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Scientific Letter

Contemporary Statewide Practice Pattern Assessment of the Palliative Treatment of Bone Metastasis

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Summary

Using a statewide initiative comprised of 20 diverse institutions that span academia and community practice, a detailed assessment of the treatment of bone metastases was captured and analyzed. Our data demonstrate that bone metastases are a heterogeneous disease state, and the treatment of this disease is similarly diverse.

Purpose: Palliative radiation therapy for bone metastases is often viewed as a single entity, despite national guidelines providing input principally only for painful uncomplicated bone metastases. Data surrounding the treatment of bone metastases are often gleaned from questionnaires of what providers would theoretically do in practice or from population-based data lacking critical granular information. We investigated the real-world treatment of bone metastases with radiation therapy.

Methods and Materials: Twenty diverse institutions across the state of Michigan had data extracted for their 10 most recent cases of radiation therapy delivered for the treatment of bone metastases at their institution between January and February 2017. Uni- and multivariable binary logistic regression was used to assess the use of single fraction (8 Gy × 1) radiation therapy.

Results: A total of 196 cases were eligible for inclusion. Twenty-eight different fractionation schedules were identified. The most common schedule was 3 Gy × 10 fractions (n = 100; 51.0%), 4 Gy × 5 fractions (n = 32; 16.3%), and 8 Gy × 1 (n = 15;

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However, even for simple painful bone metastases, the use of single fraction radiation therapy is uncommon.

7.7%). The significant predictors for the use of single fraction radiation therapy were the presence of oligometastatic disease ($P = .008$), previous overlapping radiation therapy ($P = .050$), and academic practice type ($P = .039$). Twenty-nine cases (14.8%) received >10 fractions (median 15, range 11-20). Intensity modulated radiation therapy was used in 14 cases (7.1%), stereotactic body radiation therapy in 11 (5.6%), and image guidance with cone beam computed tomography in 11 (5.6%). Of the cases of simple painful bone metastases (no previous surgery, spinal cord compression, fracture, soft tissue extension, or overlapping previous radiation therapy; n = 70), only 12.9% were treated with 8 Gy × 1.

Conclusions: Bone metastases represent a heterogeneous disease, and radiation therapy for bone metastases is similarly diverse. Future work is needed to understand the barriers to single fraction use, and clinical trials are necessary to establish appropriate guidelines for the breadth of this complex disease.

Introduction

The common indications for the use of radiation therapy for bone metastases are many. These include palliation of pain (1); spinal cord compression (2, 3); prevention of subsequent problems (eg, fracture, spinal cord compression) through durable local control (4) (eg, NRG BR-001 [phase 1 study of stereotactic body radiotherapy (SBRT) for the treatment of multiple metastases] and Radiation Therapy Oncology Group 0631); and an emerging field of treatment of oligometastatic disease (5, 6). The American Society of Radiation Oncology has published guidelines specifically for painful uncomplicated bone metastases and has recommended the use of single fraction radiation therapy (8 Gy × 1 fraction) for this entity (7). For more complex lesions, including lesions involving the spine, other groups have advocated the use of higher biologically effective doses, often delivered using stereotactic body radiation therapy (SBRT), to overcome tumor-specific radioresistance and provide more durable local control (8, 9).

The data to date on the treatment of bone metastases have come primarily from surveys of providers of how they would theoretically practice (10) or from population-based data that lack the granularity of treatment details (eg, dose per fraction) (11). This motivated our group to leverage clinical data in the treatment of bone metastases from members of the statewide Michigan Radiation Oncology Quality Consortium to examine contemporary practice patterns among radiation oncologists across a broad range of practices in the state of Michigan.

Methods and Materials

Twenty diverse institutions across the state of Michigan were provided a Case Review Form (Appendix E1; available online at www.redjournal.org) to assess the most recent 10 cases of palliative radiation therapy delivered for the treatment of bone metastases at their institution between January and February 2017. All centers provided 10 cases, with the exception of 1 center, resulting in 199 total cases. Of the 199 patients, 3 were excluded because of insufficient detail on dose and fractionation, leaving 196 cases eligible for analysis. Sixty-five percent of cases were from community practices. We collected 16 items for each case (Appendix E1; available online at www.redjournal.org).

