Advances in Radiation Oncology (2021) 6, 100720

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Radiation Therapy for Plasma Cell Disease of the Brain and Skull: Poor Palliation and Survival After Treatment for Central Nervous System Involvement

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Received December 15, 2020; revised April 19, 2021; accepted May 3, 2021

Abstract

Purpose: Myeloma lesions of the head can present with central nervous system (CNS) involvement (leptomeningeal disease or brain metastasis), cranial neuropathy (CN), or impending neurologic involvement (INI). We analyzed response and survival after palliative radiation therapy (RT) to the brain and/or skull for myeloma lesions to determine whether CNS involvement fared worse than other RT indications.

Methods and Materials: We retrospectively analyzed 54 palliative RT courses administered at our institution from 2008 to 2019. Eleven courses were administered for CNS disease, 28 for CN, and 15 for INI. Demographic, disease, and RT variables were recorded as well as clinical response, radiographic response, and survival. Univariate analyses were performed for differences between groups, effects of clinical and RT treatment factors on response, as well as dose response. Survival was analyzed with the Kaplan-Meier method and compared by the log-rank test.

Results: This heavily pretreated cohort received a median of 20 to 24 Gy, most often to the base of skull, orbit(s), calvarium, or whole brain. Any clinical response (partial or complete vs no response or progressive disease) was significantly more likely for patients with CN and INI when collectively compared with patients with CNS disease ($P < .001$). Dose response was significant for doses $\geq$15 and 20 Gy for the whole cohort ($P = .026$ and .005, respectively) and patients with CN/INI ($P = .023$ and .002, respectively). Additionally, patients with high-risk cytogenetics were less likely to clinically respond ($P = .009$). Patients with CNS disease had worse survival ($P = .005$).

Conclusions: Patients with leptomeningeal disease/brain metastasis have poor clinical response and survival after RT and their responses do not demonstrate a dose response. Given these poor outcomes, the potential benefit of RT may be limited for some patients who may be alternatively managed by supportive care or short RT courses. Patients with CN/INI have longer survival and better response rates and may benefit from RT courses $\geq$15 to 20 Gy.

Meeting presentation information: Earlier versions of this work were accepted for poster presentation at ACRO 2020 and ASTRO 2020.

Sources of support: This work had no specific funding.

Disclosures: none.

Data sharing statement: Research data are not available at this time.

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https://doi.org/10.1016/j.adro.2021.100720

Introduction

Plasma cell neoplasms represent a spectrum of diseases with a range of clinical manifestations, from solitary plasmacytoma to multiple myeloma to plasma cell leukemia. Overall management paradigms vary based on the clinical presentation, but systemic anti-plasma cell therapy remains the backbone of treatment. However, the propensity for bony involvement and radiosensitivity of plasma cell lesions offer a role for radiation therapy (RT) to palliate problematic or symptomatic lesions, and these patients are frequently referred for consideration of RT.

Clinical decision making for some cases may be relatively straightforward, as lesions of the appendicular skeleton can be targeted easily with minimal concern for clinical complications. The International Lymphoma Radiation Oncology Group guidelines recommend hypofractionated RT for bony sites treated for symptom relief or fractionated regimens totaling 20 to 30 Gy for large or reirradiated volumes.[1] Prescribing physicians may expect response rates of 80% or higher for initial treatment of symptomatic bone metastases. Lesions of the head, however, may be more challenging to treat on account of proximity of many critical structures and variable clinical presentations, which have been previously described.[2] Indications to treat may range from painful, uncomplicated bone metastases to active or impending neurologic symptoms due to advanced lesions. Actual involvement of the central nervous system (CNS) with leptomeningeal disease (LMD) or brain metastasis (BM) is a rare entity portending poor prognosis.[3] We sought to further explore how our clinical experience may inform management of these less common scenarios.

We hypothesized that patients with BM or LMD involvement of myeloma fared worse with respect to clinical responses and survival after RT compared with patients treated for other indications, specifically cranial neuropathy or impending neurologic involvement. To answer this question, we developed a clinically useful method to classify patients with myeloma of the head (excluding uncomplicated bone metastases). In analyzing their outcomes, we hoped to inform decision making for providers who may be consulted for similar patients.

