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Clinical Oncology (2008) **20:** 327–336
doi:10.1016/j.clon.2008.01.002

Original Article

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?

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ABSTRACT:
Aims: **Since 1999, randomised clinical trials and meta-analyses have reported equal efficacy of pain relief from single- and multiple-fraction radiotherapy for bone metastases. A number of factors, including limited radiotherapy resources, waiting times, and patient convenience, suggest single fraction to be the treatment of choice for patients. However, international patterns of practice indicate that multiple fractions are still commonly used. This study examined whether dose-fractionation schemes used for the treatment of bone metastases at the Rapid Response Radiotherapy Program (RRRP) at the Odette Cancer Centre have changed since 1999.**
Materials and methods: **A retrospective review of the prospective RRRP database and hospital records were conducted for all patients treated with palliative radiotherapy for uncomplicated bone metastases at the RRRP in 1999 (or baseline), 2001, 2004 and from 1 January to 31 July 2005. Data were collected on patient demographics and clinical characteristics.**
Results: **Of the 693 patients, 65 and 35% were prescribed single fraction (predominantly single 8 Gy) and multiple fractions (predominantly 20 Gy/five fractions), respectively. The administration of single treatments generally increased over time, from 51% in 1999 to 66% in 2005 ($P = 0.0001$). On the basis of multiple logistic regression analyses, patients were more likely to be prescribed single-fraction radiotherapy if they had prostate cancer, had a poorer performance status, were treated to the limbs, hips, shoulders, pelvis, ribs, scapula, sternum, or clavicle (compared with the spine), were treated by a radiation oncologist who had been trained in earlier years, and who were treated after 1999.**
Conclusions: **Between 1999 and 2005, the use of single-fraction radiotherapy increased, corresponding to publications showing equal efficacy of pain relief between single and multiple fractions in the management of uncomplicated bone metastases. However, about a third of patients still received multiple fractions. Bradley, N. M. E. *et al.* (2008). *Clinical Oncology* 20, 327–336**

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Key words: Bone metastases, dose fractionation, knowledge translation, palliative, patterns of practice, radiotherapy

Introduction

It is estimated that about 50% of cancer patients will receive palliative radiotherapy during the course of their disease [1]. Radiotherapy is highly effective and therefore commonly used in the palliation of bone metastases, with an overall and complete pain response rate of 70 and 30%, respectively [2–4]. However, controversy exists on the optimal dose-fractionation regimen for the treatment of bone metastases [5,6]. Many randomised clinical trials (RCTs) on dose-fractionation schedules have concluded that a single fraction provides equal pain relief as multiple fractions in the treatment of uncomplicated bone metastases [3,7–15]. The first two large, multicentre RCTs confirming equivalence were published in 1999 [3,8], and were followed by the publication of two meta-analyses of 12 studies in 2003 [4,16]. On the basis of these empirical results, in 2004 the Province of Ontario published

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evidence-based guidelines that recommended the use of single-fraction radiotherapy in the management of uncomplicated bone metastases [17]. However, contemporary surveys on the patterns of practice in North America, Europe, Australia and Southeast Asia suggested that radiation oncologists continue to use multiple fractions in the treatment of bone metastases [18–31].

Meanwhile, shortages in radiotherapy resources, including health care professionals, technicians and radiation equipment, have historically led to a situation of overload in Ontario, where the delivery of timely radiotherapy was compromised [32,33]. This was evident by increased waiting times for radiation services, a concern for provincial health policy decision-makers, clinicians, and patients. Limited resources may be better used if patients with bone metastases are treated with a single fraction assuming equivalence of single and multiple fractions of radiotherapy in providing pain relief [34]. Moreover, two of the three surveys on patient preference showed that patients preferred the most convenient and effective treatment modality and most preferred shorter courses of palliative radiotherapy for bone metastases [35,36].