Covariable definitions

The complexity of the bone metastases was defined as simple or complex. Complex bone metastases were defined as bone metastases with a pathologic fracture, previous surgery or planned surgery, spinal cord compression, previous radiation, or significant soft tissue extension. Previous radiation therapy was defined as direct overlap, a ≥2 cm distance from the current treatment, or no previous radiation therapy. Pain scores were collected if routinely used by the physician and/or practice. Concurrent disease was defined only by the presence of current central nervous system disease or visceral disease. Radiation sensitivity was defined according to Gerszten et al (12). The number of metastases per patient was documented as 1 to 3 lesions (eg, oligometastatic) versus >3 (polymetastatic).

Statistical analysis

Univariable odds ratios and 95% confidence intervals for the use of single fraction (8 Gy × 1) radiation therapy were calculated using a binary logistic regression model. Multivariate models were similarly constructed. Two-sided P values ≤ .05 were considered statistically significant. Statistical analysis was performed using SPSS, version 25.

Results

The pretreatment characteristics of the cohort are listed in Table 1 and demonstrate the tremendous heterogeneity of the patients treated in practice. Likewise, the treatment was

Table 1 Cohort characteristics

Characteristic	n (%)
Age (y)	
Median	65
Range	33-90
Gender	
Male	116 (59)
Female	80 (41)
Bone metastasis complexity	
Simple	112 (57)
Complex	84 (43)
Current metastases	
1-3	89 (45)
>3	105 (54)
Previous RT	
Overlap	14 (7)
≥2 cm distance	10 (5)
None	168 (86)
Unknown	4 (2)
Chemotherapy within previous month	
Yes	61 (31)
No	132 (67)
Unknown	3 (2)
Pain score collected	
Yes	163 (83)
No	32 (16)
Unknown	1 (1)
Pain score if collected	
Median	6
Range	0-10
Concurrent disease	
CNS	21 (11)
Visceral	58 (30)
Unknown	2 (1)
Histologic type	
Breast	37 (19)
Prostate	33 (17)
NSCLC	23 (12)
Myeloma/lymphoma	16 (8)
GI/liver/pancreas	17 (9)
Other	63 (32)
Unknown	7 (4)
Radiation sensitivity	
Sensitive	16 (8)
Moderately sensitive	78 (40)
Moderately resistant	43 (22)
Resistant	28 (14)
Unknown	31 (16)
Practice type	
Academic	69 (35)
Community	127 (65)

Abbreviations: CNS = central nervous system; GI = gastrointestinal; NSCLC = non-small cell lung cancer; RT = radiation therapy.

heterogeneous, with 28 different fractionation schedules identified across the 20 reporting centers (Fig. 1A). The most common schedule was 3 Gy × 10 fractions (n = 100; 51.0%), followed by 4 Gy × 5 fractions (n = 32; 16.3%), and 8 Gy × 1 (n = 15; 7.7%). A total of 29 cases (14.8%) received >10 fractions (median 15, range 11-20) of radiation therapy. Intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy was used in 14 cases (7.1%; Fig. 1B), and SBRT was used in 11 cases (5.6%). Of the 11 SBRT cases, 8 were planned using IMRT. The remaining SBRT cases were planned using 3-dimensional conformal radiation therapy. Image guidance with cone beam computed tomography was used in 11 cases (5.6%).

The heterogeneity in single fraction radiation therapy use across the 20 institutions included in the present study is shown in Figure 2A. The overall rate of single fraction use was low (7.7%), with no cases receiving 8 Gy × 1 in 13 institutions. On multivariable analysis (Table 2), significant variables associated with using single fraction radiation therapy were the presence of oligometastatic disease (P = .008), academic practice type (P = .039), and previous overlapping radiation therapy (P = .050).

In an idealized subgroup (n = 70) of patients with a pain score of >4 of 10 and no previous overlapping radiation therapy, soft tissue extension, fracture, surgery, or spinal cord compression, only 9 patients (12.86%) had received single fraction radiation therapy. Similar to the use of single fraction radiation therapy, the receipt of IMRT was also heterogeneous across the 20 institutions (Fig. 3). However, for 2 of the 15 cases (13.3%) of single fraction 8 Gy × 1 treatment, IMRT was used (Table 3).

