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Original Research Article

Effect of palliative radiation dose on symptom response in metastatic sarcomas

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ABSTRACT

Purpose: Palliative radiotherapy (RT) plays a crucial role in alleviating symptoms associated with metastatic sarcoma. However, there is a lack of consensus on the optimal palliative radiation dose and fractionation for metastatic sarcomas. We analyzed the association between biologically effective radiation dose and symptom response for patients who underwent palliative RT for metastatic sarcomas

Methods and materials: We retrospectively identified patients with metastatic sarcoma treated with palliative RT between 1999 and 2021 at our institution. We assessed the association between equivalent dose in 2 Gy fractions (EQD2) with an α/β of three and symptom relief or overall survival (OS) using univariable and multivariable analyses.

Results: Of the 198 metastatic sites treated, the most common indications for palliative radiation were pain (n = 181, 91 %) and compression of adjacent structures (n = 16, 8 %). In our analysis, an EQD2 of $>$ 20 Gy was associated with greater rates of short-term symptom relief (n = 143, 85 %) at the RT site compared to an EQD2 of $\leq$ 20 Gy (n = 14, 54 %, P = 0.001) with no reports of grade 3 or higher toxicity. However, there was no significant improvement in short-term symptom relief for higher radiation doses. Patients treated with an EQD2 of $\leq$ 20 Gy had a significantly worse performance status, but there was no significant difference in overall survival based on EQD2 on multivariable analysis.

Conclusions: An EQD2 $\leq$ 20 Gy (e.g., 8 Gy in 1 fraction) provided inadequate palliative benefit in this series. An EQD2 $>$ 20 Gy resulted in greater rates of symptom palliation in metastatic sarcomas, but further dose escalation did not improve symptom response or durability. These findings suggest standard palliative regimens such as 20 Gy in 5 fractions (EQD2 of 28 Gy) are effective for patients with metastatic sarcomas.

Introduction

Sarcomas are a rare and heterogenous group of tumors that can broadly be classified as soft tissue or bone neoplasms [1–2]. Despite aggressive multidisciplinary management, approximately one-third of patients develop metastases [3]. Metastatic disease is often treated with systemic therapy (e.g., anthracycline-based chemotherapy) but unfortunately most patients progress through treatment [4–5]. In the setting of advanced disease, RT plays a critical role in palliating symptoms and preserving quality of life.

The most common symptom requiring palliation in patients with metastatic sarcoma is pain with less common symptoms including neurological deficits, bleeding, and superior vena cava obstruction [6]. There is considerable variability in palliative RT dose and fractionation for treating metastatic sarcoma. To date, there is limited retrospective and prospective data for palliative radiation therapy in advanced sarcomas, and management has largely been extrapolated from the general palliative literature. For bone metastases in more common cancers, systematic reviews and meta-analyses have reported a single fraction of 8 Gy results in comparable pain relief to higher biologically effective dose fractionation schemes with response rates ranging from 75–90 % [7–8]. Notably, patients who were treated with a single-fraction of radiation have been reported to have higher rates of retreatment (HR 2.5; 95 % CI, 1.76–3.56) [7]. Compared to bone metastases, there is limited data evaluating appropriate dose-fractionation schemes for visceral tumors. A systematic review found 30 Gy in 10 fractions or higher doses

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led to longer symptom palliation in patients who experienced dyspnea, cough, and other symptoms related to airway compression [9].

Soft tissue and bone sarcomas are often considered radioresistant with less than one-third of patients with unresectable sarcomas controlled with radiotherapy alone [10]. Prior studies have suggested that higher doses of RT may be required to palliate patients with metastatic sarcomas [6]. As a result, some radiation oncologists routinely dose escalate when treating patients with metastatic sarcomas using palliative radiotherapy [11]. Furthermore, recent studies have reported excellent local control of metastatic sarcomas using stereotactic body radiation therapy (SBRT [12–13]), raising the possibility that higher biologically effective doses could improve the duration of symptomatic response in patients undergoing palliative radiotherapy. However, the association between biologically effective dose and symptom response in patients with metastatic sarcomas has not been analyzed in detail. Herein, we evaluated symptom response based on EQD2 and explored variables that may affect overall survival (OS).

