Curr Oncol, Vol. 20, pp. e396-405; doi: http://dx.doi.org/10.3747/co.20.1457

ORIGINAL ARTICLE

Patterns of practice in the prescription of palliative radiotherapy for the treatment of bone metastases at the Rapid Response Radiotherapy Program between 2005 and 2012

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ABSTRACT

Objective

We examined whether patterns of practice in the prescription of palliative radiation therapy for bone metastases had changed over time in the Rapid Response Radiotherapy Program (RRRP).

Methods

After reviewing data from August 1, 2005, to April 30, 2012, we analyzed patient demographics, diseases, organizational factors, and possible reasons for the prescription of various radiotherapy fractionation schedules. The chi-square test was used to detect differences in proportions between unordered categorical variables. Univariate logistic regression analysis and the simple Fisher exact test were also used to determine the factors most significant to choice of dose–fractionation schedule.

Results

During the study period, 2549 courses of radiation therapy were prescribed. In 65% of cases, a single fraction of radiation therapy was prescribed, and in 35% of cases, multiple fractions were prescribed. A single fraction of radiation therapy was more frequently prescribed when patients were older, had a prior history of radiation, or had a prostate primary, and when the radiation oncologist had qualified before 1990.

Conclusions

For patients with bone metastasis, a single fraction of radiation therapy was prescribed with significantly greater frequency.

KEY WORDS

Palliative radiation therapy, patterns of practice, bone metastasis, dose fractionation

1. INTRODUCTION

Bone metastases are a common complication of advanced cancer[1] and can progress to spinal cord compression, cauda equina syndrome, and pathologic fracture[2]. Radiation therapy has been used for the palliation of painful bone metastases, with partial responses seen in 50%–80% of patients and one third of patients achieving complete pain relief after treatment[3].

Numerous randomized trials have examined various dose fractionation schedules in palliative radiation therapy for bone metastasis[4–27]. For uncomplicated bone metastases, the most recent meta-analysis continues to report that single-fraction treatment provides pain relief equal to that achieved using a multiple-fraction treatment schedule[3]. An evidence-based clinical practice guideline from the American Society for Radiation Oncology recommends a single fraction as being more convenient for patients and their caregivers[2].

The Rapid Response Radiotherapy Program (RRRP) was established to provide timely palliative radiation therapy for symptom relief in patients with metastatic or locally advanced cancer[28]. The present retrospective study examined whether patterns of practice in prescribing palliative radiation therapy to patients seen in the RRRP with bone metastases changed over time from 2005 to 2012.

2. METHODS

General demographics and details about radiation treatment were captured in a prospective database for all patients with bone metastases who received palliative radiation therapy between August 1, 2005, and April 30, 2012. That time period was selected to update a previous study in the RRRP that reviewed patients treated for bone metastases between 1999 and July 31, 2005[29]. The primary outcome for the present study was the treatment schedule prescribed, including fractionation and dose. Secondary outcomes included an analysis of factors that may have influenced the prescribed treatment schema, including patient, organizational, and disease factors. A further analysis was conducted to determine the reasons that multiple- or single-fraction treatment schedules were prescribed.

Ten factors were hypothesized to influence the choice of dose fractionation schedule. Of those 10 factors, 6 were patient or demographic factors: age, sex, Karnofsky performance status (KPS), whether the patient had previously received radiation, where the patient had come from (for example, hospital, home, nursing home), and whether the patient arrived by ambulance. Another 3 factors pertained to the disease: primary cancer site, reason for referral, and irradiated site. The 10th factor was an organizational factor: the number of years the treating radiation oncologist had been certified for independent practice by the Royal College of Physicians and Surgeons of Ontario.

2.1 Statistical Analyses

Descriptive statistics are summarized as percentages and as means or medians with standard deviations and ranges for continuous variables. The dose fractionation schedules were categorized as single-fraction (that is, 8 Gy in 1 fraction) or multiple-fraction [that is, 20 Gy in 5 fractions (20 Gy/5), 30 Gy in 10 fractions (30 Gy/10), or others]. To determine whether the use of single-fraction radiotherapy changed over time, a chi-square test was used to detect differences in the proportions of unordered categorical variables including sex, primary cancer site, previous radiation, whether the patient arrived by ambulance, where the patient had come from, the first site of radiation therapy, and reasons for referral across time. Continuous variables such as age and KPS were tested across time using an analysis of variance.

Univariate logistic regression analyses were conducted to search for demographic and clinical characteristics significantly associated ($p < 0.05$) with the prescription of a single-fraction treatment schedule, based on the first site of radiation. The outcome of the model was a binary variable (1 or 0) for single- or multiple-fraction treatment schedules. A multiple logistic regression analysis was also used to examine the effect of year of treatment (2012 being the referent year) on the use of a single-fraction treatment schedule, after adjusting for all other independent variables (that is, sex, age, primary cancer site, and so on). Odds ratios and 95% confidence intervals were estimated for each covariate. Multi-collinearity was assessed using variance inflation factors. The Hosmer–Lemeshow goodness-of-fit test was used to determine if the data fitted the specified model.