Discussion

The present study has clearly demonstrated the significant heterogeneity in practice patterns in the treatment of bone metastases across the state of Michigan. This heterogeneity not only spans the patient demographic data and tumor types treated, but also the dose per fraction, number of fractions, use of advanced techniques, and the use of image guidance. Additionally, our data have demonstrated that IMRT use and treatment courses >10 fractions are not uncommon. Furthermore, the use of single fraction radiation therapy was low, even for simple painful bone metastases.

A previous international study asked physicians what dose fractionation schedules they would recommend for various types of bone metastases (10). Similar to our study,

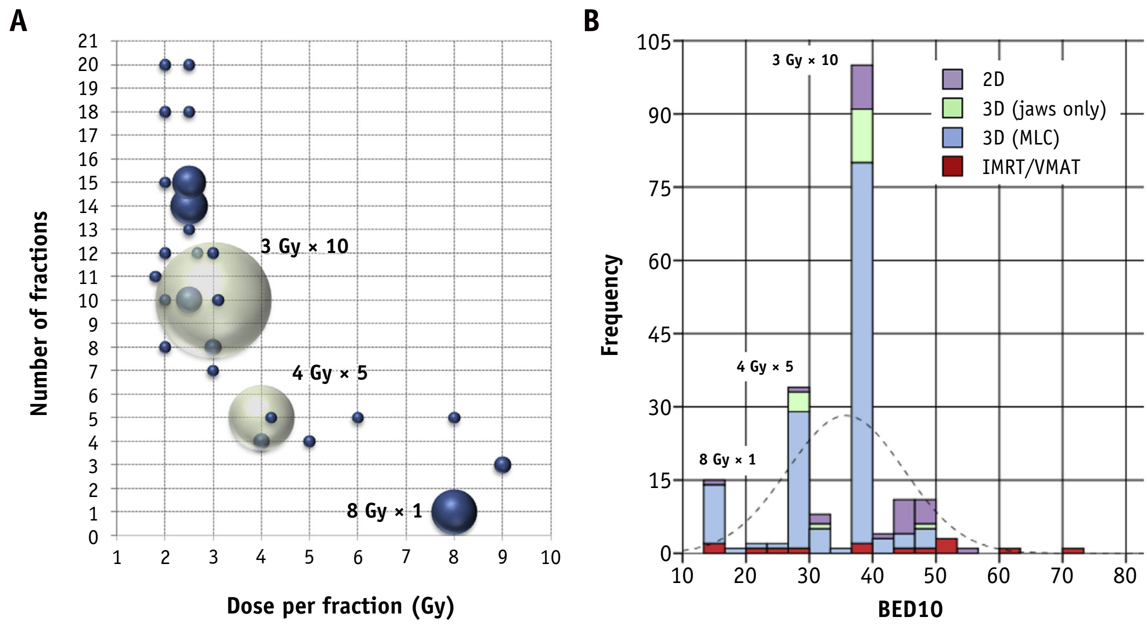

Fig. 1. Heterogeneity in dose fraction schedules. (A) Scatter plot of dose per fraction and number of fractions for all 196 cases. Size of the sphere correlates to frequency. (B) Stacked bar chart of the biologically equivalent dose using an α/β of 10 according to treatment planning technique used. *Abbreviations:* 2D = 2-dimensional; 3D = 3-dimensional; IMRT = intensity modulated radiation therapy; MLC = multileaf collimator; VMAT = volumetric modulated arc therapy.