Methods and materials

Patients

Stanford's Institutional Review Board (IRB) approved this retrospective study of patients with metastatic sarcomas treated with palliative RT between 1999 and 2021. Patients with sarcoma histology who received palliative RT were queried from the Stanford Radiation Oncology Data Warehouse which aggregates data from electronic medical records. All consecutively treated patients were included. Data were evaluated at the patient and lesion level. The primary outcome measured was symptom relief following RT and secondary outcome was OS.

Patient-level data included demographic information (e.g., age, sex), performance status, and tumor characteristics (e.g., histology, type of metastasis). Patients were treated according to physician discretion based on clinical judgment, tumor characteristics, and patient-specific factors. OS was defined as the time from the radiation start to the date of death or last follow-up date. For patients treated with multiple radiation courses, OS was calculated from the initiation of the first course. To assess OS, patients were stratified by EQD2 ($\leq$20 Gy vs $>$ 20 Gy) in Kaplan-Meier analysis. EQD2 was calculated using the formula EQD2 = D x ([d + (α/β)]/[2 Gy + (α/β)]) where D is total dose, d is dose per fraction, and α/β is assumed to be three [14–16]. Osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma were designated as pediatric sarcomas.

Symptom response

Symptomatic improvement was defined as clear documentation that the symptom(s) present before RT (e.g., pain) resolved or improved. Short-term symptom relief was defined as symptom relief documentation within 6 weeks following the completion of RT. Long-term symptom relief was defined as symptom relief documentation at 6 months following the completion of RT. Following RT, some patients experienced global symptom relief and some experienced symptom relief only at the site of RT; both levels of symptom relief were documented. Given the retrospective nature of our study, we were unable to quantify degree of symptom improvement (e.g., partial or complete pain response).

Toxicity analysis

Radiation treatment toxicities were reported according to radiation treatment summaries during and the completion of treatment. Toxicity grading was assessing using the Common Terminology Criteria for Adverse Events, version 5.0.

Table 1
Baseline patient and treatment characteristics (n = 103).

Attribute		Value (%)
Sex		
	Female	39 (38)
	Male	64 (62)
Median age at diagnosis		48.0 [IQR, 26.3–61.05]
ECOG		
	$\leq$1	42 (57)
	>1	32 (43)
Histology		
	Adult	74 (72)
	Pediatric	29 (28)
Type of metastasis		
	Bone	49 (48)
	Non-bone	54 (52)
Anatomic distribution		
	Spine	28 (27)
	Pelvis	18 (18)
	Extremities	14 (14)
	Chest	12 (12)
	Abdomen	11 (11)
	Lung	7 (7)
	Other	13 (13)
Concurrent systemic therapy		
	No	66 (64)
	Yes	37 (36)
Type of concurrent systemic therapy		
	Chemotherapy	20 (53)
	Targeted	17 (45)
	Both	1 (3)
Prior radiation to same site		
	No	90 (87)
	Yes	13 (13)
Use of pain medications		
	No	24 (12)
	Yes	174 (88)

Statistical analysis

Analyses were conducted using R version 4.3.0, and SAS version 9.4. Fisher's exact tests were used to compare categorical variables and Wilcoxon rank sum tests were used for continuous variables. Survival curves were created using Kaplan-Meier estimates. Univariable and multivariable analyses utilized Cox proportional hazards regression to identify variables associated with mortality. In our analysis, we included performance status (ECOG $>$ 1 vs ECOG $\leq$ 1), histology (adult vs pediatric), concurrent systemic therapy, EQD2 ($>$20 vs $\leq$ 20 Gy), age as a continuous variable, and sex.

Results

Patient characteristics

A total of 103 patients with sarcoma metastases treated with palliative RT were identified between 1999 and 2021 (Table 1). The median age at the time of RT was 48.0 years. Most patients were male (62 %), and most patients had ECOG performance scores $\leq$ 1 (57 %). Most patients had adult sarcoma histologies (72 %). The most common sites of metastasis were spine (27 %), pelvis (18 %), and extremities (14 %). Thirty-six percent of patients received concurrent systemic therapy. Most patients did not receive prior radiation to the same site (87 %).

A total of 198 lesions were evaluated. The most common indication for palliative radiation was pain (n = 181, 91 %). Other indications included pressure/compression secondary to tumor burden (n = 16, 8 %) and bleeding (n = 2, 1 %). Examples of pressure/compression secondary to tumor burden include nerve compression, abdominal pressure, and airway compression causing severe dyspnea.

