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Scientific Article

Effective Pain Control With Very Low Dose Palliative Radiation Therapy for Patients With Multiple Myeloma With Uncomplicated Osseous Lesions

Jeremy G. Price, MD, PhD,[a,b,*] Donna Niedzwiecki, PhD,[c] Taofik Oyekunle, MS,[c] Murat O. Arcasoy, MD,[d,e] Colin E. Champ, MD,[a] Chris R. Kelsey, MD,[a] Joseph K. Salama, MD,[a,b] and Michael J. Moravan, MD, PhD[a,b]

[a]*Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina;* [b]*Radiation Oncology Service, Durham VA Medical Health Care System, Durham, North Carolina;* [c]*Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, North Carolina;* [d]*Hematology/Oncology Service, Durham VA Medical Health Care System, Durham, North Carolina;* [e]*Section of Hematology, Department of Medicine, Duke University Medical Center, Durham, North Carolina*

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Abstract

Background: Osteolytic lesions are present in 75% of patients with multiple myeloma (MM) and frequently require palliation with radiation therapy (RT). Prior case series of patients with MM with bone pain undergoing palliative RT suggests doses ≥12 Gy (equivalent dose in 2Gy fractions, EQD2) provide excellent bone pain relief. However, recent advances in care and novel biologic agents have significantly improved overall survival and quality of life for patients with MM. We hypothesized that lower-dose RT (LDRT, EQD2 <12 Gy) offers an effective alternative to higher-dose RT (HDRT, EQD2 ≥12 Gy) for palliation of painful, uncomplicated MM bone lesions. Methods: We retrospectively identified patients with MM treated with RT for uncomplicated, painful bone lesions and stratified by EQD2 ≥/< 12 Gy. Clinical pain response (CPR) rates, acute and late toxicity, pain response duration, and retreatment rates between LDRT and HDRT groups were analyzed. Results: Thirty-five patients with 70 treated lesions were included: 24 patients (48 lesions) treated with HDRT and 11 patients (22 lesions) with LDRT. Median follow-up was 14 and 16.89 months for HDRT and LDRT, respectively. The median dose of HDRT treatment was 20 Gy versus 4 Gy in the LDRT group. The CPR rate was 98% for HDRT and 95% for LDRT. There was no significant difference in any-grade acute toxicity between the HDRT and LDRT cohorts (24.5% vs 9.1%, X^2 $P = .20$). Pain recurred in 10% of lesions (12% HDRT vs 9.5% LDRT). Median duration of pain response did not significantly differ between cohorts ($P = .91$). Five lesions were retreated, 2 (9.5%) in the LDRT cohort, and 3 (6.3%) in the HDRT cohort. Conclusion: In this study, LDRT effectively palliated painful, uncomplicated MM bony lesions with acceptable CPR and duration of palliation. These data support prospective comparisons of LDRT versus HDRT for palliation of painful, uncomplicated MM bony lesions.

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*Corresponding author: Jeremy G. Price, MD, PhD; E-mail: jeremy.price@duke.edu

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Introduction

Multiple myeloma is the most common plasma cell neoplasm, with approximately 30,000 new diagnoses annually in the United States.[1] Osteolytic lesions are present in 75% of patients with MM at diagnosis and bone pain is the most common presenting symptom.[2,3] MM is incurable, and patients historically had limited therapeutic options. During the past 20 years, however, the advent of novel systemic agents has significantly improved the overall survival and quality of life for patients with MM.[4]

Radiation therapy (RT) is a valuable adjunct for the palliation of painful MM bone lesions and is extremely effective, with clinical pain responses (CPR) in up to 97% of patients.[5] Several studies examining the relationship between CPR and RT dose suggest that doses (equivalent dose in 2Gy fractions, EQD2) of 12 Gy or more (ie, 8 Gy/1 fx, 20 Gy/5 fx, 30 Gy/10 fx) all provide similar palliation for uncomplicated bone lesions.[3,5,6] Much of these data, however, are based on case series or retrospective analyses analyzing patients before the modern era of novel systemic agents for MM. Compared with higher dose palliative RT (HDRT, EQD2 $\geq$12 Gy), low-dose palliative RT (LDRT, EQD2 <12 Gy) may facilitate more rapid initiation or concurrent administration of systemic therapy and also preserve marrow, which may become increasingly clinically important due to patients with MM significantly improved overall survival (OS). Additionally, multiple courses of LDRT could be safely delivered to the same site with minimal toxicity, should retreatment be indicated. To that end, this study reports a retrospective multi-institutional analysis of LDRT versus HDRT efficacy and safety for the management of patients with MM with painful, uncomplicated bony lesions.