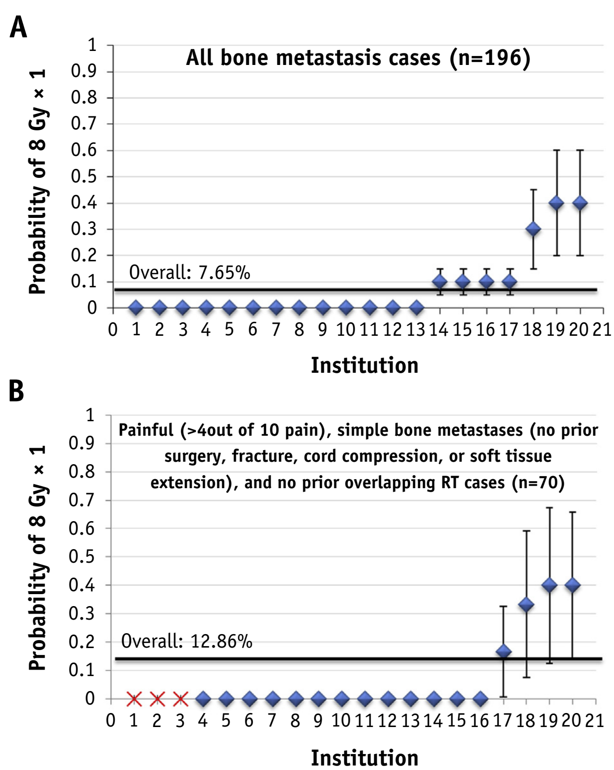

Fig. 2. Heterogeneity in use of single fraction radiation therapy (8 Gy × 1) stratified by institution. (A) Cumulative probability of single fraction radiation therapy use stratified by institution among all cases (n = 196). (B) Cumulative probability of single fraction radiation therapy use stratified by institution for only painful bone metastases (pain score >4 of 10) and no previous overlapping radiation therapy, soft tissue extension, spinal cord compression, pathologic fracture, or surgery (n = 70). Red X denotes no cases present at that center. (A color version of this figure is available at www.redjournal.org.)

Table 2 Single fraction (8 Gy × 1) use: Uni- and multivariable analyses

Variable	Univariable analysis OR	95% CI	P value	Multivariable analysis AOR	95% CI	P value
Institution (continuous)	0.99	0.90-1.09	.81	-	-	-
Gender	0.50	0.15-1.64	.25	-	-	-
Age (continuous)	1.01	0.97-1.06	.57	-	-	-
Radiosensitivity	0.95	0.52-1.72	.87	-	-	-
Complexity (simple vs complex)	0.46	0.14-1.49	.2	-	-	-
No. of metastases (1-3 vs >3)	0.05	0.01-0.40	.005*	0.06	0.01-0.46	.008*
Concomitant CNS or visceral disease	0.26	0.06-1.20	.09*	0.84	0.15-4.55	.84
Chemotherapy in previous month	1.09	0.36-3.33	.88	-	-	-
Pain score (continuous)	1.08	0.89-1.28	.45	-	-	-
Previous RT				-	-	-
None	Reference	-	-	Reference	-	-
Overlap	3.85	0.94-16.67	.06*	5.88	1.00-35.71	.05*
>2 cm distance	1.59	0.18-14.29	.68	1.19	0.12-11.90	.89
Practice type (academic vs community)	0.12	0.02-0.93	.042*	0.09	0.01-0.89	.039*

Abbreviations: AOR = adjusted odds ratio; CI = confidence interval; CNS = central nervous system; OR = odds ratio; RT = radiation therapy.
* Statistically significant.

the most common dose fractionation schedule in their study was 3 Gy × 10. The strength of our study, however, was that it was based on the diverse practices across 1 state, reflecting actual treatment data, instead of merely querying what physicians theoretically would do. Additionally, we were able to capture data on treatment planning and image guidance techniques. Furthermore, the present study was not restricted to those with only painful bone metastases, further underlining real-world practice and the diverse goals of care when treating patients with bone metastases.

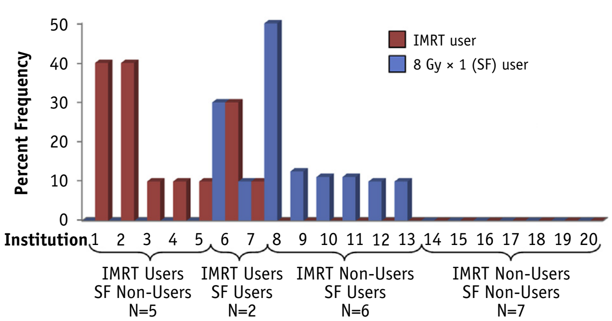

Fig. 3. Distribution of intensity modulated radiation therapy (IMRT) and single fraction (SF) use stratified by institution.

