Original Article

Single-Fraction Radiotherapy Versus Multifraction Radiotherapy for Palliation of Painful Vertebral Bone Metastases—Equivalent Efficacy, Less Toxicity, More Convenient

A Subset Analysis of Radiation Therapy Oncology Group Trial 97-14

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BACKGROUND: The Radiation Therapy Oncology Group (RTOG) trial 97-14 revealed no difference between radiation delivered for painful bone metastases at a dose of 8 gray (Gy) in 1 fraction (single-fraction radiotherapy [SFRT]) and 30 Gy in 10 fractions (multifraction radiotherapy [MFRT]) in pain relief or narcotic use 3 months after randomization. SFRT for painful vertebral bone metastases (PVBM) has not been well accepted, possibly because of concerns about efficacy and toxicity. In the current study, the authors evaluated the subset of patients that was treated specifically for patients with PVBM. **METHODS:** PVBM included the cervical, thoracic, and/or lumbar spine regions. Among patients with PVBM, differences in retreatment rates and in pain relief, narcotic use, and toxicity 3 months after randomization were evaluated. **RESULTS:** Of 909 eligible patients, 235 (26%) had PVBM. Patients with and without PVBM differed in terms of the percentage of men (55% vs 47%, respectively; $P = .03$) and the proportion of patients with multiple painful sites (57% vs 38%, respectively; $P < .01$). Among those with PVBM, more patients who received MFRT had multiple sites treated (65% vs 49% for MFRT vs SFRT, respectively; $P = .02$). There were no statistically significant treatment differences in terms of pain relief (62% vs 70% for MFRT vs SFRT, respectively; $P = .59$) or freedom from narcotic use (24% vs 27%, respectively; $P = .76$) at 3 months. Significant differences in acute grade 2 through 4 toxicity (20% vs 10% for MFRT vs SFRT, respectively; $P = .01$) and acute grade 2 through 4 gastrointestinal toxicity (14% vs 6%, respectively; $P = .01$) were observed at 3 months, with lower toxicities seen in the patients treated with SFRT. Late toxicity was rare. No myelopathy was recorded. SFRT produced higher 3-year retreatment rates (5% vs 15%; $P = .01$). **CONCLUSIONS:** Results for the subset of patients with PVBM in the RTOG 94-17 randomized controlled trial were comparable to those for the entire population. SFRT produced less acute toxicity and a higher rate of retreatment than MFRT. SFRT and MFRT resulted in comparable pain relief and narcotic use at 3 months. ***Cancer*** **2013;119:888-96.** © *2012 American Cancer Society.*

KEYWORDS: radiation oncology, bone metastases, palliative care, pain management, supportive care, metastases, single-fraction radiation, stereotactic radiation therapy, spine malignancy, late effects.

INTRODUCTION

Pain secondary to osseous metastases is a serious problem in many patients with stage IV cancer. There are several options for the treatment of painful bone metastases. Radiation therapy is an effective treatment, providing pain relief and reducing the need for narcotics and other analgesics to manage symptomatic bone metastases. Many randomized trials have demonstrated that various dose/fractionation schedules of radiation can provide comparable pain relief.[1-3] Several randomized controlled trials have indicated equivalency in endpoints measured, such as pain relief and need for narcotic use after the delivery of a single, higher dose of radiation compared with several smaller doses of radiation delivered over $\geq$10 treatments.[1-3]

In 2005, Hartsell et al[4] reported on Radiation Therapy Oncology Group (RTOG) Study 97-14, which investigated patients with breast cancer and prostate cancer who were diagnosed with painful osseous metastases and had an expected median survival of at least 3 months. Those patients received palliative radiation and were randomized to 2 different

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fractionation schedules: 8 Gray (Gy) in a single fraction (8 Gy/1) versus 30 Gy delivered in 10 fractions (30 Gy/10). The results from that study revealed no substantive differences in the endpoints of pain relief and narcotic use 3 months postrandomization. The 8 Gy/1 group had a lower incidence of acute toxicities but higher rates of retreatment than the 30 Gy/10 group. RTOG 97-14 included patients who had osseous metastases to a wide range of bones throughout the body, excluding the skull, hands, and feet. Despite overwhelming evidence that equivalent pain relief from painful bone metastases could be achieved from a single radiation treatment, practice patterns among US radiation oncologists still favor a multifraction course of radiation.[5-7]