The final procedure conducted was a simple Fisher exact test to determine whether any referral reason was significantly associated with the prescription of 20 Gy/5, 30 Gy/10, and other multiple-fraction schedules. All analyses were conducted using the Statistical Analyses System (SAS version 9.2 for Windows: SAS Institute, Cary, NC, U.S.A.).

3. RESULTS

During the study period, 2549 courses of radiation therapy were administered in the RRRP to patients with bone metastases. A single fraction of radiation therapy was prescribed in 65% of cases, and multiple fractions were prescribed in the remaining 35% (Figure 1). Of the 888 courses of radiation therapy in patients receiving multiple fractions, 738 courses used a prescription of 20 Gy/5, and 75 courses used 30 Gy/10. The most commonly irradiated sites were the spine (46%) and the limbs, hip, and skull (35% combined, Table I).

Median age of the patients was 70 years (range: 27–101 years), and 57% were men. The median KPS was 60 (range: 10–100). Overall, 29% were hospital inpatients, and 23% arrived at the RRRP by ambulance. Prior radiation therapy (not necessarily to the same site) had been administered in 48% of patients before they received radiation therapy for their bone metastases. In terms of primary cancer site, 26% of the patients had a lung primary; prostate (25%) and breast (22%) primaries were the next most frequent. The most common reasons for referral to the RRRP were bone pain (83%), spinal cord compression, postoperative radiation therapy, and others (Table II).

A significant difference in the prescription of a single fraction of radiation therapy occurred over time ($p = 0.036$). Patients receiving a single fraction were significantly older ($p < 0.0001$, Table III). Patients with prostate cancer were most likely to receive a single fraction. In addition, compared with patients receiving radiation therapy for the first time, those with a prior history of radiation had 1.55 times the odds of receiving a single fraction. In contrast, women, inpatients, and patients arriving at the RRRP by ambulance were less likely to receive a single fraction of radiation therapy. A single fraction was less frequently used in the spine than in other sites ($p < 0.0001$), being less frequently administered to patients referred for spinal cord compression, impending cord compression, cauda equina syndrome, or pathologic fracture ($p < 0.0001$). Lastly, radiation oncologists certified from the year 1990 onward were more likely to prescribe multiple-fraction treatment schedules.

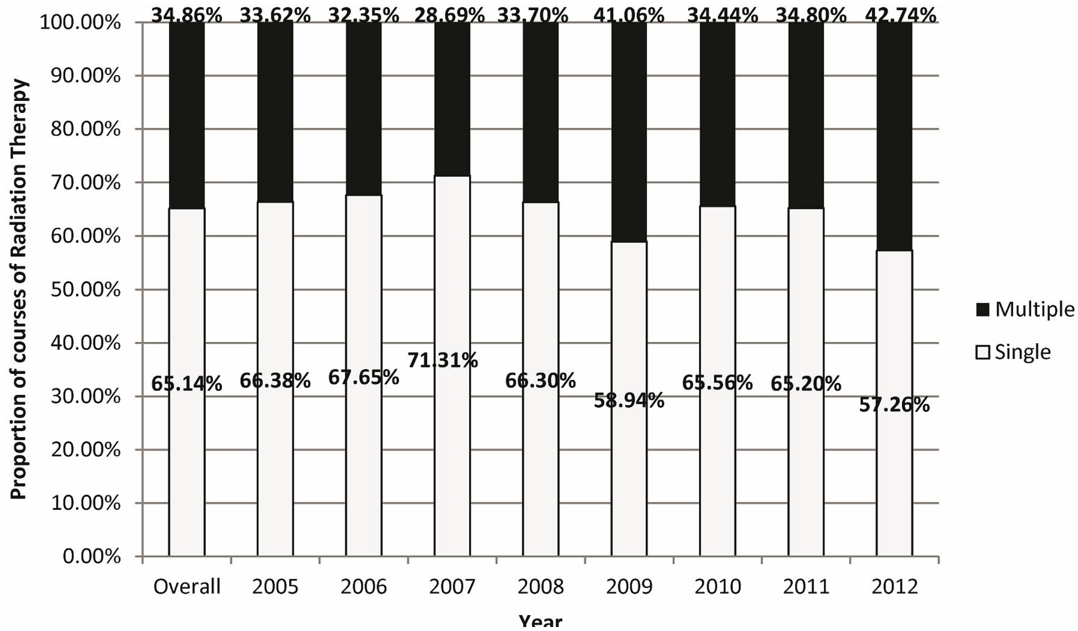

FIGURE 1 Prescription of single and multiple fractions of palliative radiation therapy for bone metastases administered in the Rapid Response Radiotherapy Program over time.

In the multiple logistic regression analyses, the likelihood of using single-fraction radiation did not significantly change over time ($p = 0.30$) after adjustment for other parameters. There was no collinearity present; variance inflation factors ranged from 1.02 to 3.78. The results of the Hosmer–Lemeshow goodness-of-fit test did not demonstrate any evidence of gross lack of fit for the model ($p = 0.62$).