Methods and Materials

Study setting

We retrospectively identified RT courses delivered with palliative intent at our institution between January 2008 and January 2019 associated with International Classification of Diseases (ICD) codes for plasma cell neoplasms (ICD-9 codes 198, 203; ICD-10 C90) and secondary neoplasms of bone (C79.51) from plasma cell disease. All courses to the head and neck were identified and reviewed to identify RT treatment for the following indications: (1) nervous system involvement including LMD or BM, (2) osseous or soft tissue lesions with symptomatic cranial neuropathy (CN), or (3) osseous or soft tissue lesions with risk of impending neurologic involvement (INI) including brain mass effect, focal dural involvement, or disease encroaching critical neurologic structures. Courses delivered for uncomplicated, painful lesions without significant local control concerns were excluded from the analysis. This study was approved by our institutional review board.

Data abstraction

For all RT courses meeting inclusion criteria, the electronic medical record (EMR) and radiation treatment planning system (Eclipse; Varian, Palo Alto, CA) were reviewed to document patient demographic information, clinicopathologic features, clinical symptoms before treatment, radiography before treatment, prior and concurrent therapies, RT treatment details, clinical and radiographic responses, and, when available, survival and cause of death. Plasma cell leukemia diagnosis was obtained from clinical notes or labs at time of treatment.[4] Patients lost to follow-up greater than or equal to 12 months before analysis and living patients had last follow-up dates recorded.

Outcomes

Outcomes of interest included clinical response, radiographic response, and survival. Treatment responses were recorded based on documented clinical assessment and follow-up imaging when available, with responses recorded categorically as progressive disease (new lesions or progressive symptoms), stable disease, partial response (lesions smaller but present or improved but still present symptoms), or complete response (radiographic resolution or resolution of symptoms prompting treatment). These categories were additionally recorded as binary variables representing any response (partial or complete response) versus none (progressive or stable disease).

Clinical responses were recorded by review of the EMR for specific documentation regarding the symptoms attributed to disease sites for which RT was prescribed. The EMR was reviewed for best clinical response, which could happen during treatment or in follow-up. All dates were documented in relation to end of RT, with negative

values reflecting responses documented before end of treatment. Radiographic responses were also not obtained in a standardized fashion, and any follow-up head imaging was reviewed to assess response.

Statistical analysis

Analyses were performed using the Stata/IC software suite, version 15.1 (StataCorp, College Station, TX). Descriptive statistics were generated for abstracted variables. Only first radiation courses to the head (n = 54) were used for descriptive statistics and testing. Fisher's exact test was used to analyze categorical and binary response outcomes. Univariate logistic regression was used to identify factors predictive of clinical response. Based on the small number of outcomes multivariate regression was not performed. Dose response for clinical responses was analyzed with Fisher's exact test. Survival analyses, including Kruskal-Wallis test for mean survival among 3 groups, *t* test among 2 groups, and Kaplan-Meier method with log-rank test for overall survival between groups, were performed. A significance level of $P = .05$ was used for all calculations.

Results

We identified 53 patients receiving 61 RT courses within the study period. Six patients received 2 eligible courses and 1 patient received 3 (2 of which were delivered concurrently). Fifty-four first courses were included for statistical analyses. Regarding RT, 20.4% of RT courses were delivered to the head and neck for LMD/BM (group 1; n = 11), 51.9% for CN (group 2; n = 28), and 27.8% for INI (group 3; 15). Patients with CN could have multiple nerves affected, but most often presented with involvement of cranial nerves III/IV/VI (n = 17; symptoms including ocular palsy), II (9; visual acuity), and V (8; pain or paresthesia). Additional baseline demographic and clinical characteristics are included in Table 1.