The United States radiation oncology community has not well accepted single-fraction conventional radiation (SFRT) for use in the treatment of painful vertebral bone metastases, possibly because of provider concerns about efficacy and toxicity. Radiation oncologists have cited concerns about increased risks of acute gastrointestinal (GI) toxicity, such as esophagitis, nausea, and vomiting; late central nervous system (CNS) toxicity, such as myelopathy; and potential greater needs for retreatment as reasons not to use SFRT.

The use of a shorter course of radiation for supportive care in this palliative situation makes it easier for patients and their caregivers to arrange for the logistics of therapy. One or 2 visits to the treatment facility for planning and treatment save time and resources for patients, caregivers, and health care providers compared with $\geq$10 visits. The concerns about efficacy and toxicity because of 8 Gy/1 vs 30 Gy/10 in patients who were treated specifically for painful vertebral bone metastases prompted a retrospective subset analysis of patients from RTOG 97-14 who had painful vertebral bone metastases.

MATERIALS AND METHODS

Patient Population

Patients were randomized to receive 8 Gy/1 on 1 day or 30 Gy/10 over 2 weeks. Patients were treated for no more than 3 separate painful sites (multiple spine sites were allowed). Patients were identified as those with painful vertebral bone metastases (PVBM) if any of the treated sites were at the cervical, thoracic, or lumbar spine. Patients who had spinal cord compression or a Karnofsky performance status $<$40 were excluded from the study.

The Brief Pain Inventory (BPI) worst pain score was used to assess pain response.[8] Eligible patients had a baseline BPI worst pain score $\geq$5 or a score $<$5 while they were receiving a daily equivalent of $\geq$60 mg morphine. Pain response was determined by the BPI worst pain score at a follow-up assessment that occurred 3 months after the initiation of radiation. Pain response was categorized as follows: 1) complete response–a post-treatment pain score of 0; 2) partial response–a post-treatment improvement of at least 2 points; 3) stable response–post-treatment pain score within 1 point of the initial pain score; or 4) progression of pain–a post-treatment increase of at least 2 points.

The BPI worst pain score does not incorporate narcotic use. Narcotic use was assessed 3 months after the start of radiation using the following criteria: 1) no pain medication, 2) non-narcotic analgesics (aspirin, buffered aspirin, acetaminophen, ibuprofen, and others), 3) mild narcotics ($\leq$0.5 g), 4), moderate narcotics (0.5-1.0 g), or 5) strong narcotics ($\geq$1 g) per day.

The decision to retreat patients and the retreatment dose and fractionation were left to the discretion of the treating radiation oncologist. Retreatment was not permitted within 4 weeks of completion of initial treatment unless a patient experienced progressive pain.

Adverse events that occurred before 90 days after the start of treatment were reported according to the Acute Radiation Morbidity Scoring Criteria. and adverse events that occurred at least 90 days after start of treatment were reported according to the RTOG/European Organization for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Scheme.[9]

Statistical Methods

The chi-square test was used to test for treatment differences (8 Gy/1 vs 30 Gy/10) in the distribution of pain response at the .05 significance level. The chi-square test also was used to test for treatment differences in the distribution of narcotic use at the .05 significance level.

Retreatment rates were estimated using the cumulative incidence method to account for death as a competing risk. Gray's test was used to test for treatment differences in retreatment rates at the .05 significance level (2-sided). Overall survival was estimated using the Kaplan-Meier method. The log-rank test was used to test for treatment differences in overall survival at the .05 significance level (2-sided). All data were analyzed using SAS statistical software (version 9.1 for Windows; SAS Institute Inc., Cary, NC).