The Odette Cancer Centre is one of two large cancer centres providing radiotherapy in the Greater Toronto Area. The Rapid Response Radiotherapy Program (RRRP) is an outpatient clinic at the Odette Cancer Centre that started in 1996 as a pilot programme in Ontario to provide timely palliative radiotherapy and to reduce waiting times for radiotherapy services in Ontario [37]. Patients with advanced cancer are referred to the programme to relieve suffering and to improve symptoms and quality of life. About 70% of referrals to the RRRP are patients with painful bone metastases [37]. Most patients begin treatment on the day of initial consultation with the radiation oncologist. Therefore, if patients are prescribed a single fraction, they will typically be in the cancer centre for 1 day only.

This study was conducted to determine whether fractionations used for the treatment of uncomplicated bone metastases at the RRRP changed between 1999 and 2005. This will determine if evidence-based research findings are translated into clinical practice among radiation oncologists specialising in palliative radiotherapy at a large radiation treatment centre in Ontario. The effect of patient, disease, treatment, and organisational factors on the use of single vs multiple courses of palliative radiotherapy will also be considered.

Materials and Methods

A retrospective review of the prospective database of electronic treatment records and physician-dictated progress notes was conducted for all bone metastases patients who were prescribed palliative radiotherapy at the RRRP in 1999, 2001, 2004 and from 1 January to 31 July 2005. These years were chosen because they included time periods before and after the publication of the landmark RCTs and meta-analyses. Data from patient charts before 1999 were not available in electronic form so could not be included in the review. The year of 2001 was selected as an intermediary year used to determine changes in radiotherapy prescription after the publication of the two RCTs; as such, data from 2000 and 2002 were not collected. Data from 2003 were not collected given the severe acute respiratory syndrome (SARS) outbreak in Toronto, a period when radiation oncologists were more likely to prescribe single-fraction radiotherapy due to the increased chance of infection with longer stays in hospital. Furthermore, data were collected only until 31 July for 2005, given the time constraints of the data collection process. The primary outcome of interest was the dose-fractionation regimen prescribed (Gy/number of fractions).

Eight demographic and clinical variables shown to be associated with the dose-fractionation regimens prescribed were extracted from the medical records, including gender, age at radiation for bone metastases, primary cancer site, Karnofsky Performance Status (KPS) score [38] (if recorded at the time of consultation), distance from residence (derived from residential postal code) to cancer centre, date of initial consultation with the radiation oncologist, bony site irradiated, and the year of certification with the Royal College of Physicians and Surgeons of Ontario of each radiation oncologist.

Primary cancer sites were categorised as cancer of the lung, breast, prostate, and others. The KPS is a validated functional assessment tool often used for oncology patients, with an 11-point categorical interval scale ranging from 0 (death) to 100 (no functional impairment) [38]. KPS scores were analysed as a continuous variable. The distance travelled from residence to cancer clinic was summarised: (1) continuously; (2) as an ordinal categorical variable as: near (0 to $<$40 km), intermediate ($>$40 to $<$80 km), distant ($>$80 to $<$120 km), and very distant ($>$120 km); and (3) as a dichotomous variable as: near (0 to $<$45 km) and distant ($>$45 km). Irradiated bone metastases sites were grouped into five categories: (1) spine; (2) pelvis; (3) ribs, scapula, sternum and clavicle (chest); (4) limbs, hips, and shoulders; and (5) skull and hemi-body irradiation. The year of certification for the treating radiation oncologist was recorded for each patient case and was categorised by decade: 1970–1979; 1980–1989; 1990–1999; 2000–2005.

Excluded from the analysis were patients who had documented spinal or cauda equina compression, nerve root impingement, actual or impending pathological fracture(s) of an extremity, previously irradiated bony lesions, or referrals for postoperative radiotherapy to the bone. Any uncertainty of the presence of spinal cord compression, pathological fracture, or impending cord compression and fracture were cross-checked with available imaging reports. Data were collected for each episode of radiotherapy for bone metastases in 1999, 2001, 2004 and 1 January to 31 July 2005. Ethical approval for research involving humans was obtained from the hospital Research Ethics Board.