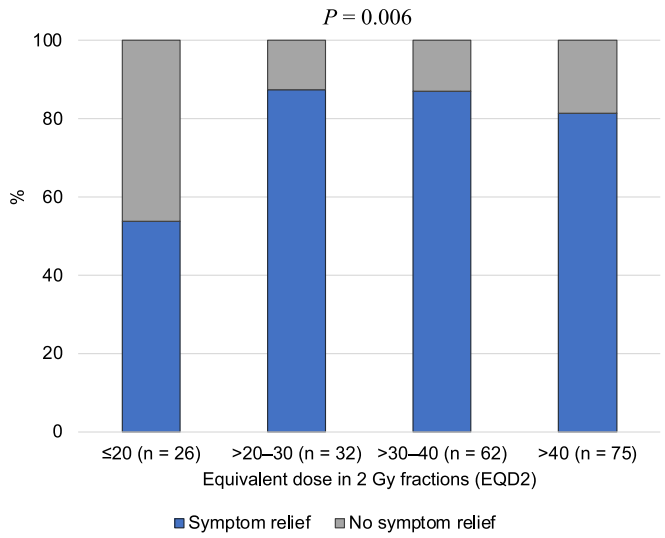

Fig. 1. Association between EQD2 and short-term (6 weeks) symptom relief to palliative radiotherapy at the treatment site.

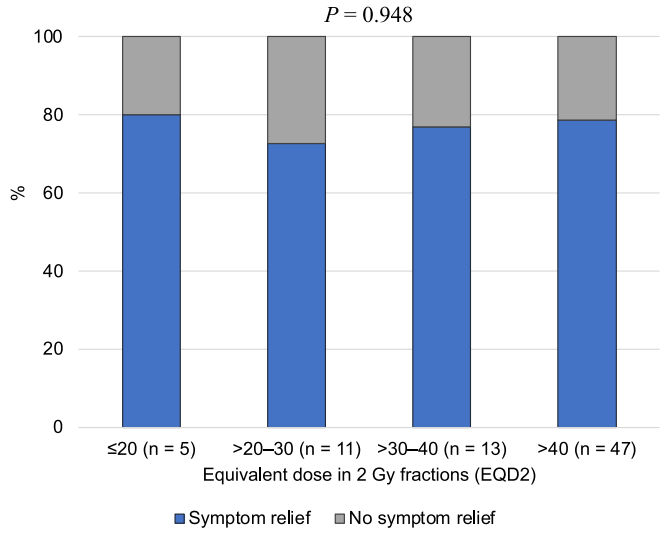

Fig. 2. Association between EQD2 and long-term (6 month) symptom relief to palliative radiotherapy at the treatment site.

Symptom relief

Stratifying by an EQD2 of ≤ 20, >20–30, >30–40, and > 40 Gy, the rates of short-term symptom relief at the RT site increased from an EQD2 ≤ 20 Gy (54 %, n = 14) to an EQD2 > 20–30 Gy (88 %, n = 28, P = 0.006, Fig. 1). However, there was no further increase in short-term symptom relief at the RT site at an EQD2 of > 30–40 Gy (87 %, n = 54) or > 40 Gy (81 %, n = 61). Of the patients treated with an EQD2 > 40 Gy, 69 % received SBRT. Only 76 of 198 lesions were evaluable at 6 months because of patients being lost to follow up or succumbing to disease, but there were no significant differences in long-term symptom response based on EQD2 (P = 0.948, Fig. 2). There were no incidents of grade 3 or higher toxicities documented in any patients. The most common toxicities noted were fatigue (n = 26, 13 %), nausea (n = 15, 8 %), and dermatitis (n = 14, 7 %). Given the lack of improvement in short-term symptom relief for an EQD2 > 30 Gy, we grouped together patients with an EQD2 > 20 Gy for further analysis.

Twenty-six (13 %) and 172 (87 %) lesions were treated with an EQD2 of ≤ 20 Gy and > 20 Gy, respectively (Table 2). There was a significant difference in performance status at the time of radiation between the two groups where 9 % of patients treated with an EQD2 ≤ 20 Gy had an ECOG ≤ 1 whereas 66 % of patients treated with an EQD2 > 20 Gy had an ECOG ≤ 1 (P = <0.001). There was a significant difference in short-term overall symptom relief between the EQD2 ≤ 20 Gy and EQD2 > 20 Gy groups of 39 % and 69 %, respectively (P = 0.005). There was also a significant difference in short-term symptom relief at the RT site with 54 % symptom relief in the EQD2 ≤ 20 Gy group and 85 % in the EQD2 > 20 Gy group (P = 0.001). There was a trend towards decreased use of pain medications at 6 weeks (EQD2 ≤ 20 Gy 4 % vs. EQD2 > 20 Gy 18 %), but this was not statistically significant (P = 0.152). There were no statistically significant differences in long-term overall symptom relief, symptom relief at RT site, or decrease in pain medications. When considering all sites, there was no difference in repeat RT at the same site or hospitalization within 6 months between the two groups.