RESULTS

RTOG 97-14 accrued 949 patients (909 eligible), of which 235 had PVBM. Most patients received treatment to the lumbar (51%) or thoracic (36%) spine. Patients

Table 1. Pretreatment Characteristics for All Eligible Patients: Radiation Therapy Oncology Group Trial 9714

Characteristic	No. of Patients (%)		P^a
	Without Vertebral Metastases, n = 674	With Vertebral Metastases, n = 235	
Age: Median [range], y	66 [31-92]	68 [33-92]	<.01
Treatment arm			
8 Gy	336 (50)	124 (53)	.45
30 Gy	338 (50)	111 (47)	
Sex			
Men	318 (47)	130 (55)	.03
Women	356 (53)	105 (45)	
Race/ethnicity			
White	488 (72)	166 (71)	.27
Black	101 (15)	41 (17)	
Hispanic	34 (5)	6 (3)	
Other	51 (8)	22 (9)	
KPS			
40-60	159 (23)	56 (24)	.65
70-80	355 (53)	134 (57)	
90-100	160 (24)	45 (19)	
Receiving bisphosphonates			
Yes	170 (25)	51 (22)	.28
No	504 (75)	184 (78)	
Painful sites			
Solitary	415 (62)	102 (43)	<.01
Multiple	259 (38)	133 (57)	
BPI worst pain score, baseline			
<5	15 (2)	3 (1)	.39
5-6	194 (29)	60 (26)	
7-10	465 (69)	172 (73)	

Abbreviations: BPI, Brief Pain Inventory; Gy, Gray; KPS, Karnofsky performance status; RT, radiation therapy.
[a] *P* values were determined using the chi-square test for all variables except age (*t* test).

Table 2. Pretreatment Characteristics

Characteristic	All Patients With Vertebral Metastases: No. (%)		P^a
	8-Gy Arm, n = 124	30-Gy Arm, n = 111	
Age: Median [range], y	69 [36-92]	68 [33-91]	.85
Sex			
Men	68 (55)	61 (55)	.96
Women	55 (45)	50 (45)	
Race/ethnicity			
White	86 (69)	80 (72)	.35
Black	26 (21)	15 (13)	
Hispanic	2 (2)	4 (4)	
Other	10 (8)	12 (11)	
KPS			
40-60	29 (23)	27 (24)	.80
70-80	73 (59)	61 (55)	
90-100	22 (18)	23 (21)	
Receiving bisphosphonates			
Yes	23 (19)	28 (25)	.22
No	101 (81)	83 (75)	
Painful sites: Vertebral and nonvertebral			
Solitary	63 (51)	39 (35)	.02
Multiple	61 (49)	72 (65)	
Treatment site			
Weight bearing	48 (39)	36 (32)	.32
Nonweight bearing	76 (61)	75 (68)	
Vertebral site			
Cervical	12 (10)	7 (6)	0.78
Thoracic	44 (35)	40 (36)	
Lumbar	63 (51)	58 (53)	
Multiple sites	5 (4)	6 (5)	
BPI worst pain score, baseline			
<5	2 (2)	1 (1)	.68
5-6	34 (27)	26 (23)	
7-10	88 (71)	84 (76)	

Abbreviations: BPI, Brief Pain Inventory; Gy, Gray; KPS, Karnofsky performance status.
[a] *P* values were determined using the chi-square test for all variables except age (*t* test).

also received radiation to the cervical spine or to multiple spine sites. PVBM patients were similar to the general RTOG 97-14 population (Table 1), although there were some differences. PVBM patients were older (median age, 68 years vs 66 years for patients with nonvertebral bone metastases [non-PVBM]; $P < .01$), were mostly men (55% vs 47% of non-PVBM; $P = .03$), and were more likely to have received treatment at multiple painful sites (57% vs 38% non-PBVM; $P < .01$).

Among patients with PVBM, most pretreatment characteristics did not differ between patients who received 8 Gy/1 or 30 Gy/10, as expected because of randomization (Table 2). However, patients with PVBM who received 30 Gy/10 were more likely to have multiple treatment sites (65% vs 49% for patients who received 8 Gy/1; $P = .02$).