Reasons for treating bone metastases with multiple fractions were also examined based on common fractionation schedules: 20 Gy/5, 30 Gy/10, and others (Table IV). The most common reasons for prescribing 20 Gy/5 included impending cord compression (17%), postoperative radiation therapy (16%), and cord or nerve root compression (16%). In comparison, the most common reasons for prescribing 30 Gy/10 included the presence of primary renal cell cancer (36%), postoperative radiation therapy (14%), and impending cord compression (13%). The Fisher exact test revealed a few significant correlations between the reason for referral to the RRRP and the prescription of common multiple fractionation schedules (Table V). A dose fractionation schedule of 20 Gy/5 was more likely to be prescribed for patients referred for spinal cord compression. In addition, patients referred for an impending fracture were more likely to be prescribed 30 Gy/10.

4. DISCUSSION

Our previous study of the RRRP between 1999 and 2005 revealed that in 65% of palliative radiation therapy cases, a single fraction was prescribed, and that in 35%, multiple fractions were prescribed[29], findings identical to those in the present study. Furthermore, in both time periods, a single fraction was more likely to be prescribed for patients with a prostate cancer primary or for older patients, and by radiation oncologists with a greater number of years of certification for independent practice. This time, we also analyzed the physician-dictated notes that were transcribed after each RRRP clinic to further examine the reasons that radiation oncologists prescribed multiple fractions of radiation therapy. That analysis had not been conducted in the earlier study, and it revealed that dose fractionation schedules of 20 Gy/5 and 30 Gy/10 were commonly prescribed for complicated bone metastases: for example, in cord compression or pathologic fracture requiring postoperative radiation therapy. Several studies examining radiation therapy used to treat spinal cord compression revealed that no specific treatment schedules proved to be more advantageous than others[30]. Fractionated treatment schedules such as 30 Gy/10 and 20 Gy/5 are typically administered to manage spinal cord compression in patients receiving only radiation therapy[2,31,32].

A dose fractionation schedule of 30 Gy/10 was specifically more commonly prescribed in patients with a primary renal cell cancer. Studies have suggested that metastatic renal cell cancers often require higher doses of radiation therapy because they are typically more radioresistant[33]. In bony metastatic renal cell cancer, Halperin and Harisiadis[34] used dose fractionation schedules with a total dose ranging from 30 Gy to 60 Gy. They showed that a total dose ranging

TABLE I Cases of radiation therapy for bone metastases, including fractionation and site of radiation, overall and by year

Variable	Overall		2005		2006		2007		2008		2009		2010		2011		2012	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Radiation fraction																		
Single	1659	65.14	77	66.38	184	67.65	256	71.31	299	66.30	267	58.94	297	65.56	208	65.20	71	57.26
Multiple	888	34.86	39	33.62	88	32.35	103	28.69	152	33.70	186	41.06	156	34.44	111	34.80	53	42.74
Radiation fraction details																		
Single	1659	65.08	77	66.38	184	67.40	256	71.31	299	66.15	267	58.94	297	65.56	208	65.20	71	57.26
Multiple																		
20 Gy in 5 fractions	738	28.95	28	24.14	66	24.18	92	25.63	129	28.54	161	35.54	128	28.26	92	28.84	42	33.87
30 Gy in 10 fractions	75	2.94	3	2.59	5	1.83	4	1.11	9	1.99	11	2.43	21	4.64	13	4.08	9	7.26
Others	75	2.94	8	6.90	17	6.23	7	1.95	14	3.10	14	3.09	7	1.55	6	1.88	2	1.61
Unknown	2	0.08	0	0.00	1	0.37	0	0.00	1	0.22	0	0.00	0	0.00	0	0.00	0	0.00
Radiation site																		
Spine	1172	45.98	48	41.38	125	45.79	160	44.57	217	48.01	203	44.81	205	45.25	154	48.28	60	48.39
Limbs, hip, skull	649	25.46	36	31.03	62	22.71	83	23.12	113	25.00	131	28.92	111	24.50	79	24.76	34	27.42
Ribs, scapula, sternum, clavicle	388	15.22	14	12.07	42	15.38	61	16.99	63	13.94	66	14.57	77	17.00	51	15.99	14	11.29
Pelvis	325	12.75	18	15.52	42	15.38	48	13.37	54	11.95	53	11.70	60	13.25	34	10.66	16	12.90
Unknown	15	0.59	0	0.00	2	0.73	7	1.95	5	1.11	0	0.00	0	0.00	1	0.31	0	0.00

between about 30 Gy and 40 Gy controlled bone pain within normal tissue tolerance and that higher doses were not necessary for achieving bone pain palliation in this patient population. Another prospective study conducted by Lee *et al.*[35] also revealed that a dose of 30 Gy/10 for patients with renal cell cancer metastatic to bone resulted in significant relief from local symptoms. Those findings reflect the rationale behind the prescription of 30 Gy/10 in patients with a primary renal cell cancer attending the RRRP.

Our study also revealed that patients with prostate cancer were commonly prescribed a single fraction of radiation therapy. That finding reflects the results of an international pattern-of-practice survey conducted by Fairchild *et al.*[36], in which one scenario described a patient with hormone-refractory prostate cancer. The most common dose fractionation schedule selected for that scenario by the radiation oncologists surveyed was 8 Gy in 1 fraction. Fairchild *et al.* also demonstrated that Canadian radiation oncologists were significantly more likely to prescribe a single fraction of radiation therapy. The same patterns were reflected among radiation oncologists in the United Kingdom, Australia, and New Zealand. Members of the American Society for Radiation Oncology were less likely to prescribe a single fraction of radiation therapy. The authors speculated that such differences could potentially be attributed to financial compensation[36].