Methods and Materials

We retrospectively identified all consecutively treated patients with MM treated with RT for painful, uncomplicated bone lesions at Duke University Hospital (DUH) and the Durham Veterans Affairs Medical Center (VA) by query of electronic radiation treatment records from 2013 to 2019. Uncomplicated osseous lesions were defined as all lesions without impending risk of pathologic fracture, prior orthopedic fixation, or spinal lesions with malignant epidural involvement. Epidural disease was excluded as longer course of RT may benefit this subset of patients.[7] Likewise, patients with pathologic fractures were excluded as RT would not be expected to alleviate pain. Impending pathologic fractures were identified using Mirels' criteria. All patients underwent CT simulation and were treated with standard palliative RT fields. Gross tumor volume (GTV) volume encompassed only areas of osseous lesions within involved bones and was delineated using Eclipse (Varian, Palo Alto, CA). A treatment site was defined as a bony lesion(s) able to be treated by a single set of radiation fields. Reirradiation was defined as a subsequent palliative RT overlapping the prescription dose of a previous RT course.

Clinical practice at the VA incorporated both LDRT and HDRT based on physician/patient preference; only HDRT was used at DUH. Patients were grouped into the LDRT cohort with EQD2 <12 Gy, with all others treated with EQD2 $\geq$12 Gy comprising the HDRT cohort. For EQD2 calculations an α/β ratio of 10 was used. Patients were routinely seen in follow-up after the completion of RT and assessed for pain response and toxicity beginning at 1 to 3 months post-RT, and typically again at 6 months per clinic standards using both physician and patient reported pain response metrics after which patients were either followed in radiation oncology or discharged for long-term medical oncology follow-up.

Pain responses were reported as complete (absence of presenting pain without opiates), partial (improved pain with stable/decreased opiates), or none (worsened pain or increased opiates). Complete and partial responses were considered CPRs. No patients began new systemic therapies or steroids during RT. Clinical data were collected compositely by chart review of radiation and medical oncology clinic notes and inpatient admission notes. The primary endpoint was CPR at each specific treated site. Secondary endpoints were acute and late toxicity, duration of pain response, retreatment rates, and overall survival from date of RT initiation. This retrospective protocol was approved by both the DUH and VA Institutional Review Boards.

Toxicities were recorded retrospectively using the Common Terminology Criteria for Adverse Events, version 5.0 and reported by type and grade. If patients required retreatment, the additional course of RT was noted and included in the analysis. Patients were recorded as having received systemic therapy prior- or post-RT if administered within 3 months of RT initiation.

Patient demographic and disease characteristics were summarized using descriptive statistics. Baseline differences in patient characteristics were assessed using the χ^2 test. Actuarial rates of CPR, acute toxicity, and retreatment were calculated based on assessment at acute toxicity visits and up to 90 days post-RT. Differences in CPR between RT regimens were compared using the χ^2 test. Median time to event for pain recurrence was determined by the Kaplan-Meier method. All statistical tests were 2-sided with $\alpha = 0.05$ considered significant. Statistical analyses were performed using R software.

Results

Thirty-five patients with 70 treated lesions were included; 11 patients received LDRT to 22 lesions and 24 patients received HDRT to 48 lesions (Table 1). The LDRT cohort includes one patient that subsequently received HDRT

Table 1 Patient demographic and disease characteristics (n = 35 patients)

	HDRT (N = 24)	LDRT (N = 11)	*P* value
Age at RT			.3928*
Median (range)	63.5 (42.0-88.0)	66.0 (57.0-86.0)	
Sex			.6399†
Female	5 (20.8%)	1 (9.1%)	
Male	19 (79.2%)	10 (90.9%)	
Race			.0206†
White	16 (66.7%)	3 (27.3%)	
Black	4 (16.6%)	7 (63.6%)	
Hispanic	3 (12.5%)	0 (0.0%)	
Unknown/other	1 (4.2%)	1 (9.1%)	
MM Revised International Staging System (rISS) stage			.0757‡
1	12 (50.0%)	2 (18.2%)	
2	3 (12.5%)	5 (45.4%)	
3	9 (37.5%)	4 (36.4%)	
GTV volume (cm^3)			.0003‡
	20.7 (1-1000)	104.5 (8.9-640)	
ECOG			.2572†
0	2 (8.3%)	2 (18.2%)	
1	13 (54.2%)	3 (27.3%)	
2	7 (29.2%)	3 (27.3%)	
3	2 (8.3%)	3 (27.3%)	
Prior chemotherapy			.2831†
Yes	16 (66.7%)	5 (45.5%)	
No	8 (33.3%)	6 (54.5%)	
Post-RT chemotherapy			1.0000†
Yes	22 (91.7%)	11 (100.0%)	
No	2 (8.3%)	0 (0.0%)	

Abbreviations: GTV = gross tumor volume; HDRT = higher-dose radiation therapy; LDRT = higher-dose radiation therapy; MM = multiple myeloma; RT = radiation therapy.