Median age at time of treatment for the entire cohort was 60 years (range, 33-82). Patients were heavily pretreated, with greater than 90% of patients in all groups having previously received a proteasome inhibitor (96%, 52 of 54) and immunomodulatory drug (93%, 50 of 54) such as thalidomide, lenalidomide, or pomalidomide. Overall, fewer patients had received prior daratumumab, which was Food and Drug Administration approved for use in relapsed/refractory MM in November 2015.[5] Among patients treated with RT after Food and Drug Administration approval, 6 of 6 (100%), 10 of 18 (56%), and 8 of 10 (80%) had prior daratumumab in groups 1 to 3, respectively. Of the 13 patients who tested positive for any high-risk genetic mutations, 8 had gain1q, 3 had t(14;16), 3 had del17p, and 2 had t(4;14). Plasma cell leukemia, although rare in this cohort, was more common in patients treated for LMD/BM (2 of 11 patients).

Radiation dose, fractionation, and treatment fields were at the discretion of the treating radiation oncologist. Treatment characteristics and outcomes are included in Table 2. Commonly employed treatment fields included base of skull (n = 21; see Fig 1), orbit(s) (11), calvarium (10), and whole brain (10). Specifically, patients with CNS disease were treated with fields to the whole brain (n = 5), base of skull (2), and unilateral calvarium, unilateral orbit, pineal region, or craniospinal region (1 each). Eighty-nine percent of courses were treated with photons (n = 48), 9% with electrons (5), and 2% with protons (1). Nonelectron planning techniques included 2-dimensional (n = 29), 3-dimensional (13), volumetric modulated arc therapy (5), intensity modulated proton therapy (1), and volumetric modulated arc therapy via 6-MV flattening-filter-free O-ring linear accelerator (1). Of 3 treatment courses for LMD/BM that terminated early, 2 patients

Table 1 Patient and disease characteristics

Treatment indication	Group 1 - LMD or BM	Group 2 - CN	Group 3 - INI
Courses (n)	11	28	15
Median age (range)	60 (41-69)	59 (33-82)	63 (44-81)
High-risk cytogenetics (% of patients tested)	6/7 (85.7)	3/15 (20.0)	4/11 (36.4)
PCL	2	2	0
Positive LP (% of courses)	6 (54.5)	2 (7.1)	0 (0.0)
Median prior lines systemic therapy (range)	6 (0-11)	4.5 (0-11)	7 (3-14)
Prior therapy exposure rate (%)			
Protease inhibitor	10 (90.9)	27 (96.4)	15 (100.0)
IMiD	10 (90.9)	25 (89.3)	15 (100.0)
Daratumumab	6 (54.5)	10 (35.7)	8 (53.3)
Prior ASCT (%)	7 (63.6)	16 (57.1)	14 (93.3)

Abbreviations: ASCT = autologous stem cell transplant; BM = brain metastases; CN = cranial neuropathy; IMiD = immunomodulatory drug; INI = impending neurologic involvement; LMD = leptomeningeal disease; LP = lumbar puncture; PCL = plasma cell leukemia.

Table 2 Radiation treatment characteristics and outcomes

		Group 1 LMD or BM (n = 11)	Group 2 CN (n = 28)	Group 3 INI (n = 15)
Treatment characteristics				
Median dose (range), Gy		20 (3-45)	24 (9-40)	20 (8-30)
Median fractions (range)		7 (1-25)	10 (3-20)	8 (1-10)
Median dose per fraction (range), Gy		2.5 (1.8-4)	3 (2-4)	2.5 (2-8)
Incomplete courses (n)		3	3	2
Courses with systemic therapy within 2 weeks of RT start (%)		5 (45.5)	14 (50.0)	10 (66.7)
Courses with intrathecal therapy within 30 days of RT start (%)		3 (27.3)	1 (3.6)	0 (0.0)
Treatment outcomes				*P* value
Median survival days (range)	76 (10-151)	166.5 (6-1640)	95 (7-1342)	.11
Courses with <60 days survival (%)	5 (45.4)	7 (25.0)	6 (40.0)	.39
Courses with <120 days survival (%)	10 (90.9)	11 (39.2)	9 (60.0)	.013
Patients living or lost to follow-up	0	2	3	-
Partial or complete clinical response (%)*	2 (25.0)	25 (89.3)	10 (90.9)	< .001
Partial or complete radiographic response (%)†	3 (50.0)	14 (66.7)	6 (54.5)	.73

Abbreviations: BM = brain metastases; CN = cranial neuropathy; INI = impending neurologic involvement; LMD = leptomeningeal disease; RT = radiation therapy.