Treatment was appropriately delivered according to protocol. A random sample of 71 patients (30%) was selected for quality-assurance review. Ninety-three percent of patients received treatment within protocol borders, 96% received the total protocol dose, 99% received all fractions, and 99% did not have any treatment delays. Patients received 4 to 9 megavoltage (MV) photons (63%), 10 to 20 MV photons (23%), 60-Cobalt (11%),

Table 3. Narcotic Use 3 Months After the Start of Radiation Therapy[a]

	8-Gy Arm		30-Gy Arm		
Narcotic Use at 3 Months	No.	%	No.	%	P[b]
All vertebral patients	84	100	89	100	
None	17	20	15	17	.76
Analgesics	6	7	6	7	
Mild narcotic	8	10	12	13	
Moderate narcotic	21	25	17	19	
Strong narcotic	32	38	39	44	
Cervical spine patients	9		5		
None	2	22	1	20	.86
Analgesics	1	11	0	0	
Moderate narcotic	1	11	1	20	
Strong narcotic	5	56	3	60	
Thoracic spine patients	28		33		
None	7	25	8	24	.97
Analgesics	4	14	3	9	
Mild narcotic	3	11	3	9	
Moderate narcotic	4	14	5	15	
Strong narcotic	10	36	14	42	
Lumbar spine patients	42		47		
None	5	12	5	11	.13
Analgesics	1	2	3	6	
Mild narcotic	3	7	9	19	
Moderate narcotic	16	38	8	17	
Strong narcotic	17	41	22	47	
Patients with multiple spine sites	5		4		
None	3	60	1	25	.08
Mild narcotic	2	40	0	0	
Moderate narcotic	0	0	3	75	

Abbreviations: Gy, Gray.
[a] Mild narcotic indicated $\leq$ 0.5 gm/day; moderate narcotic indicates 0.5 gm to 1 gm/day; strong narcotic indicates $\geq$ 1 gm/day.
[b] P values were determined using the chi-square test except for multiple spine sites (Fisher exact test).

or other energies (3%). Acute and late adverse events were minimal. For patients who received 8 Gy/1, there were no grade 4 adverse events, there was 1 grade 3 acute nonhematologic (lung) adverse event, and there were two grade 3 late nonhematologic (CNS) adverse events (grade 3 CNS adverse events were defined as neurologic findings that required hospitalization for initial management). For patients who received 30 Gy/10, there was 1 grade 4 acute hematologic adverse event, 1 grade 4 late nonhematologic (lung) adverse event, and there were 3 grade 3 acute nonhematologic (GI) adverse events. Radiation myelopathy was not reported in any patient. Significant treatment differences (8 Gy/1 vs 30 Gy/10) in acute overall grade 2 through 4 toxicity (10% vs 20%, respectively; $P = .01$) and acute grade 2 through 4 GI toxicity (6% vs 14%, respectively; $P = .01$) were observed at 3 months, with less toxicity in the 8 Gy/1 group.

No significant difference between treatment arms was reported in narcotic use or pain response 3 months after initiation of radiation (Tables 3 and 4). Sixty-three percent of patients on each treatment arm reported moderate or strong narcotic use ($P = .76$). Seventy percent and 62% of patients on the 8 Gy/1 and 30 Gy/10 treatment arms, respectively, experienced a partial or complete pain response ($P = .59$).

Patients who received 8 Gy/1 had significantly higher retreatment rates at 3 years after their initial radiation (15% vs 5%; $P = .01$), and differences were evident 3 months after their initial radiation course (Table 5). There were no differences among patients who had cervical, thoracic, or multiple spine sites; the differences in retreatment in the overall PVBM population were attributable to patients who had lumbar spine metastases. Sixty-eight percent (17 of 25 patients) of retreated patients were lumbar spine patients. There were no differences in overall survival attributable to treatment. The median survival was 9.3 months in the 8 Gy/1 treatment arm and 10.6 months in the 30 Gy/10 treatment arm ($P = .51$).