Table 2
Association of EQD2 with patient outcomes.

	Overall (%)	EQD2 ≤ 20 Gy (%)	EQD2 > 20 Gy (%)	P value
Total	198	26	172	
Performance status				**<0.001**
ECOG ≤ 1	97 (58)	2 (9)	95 (66)	
ECOG > 1	69 (42)	20 (91)	49 (34)	
Short-term symptom relief				**0.005**
No	68 (35.2)	16 (61.5)	52 (31.1)	
Yes	125 (64.8)	10 (38.5)	115 (68.9)	
Short-term symptom relief at RT site				**0.001**
No	38 (19.5)	12 (46.2)	26 (15.4)	
Yes	157 (80.5)	14 (53.8)	143 (84.6)	
Decrease in pain medications at 6 weeks				0.152
No	146 (84.4)	24 (96.0)	122 (82.4)	
Yes	27 (15.6)	1 (4.0)	26 (17.6)	
Long-term symptom relief				0.903
No	40 (52.6)	2 (40.0)	38 (53.5)	
Yes	36 (47.4)	3 (60.0)	33 (46.5)	
Long-term symptom relief at RT site				1.000
No	17 (22.4)	1 (20.0)	16 (22.5)	
Yes	59 (77.6)	4 (80.0)	55 (77.5)	
Decrease in pain medications at 6 months				0.657
No	53 (82.8)	5 (100.0)	48 (81.4)	
Yes	11 (17.2)	0 (0.0)	11 (18.6)	
Repeat RT at site				0.633
No	191 (96.5)	26 (100.0)	165 (95.9)	
Yes	7 (3.5)	0 (0.0)	7 (4.1)	
Hospitalization within 6 months				0.300
No	72 (51.8)	4 (33.3)	68 (53.5)	
Yes	67 (48.2)	8 (66.7)	59 (46.5)	

Overall survival

The median OS of the entire cohort was 6.8 months (CI 2.6–12.2 months) (Fig. 3). By Kaplan-Meier analysis, there was greater OS with an

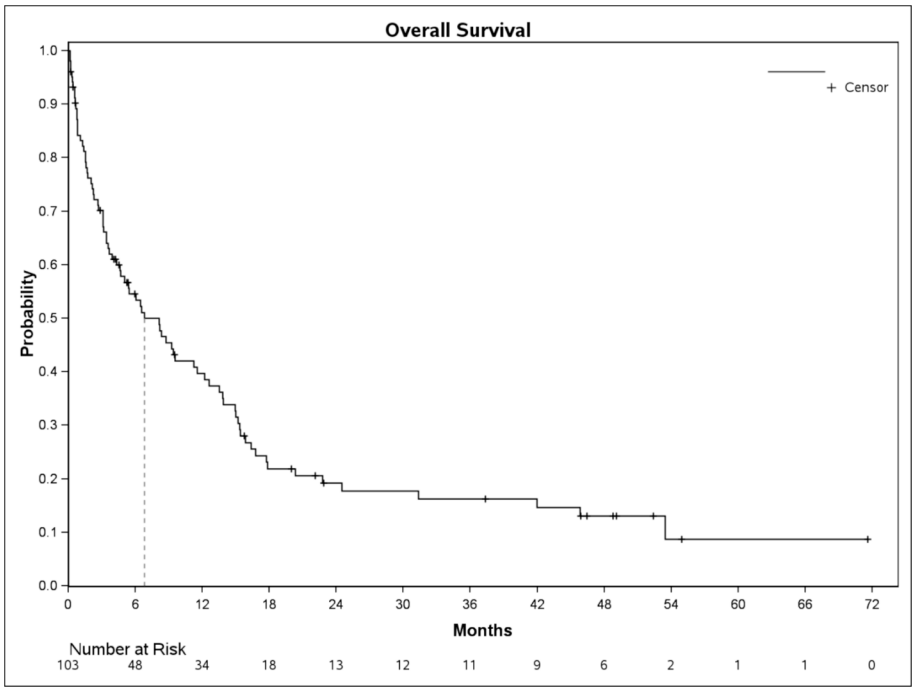

Fig. 3. Overall survival for the entire patient cohort.