Statistical Analyses

Descriptive statistics were recorded as percentages for proportions and as means, medians, standard deviations, and ranges for continuous variables. For the purpose of this study, the dose-fractionation regimen for each patient was coded as a binary variable, where 1 = single fraction and 0 = multiple fractions. For patients who had more than one independent course of radiotherapy for bone metastases during the study period, one course of radiation was randomly selected using a table of random numbers. To determine whether the use of single-fraction radiotherapy changed over time, the chi-square test was used. The chi-square test was also used to detect differences in proportions between unordered categorical variables, including gender, travel distance, primary cancer site, site of radiotherapy, prescription of single or multiple fractions, radiation oncologist, and year of certification of radiation oncologist across time. Continuous interval variables, such as age and travel distance, were tested across time using the analysis of variance (ANOVA). Univariate logistic regression analyses were conducted to identify patient, treatment and organisational variables significantly associated ($P \leq 0.05$) with the use of single-fraction regimens. In these models, multilevel categorical variables were dummy coded with the following reference groups: female for gender; lung for primary cancer site; near for travel distance; spine for radiotherapy site group; and 2000—2005 for year of certification of radiation oncologist. We then carried out a multiple logistic regression analysis to examine the effect of the year of treatment (1999 was the referent group) on the use of single radiotherapy, after adjusting for gender, age, primary cancer site, KPS, travel distance to cancer centre, site of radiotherapy, and year of certification of radiation oncologist. Covariates were included in the final model if they were hypothesised to be related to the prescription of single-fraction radiation across time and the final model was selected based on the highest r^2 value, a statistical indicator of the best fit of a model. Patients with missing values for any covariates were excluded from the multiple logistic regression analysis.

Multi-collinearity was assessed using correlation coefficients, variance inflation factors, and condition indices. The Hosmer—Lemeshow goodness-of-fit test was conducted to determine if the data fitted the specified model [39]. All analyses were carried out using the Statistical Analysis System (SAS), version 9.1.3. Tests were considered statistically significant if the P value was ≤ 0.05, if the 95% confidence interval did not include one, and all tests were two-sided.

Results

The study sample consisted of 693 patients with symptomatic, uncomplicated bone metastases. In total, 965 courses of palliative radiotherapy were prescribed. Table 1 presents the clinic activity, demographic, disease and treatment-related characteristics of the patients for each year under study. Clinic activity refers to the number of patients who were prescribed radiotherapy for bone metastases as well as the number of courses of radiotherapy for bone metastases prescribed for each year under study. After randomly selecting one course of radiotherapy per patient, 451 (65.08%) and 242 (34.92%) patients were prescribed single and multiple fractions of radiation, respectively. Single-fraction treatments were predominantly prescribed as 8 Gy (92%), with doses ranging from 4 to 10 Gy. Ninety per cent of multiple-fraction treatments were prescribed as 20 Gy/five fractions and 6% were 30 Gy/10 fractions (range 12 Gy/two fractions to 30 Gy/10 fractions). The proportions of single fractions used over time are presented in Fig. 1. The administration of single treatments generally increased across time, from 51% in 1999, to 70% in 2001, to 71% in 2004 and 66% in 2005 ($P < 0.0001$).

Overall, 57% of the sample were men, with a mean age of 67.4 years. The three most common primary cancer sites were lung, prostate and breast (respectively), and the median KPS score was 60, indicating that most patients required occasional assistance from others, but were able to care for most needs [38]. About 87% of radiotherapy episodes were to the spine, pelvis, or limbs. The median travel distance to the clinic was 25.1 km and most patients (66.1%) resided 'near' the cancer centre (at a distance of less than 40 km). Tests for heterogeneity found significant differences in the proportion of men and women who were prescribed radiotherapy ($P = 0.037$) across time, with the proportion of men increasing. The distribution of primary cancer sites also changed ($P = 0.004$) across time, with an increasing proportion of both lung and prostate cancers and a decreasing frequency of breast cancer and other cancer types. Furthermore, patients prescribed radiotherapy in 1999 and 2001 had a poorer performance status (median of 60) than patients seen in 2004 and 2005 (median of 70) ($P < 0.0001$, Table 1).