Table 4. Pain Response 3 Months After the Start of Radiation Therapy[a]

	8-Gy Arm		30-Gy Arm		
Pain Response at 3 Months	No.	%	No.	%	*P*[b]
All vertebral patients	77	100	76	100	
Complete	15	19	13	17	.59
Partial	39	51	34	45	
Stable	14	18	21	28	
Progressive	9	12	8	10	
Cervical spine patients	10		5		
Complete	1	10	0	0	.42
Partial	5	50	1	20	
Stable	2	20	3	60	
Progressive	2	20	1	20	
Thoracic spine patients	26		25		
Complete	6	23	5	20	.75
Partial	14	54	13	52	
Stable	5	19	4	16	
Progressive	1	4	3	12	
Lumbar spine patients	38		44		
Complete	6	16	7	16	.45
Partial	20	52	20	45	
Stable	6	16	13	30	
Progressive	6	16	4	9	
Patients with multiple spine sites	3		2		
Complete	2	67	1	50	—
Stable	1	33	1	50	

Abbreviations: Gy, Gray.
[a] Pain response was based on the Brief Pain Inventory worst pain score: a complete response indicates a post-RT pain score of 0; partial response, post-RT pain score decrease ≥2 points from baseline score; stable response, post-RT pain score within 1 point of baseline score; progressive response, post-RT pain score increase ≥2 points from baseline score.
[b] *P* values were determined using the chi-square test.

Survival estimates at 3 months and 6 months were 83% and 62%, respectively, in the 8 Gy/1 arm and 85% and 67%, respectively, in the 30 Gy/10 arm (Table 6).

DISCUSSION

To our knowledge, this is the largest series to date comparing conventionally planned single-fraction radiation (SFRT) and conventionally planned multifraction radiation (MFRT) in patients with PVBM. Radiation delivered by SFRT or MFRT was equally effective at palliating pain from metastases to the vertebral bone. This result is similar to what was observed in the total population of patients with bone metastases in RTOG 97-14.[4] The pain control observed was comparable to that reported in a group of 117 Canadian patients who received radiation for spinal metastases.[10] The largest series of patients treated with radiation for spinal column metastases (603 patients) comes from Japan.[11] Although Mizumoto et al discuss prognostic factors, local control, and survival for this population,[11] there is little information on pain relief.

SFRT has not yet gained overwhelming support in practice in the United States. There may be many reasons for this—among them a reluctance to adapt a new practice after long experience with MFRT, concerns about risks of acute morbidity, and concerns about late CNS toxicity. MFRT also is reimbursed at a higher rate in the United States than SFRT.[12] The current analysis provides further evidence that SFRT for vertebral bone metastases is safe and effective, has less acute effects, and produces no difference in late effects compared with MFRT.

Radiation-induced myelopathy is the radiation oncologist's greatest concern of iatrogenic toxicity of all concerns about the potential morbidity of radiation. The consequences of radiation damage to the spinal cord can be devastating. Consequently, radiation oncologists are loath to give a radiation dose anywhere near what would be associated with a low risk of damage. It might be uncertainty about the effects of 8 Gy/1 to the spinal cord that worries some US radiation oncologists regarding this technique. Studies from Maranzano et al using 8 Gy/1 and even two 8-Gy fractions spaced 1 week apart (16 Gy

Table 5. Retreatment Rates

Patient Subgroup	8-Gy Arm		30-Gy Arm	
	% Retreated[a]	Number At Risk	% Retreated[a]	Number At Risk
All vertebral patients				
Time to retreatment, mo				
3	10	94	2	93
6	10	68	2	74
12	15	40	3	53
36	15	15	5	16
60	15	4	5	7
No. of failures/total	19/124		6/111	
$P = 0.01$[b]				
Cervical spine patients				
Time to retreatment, mo				
3	25	9	0	5
6	25	8	0	2
12	25	4	0	2
36	25	2	0	0
60	25	1	0	0
No. of failures/total	3/12		0/7	
$P = .16$[b]				
Thoracic spine patients				
Time to retreatment, mo				
3	0	35	0	33
6	0	22	0	27
12	2	16	0	17
36	5	6	3	2
60	5	2	5	1
No. of failures/total	2/44		2/40	
$P = .94$[b]				
Lumbar spine patients				
Time to retreatment, mo				
3	14	45	3	49
6	14	33	3	39
12	21	18	5	30
36	21	5	7	12
60	21	1	7	4
No. of failures/total	13/63		4/58	
$P = .03$[b]				
Patients with multiple spine sites				
Time to retreatment, mo				
3	0	5	0	6
6	0	5	0	6
12	20	2	0	4
36	20	2	0	2
60	20	0	0	2
No. of failures/total	1/5		0/6	
$P = .27$[b]				