Protracted dose fractionation schedules have been found to be more commonly prescribed in countries that offer financial compensation based on the number of fractions administered than in countries—such as Canada—that do not use any sort of financial incentive[37,38]. Radiation oncologists certified from 1990 onward were more likely to prescribe multiple fractions of radiation therapy to patients, which accords with the findings of the previous RRRP study[29].

The age of the patient also appeared to be a significant factor: older patients had a 1.02 greater chance of receiving a single fraction of radiation therapy. A British study by Crellin *et al.*[39] made similar findings and concluded that radiation oncologists who typically prefer prescribing a single fraction of radiation therapy for bone metastases tend to prescribe multiple fractions in younger patients (≤40 years of age). Similarly, radiation oncologists who prefer prescribing multiple fractions of radiation therapy typically prescribe a single fraction in older patients (≥70 years of age).

5. CONCLUSIONS

In this updated review of patterns of practice in the RRRP for 2005–2012, most radiation therapy for bone metastases continued to be delivered in a single fraction, which accords with established practice guidelines[2,30].

TABLE II Patient demographics, organizational, disease factors, and reasons for prescribing multiple fractions of radiation therapy over time

Variable	*Overall*		*2005*		*2006*		*2007*		*2008*		*2009*		*2010*		*2011*		*Jan-Apr 2012*		p *Value*[a]
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	
Patients	1995		105	5	231	12	281	14	356	18	340	17	323	16	263	13	96	5	
First radiotherapy																			**0.03**
Single	1288	64.56	67	63.81	152	65.80	195	69.40	235	66.01	196	57.65	217	67.18	171	65.02	53	55.21	
Multiple	707	35.44	38	36.19	79	34.20	86	30.60	121	33.99	144	42.35	106	32.82	92	34.98	43	44.79	
First radiotherapy																			**0.0003**
Single	1288	64.56	67	63.81	152	65.80	195	69.40	236	66.29	196	57.65	217	67.18	171	65.02	54	56.25	
Multiple																			
20 Gy in 5 fractions	582	29.17	27	25.71	59	25.54	75	26.69	102	28.65	123	36.18	87	26.93	76	28.90	33	34.38	
30 Gy in 10 fractions	57	2.86	3	2.86	4	1.73	4	1.42	7	1.97	8	2.35	13	4.02	10	3.80	8	8.33	
Other	68	3.41	8	7.62	16	6.93	7	2.49	11	3.09	13	3.82	6	1.86	6	2.28	1	1.04	
Age (years)																			0.91
Mean	68.7±12.8		70.0±12.2		68.6±12.6		69.2±13.4		68.8±12.2		67.6±12.8		68.1±13.1		69.7±13.6		69.6±11.4		
Median	70		73		69		70		71		68		69		70		71		
Range	(27–101)		(39–92)		(34–101)		(30–95)		(27–92)		(29–94)		(33–95)		(29–96)		(44–94)		
Sex																			0.83
Women	863	43.26	37	35.24	100	43.29	123	43.77	151	42.42	151	44.41	140	43.34	119	45.25	42	43.75	
Men	1132	56.74	68	64.76	131	56.71	158	56.23	205	57.58	189	55.59	183	56.66	144	54.75	54	56.25	
Karnofsky performance status																			0.83
Mean	60.3±17.0		NA		61.2±20.0		59.0±16.2		59.3±16.3		61.9±17.1		61.9±17.2		58.8±16.6		59.9±17.7		
Median	60		NA		60		60		60		60		60		60		60		
Range	(10–100)		NA		(10–100)		(10–90)		(20–90)		(20–100)		(10–100)		(10–100)		(20–90)		
Primary cancer site																			**0.008**
Lung	515	25.81	25	23.81	60	25.97	69	24.56	91	25.56	90	26.47	84	26.01	73	27.76	23	23.96	
Prostate	506	25.36	31	29.52	51	22.08	77	27.40	100	28.09	84	24.71	67	20.74	71	27.00	25	26.04	
Breast	447	22.41	19	18.10	58	25.11	64	22.78	78	21.91	96	28.24	75	23.22	49	18.63	8	8.33	
Others	527	26.42	30	28.57	62	26.84	71	25.27	87	24.44	70	20.59	97	30.03	70	26.62	40	41.67	
Arrival by ambulance																			0.1908
No	1507	76.54	77	73.33	180	77.92	205	76.21	273	77.34	263	77.58	247	77.43	181	70.43	81	84.38	
Yes	462	23.46	28	26.67	51	22.08	64	23.79	80	22.66	76	22.42	72	22.57	76	29.57	15	15.63	
Patients originating from																			**0.0008**
Home	1381	70.28	77	73.33	173	75.22	195	73.86	252	71.19	239	70.29	220	68.97	159	61.87	66	68.75	
Hospital	564	28.70	27	25.71	49	21.30	66	25.00	99	27.97	99	29.12	96	30.09	98	38.13	30	31.25	
Other	20	1.02	1	0.95	8	3.48	3	1.14	3	0.85	2	0.59	3	0.94	0	0.00	0	0.00	
Previous radiation																			0.0532
No	1025	52.40	61	58.10	132	57.39	151	56.77	189	53.39	165	48.82	164	51.57	111	44.58	52	54.17	
Yes	931	47.60	44	41.90	98	42.61	115	43.23	165	46.61	173	51.18	154	48.43	138	55.42	44	45.83	

