. Overall survival (OS) was calculated as the time from initiation of treatment to death from any cause. Patients without an event were censored at the time of last follow-up. The Kaplan–Meier method was used to assess the EFS and OS. A competing-risks analysis was used to assess the cumulative incidence of bone failures from time of bone RT to relapse. A bone failure was defined as recurrence of tumor within the RT field of a treated bone, at any point after RT. To determine local recurrence at irradiated sites, all images (anatomic and functional) of the bone post-RT were reviewed and compared to pretreatment imaging and RT plans. One patient did not have post-treatment imaging of his treated site and thus was excluded from all analyses evaluating local control at metastatic sites. Survival curves among different subgroups of patients were compared with the Mantel log-rank test. Cumulative incidence curves were compared with Gray's method, with $P = 0.05$ considered significant. The Common Terminology Criteria for Adverse Events (version 4.0) was used to grade acute toxicities.

Results

Patient and Tumor Characteristics

Patient and tumor characteristics are shown in Table I. Twenty-two patients had ES and eight had RMS. Median age at bone RT was 19.5 years (range, 1.6–34.6). The most common site of primary disease was the pelvis ($n = 10$) followed by extremity ($n = 7$). All patients were stage IV at diagnosis. Fifty-percent of patients had greater than three sites of bone metastases at presentation and 33% had greater than five. Sixty-seven percent of patients had metastases outside of the bone, most commonly in the lung.

Radiotherapy

Among the 30 patients, 49 bone metastases were irradiated (36 ES, 13 RMS). The most common site of bone irradiation was the spine ($n = 20$), followed by the femur ($n = 16$). Seventeen patients had 1 bone irradiated, eight patients had 2 bones irradiated, four patients had 3 bones irradiated, and one patient had 4 bones irradiated. Fifty-percent of patients received RT to all affected bones. Of the patients who did not receive radiation to all affected bones, 80% had ≥ 5 involved sites at diagnosis.

Bone RT occurred at a median time of 21 weeks from chemotherapy initiation (range, 9–66). Thirty of 49 (61%) bone metastases were irradiated concurrently with the primary site, 16 of which were included in the primary RT field. One patient underwent bone RT prior to primary site RT due to pain at the site of metastases. The remaining bone metastases were irradiated after local treatment of the primary site.

Median BED was 48.0 Gy: 42.4 Gy (range, 34.9–59.7) for RMS and 50.7 Gy (range 31.3–65.8) for ES. Thirty-five of 49 (71%) bone metastases received less than BED of 59.7 Gy for RMS (50.4 Gy in fractions of 1.8 Gy) or BED of 65.8 Gy for ES (55.8 Gy in fractions of 1.8 Gy). All 14 bones that received standard doses for gross disease in RMS and ES were treated with or at the same time as the primary site. Hypofractionation with 3.0–8.0 Gy per fraction was utilized in 10/49 bones, conventional fractionation in 34/49 bones, and hyperfractionation with 1.5 Gy twice per day in 5/49 bones. Median time to complete bone RT was 27 days (range, 4–48). See Table II for more information on RT for bone metastases.

Clinical Outcomes

Six local relapses at previously irradiated sites were observed among five patients (4 ES, 1 RMS). Median time from bone RT to local recurrence was 0.9 years (range, 0.2–7.1). Two patients relapsed in a treated bone after multiple prior recurrences elsewhere. Bony sites of relapse were the femur ($n = 3$), spine ($n = 2$), and pelvis ($n = 1$). Median BED at site of recurrence was 50.6 Gy (range, 39.0–65.9).

Cumulative incidence of local failures at an irradiated bone site was 6.6% at 1 year and 9.0% at 3 years. Diagnosis (RMS vs. ES), technique of RT, and fractionation had no impact on local control. Additionally, BED had no effect on local control ($P = 0.93$, Fig. 1). Among the subgroups of patients with RMS and ES, BED similarly did not influence local control. There was a trend toward increased bone relapse at an irradiated site when there were >5 bone metastases: 1-year incidence was 15.4% with >5 bone metastases versus 5.3% with ≤ 5 bone metastases ($P = 0.07$). See Table III for more information on the local recurrences.