Abbreviations: Gy, Gray.
[a] Estimates were based on cumulative incidence with death considered as a competing risk.
[b] *P* values were determined using the Grey test.

total) for vertebral bone metastases causing spinal cord compression have not reported any late cases of radiation-induced myelopathy.[13,14] Macbeth et al[15] reported 5 cases of radiation myelopathy among 1048 patients who had received radiation for inoperable nonsmall cell lung cancer. In that study, there were 3 cases of radiation-induced myelopathy among 524 patients who had received 17 Gy in two 8.5 Gy fractions spaced 1 week apart, and there were 2 cases of radiation-induced myelopathy among 153 patients who had received 39 Gy in thirteen 3 Gy

Table 6. Overall Survival

Patient Subgroup	8-Gy Arm		30-Gy Arm	
	% Alive[a]	Number At Risk	% Alive[a]	Number At Risk
All vertebral patients				
Overall survival, mo				
3	83	103	85	94
6	62	77	67	74
12	40	50	49	54
24	26	32	26	29
60	5	5	8	8
No. of failures/total	116/124		102/111	
Median survival, mo	9.3		10.6	
$P = .50$[b]				
Cervical spine patients				
Overall survival, mo				
3	92	11	71	5
6	83	10	29	2
12	33	4	29	2
24	17	2	0	0
60	8	1	0	0
No. of failures/total	11/12		7/7	
Median survival, mo	9.1		4.5	
$P = .11$[b]				
Thoracic spine patients				
Overall survival, mo				
3	80	35	83	33
6	50	22	68	27
12	36	16	43	17
24	27	12	25	10
60	5	2	3	1
No. of failures/total	42/44		39/40	
Median survival, mo	6.0		8.3	
$P = .89$[b]				
Lumbar spine patients				
Overall survival, mo				
3	83	52	86	50
6	63	40	67	39
12	43	27	53	31
24	24	15	29	17
60	5	2	10	5
No. of failures/total	58/63		52/58	
Median survival, mo	10.3		12.4	
$P = .29$[b]				
Patients with multiple spine sites				
Overall survival, mo				
3	100	5	100	6
6	100	5	100	6
12	60	3	67	4
24	60	3	33	2
60	0	0	33	2
No. of failures/total	5/5		4/6	
Median survival, mo	26.6		17.3	
$P = .46$[b]				

Abbreviations: Gy, gray.
[a] Kaplan-Meier estimates are listed.
[b] *P* values were determined using the log-rank test.

fractions over 17 days. There were no reports of radiation-induced myelopathy in the RTOG 97-14 patients.

There have been many randomized comparisons of 1 or 2 fractions of radiation versus ≥10 fractions as palliative therapy for painful bone metastases.[1-3] Wu et al[3] conducted a meta-analysis that included all randomized controlled trials reported between 1966 and 2000 and observed no difference in response rates between SFRT and MFRT. There were differences in the rates of retreatment: Patients who received SFRT had rates of retreatment between 11% and 25% versus patients who received MFRT, who had retreatment rates between 0% and 12%. The subset of patients with PVBM from RTOG 97-14 also had similar rates of retreatment between those who received 8 Gy/1 (15%) and those who received 30 Gy/10 (5%)