TABLE II Continued

Variable	*Overall*		*2005*		*2006*		*2007*		*2008*		*2009*		*2010*		*2011*		*Jan-Apr 2012*		p *Value*[a]
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	
First radiation sites																			0.4710
Spine	976	49.19	47	44.76	110	48.03	132	47.48	192	54.70	161	47.35	153	47.37	134	51.15	47	48.96	
Limbs, hip, skull	478	24.09	31	29.52	51	22.27	62	22.30	80	22.79	91	26.76	77	23.84	60	22.90	26	27.08	
Ribs, scapula, sternum, clavicle	266	13.41	11	10.48	30	13.10	47	16.91	35	9.97	40	11.76	53	16.41	39	14.89	11	11.46	
Pelvis	264	13.31	16	15.24	38	16.59	37	13.31	44	12.54	48	14.12	40	12.38	29	11.07	12	12.50	
First referral reasons																			**<0.0001**
Pain, bone	1663	83.48	89	84.76	197	85.28	249	88.61	306	85.96	262	77.29	267	82.92	214	81.68	79	82.29	
Cord compression	68	3.41	4	3.81	14	6.06	8	2.85	13	3.65	10	2.95	8	2.48	6	2.29	5	5.21	
Postsurgical	64	3.21	3	2.86	4	1.73	4	1.42	3	0.84	16	4.72	17	5.28	9	3.44	8	8.33	
Assess need	59	2.96	0	0.00	0	0.00	0	0.00	1	0.28	26	7.67	13	4.04	19	7.25	0	0.00	
Cord compression, impending	49	2.46	0	0.00	6	2.60	7	2.49	14	3.93	10	2.95	6	1.86	4	1.53	2	2.08	
Fracture, pathologic	38	1.91	2	1.90	5	2.16	9	3.20	5	1.40	8	2.36	5	1.55	2	0.76	2	2.08	
Pain, neuropathic	15	0.75	3	2.86	2	0.87	1	0.36	0	0.00	5	1.47	0	0.00	4	1.53	0	0.00	
Cauda equina syndrome	12	0.60	0	0.00	1	0.43	1	0.36	9	2.53	1	0.29	0	0.00	0	0.00	0	0.00	
Fracture, impending	11	0.55	1	0.95	2	0.87	2	0.71	3	0.84	1	0.29	1	0.31	1	0.38	0	0.00	
Others	13	0.65	3	2.86	0	0.00	0	0.00	2	0.56	0	0.00	5	1.55	3	1.15	0	0.00	
Reason for multiple treatments																			**<0.0001**
Cord compression, impending	97	16.25	0	0.00	7	10.45	13	18.31	16	14.95	27	20.77	12	13.33	14	19.72	8	27.59	
Postsurgical	97	16.25	3	9.38	4	5.97	10	14.08	10	9.35	25	19.23	23	25.56	16	22.54	6	20.69	
Cord or nerve root compression	87	14.57	4	12.50	14	20.90	10	14.08	22	20.56	12	9.23	9	10.00	10	14.08	6	20.69	
Re-treat	76	12.73	7	21.88	11	16.42	7	9.86	16	14.95	16	12.31	7	7.78	10	14.08	2	6.90	
Fracture, pathologic	65	10.89	1	3.13	9	13.43	12	16.90	11	10.28	11	8.46	9	10.00	8	11.27	4	13.79	
Soft-tissue component	36	6.03	5	15.63	2	2.99	4	5.63	9	8.41	6	4.62	9	10.00	1	1.41	0	0.00	
Renal cell cancer	35	5.86	1	3.13	4	5.97	4	5.63	7	6.54	5	3.85	9	10.00	3	4.23	2	6.90	
Prophylaxis	27	4.52	3	9.38	4	5.97	4	5.63	1	0.93	6	4.62	6	6.67	3	4.23	0	0.00	
Cauda equina syndrome	23	3.85	0	0.00	2	2.99	2	2.82	8	7.48	6	4.62	4	4.44	1	1.41	0	0.00	
Fracture, impending	23	3.85	1	3.13	6	8.96	1	1.41	1	0.93	6	4.62	2	2.22	5	7.04	1	3.45	
Sensitive organs or tissues within treatment field	8	1.34	1	3.13	2	2.99	3	4.23	1	0.93	1	0.77	0	0.00	0	0.00	0	0.00	
Patient preference or randomized clinical trial	2	0.34	0	0.00	0	0.00	1	1.41	1	0.93	0	0.00	0	0.00	0	0.00	0	0.00	

[a] By chi-square test for categorical variables and by analysis of variance for age and KPS. Boldface type indicates significance ($p<0.05$).
NA = not available.