* There were 8, 28, and 11 courses evaluable for clinical response in groups 1-3, respectively.

† There were 6, 21, and 11 courses evaluable for radiographic response in groups 1-3, respectively.

with failure to thrive enrolled in hospice, and 1 completed craniospinal irradiation at another center for which RT details were not available. Of 3 incomplete courses for CN, 2 patients had failure to thrive due to disease progression, and 1 had good clinical response and elected to return to systemic therapy. Of 2 incomplete courses for INI, 1 had progressive disease and enrolled in hospice whereas 1 had good clinical response. Systemic agents most often administered concurrently with RT (alone or in combination with other agents) included bortezomib, carfilzomib, cyclophosphamide, and daratumumab (n = 6, 10, 10, and 7, respectively). All 4 patients who received intrathecal chemotherapy within 30 days of RT start received cytarabine, with 2 of these patients also receiving methotrexate.

Clinical and radiographic follow-up varied widely between patients with response assessments available for 8 of 11, 28 of 28, and 11 of 15 courses in groups 1, 2, and 3, respectively, at median time points of 22 (interquartile range [IQR], 6-78), 16.5 (IQR, 1-38), and 4 (IQR, -5-44) days.

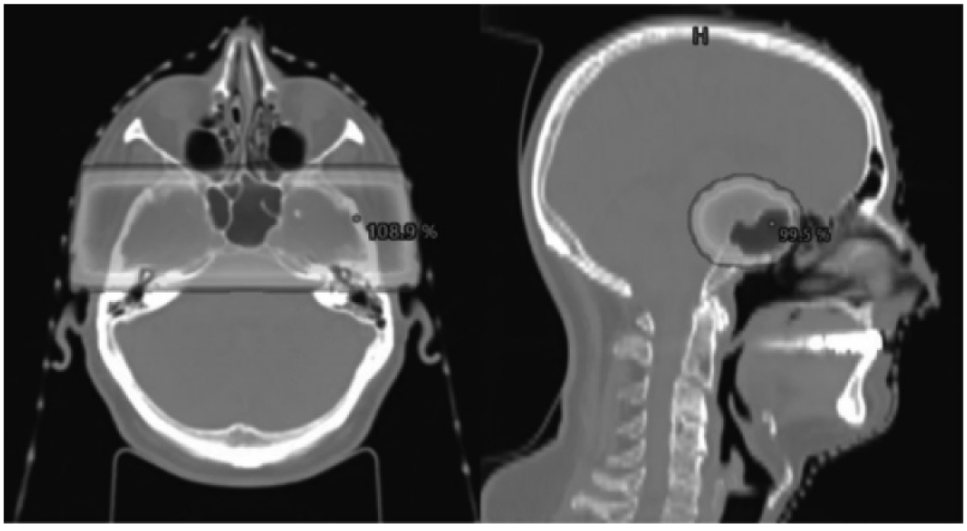

Fig. 1 Example base of skull treatment fields.

Table 3 Graded clinical and radiographic responses

	Progressive disease	Stable disease	Partial response	Complete response	*P* value
	Clinical response (number of courses)*				
Group 1 – LMD or BM	1	5	2	0	.010
Group 2 – cranial neuropathy	1	2	20	5	
Group 3 – INI	0	1	8	2	
	Radiographic response (number of courses)*				
Group 1 – LMD or BM	1	2	3	0	.20
Group 2 – cranial neuropathy	1	6	7	7	
Group 3 – INI	0	5	1	5	

Abbreviations: BM = brain metastases; INI = impending neurologic involvement; LMD = leptomeningeal disease.
* In total, 47 of 54 courses evaluable for clinical response; 38 of 54 evaluable for radiographic response.