* Wilcoxon rank-sum test.

† Fisher exact test.

‡ Mann-Whitney *U* test.

reirradiation. Median follow-up was 16.8 months (interquartile range [IQR] = 2.3-29.1 months) versus 14.0 months (IQR = 5.9-31.2), respectively. Median age at first palliative RT was 66 (range, 57-86) for LDRT and 63.5 (range, 42-88) for HDRT. The median time from diagnosis to start of RT was longer in the HDRT cohort (65.7 vs 5.1 months, $P < .0001$), as was the percentage of patients receiving RT within 1 year of diagnosis (77.5% vs 22.7%, Fig. E1). Most patients were male (79% HDRT, 90.9% LDRT). LDRT patients were more likely to be Black ($P = .02$). Seventy-one percent of patients received prior systemic therapy (45% of LDRT and 79% of HDRT, detailed by patient in Table E1). With respect to concurrent administration of chemotherapy, 18% of the LDRT cohort and 12.5% of the HDRT cohort remained on their existing chemotherapy regimens. Ninety-four percent of patients received systemic therapy after their initial palliative RT (100% of LDRT and 91.7% of HDRT). The most common treatment sites included the spine, pelvis, extremities, and rib cage (Table 2). The median dose of HDRT was 20 Gy (range, 8-30 Gy; EQD2 = 12-32.5 Gy) versus 4 Gy for LDRT (range, 4-8 Gy; EQD2 = 4.67-9.3 Gy;

Table 2 Treatment related characteristics (n = 70 sites)

	HDRT (N = 48 sites)	LDRT (N = 22 sites)
	N (%)	
Location		
Spine	11 (22.9)	6 (27.2)
Pelvis	5 (10.4)	3 (13.6)
Leg	7 (14.6)	4 (18.2)
Rib/chest wall	9 (18.8)	4 (18.2)
Arm	6 (12.5)	2 (9.1)
Clavicle	5 (10.4)	1 (4.5)
Skull	3 (6.3)	1 (4.5)
Shoulder	2 (4.2)	1 (4.5)
	Median (range)	
Total RT dose		
Gy	20 (8-30)	4 (4-8)
EQD2	23.33 (12-32.5)	4.67 (4.67-9.3)
No. of fractions		
	5 (1-10)	1 (1-2)

Abbreviations: HDRT = higher-dose radiation therapy; LDRT = higher-dose radiation therapy; RT = radiation therapy.

Table E2). The median GTV volume was significantly greater in the LDRT cohort (median = 104.5, IQR = 34.9-197.3) versus the HDRT cohort (median = 20.7, IQR = 9.0-43.9, $P < .001$).

The overall effectiveness of HDRT versus LDRT was evaluated based on CPR at 6 months post-RT and pain response duration. The overall CPR rate was 97%, with 98% of HDRT and 95% of LDRT responding either partially or completely (Fig. 1, $P = .53$). Median time to pain response was 37.5 and 39 days, respectively. There was no significant difference in the duration of pain response between HDRT and LDRT cohorts ($P = .91$, Fig. 2). The median pain response duration was not yet reached for either cohort. Additionally, there was no difference in OS between the patient cohorts ($P = .74$, Fig. E2).

There was no significant difference in all grades of acute or late toxicity between the HDRT (24.5%) and LDRT cohorts (9.5%, $P = .20$, Fig. 3, Table E3). In the overall cohort, pain recurred in 10% of lesions (12.5% HDRT vs 9.1% LDRT). Five lesions were retreated, 2 (9.1%) in the LDRT cohort and 3 (6.3%) in the HDRT cohort (Table 3). Of the retreated LDRT patients, one had pathologic fracture and the other had subsequent CPR with HDRT reirradiation.

Discussion

In this study LDRT, often delivered in a single 4 Gy fraction, was effective for palliation of painful, uncomplicated MM lesions. The rates of CPR and pain response duration were similar between LDRT and HDRT despite larger overall GTV volumes for the patients with LDRT. Moreover, pain recurrence rates were not increased in patients with LDRT. A lower percentage of patients with LDRT experienced acute toxicity. Our data suggest that LDRT has the potential to effectively palliate painful MM bony lesions with acceptable CPR and duration of palliation.