To put the issue of need for retreatment in perspective, we illustrate the relative difference in total visits for radiation between the 8 Gy/1 population and the 30 Gy/10 population. Consider a hypothetical sample of 200 patients with PVBM in which 100 patients receive 8 Gy in a single fraction and 100 patients receive 30 Gy in 10 fractions. Assume that there is an additional visit required to the radiation therapy department in each case for consultation, simulation, and planning. The 8 Gy/1 group will have made 200 visits to the department; and the 30 Gy/10 group will have made 1100 visits; Then, factor in retreatments: 15 from the 8 Gy/1 group will make 2 additional visits each (30 total), and 5 patients from the 30 Gy/10 group, who will each make 11 additional visits (55 total). In aggregate, the 8 Gy/1 group will have made 230 visits to the radiation department, whereas the 30 Gy/10 group will have made 1155 visits—a 5-fold difference in trips to the radiation department. The 30 Gy/10 patient, on average, makes 9 more visits for treatment than the SFRT patient.

The retreatment rates were greatest in those patients who had PVBM involving the lumbar spine. Decisions on retreatment were left to the discretion of the treating physician. The higher lumbar spine retreatment rate may have been influenced by the absence of the spinal cord below lumbar segment 1 (L1), which may have had an impact on decisions to retreat. Only 23% of patients received initial treatment with photon energies ≥10 MV. Higher photon energy allows for a greater depth of penetration for a given dose, which generally portends a better dose distribution at depth. The lumbar spine extends deeper into the body than the thoracic or cervical spine. In addition, more information may be gleaned by examining allowable treatment techniques under the radiation therapy treatment plan outlined by the RTOG 97-14 treatment protocol. For the cervical spine, either a posterior field (treated to a depth of 5 cm or another depth, as determined from a lateral simulation film) or parallel opposed lateral fields with the isocenter set at mid-plane were allowed. For the thoracic spine, a single posterior field was to be used with the treatment depth set at the middle of the vertebral body. For the lumbar spine, anterior and posterior parallel opposed fields were suggested with equal weighting. However, unequal weighting could be used with a ratio of doses of 1:2 anterior:posterior, with dose prescribed to mid-thickness of the central axis or at the center of the target volume if unequal weighting was to be used. Alternatively, a third option for the lumbar spine would have been to treat with a single posterior-anterior (PA) field, with dose prescribed to the mid-vertebral body. Treatment volumes were to include the radiographic abnormalities with at least a 2-cm margin. Treatment of the entire bone was not required.[1]

It is reasonable to wonder, with the parameters set for treatment, the percentages of patients who received treatment with lower energy photons, and the treatment volumes specified, whether the more centrally located lumbar spine lesions would have received the desired full and homogeneous dose of radiation. Alternately, there may have been some form of bias on the part of participating physicians to perhaps use smaller volumes or different dose parameters to reduce dose homogeneity in light of concerns about the potential toxicities of SFRT. There was nothing in the study design that required the treating physicians to plan the field to be used before randomization. Whether there may have been a bias in the size or orientation of the fields planned based on the randomization to SFRT or MFRT is unknown.

Another factor that was not controlled in the RTOG 97-14 trial was initial pain management techniques and pain control in the time before initiation of radiation, and also how pain was managed during the course of treatment and thereafter. Only 3 in 235 patients (1%) reported baseline narcotic use. Randomized patients who worked with a radiation oncologist or other health care professional who was more cognizant of various pain management strategies, including 1) appropriate narcotic and non-narcotic pharmacologic pain management with frequent pain assessment, 2) application of long-acting analgesics, 3) judicious use of short-acting medications for breakthrough pain, 4) the appropriate use of coanalgesics and non-narcotic interventions, and 5) the use of pain diary monitoring and other pain-management techniques would likely have had better pain control. Various applications of non-radiation methods of management of pain may have confounded information on pain control as impacted by radiation technique.

Can these data be extrapolated to patients with other histologies? The RTOG 97-14 study enrolled only patients with breast and prostate cancer histologies. However, in the absence of any contrary data, it appears that the results from this study could be extrapolated to patients who have vertebral bone metastases of other histologies.[13,14]

Can these data be extrapolated to patients who have had other local interventions such as vertebroplasty, kyphoplasty, corpectomy or other form of stabilization procedure? Currently the answer is unknown.