Including local failures at the primary site and distant failures outside of treated bones, 21/30 patients progressed and/or relapsed. Site of first relapse involved the bone in 16/21 patients. Among the entire cohort, the 3-year EFS was 21% and OS was 40%. For ES, EFS and OS were 16% and 38%; and for RMS, EFS and OS were 33% and 45%. EFS was not influenced by the number of bone metastases at diagnosis or the ability to irradiate all sites of bone metastases. Two patients without evidence of disease died from toxicity related to bone marrow transplant and chemotherapy. Five of 21 patients who relapsed are alive, one of whom is without evidence of disease 3 years from last recurrence.

Toxicity

Acute toxicities were mostly grade 1 and depended on site of bone irradiation: dermatitis ($n = 7$), fatigue ($n = 7$), diarrhea ($n = 4$), nausea ($n = 5$), vomiting ($n = 4$), mucositis ($n = 1$), dysphagia ($n = 1$), cough ($n = 1$), esophagitis ($n = 1$), and cystitis ($n = 1$). Grade 2 toxicities included dermatitis ($n = 2$), diarrhea ($n = 2$), and proctitis ($n = 2$). Two patients developed grade 3 mucositis, one of whom received concurrent RT to his primary parameningeal RMS. No patients required a break in treatment due to cytopenias.

With a median follow-up of 4.0 years from bone RT, 11/12 survivors are without late sequelae from bone RT. No patients have developed a fracture in an irradiated bone. One long-term survivor who was treated at the age of 3 years has hearing loss, growth hormone deficiency, thyroid stimulating hormone deficiency, and decreased processing speed 9 years post-RT to the skull base.

Discussion

The most important negative prognostic factor in RMS and ES is the presence of metastatic disease [1,14], especially the presence of bone metastases [5,6]. Although the prognosis for localized ES and RMS has improved over the past few decades, prognosis for patients with metastatic disease has remained poor. Multiple studies have evaluated the potential benefit of WLI for treatment of pulmonary metastases in ES and RMS [6,8,9]. A recent retrospective report from EURO-E.W.I.N.G 99 demonstrated that treatment with radiation for extrapulmonary sites of metastatic disease may also improve outcomes in Stage IV ES. Among 120 patients with extrapulmonary metastases (bone and other), 33 patients underwent definitive RT for treatment of metastatic sites of disease. Patients receiving radiation for local treatment of their metastases had a 3-year EFS of 35% versus 16% in those without local treatment [10]. This study did not evaluate local control at treated metastatic sites, and RT details such as dose, fractionation, and number of irradiated sites per patient are not described in the paper. However, the original protocol called for a minimum of 45 Gy to all clinically detectable extrapulmonary metastases, with the restriction that no more than 30% of a patient's bone marrow be irradiated.

Two other small studies have confirmed the potential efficacy of RT for bone metastases. At University of Iowa Hospitals and Clinics, there was tumor progression in only 1/17 (5.9%) irradiated ES bones versus 15/22 (68.2%) non-irradiated bones [11]. At Children's Hospital in Denver, among five patients with ES and eight patients with RMS who received treatment for extrapulmonary metastases, only one patient failed at a treated metastatic site after a median follow-up of 17 months; the local control as per Kaplan–Meier methods was 92% [12]. Our study is the first to calculate cumulative incidence of local relapses at an irradiated site for ES and RMS; a competing-risk analysis assessing cumulative incidence best takes into account death as a competing risk and thus is a better measure of local failure than Kaplan–Meier in this unfavorable patient population [15]. Moreover, our study is the first to evaluate the influence of potential prognostic factors such as RT dose and number of bone metastases.