TABLE III Factors potentially influencing schedule choice, by dose fractionation schedule prescribed

Variable	*Single fraction*		*Multiple fractions*		*Logistic regression*					
					Univariate			*Multivariate*		
	(n)	(%)	(n)	(%)	OR	95% CI	p Value	Adjusted OR	95% CI	p Value
Year of treatment							**0.04**			0.30
Overall	1286	64	709	36						
2005	67	63.81	38	36.19	1.43	0.81 to 2.52	0.22	—	—	NA[a]
2006	152	65.80	79	34.20	1.56	0.96 to 2.54	0.07	1.57	0.81 to 3.06	0.18
2007	195	69.40	86	30.60	1.84	1.14 to 2.96	**0.01**	1.79	1.00 to 3.20	0.05
2008	235	66.01	121	33.99	1.58	1.00 to 2.49	0.05	1.61	0.92 to 2.80	0.09
2009	196	57.65	144	42.35	1.10	0.70 to 1.74	0.67	1.20	0.69 to 2.09	0.52
2010	217	67.18	106	32.82	1.66	1.04 to 2.64	**0.03**	1.59	0.91 to 2.77	0.11
2011	171	65.02	92	34.98	1.51	0.94 to 2.43	0.09	1.38	0.78 to 2.46	0.27
2012	53	55.21	43	44.79	Reference		—	Reference		—
Demographic factors										
Age (years)					1.02	1.01 to 1.03	**<.0001**	1.01	1.00 to 1.02	**0.007**
Mean	69.9±12.6		66.7±13.0							
Median	71		68							
Range	29–101		27–94							
Sex					1.34	1.12 to 1.62	**0.002**	0.87	0.63 to 1.19	0.38
Female	523	60.60	340	39.40						
Male	763	67.40	369	32.60						
Karnofsky performance status					1.00	0.99 to 1.002	0.16	0.98	0.97 to 0.99	**<0.0001**
Mean	59.9±16.8		61.1±17.4							
Median	60		60							
Range	10–100		20–100							
Appointment type							**0.012**			0.73
Special	605	67.60	290	32.40	1.36	1.11 to 1.67	**0.003**	0.88	0.63 to 1.22	0.43
Follow-up	230	64.79	125	35.21	1.20	0.92 to 1.56	0.17	0.92	0.61 to 1.38	0.69
New patient	451	60.54	294	39.46	Reference		—	Reference		—
Arrival by ambulance					0.75	0.60 to 0.93	**0.008**	1.23	0.78 to 1.92	0.37
Yes	275	59.52	187	40.48						
No	999	66.29	508	33.71						
Patients arriving from							**0.002**			0.08
Home	926	67.05	455	32.95	1.43	1.17 to 1.75	**0.0005**	1.62	1.04 to 2.50	0.03
Others	13	65.00	7	35.00	1.31	0.51 to 3.33	0.57	0.90	0.24 to 3.29	0.87
Hospital	331	58.69	233	41.31	Reference		—	Reference		—

TABLE III Continued

Variable	*Single fraction*		*Multiple fractions*		*Logistic regression*					
					Univariate			*Multivariate*		
	(n)	(%)	(n)	(%)	OR	95% CI	p Value	Adjusted OR	95% CI	p Value
Prior radiation					1.55	1.28 to 1.87	**<0.0001**	1.53	1.13 to 2.08	**0.006**
Yes	646	69.39	285	30.61						
No	609	59.41	416	40.59						
Disease factors										
Primary cancer site							**<0.0001**			**<0.0001**
Lung	318	61.75	197	38.25	0.39	0.29 to 0.52	**<0.0001**	0.49	0.33 to 0.73	**0.0005**
Breast	277	61.97	170	38.03	0.39	0.29 to 0.52	**<0.0001**	0.44	0.27 to 0.72	**0.001**
Others	283	53.70	244	46.30	0.28	0.21 to 0.37	**<0.0001**	0.29	0.20 to 0.42	**<0.0001**
Prostate	408	80.63	98	19.37		Reference	—		Reference	—
First referral reasons							**<0.0001**			**<0.0001**
Assess need	28	47.46	31	52.54	0.34	0.20 to 0.58	**<0.0001**	0.44	0.24 to 0.81	**0.008**
Cauda equina syndrome	1	8.33	11	91.67	0.04	0.004 to 0.27	**<0.0001**	0.06	0.009 to 0.41	**0.004**
Cord compression	9	13.24	59	86.76	0.06	0.03 to 0.12	**0.0013**	0.078	0.035 to 0.175	**<0.0001**
Cord impression, impending	9	18.37	40	81.63	0.09	0.04 to 0.18	**<0.0001**	0.131	0.060 to 0.286	**<0.0001**
Fracture, impending	4	36.36	7	63.64	0.22	0.06 to 0.75	**<0.0001**	0.14	0.03 to 0.59	**0.007**
Fracture, pathologic	15	39.47	23	60.53	0.25	0.13 to 0.48	**0.0154**	0.23	0.10 to 0.53	**0.0005**
Pain, neuropathic	3	20.00	12	80.00	0.10	0.03 to 0.34	**<0.0001**	0.27	0.07 to 1.05	0.06
Postsurgical	6	9.38	58	90.63	0.04	0.02 to 0.09	**0.0003**	0.05	0.02 to 0.12	**<0.0001**
Others	7	53.85	6	46.15	0.45	0.15 to 1.33	**<0.0001**	0.85	0.18 to 4.03	0.83
Pain, bone	1204	72.40	459	27.60		Reference	—		Reference	—
First radiation sites							**<0.0001**			**<0.0001**
Limbs, hip, skull	296	61.92	182	38.08	1.13	0.91 to 1.42	0.27	1.13	0.84 to 1.51	0.41
Ribs, scapula, sternum, clavicle	218	81.95	48	18.05	3.17	2.26 to 4.44	**<0.0001**	2.81	1.87 to 4.22	**<0.0001**
Pelvis	193	73.11	71	26.89	1.90	1.40 to 2.56	**<0.0001**	1.44	1.00 to 2.09	0.05
Spine	575	58.91	401	41.09		Reference	—		Reference	—
Organizational factor										
Year of certification of radiation oncologist							**<0.0001**			**<0.0001**
2000–2009	199	48.77	209	51.23	0.23	0.17 to 0.31	**<0.0001**	0.22	0.15 to 0.32	**<0.0001**
1990–1999	713	63.27	414	36.73	0.41	0.32 to 0.54	**<0.0001**	0.45	0.32 to 0.63	**<0.0001**
1980–1989	12	100.00	0	0.00	5.98	0.31 to 114.6	0.24	—	—	—
1970–1979	362	80.80	86	19.20		Reference	—		Reference	—