The current American Society of Radiation Oncology guidelines for bone metastases were based on the randomized trials that were included in the multiple bone metastases meta-analyses (1, 13). However, these randomized trials on optimal dose fractionation schedules were limited to those with only painful metastatic disease. Furthermore, these trials were completed before the advent of more effective systemic therapies (eg, targeted monoclonal antibodies, small molecule inhibitors, and immunotherapy), and none assessed the comparison of much greater biologically effective doses. Additionally, these trials had very short primary endpoints of 1 to 3 months of pain control, and none systematically performed serial imaging to document local tumor progression. Finally, the field of metastasis-directed therapy is growing, and these historical trials cannot provide insight into this new exciting field. These many differences in the historical bone metastases trials provide more questions than answers in the landscape of treating bone metastasis in 2018. Going forward, the Michigan Radiation Oncology Quality Consortium is expanding data collection efforts to better understand the barriers to adopting single fraction radiation therapy and to better understand and study the framework for the use of alternative dose fractionation schedules and advanced treatment techniques for diverse goals of care.

Table 3 Details of cases using either IMRT and/or SBRT

Case No.	Practice type	Age (y)	Histologic type	Bone metastasis complexity	Concurrent disease	Metastatic burden	Pain score taken	Pain score (0-10)	Previous RT	Treatment planning technique	SBRT	Total dose (Gy)	Fx (n)	Dose/Fx (Gy)	Image guidance
1	Academic	57	RCC	Simple	No	Poly	No		No	IMRT	Yes	30	3	10	CBCT
2	Community	70	NSCLC	Complex	Yes	Poly	No		No	IMRT	Yes	27	3	9	CBCT
3	Academic	75	NSCLC	Complex	No	Oligo	Yes	5	No	IMRT	Yes	40	5	8	CBCT
4	Academic	59	Prostate	Simple	No	Oligo	Yes	2	No	IMRT	Yes	27	3	9	CBCT
5	Community	77	Breast	Simple	Yes	Poly	Yes	2	No	IMRT	Yes	18	1	18	CBCT
6	Community	70	Penile	Complex	No	Oligo	Yes	4	No	IMRT	Yes	20	5	4	KV
7	Community	70	Prostate	Complex	No	Oligo	No		Yes, >2 cm distance	IMRT	Yes	30	5	6	CBCT
8	Academic	60	Unknown ACA	Complex	Yes	Oligo	Yes	8	No	3D-CRT with MLCs	Yes	20	5	4	KV
9	Community	61	NSCLC	Complex	No	Poly	Yes	7	No	3D-CRT with MLCs	Yes	16	4	4	KV
10	Community	71	PACC	Simple	Yes	Oligo	No		No	3D-CRT with MLCs	Yes	30	10	3	KV
11	Academic	66	Unknown ACA	Simple	Yes	Oligo	No		Yes	IMRT	Yes	16	4	4	CBCT
12	Academic	63	Liver	Simple	Yes	Oligo	Yes	0	No	IMRT	No	50	20	2.5	CBCT
13	Academic	48	Breast	Complex	No	Poly	Yes	9	Yes	IMRT	No	19.8	11	1.8	CBCT
14	Community	68	Prostate	Simple	No	Oligo	Yes	10	No	IMRT	No	8	1	8	KV
15	Community	55	GI	Complex	No	Poly	Yes	7	Yes, >2 cm distance	IMRT	No	30	10	3	KV
16	Community	73	NSCLC	Simple	No	Oligo	Yes	1	No	IMRT	No	8	1	8	KV
17	Community	64	Unknown ACA	Complex	Yes	Poly	Yes	9	No	IMRT	No	36	15	2.4	CBCT

Abbreviations: ACA = adenocarcinoma; CBCT = cone beam computed tomography; 3D-CRT = 3-dimensional conformal radiation therapy; Fx = fraction; IMRT = intensity modulated radiation therapy; MLCs = multileaf collimators; NSCLC = non-small cell lung cancer; Oligo = oligometastatic (1-3 metastases); PACC = parotid adenoid cystic carcinoma; Poly = polymetastatic (>3 metastases); RCC = renal cell carcinoma; SBRT = stereotactic body radiation therapy.

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