Table 2 presents the univariate relationship between individual clinical and demographic variables and single-fraction radiotherapy. As shown, patients treated with single-fraction radiotherapy were significantly older (mean age 68.26 years) than patients treated with multiple fractions (mean age 65.64 years). For each increasing year of age, patients had 1.02 times greater the odds of receiving single-fraction radiation. Patients with prostate cancer had 1.623 times the odds of receiving single-fraction radiation, compared with patients with lung cancer. There were no significant differences in the use of single or multiple fractions for patients with breast or other types of cancer, with odds ratios of 0.767 and 0.981, respectively (Table 2). Patients who had a higher KPS had lower odds of receiving single-fraction radiation than patients with a poorer performance status (odds ratio = 0.984, 95% confidence interval 0.972—0.996). Also, patients who lived 'very distant' from the treatment centre had 1.951 times the odds (95% confidence interval 1.050—3.864) of receiving a single fraction of radiotherapy compared with patients who lived 'near' the cancer centre. Overall, there were significant differences in the use of single-fraction radiotherapy by bony sites of metastases ($P < 0.0001$); single

Table 1 — Clinic activity, demographic, disease and treatment characteristics of patients by year of radiotherapy treatment

	Overall ($n = 693$)	1999 ($n = 169$; 24.4%)	2001 ($n = 186$; 26.8%)	2004 ($n = 236$; 34.1%)	January to July 2005 ($n = 102$; 14.7%)	P value
Clinical activity						
Patients prescribed radiotherapy	693	169 (24.4%)	186 (26.8%)	236 (34.1%)	102 (14.7%)	0.05264
Courses of radiotherapy rrescribed	965	229 (23.7%)	245 (25.4%)	346 (35.9%)	145 (15.0%)	0.03169*
Gender						
Male	395 (57.0%)	82 (48.5%)	110 (59.1%)	136 (57.6%)	67 (65.7%)	0.0370*
Female	298 (43.0%)	87 (51.5%)	76 (40.9%)	100 (46.4%)	35 (34.3%)	
Age at radiation (in years)						
Mean ± standard deviation	67.4 ± 11.3	66.8 ± 10.2	67.5 ± 10.8	67.2 ± 11.8	68.4 ± 12.7	0.7314
Median (range)	69 (31—95)	68 (31—88)	69 (35—88)	69.5 (33—95)	69.5 (31—94)	
Primary cancer site						
Lung	173 (25.0%)	33 (19.5%)	45 (24.2%)	61 (25.8%)	34 (33.3%)	0.0045*
Breast	159 (22.9%)	49 (29.0%)	37 (19.9%)	52 (22.0%)	21 (20.6%)	
Prostate	168 (24.2%)	31 (18.3%)	41 (22.0%)	72 (30.5%)	24 (23.5%)	
Others	193 (27.8%)	56 (33.1%)	63 (33.9%)	51 (21.6%)	23 (22.5%)	
Karnofsky Performance Status score						
Number of evaluable patients	590 (85.1%)	163 (96.4%)	151 (81.2%)	212 (89.8%)	64 (62.7%)	<0.0001*
Median (range)	60 (10—90)	60 (10—90)	60 (30—90)	70 (30—90)	70 (40—90)	
Distance between residence and cancer centre (km)						
Number of evaluable patients	688 (99.3%)	167 (98.8%)	186 (100.0%)	235 (99.6%)	100 (98.0%)	
Continuous						
Mean ± standard deviation	43.2 ± 49.3	40.5 ± 45.2	46.9 ± 50.9	42.9 ± 51.2	41.8 ± 48.5	0.6543
Median (range)	25.1 (1.1—442.0)	26.7 (1.5—376.0)	26.8 (1.9—442.0)	24.2 (1.1—402.0)	22.1 (4.7—343.0)	
Ordinal						
Near (0 to <40 km)	455 (66.1%)	115 (68.9%)	115 (61.8%)	159 (67.7%)	66 (66.0%)	0.7444
Intermediate (>40 to <80 km)	120 (17.4%)	29 (17.4%)	32 (17.2%)	39 (16.6%)	20 (20.0%)	
Distant (>80 to <120 km)	113 (16.4%)	12 (7.2%)	21 (11.3%)	16 (6.8%)	6 (6.0%)	
Very distant (>120 km)	55 (8.0%)	11 (6.6%)	18 (9.7%)	21 (8.9%)	8 (8.0%)	
Dichotomous						
Near (0 to <45 km)	491 (71.4%)	123 (73.6%)	124 (66.7%)	174 (74.0%)	70 (70.0%)	0.3404
Distant (>45 km)	187 (28.6%)	44 (26.4%)	62 (33.3%)	61 (26.0%)	30 (30.0%)	
Site of radiotherapy						
Spine	217 (31.3%)	50 (29.6%)	61 (32.8%)	63 (26.7%)	43 (42.2%)	0.1732
Pelvis	174 (25.1%)	40 (23.7%)	56 (30.1%)	58 (24.6%)	20 (19.6%)	
Ribs, scapula, sternum and clavicle	77 (11.1%)	19 (11.2%)	19 (10.2%)	26 (11.0%)	13 (12.8%)	
Limbs, hips and shoulders	210 (30.3%)	56 (33.1%)	48 (25.8%)	83 (35.2%)	23 (22.6%)	
Cranium, hemi-body	15 (2.2%)	4 (2.4%)	2 (1.1%)	6 (2.5%)	3 (2.9%)	
Year of certification of radiation oncologist						
1970—1979	177 (25.7%)	48 (28.4%)	36 (19.4%)	65 (27.5%)	28 (28.3%)	<0.0001*
1980—1989	185 (26.8%)	48 (28.4%)	66 (35.5%)	45 (19.1%)	26 (26.3%)	
1990—1999	250 (36.2%)	73 (43.2%)	68 (36.6%)	84 (35.6%)	25 (25.2%)	
2000—2006	78 (11.3%)	0 (0.0%)	16 (8.6%)	42 (17.8%)	20 (20.2%)	