Radiographic response data were available for 6 of 11, 21 of 28, and 11 of 15 courses for groups 1, 2, and 3, respectively, at median time points of 23 (IQR, 2-76), 37 (IQR, 17-141), and 36 (IQR, 11-335) days. Among 38 patients who had follow-up imaging, 5 did not have any cranial imaging until at least 1 year after RT completion. Graded treatment responses are shown in Table 3. There was no significant difference in radiographic categorical responses between groups (P = .20), but clinical categorical responses differed between groups (P = .010). Further analysis was performed with clinical responses consolidated to a binary variable (partial response or better vs no response) to compare groups. When groups 2 and 3 (CN and INI, respectively) were combined, the analysis demonstrated that patients in group 2 or 3 (no CNS involvement) were more likely to achieve at least a partial clinical response compared with patients in group 1 (LMD/BM; 90% vs 25%; P < .001), with the only complete responders in groups with CN or INI (Fig. 2). Similarly, radiographic responses were no different between groups when considered as either binary or categorical variables, but the only radiographic complete responders were in groups 2 and 3. Logistic regression modeling to identify factors predictive of any clinical response are shown in Table 4. Patients in the combined CN/INI group (P < .001) and those without high-risk cytogenetics (P = .009) were more likely to have a clinical response, and total dose trended toward significance (P = .087). Small patient numbers limited the ability to perform multivariate analysis, and limited follow-up imaging for most patients precluded assessment of local control.

To determine the potential role of dose in clinical response, dose-response analyses were performed with cutoffs in 5 Gy increments from 5 to 40 Gy. Among patients in all 3 groups, 15 and 20 Gy emerged as significant cutoffs (P = .026 and .005, respectively), which is predictive of increased probability of any clinical response (Table E5). These dose levels were also significant for the combined patient group with CN/INI (P = .023 and .002). Doses ≥20 Gy were predictive of response in patients with CN (P = .008).

Dates of death were available for 48 patients (90.6%). Three patients were confirmed alive in ongoing follow-up, and 2 patients were censored at last follow-up greater

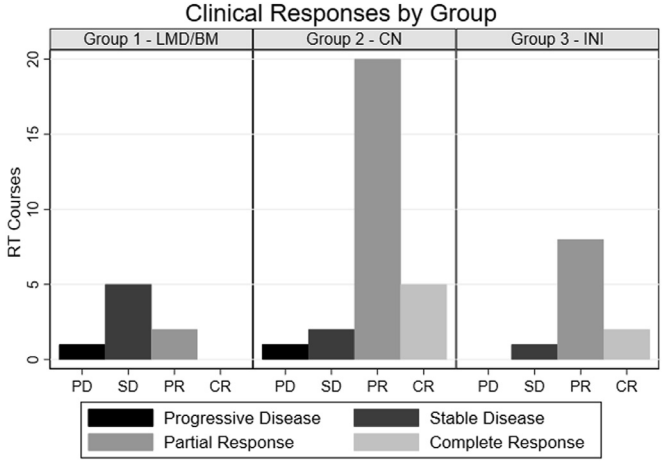

Fig. 2 Clinical responses by group.

Table 4 Logistic regression results for any clinical response

	Univariate	
Patient baseline characteristics*	Coeff (95% CI)	*P* value
Group number (all 3 groups)	2.27 (0.71-3.82)	< .001
Group number (1 vs 2/3 combined)	3.27 (1.36-5.17)	< .001
Age	0.002 (-0.069-0.073)	.95
High-risk cytogenetics	−2.71 (−5.08 to −0.33)	.009
PCL	−0.66 (−3.17 to 1.84)	.62
Prior lines of therapy	−0.12 (−0.33 to 0.09)	.27
Daratumumab	−0.27 (−1.67 to 1.13)	.70
ASCT	−0.89 (−2.58 to 0.80)	.27
Positive LP	−0.72 (−2.59 to 1.14)	.46
Treatment factors†	Coeff (95% CI)	*P* value
Dose	0.0008 (−0.0002 to 0.0019)	.087
Dose per fraction	−0.0002 (−0.0070 to 0.0074)	0.95
Concurrent systemic therapy	−0.58 (−2.08 to 0.93)	.44

Abbreviations: ASCT = autologous stem cell transplant; CI = confidence interval; IMiD = immunomodulatory drug; LP = lumbar puncture; PCL = plasma cell leukemia.