[a] Karnofsky performance status was not collected in 2005; and therefore patients with missing values were excluded from the multiple regression analysis.
NA = not available.

TABLE IV Reasons for prescribing multiple treatments, by dose fractionation schedule

Schedule	Reason	Patients (n)	Patients (%)
20 Gy/5		572	—
	Cord compression, impending	95	16.61
	Postsurgical	94	16.43
	Cord or nerve root compression	89	15.56
	Fracture, pathologic	77	13.46
	Re-treat	54	9.44
	Soft-tissue component	39	6.82
	Prophylaxis	29	5.07
	Fracture, impending	27	4.72
	Cauda equina syndrome	21	3.67
	Renal cell cancer	18	3.15
	Patient preference or randomized clinical trial	10	1.75
	Sensitive organs or tissues within treatment field	4	0.70
	Others	15	2.62
30 Gy/10		58	—
	Renal cell cancer	21	36.21
	Postsurgical	8	13.79
	Cord compression, impending	7	12.07
	Fracture, impending	6	10.34
	Fracture, pathologic	4	6.90
	Prophylaxis	3	5.17
	Soft-tissue component	2	3.45
	Cauda equina syndrome	1	1.72
	Cord or nerve root compression	1	1.72
	Re-treat	1	1.72
	Others	4	6.90
Others		71	—
	Re-treat	32	45.07
	Renal cell cancer	7	9.86
	Cord or nerve root compression	6	8.45
	Postsurgical	6	8.45
	Cord compression, impending	4	5.63
	Fracture, pathologic	4	5.63
	Sensitive organs or tissues within treatment field	4	5.63
	Cauda equina syndrome	2	2.82
	Soft-tissue component	2	2.82
	Prophylaxis	1	1.41
	Others	3	4.23

6. ACKNOWLEDGMENTS

The author acknowledge the generous support of the Bratty Family Fund, the Michael and Karyn Goldstein Cancer Research Fund, the Joseph and Silvana Melara Cancer Research Fund, and the Ofelia Cancer Research Fund.

TABLE V Reasons for referral influencing the prescription of multiple-fraction schedules

Reason	p Value[a]
Bone pain	**0.0006**
Cord compression, impending	**0.0467**
Postsurgical	0.2564
Cord compression	**0.0104**
Fracture, pathologic	0.3334
Assess need	0.1163
Fracture, impending	**0.0180**
Cauda equina syndrome	0.5775
Pain, neuropathic	0.4186

[a] By the simple Fisher exact test.

7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to disclose.

8. REFERENCES

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res* 2006;12:6243s–9s.
2. Lutz S, Berk L, Chang E, *et al.* Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79:965–76.
3. Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;25:1423–36.
4. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the Study by the Radiation Therapy Oncology Group. *Cancer* 1982;50:893–9.
5. Madsen EL. Painful bone metastasis: efficacy of radiotherapy assessed by the patients: a randomized trial comparing 4 Gy×6 versus 10 Gy×2. *Int J Radiat Oncol Biol Phys* 1983;9:1775–9.
6. Teshima T, Chatani M, Inoue T, *et al.* A multi-institutional prospective randomized study of radiation therapy of bone metastasis. II. Prognostic factors [Japanese]. *Nihon Igaku Hoshasen Gakkai Zasshi* 1989;49:439–44.
7. Okawa T, Kita M, Goto M, Nishijima H, Miyaji N. Randomized prospective clinical study of small, large and twice-a-day fraction radiotherapy for painful bone metastases. *Radiother Oncol* 1988;13:99–104.
8. Hoskin PJ, Price P, Easton D, *et al.* A prospective randomised trial of 4 Gy or 8 Gy single doses in the treatment of metastatic bone pain. *Radiother Oncol* 1992;23:74–8.
9. Rasmusson B, Vejborg I, Jensen AB, *et al.* Irradiation of bone metastases in breast cancer patients: a randomized study with 1 year follow-up. *Radiother Oncol* 1995;34:179–84.
10. Niewald M, Tkocz HJ, Abel U, *et al.* Rapid course radiation therapy vs. more standard treatment: a randomized trial for bone metastases. *Int J Radiat Oncol Biol Phys* 1996;36:1085–9.
11. Jeremic B, Shibamoto Y, Acimovic L, *et al.* A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. *Int J Radiat Oncol Biol Phys* 1998;42:161–7.