What is clear is that both regimens studied are safe and effective for palliation of PVBM. No late grade 4 CNS toxicity was observed in either group. There were no reports of radiation myelopathy in RTOG 97-14 patients. GI toxicity was less in the 8 Gy/1 group. Ten percent more patients (1 in 10) in the 8 Gy/1 group received retreatment than in the 30 Gy/10 group. The 30 Gy/10 group required 9 more visits, on average, in the hypothetical population sample described above (allowing for retreatment rates appropriate to each group) than the 8 Gy/1 group. Howell et al[12] reported a cost analysis for Medicare Region 1 allowable reimbursement for 7 different schemas for the treatment of bone metastases and demonstrated a nearly 10-fold difference in Medicare reimbursement, depending on the technology used for treatment, the setting for treatment delivery, and the number of fractions used.

On a humanitarian note, the use of SFRT in this clinical setting saves the patient and their caregivers from having to make an additional 9 visits to the radiation oncology facility. It saves direct and indirect costs of additional time off of work, transportation, lodging, childcare, and other costs. The use of SFRT also saves time for health care providers and radiation therapists, and it reduces linear accelerator use.

On the basis of the results from RTOG 97-14, SFRT is safe and effective for the treatment of vertebral bone metastases.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol*. 2007;25:1423-1436.
2. Sze WM, Shelley MD, Held I, et al. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy—a systematic review of randomised trials. *Clin Oncol (R Coll Radiol)*. 2003; 15:345-352.
3. Wu JS, Wong R, Johnston M, et al. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys*. 2003;55:594-605.
4. 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.
5. Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol*. 2008;26:4001-4011.
6. Hartsell WF, Konski AA, Lo SS, Hayman JA. Single fraction radiotherapy for bone metastases: clinically effective, time efficient, cost conscious and still underutilized in the United States? *Clin Oncol (R Coll Radiol)*. 2009;21:652-654.
7. Kachnic L, Berk L. Palliative single-fraction radiation therapy: how much more evidence is needed? *J Natl Cancer Inst.* 2005;97:786-788. Erratum in: *J Natl Cancer Inst*. 2005;97:1095.
8. Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. Issues in Pain Measurement, Volume 12: Advances in Pain Research and Therapy. New York: Raven Press; 1989:391-403.
9. Trotti A, Byhardt R, Stetz J, et al. Common Toxicity Criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47:13-47.
10. Nguyen J, Chow E, Zeng L, et al. Palliative response and functional interference outcomes using the brief pain inventory for spinal bony metastases treated with conventional radiotherapy. *Clin Oncol (R Coll Radiol)*. 2011;23:485-491.
11. Mizumoto M, Harada H, Asakura H, et al. Radiotherapy for patients with metastases to the spinal column: a review of 603 patients at Shizuoka Cancer Center Hospital. *Int J Radiat Oncol Biol Phys*. 2011;79:208-213.
12. Howell DD, Lutz ST, Wood SL, Jagsi R. Cost comparisons for a course of radiation therapy for painful bone metastases from breast cancer using different technologies and fraction schema [abstract 152]. Paper presented at: American Society of Clinical Oncology Breast Cancer Symposium; San Francisco, CA; October 8-10, 2009.
13. Maranzano E, Trippa F, Casale M, et al. Eight-gray single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. *Radiother Oncol*. 2009;93:174-179.
14. Maranzano E, Latini P, Perrucci E, et al. Short-course radiotherapy (8 Gy ×2) in metastatic spinal cord compression: an effective and feasible treatment. *Int J Radiat Oncol Biol Phys*. 1997;38:1037-1044.
15. Macbeth FR, Wheldon TE, Girling DJ, et al. Radiation myelopathy: estimates of risk in 1048 patients in 3 randomized trials of palliative radiotherapy for non-small cell lung cancer. The Medical Research Council Lung Cancer Working Party. *Clin Oncol (R Coll Radiol)*. 1996;8:176-181.