* Proteasome inhibitor and IMiD use excluded for collinearity.

† Recent intrathecal therapy excluded for collinearity.

than 1 year before analysis without confirmed date of death. There were no statistically significant differences in mean survival between all 3 groups ($P = .11$) as determined by Kruskal-Wallis. After consolidating groups 2 and 3, Student's *t* test demonstrated mean survival trending toward significance ($P = .058$). The longest survival in group 1 was 151 days. In contrast, 11 of 42 (26.2%) patients in groups 2 and 3 survived for more than 1 year. Kaplan-Meier survival analysis for all 3 groups was significantly different by log-rank test ($P = .017$), and log-rank for group 1 versus 2 and 3 combined (Fig. 3) demonstrated significantly worse survival among patients with LMD or BM ($P = .005$). Median survival in group 1 was 76 days versus 142 days for groups 2 and 3.

All subsequent radiation courses were excluded from these analyses. Of the 7 patients who received multiple courses, 5 received multiple courses for the same indication. Two patients received an initial course for CN and a second course for INI. For patients who received multiple courses, the median time between RT courses was 92 days (range, 26-1132).

Discussion

In this review of patients treated with RT at our institution for myeloma of the head, we demonstrate poor response rates and survival for patients with BM and

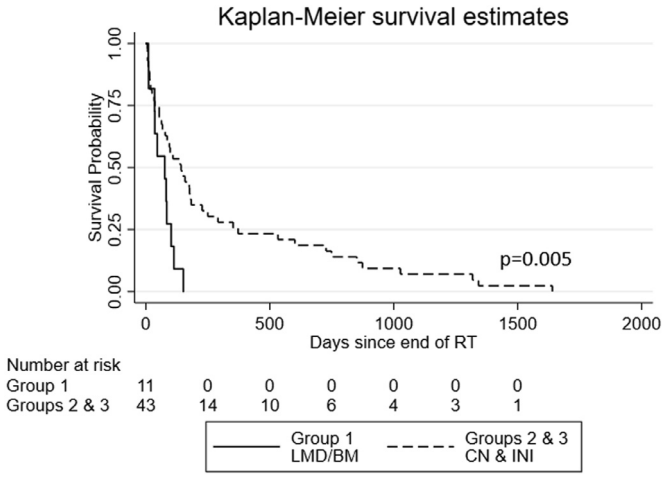

Fig. 3 Kaplan-Meier survival analysis (group 1 vs groups 2 and 3).

LMD compared with patients treated for CN or INI. The results of our series of patients corroborate prior literature demonstrating the poor prognosis for CNS myeloma, likely reflecting aggressive underlying disease biology. In a recent similarly conducted review from the United Kingdom, Egan et al[6] noted CNS relapses of myeloma affect <1% of patients and confer a survival of 7 or fewer months. They also highlighted the improved prognosis of lesions resulting from an osseous primary, similar to our patients in the CN and INI groups. Our results from treating patients with CNS involvement are also consistent with an older review from the Netherlands demonstrating median survival of approximately 2 months in 109 patients. In comparison to our study, this series noted a significant—albeit small—survival improvement with cranial RT compared with no RT (median survival 3 months vs 0.81 months),[7] although this improvement may be less generalizable in the current era of novel systemic agents. Conversely, Chen et al[8] from the Princess Margaret Hospital reported long-term survival in 9 out of 37 patients (median, 17.1 months) with aggressive combination therapies consisting of systemic therapies, RT, and transplant, suggesting that aggressive multimodal therapy may provide durable control of disease in a small number of patients. However, the absolute number of patients who acquired long-term survival in this series survival was small, and no cytogenetic information was provided. Additionally, these patients may have been less heavily pretreated with systemic therapy than those included in our series. Several other small retrospective series have also been published, again corroborating limited survival in patients with CNS myeloma.[9,10]