Among 49 bone metastases irradiated in our cohort, the cumulative incidence of local failures at an irradiated site was 6.6% at 1 year and 9.0% at 3 years. We did not compare our cohort of patients who received local treatment for bone metastases with those who did not due to a selection bias. Patients with bone metastases who did not receive RT with a curative intent at our institution were often either treated palliatively and/or progressed before time of bone RT. Thus, the patients who were not eligible for definitive RT to sites of bone metastases represent an unfavorable group. However, given the low incidence of local relapses, RT appears to be an effective modality of local control for bone metastases in ES and RMS.

Local control at bone metastases in our cohort is similar to if not slightly better than local control of ES and RS at the primary site after definitive RT. For RMS, local failure was 19% in Intergroup Rhabdomyosarcoma Study (IRS)-III [16] and 13% in IRS-IV [17] for patients with group III RMS. For ES, local failure was 22% after definitive RT at our institution [18], and ranges from 26% to 35% in other series [19–21]. Given the similarities between rates of local control at metastatic and primary sites, it appears that both respond similarly to RT. Four of six relapses in our cohort occurred after sub-therapeutic doses (i.e., doses lower than typical doses used for gross disease in RMS and ES). Although local control did not depend on dose on univariate analysis, multivariate analysis in a larger sample size is necessary to further evaluate these findings.

Without a prospective trial analyzing the optimal dose for bone metastases in RMS or ES, it may be appropriate to extrapolate from primary site data when planning RT for metastatic sites. We recommend treatment of bone metastases with biologically effective doses known to be appropriate for definitive control of primary disease in ES (55.8 Gy, BED₁₀ of 65.8 Gy) and RMS (50.4 Gy, BED₁₀ of 59.7 Gy). For patients whose bone metastases are not treated concurrently with the primary site, an important consideration is the limitation of the number of RT sessions necessary for treatment. Given the ability to target lesions precisely with image-guided techniques, hypofractionation is an appropriate technique to reduce the number of RT sessions for these patients. For example, 10 fractions of 4Gy each for RMS (BED of 56 Gy) or 4.5 Gy each for ES (BED of 65.3 Gy) provides sufficient dose while limiting the length of treatment. Other appropriate regimens may include 5 fractions of 7 Gy each for RMS (BED of 59.5 Gy) or 7.5 Gy each for ES (BED of 65.6 Gy).

Almost half of the patients in our cohort presented with five or more bone metastases at diagnosis. The number of bone metastases was not prognostic of EFS in our cohort, most likely due to the small sample size. There was a trend toward worse local control at an irradiated site when there were >5 sites of metastatic disease at diagnosis. Additionally, the number of bone metastases in EURO-E.W.I.N.G 99 was prognostic of EFS [10]. For patients with ≤5 sites of disease, it is possible to irradiate all lesions during frontline therapy. However, the optimal management strategy for >5 metastatic sites is not clearly defined. Although the goal is to eradicate all viable tumor and decrease further tumor seeding, for patients with >5 sites of disease, it is not feasible to irradiate all sites; this would exceed bone marrow tolerance and delay or prohibit further systemic therapy, which is most likely the more critical treatment for disease control in these patients. For this subgroup, it is advisable to treat bone metastases that respond poorly to induction chemotherapy and/or initially bulky lesions in weight-bearing bones. FDG-PET response at the primary tumor after induction chemotherapy can predict outcomes in RMS [22] and ES [23]. Whether or not FDG-PET response at metastatic sites can also predict outcomes must be further explored and may validate which bones are most important to irradiate.

One of the most serious complications post-RT in children are second cancers. RT-induced cancers are dose-dependent, with a dose of ≥60 Gy found to portend the highest risk of developing a secondary bone cancer in ES [24]. Other late effects seen after bone RT include bone growth abnormalities such as limb length discrepancy, fracture, scoliosis, and muscular atrophy [25]. The long-term survivors in our cohort need additional follow-up before any

definitive conclusions regarding the risk of late effects can be made. Although control of disease is and will remain the primary goal for Stage IV RMS and ES, the potential consequences of multi-site irradiation must not be underestimated, and hypofractionation with dose escalation should be undertaken with caution, especially in young children.