12. Foro P, Algara M, Reig A, Lacruz M, Valls A. Randomized prospective trial comparing three schedules of palliative radiotherapy. Preliminary results. *Oncologia* 1998;21:55–60.
13. Koswig S, Budach V. Remineralization and pain relief in bone metastases after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study [German]. *Strahlenther Onkol* 1999;175:500–8.
14. Ozsaran Z, Yalman D, Anacak Y, *et al.* Palliative radiotherapy in bone metastases: results of a randomized trial comparing three fractionation schedules. *J Balkan Union Oncol* 2001;6:43–8.
15. Sarkar SK, Sarkar S, Pahari B, Majumdar D. Multiple and single fraction palliative radiotherapy in bone secondaries—a prospective study. *Indian J Radiol Imaging* 2002;12:281–4.
16. Badzio A, Senkus–Konefka E, Jereczek–Fossa BA, *et al.* 20 Gy in five fractions versus 8 Gy in one fraction in palliative radiotherapy of bone metastases. A multicenter randomized study. *Nowotwory* 2003;53:261–4.
17. van der Linden YM, Lok JJ, Steenland E, *et al.* Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. *Int J Radiat Oncol Biol Phys* 2004;59:528–37.
18. Amouzegar–Hashemi F, Behrouzi H, Kazemian A, Zarpak B, Haddad P. Single versus multiple fractions of palliative radiotherapy for bone metastases: a randomized clinical trial in Iranian patients. *Curr Oncol* 2008;15:151.
19. Steenland E, Leer JW, van Houwelingen H, *et al.* The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;52:101–9.
20. Amichetti M, Orrù P, Madeddu A, *et al.* Comparative evaluation of two hypofractionated radiotherapy regimens for painful bone metastases. *Tumori* 2004;90:91–5.
21 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. *Radiother Oncol* 1999;52:111–21.
22. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989;1:59–62.
23. Gaze MN, Kelly CG, Kerr GR, *et al.* Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiother Oncol* 1997;45:109–16.
24. Hartsell WF, Scott CB, Bruner DW, *et al.* Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005;97:798–804.
25. Kaasa S, Brenne E, Lund JA, *et al.* Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy×1) versus multiple fractions (3 Gy×10) in the treatment of painful bone metastases. *Radiother Oncol* 2006;79:278–84.
26. Kagei K, Suzuki K, Shirato H, Nambu T, Yoshikawa H, Irie G. A randomized trial of single and multifraction radiation therapy for bone metastasis: a preliminary report [Japanese]. *Gan No Rinsho* 1990;36:2553–8.
27. Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol* 1998;47:233–40.
28. Danjoux C, Chow E, Drossos A, *et al.* An innovative rapid response radiotherapy program to reduce waiting time for palliative radiotherapy. *Support Care Cancer* 2006;14:38–43.
29. Bradley NM, Husted J, Sey MS, *et al.* Did the pattern of practice in the prescription of palliative radiotherapy for the treatment of uncomplicated bone metastases change between 1999 and 2005 at the rapid response radiotherapy program? *Clin Oncol (R Coll Radiol)* 2008;20:327–36.
30. Loblaw DA, Mitera G, Ford M, Laperriere NJ. A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys* 2012;84:312–17.
31. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol* 2005;23:2028–37.
32. Dennis K, Vassiliou V, Balboni T, Chow E. Management of bone metastases: recent advances and current status. *J Radiat Oncol* 2012;1:201–10.
33. Vaeth JM. Proceedings: cancer of the kidney—radiation therapy and its indications in non-Wilms' tumors. *Cancer* 1973;32:1053–5.
34. Halperin EC, Harisiadis L. The role of radiation therapy in the management of metastatic renal cell carcinoma. *Cancer* 1983;51:614–17.
35. Lee J, Hodgson D, Chow E, *et al.* A phase II trial of palliative radiotherapy for metastatic renal cell carcinoma. *Cancer* 2005;104:1894–900.
36. Fairchild A, Barnes E, Ghosh S, *et al.* International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice? *Int J Radiat Oncol Biol Phys* 2009;75:1501–10.
37. Lievens Y, Kesteloot K, Rijnders A, Kutcher G, Van den Bogaert W. Differences in palliative radiotherapy for bone metastases within Western European countries. *Radiother Oncol* 2000;56:297–303.
38. Lievens Y, Van den Bogaert W, Rijnders A, Kutcher G, Kesteloot K. Palliative radiotherapy practice within Western European countries: impact of the radiotherapy financing system? *Radiother Oncol* 2000;56:289–95.
39. Crellin AM, Marks A, Maher EJ. Why don't British radiotherapists give single fractions of radiotherapy for bone metastases? *Clin Oncol (R Coll Radiol)* 1989;1:63–6.

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