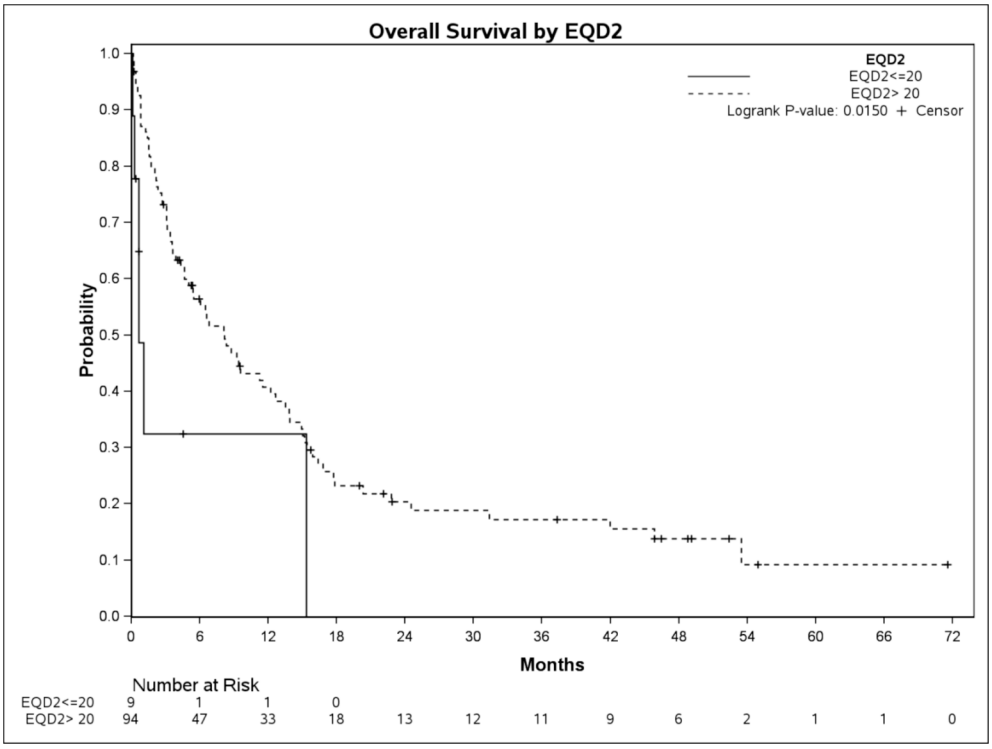

Fig. 4. Overall survival comparing EQD2 $\leq$ 20 and $>$ 20.

EQD2 $>$ 20 vs $\leq$ 20 Gy (P = 0.015, Fig. 4). On univariable analysis, EQD2 $\leq$ 20 Gy was associated with an increased risk of mortality, while ECOG $\leq$ 1 and female sex were associated with a decreased risk (Table 3). However, there were no significant predictors of mortality in the adjusted multivariable model.

Discussion

Radiation plays a critical role in the symptomatic management of metastatic sarcoma in the palliative setting. To date, there are limited data supporting the optimal dose-fractionation schedule for patients with advanced sarcomas. In this study, we present the largest series of patients with metastatic sarcomas treated with RT. Our findings demonstrate an EQD2 $>$ 20 Gy results in excellent symptom relief while

Table 3
Overall survival univariable and multivariable analysis.

Covariables	Univariable			Multivariable		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age	0.99	0.98–1.00	**0.035**	0.99	0.98–1.01	0.312
Gender (female vs male)	0.57	0.35–0.91	**0.019**	0.66	0.37–1.18	0.162
Performance status (ECOG ≤ 1 vs > 1)	0.51	0.31–0.84	**0.009**	0.61	0.36–1.05	0.073
Histology (pediatric vs adult)	1.55	0.95–2.53	0.080	1.41	0.78–2.56	0.256
Concurrent chemotherapy (no vs yes)	0.97	0.61–1.53	0.895	1.13	0.64–2.00	0.681
EQD2 (≤20 vs > 20)	2.74	1.17–6.39	**0.020**	1.6	0.58–4.47	0.368

an EQD2 of ≤ 20 Gy (e.g., 8 Gy in 1 fraction) provided inadequate benefit in this series.