Thus, given the limited median survival for patients with CNS disease (76 days), a short course (ie, 5 or fewer fractions) of RT may be most appropriate if treating at all. Alternatively, providers may terminate treatment courses early if clinical benefit has been attained or defer radiation altogether in favor of best supportive care. Ultimately, the decision depends on many factors, including remaining systemic options, prognostic factors as indicated by cytogenetics or bloodwork, as well as the patient's wishes.[11,12]

On the other hand, some patients with CN or INI involvement had prolonged survival (up to years in some cases) and therefore may benefit from treatment for symptoms or lesions encroaching critical structures. Notably, our results confirm already published data on the varied natural history of myeloma, with isolated lesions near neurologic structures associated with improved outcomes compared with patients with parenchymal lesions or LMD.[6,13,14] Furthermore, in our series, responses for patients with CN or INI were improved with doses above 15 to 20 Gy, and patients with anticipated long-term survival may benefit from these or higher doses. The presence of high-risk cytogenetics may also help guide decision making, as patients with poor molecular markers had worse clinical responses in our series. Altogether, modest doses of 20 to 30 Gy may provide the optimal balance between achieving the desired clinical response and minimizing treatment burden. These results are also consistent with International Lymphoma Radiation Oncology Group guidelines, which recommend a more protracted regimen of 20 to 30 Gy for epidural disease with cord compression, a bulky mass when local control is desired, large volumes, or reirradiation.[1] Additionally, keeping doses below the range used for plastmacytomas (40-50 Gy) may minimize breaks from systemic therapy and potential toxicities associated with escalated doses.

Limitations of this study are largely a result of its retrospective nature and small sample size. This may lead to bias regarding patient selection, variable response assessments and documentation, inconsistent follow-up, and inability to account for systemic burden of disease in many cases. Due to inconsistent documentation we are also unable to account for performance status as a potential confounder of survival and clinical outcomes. Moreover, this series includes only patients seen by and treated with RT and does not account for patients for whom RT was not recommended at initial consultation as well as patients never referred for RT.

Regardless of such limitations, we assert that our analysis offers a valuable clinical paradigm that providers can use to categorize patients and guide clinical decision making. As CNS involvement is rarely encountered in patients with myeloma, of whom only a subset are referred for consideration of RT, few large experiences have been reported. This work adds to the clinical literature by not only redemonstrating poor outcomes associated with CNS relapses, but also developing a useful clinical system to help understand which patients may benefit from RT. Differentiating CNS disease from other head and neck presentations of myeloma offers a simple heuristic that physicians can employ to counsel patients and advise colleagues on the utility of RT. We hope to collaborate in a multi-institutional setting to expand the cohort and retest our hypothesis with a broader patient population.

Conclusions

CNS myeloma is a rare diagnosis with a poor prognosis. Clinical presentations of myeloma in the head and neck differ in terms of symptoms and prognosis. Patients with LMD or BM may not strongly benefit from RT either in terms of clinical response or survival. Moreover, RT may delay next-line systemic therapy and expose patients to potential RT-related toxicities. Therefore, a reasonable alternative option may be supportive care or a short palliative RT course, as these patients do now show any dose-response trend. Alternatively, patients with CN or lesions approaching critical neurologic structures can have significantly better survival and may benefit from courses of at least 15 to 20 Gy. Thus,

when evaluating a patient with myeloma involving the head, identifying the extent and symptoms of disease can help radiation oncologists determine whether treatment may benefit the patient and, if so, what dose to prescribe.

Acknowledgments

The authors would like to thank the Abramson Cancer Center clinical informatics team for their assistance in collecting data for this study, as well as the Perelman School of Medicine Center for Clinical Epidemiology and Biostatistics for their review of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.adro.2021.100720.

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