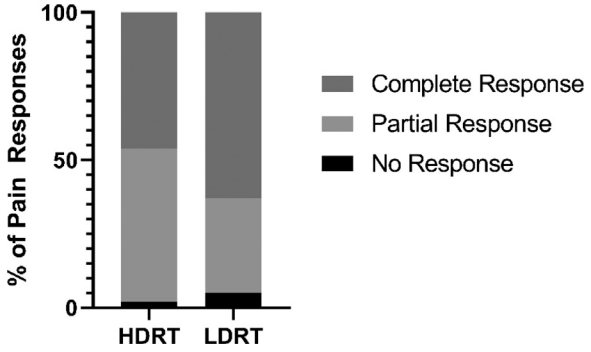

Fig. 1 Percentage of clinical pain responses in patients receiving higher-dose radiation therapy and lower-dose radiation therapy. There was no significant difference between the number of patients experiencing a pain response (complete/partial) versus those with no pain response to radiation therapy (Fisher exact $P = .53$).

Although some previous reports[8,9] suggested higher doses of palliative RT may provide superior CPR or more durable pain responses for uncomplicated bony lesions, others[3,5,6] have not. Additionally, none have examined the use of LDRT. Our findings are consistent with a recent retrospective osseous plasmacytoma series, in which RT doses as low as 20 Gy, ~50% lower than typical International Lymphoma Radiation Oncology Group (ILROG) recommendations of 35 to 50 Gy, provided effective local control.[2,10] Together, these data suggest a need to assess RT deintensification in MM and plasmacytoma.

LDRT possesses many hypothetical advantages to HDRT. These include less toxicity, shorter treatment course, and lower cost.[11] The LDRT dose we commonly used was sufficiently low that salvage reirradiation with LDRT or HDRT would be feasible based on the initial CPR.[12] LDRT may be a good option for newly diagnosed patients with MM as they will likely respond to planned systemic therapy. This is consistent with the noted imbalance in our patient cohort that patients with LDRT were more likely to have recently diagnosed disease, that is not relapsed of refractory to prior lines of therapy. Additionally, lower RT doses may theoretically preserve marrow for subsequent stem cell transplantation,[13] which becomes a more pertinent concern in an era of increased patient survival with MM. Future analyses may assess long-term peripheral blood counts to examine this hypothesis as this requires long-term follow-up not feasible in the retrospective setting.

Additionally, medical oncologists may more comfortably continue systemic therapy during LDRT for low-risk disease sites, thereby avoiding treatment breaks, given reports of the safety of concurrent therapy.[14,15] Indeed, 18% of patients receiving LDRT received concurrent systemic therapy. Even if the pain response duration were shorter with LDRT than HDRT, LDRT could potentially spare a subset of patients from a higher total RT dose. Given the prior delivered dose, retreatment would likely be straightforward. Although it is possible that retreatment rates may be higher with LDRT, this was not observed in our, albeit small, LDRT patient cohort.

There are multiple limitations to our study. Clinical endpoints were assessed retrospectively from a relatively small cohort. Patients were also seen by multidisciplinary teams including radiation and medical oncology, and palliative care, allowing for potential variations in pharmacologic pain management which may have influenced CPR. Clinical correlation of CPR with subsequent imaging studies to visualize a corresponding radiographic response or recurrence was also unavailable. Notably, all patients receiving LDRT were treated at the VA, were more commonly Black and male, and therefore may not be representative of the general population.[16] Based on the limited sample size, statistical modeling of these imbalances were not possible. Although dose selection was physician driven, we cannot exclude the possibility that other