Currently, retrospective and prospective studies have evaluated adequate radiation doses to achieve symptom palliation, particularly in bone metastases. Although sarcoma metastases have been included in prior studies, there are few reports that focus on the ideal dose and fractionation specifically for these tumors. A recent study by Tween *et al.* retrospectively analyzed 137 sites treated with wide range of dose fractionation schedules for advanced sarcomas requiring palliative RT [6]. Of the 114 soft tissue and 23 bone sarcomas, data on symptom response were available for only 56 % and 67 % of the lesions, respectively. Approximately two-thirds of patients reported symptom improvement with the authors concluding a biological effective dose (BED) of 50 or greater results in higher symptomatic response rates. For comparison, 30 Gy in 10 fractions has a BED of 60 Gy and an EQD2 of 36 Gy whereas 20 Gy in 5 fractions has a BED of 46.7 Gy and an EQD2 of 28 Gy [17–19].

In our patient cohort, there was a significant short-term benefit with an EQD2 of > 20 Gy. While 54 % of patients treated with an EQD2 ≤ 20 Gy experienced symptom relief, all groups with an EQD2 > 20 Gy had > 80 % response rate. Most patients in the EQD2 ≤ 20 Gy cohort were treated with 8 Gy in 1 fraction. Common dose-fractionation schemes in the EQD2 > 20 Gy cohort included 20 Gy in 5 fractions, 30 Gy in 10 fractions, 25 Gy in 5 fractions, 30 Gy in 5 fractions, 40 Gy in 5 fractions, and 20 Gy in 1 fraction. Unfortunately, most patients passed away within 6 months of receiving RT, making it difficult to draw conclusions on the long-term symptom outcomes. In our cohort, there were no benefits seen in long-term symptom response or decrease in pain medication usage with an EQD2 > 20 Gy. Collectively, these findings suggest targeting an EQD2 of > 20 Gy for patients with metastatic sarcoma is appropriate for adequate symptom palliation. Although lower biologically effective doses (e.g., single 8 Gy fraction) may palliate the symptoms of certain metastatic lesions, our findings suggest that higher doses are required to maximize symptom relief [15,20]. The worse OS observed in patients treated with an EQD2 ≤ 20 Gy likely reflects selection biases for patients treated with this regimen. Patients in this group had a lower performance status pre-treatment, and EQD2 was not significantly associated with OS on multivariable analysis.

The retrospective nature of this study results in several limitations. A major limitation of this study is assessment of symptom relief from medical records, limiting the ability to thoroughly and systematically determine the degree of relief (e.g., partial or complete). Although this is a single institution study, there was significant heterogeneity in the dose-fractionation schedules, making it difficult to draw correlations between specific RT schedules and outcomes. The reported findings inform short-term palliation and do not inform long-term palliation, tumor control, or other objectives for the incorporation of RT. Additionally, the decisions of which patients received higher biologically effective doses were likely impacted by patient selection bias. Lastly, we were unable stratify patients by individual histology given the numerous sarcoma histologies and limited number of patients in the cohort.

Conclusions

In conclusion, our study found patients with metastatic sarcoma treated with RT experienced significantly greater rates of symptom relief with an EQD2 of > 20 Gy, but there was no further improvement at higher biologically effective doses. These findings suggest that common palliative regimens such as 20 Gy in 5 fractions or 30 Gy in 10 fractions are adequate for symptom relief in patients with metastatic sarcomas, while an EQD2 of ≤ 20 Gy (e.g., 8 Gy in 1 fraction) provided inadequate palliative benefit.

Author contribution Statement

Jennifer Matsui designed the study, performed data collection, and interpretation of the results. She drafted the initial manuscript and integrated feedback from all co-authors. Everett Moding conceptualized and designed the study, contributed to the acquisition of funding, and oversaw the research project. He was responsible for the critical revision of the manuscript for important intellectual content. Scott Jackson and Judy Fang conducted the statistical analysis and interpretation of the results. Lynn Million, Alexander Chin, Susan Hiniker, and Anusha Kalbasi participated in the study design, data interpretation, critical review of the manuscript, and provided expertise in radiation oncology.

All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: E. J.M. has served as a paid consultant for Guidepoint and GLG. The other authors declare no competing interests.

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