*Statistical significance using the chi-square test for proportions and the ANOVA test for continuous variables, defined as $P \leq 0.05$.

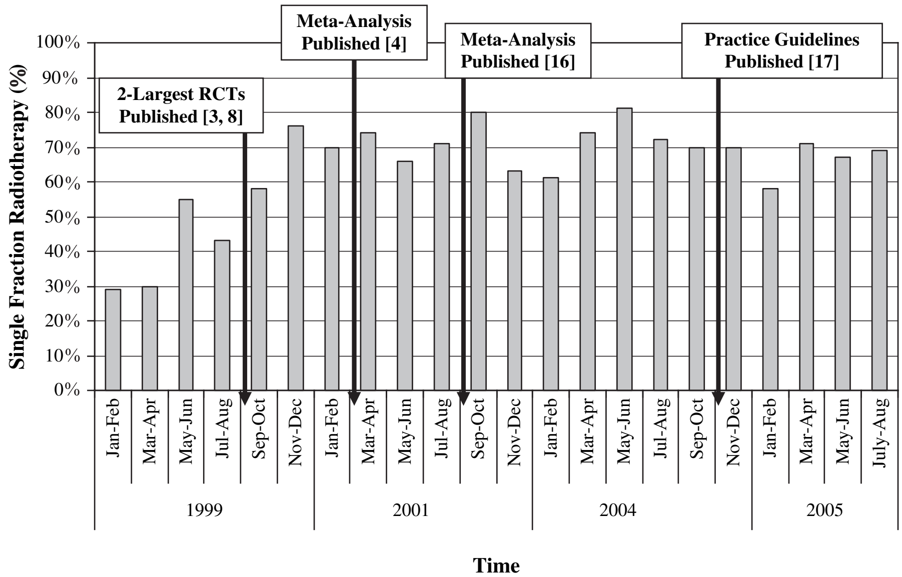

Fig. 1 — Relative frequency of single-fraction radiotherapy at the Rapid Response Radiotherapy Program (RRRP) over time, in relation to the publication of the large randomised clinical trials [3,8], meta-analyses [4,16], and evidence-based practice guidelines in Ontario [17].