The 3-year EFS and OS were 21% and 40%, respectively. It is evident that for a survival benefit (and not just a local control benefit) to be seen after bone RT, other systemic therapies must be employed for patients with extrapulmonary metastases. RT for metastatic bone lesions appears to alter the pattern of distant relapse rather than prevent relapse.

Limitations of this analysis include the retrospective design, small sample size, heterogeneous treatment for bone metastases, and dependence on available imaging for the detection of bone disease. In summary, RT for bone metastases in RMS and ES is important for control of these sites, with local control similar to that of the primary site after definitive RT. It will be important to evaluate the long-term benefits versus risks of targeting up to five metastatic sites of disease with high doses, as is mandated on recent protocols.

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Fig. 1.
Cumulative incidence of bone failures at an irradiated metastatic site after <48 Gy versus 48 Gy. BED = biologically effective dose ($P = 0.93$).

Table I
Patient and Tumor Characteristics

	N (%)
Total patients	30 (100)
Gender	
Female	6 (20)
Male	24 (80)
Diagnosis	
Ewing sarcoma	22 (73)
Rhabdomyosarcoma	8 (27)
Site of primary disease	
Extremity	7 (23)
Pelvis	10 (33)
Spine	4 (13)
Chest wall/mediastinum	4 (13)
Parameningeal	2 (7)
Bladder/prostate	1 (3)
Other ^a	2 (7)
Metastases	
Bone only	10 (33)
Bone and lung	12 (40)
Bone and bone marrow	4 (13)
Bone and other ^b	4 (13)

RT, radiotherapy

^aDiaphragm, unknown;

^bPeritoneum, muscle, kidney.

Table II
Bone Metastases and Treatment Characteristics

	N (%)
Number of bone metastases at diagnosis per patient	
1	8 (27)
2	5 (17)
3	2 (7)
4	3 (10)
5	2 (7)
>5	10 (33)
Number of irradiated bones per patient	
1	17 (57)
2	8 (27)
3	4 (13)
4	1 (3)
Location of irradiated bone	
Spine	20 (41)
Pelvis	6 (12)
Extremity	17 (35)
Skull	4 (8)
Rib	2 (4)
RT technique	
AP/PA	25 (51)
IMRT	20 (41)
Electrons	4 (8)
RT fractionation	
Hyperfractionation (1.5 Gy twice per day)	5 (10)
Conventional fractionation	34 (69)
Hypofractionation	
3 Gy × 10 fractions	4 (8)
3 Gy × 12 fractions	4 (8)
8 Gy × 3 fractions	2 (4)

RT, radiotherapy; AP/PA, anterior–posterior/posterior–anterior; IMRT, intensity-modulated radiotherapy.

Table III

Six Bone Relapses in Five Patients

Diagnosis	Patient age	Sites of metastatic disease at diagnosis	Total number of bones involved at diagnosis	Total number of bones irradiated	Dose/fractionation in bone where failed (Gy)	BED ₁₀ (Gy)	Site of irradiated bone failure	Years from RT to bone recurrence	Vital status
ES	12	Bone	1	1	55.8/1.8	65.8	Iliac bone	0.7	Deceased
ES	17	Bone, lungs	1	1	45/1.8	53.1	Lumbar spine	1.1	Deceased
ES	20	Bone, lungs	>5	1	35/2.5	43.4	Femur	7.1	Alive, with disease
ES	33	Bone	>5	2	40/2.0	48	Lumbar spine	3.1	Deceased
RMS	15	Bone, muscle	>5	3	50.4/1.8	59.7	Distal femur	0.5	Deceased
RMS	15	Bone, muscle	>5	3	30/3.0	39	Femoral head	0.2	Deceased

ES, Ewing sarcoma; RMS, rhabdomyosarcoma; RT, radiotherapy; BED₁₀, biologically effective dose.