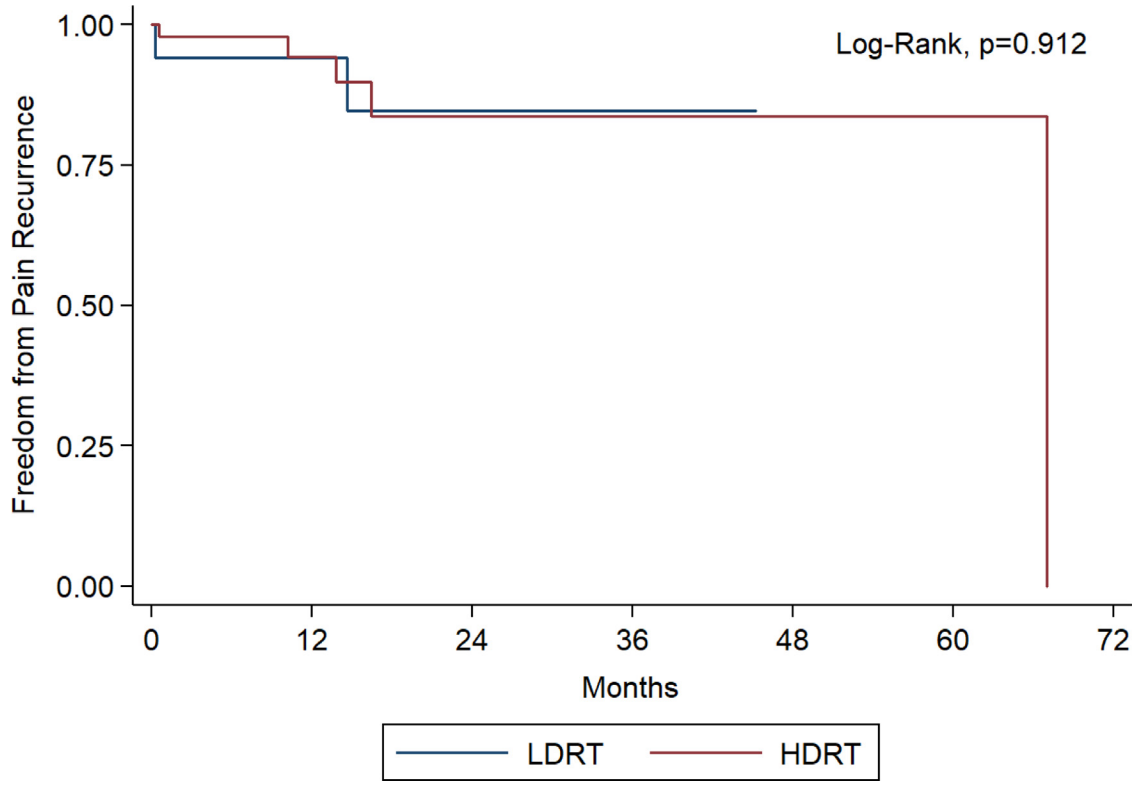

Fig. 2 Freedom from pain recurrence was calculated by the Kaplan-Meier method for the higher-dose radiation therapy and lower-dose radiation therapy cohorts. There was no statistically significant difference in the duration of pain responses to radiation therapy (log-rank $P = .91$).

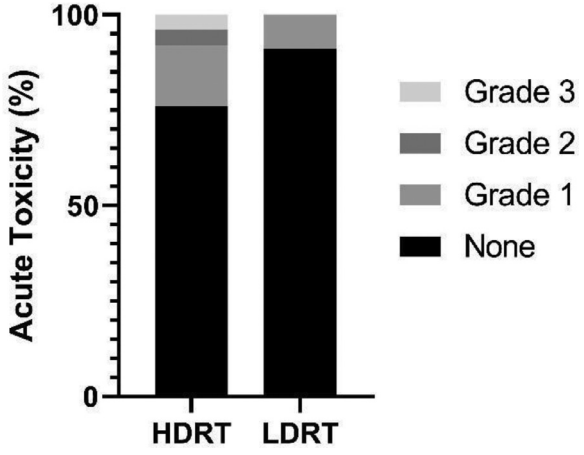

Fig. 3 Acute toxicity events after lower-dose radiation therapy and higher-dose radiation therapy. There was no statistically significant difference in episodes of acute toxicity after radiation therapy (Fisher exact $P = .20$).

patient or disease attributes were considered. Similarly, patients with HDRT had longer times to RT from diagnosis, suggesting greater percentages had relapsed or refractory disease. In addition to evaluating the efficacy of LDRT prospectively, future studies should identify patient factors to determine which patients would benefit from LDRT versus HDRT.

Table 3 Treatment related outcomes (n = 70 sites)

	HDRT (N = 48 sites)	LDRT (N = 22 sites)
	N (%)	
Retreatment	3 (6.3)	2 (9.1)
Pain recurrence	6 (12.5)	2 (9.1)

Abbreviations: HDRT = higher-dose radiation therapy; LDRT = higher-dose radiation therapy.

Conclusions

LDRT resulted in effective palliation of uncomplicated MM bony lesions in our patient cohort with favorable toxicity and retreatment rates. These data support other studies using reduced-dose RT for hematologic malignancies and support further inquiry into the use of palliative LDRT for low-risk patients with MM with uncomplicated MM bony lesions.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2021.100729.

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