fractions were used more frequently to irradiate the limbs, hips, pelvis and ribs compared with treatments to the spine (Table 2). There were significant differences in the prescription of single- or multiple-fraction radiation according to the year of certification of the radiation oncologists. Oncologists certified in the 1970s and 1980s were more likely to prescribe single-fraction radiation than those certified in the 2000s (odds ratio = 4.07 and 2.50, respectively). However, there was no difference in the prescription patterns of oncologists certified in the 1990s compared with their year 2000s counterparts. Gender was not found to be associated with single-fraction radiation (Table 2).

The results of the multivariable logistic regression analyses are also presented in Table 2. After adjusting for gender, age, primary cancer site, KPS, distance travelled (ordinal measurement), site of radiotherapy, and year of certification of radiation oncologist, there was a significantly increased likelihood of single-fraction radiation being prescribed after 1999. The odds of using single-fraction radiation were about 1.5 times greater overall than in 1999 (Table 2). The increased use of single-fraction radiation was observed in 2002, 2004 and 2005. KPS, the site of radiation, and the year of certification of the oncologist were also significantly associated with the dose-fractionation regimen. Treatments to the pelvis had 5.6 times the odds of receiving single-fraction radiation, whereas treatments to the ribs, scapula, sternum and clavicle had about 3.2 times the odds of receiving single-fraction radiation compared with treatments to the spine. Also, treatments to the limbs, hips and shoulders had 1.9 times the odds of receiving single-fraction radiation compared with treatments to the spine. After controlling for age, the primary cancer site overall was not found to be related to single-fraction radiation, although prostate cancer patients had a greater likelihood (odds ratio = 2.089) of being prescribed single-fraction radiation compared with other cancer sites. Oncologists trained in earlier years (i.e. 1970s and 1980s) had significantly higher odds of prescribing single-fraction radiation than oncologists trained later. There was no collinearity present in the multivariable model, with variance inflation factors ranging from 1.00853 to 1.12102. The results of the Hosmer—Lemeshow goodness-of-fit test did not indicate any evidence of gross lack of fit of the model ($P = 0.1489$).

Discussion

This study provides insight into the knowledge translation of empirical evidence from RCTs to the palliative radiotherapy clinical setting. On the basis of our review of practice in the RRRP, the use of single-fraction radiation did increase significantly over time, particularly in 2001 and 2004 after the publication of the two large RCTs [3,8] and the two meta-analyses [4,16]. Similarly, a rapid change in the pattern of practice of concurrent chemotherapy and radiation in cervical cancer in Ontario has also been shown in response to the publication of RCTs and recommendations of the National Cancer Institute [40].

There was a decline in the prescription of single-fraction radiation in 2005 compared with 2001 and 2004, although the odds of administration of single-fraction radiotherapy were significantly higher than in 1999 (odds ratio 2.236, 95% confidence interval 1.079—4.633). This may not be a true reflection of the prescription patterns of oncologists in the RRRP in 2005. First, data were only collected until 31 July 2005, resulting in few courses of radiotherapy during the 2005 time period included in the study compared with other years. As such, cases have been overlooked, which may

Table 2 — Univariate and multivariable logistic regression analyses examining the relationship between demographic and clinical variables and the use of single-dose fractionation for bone metastases

	Single fraction (*n* = 451, 65.1%)	Multiple fractions (*n* = 242, 34.9%)	Univariate logistic regression: Odds ratio (95% CI)	Univariate logistic regression: *P* value	Multivariable logistic regression*: Adjusted odds ratio (95% CI)	Multivariable logistic regression*: *P* value
Year of treatment				0.0002	1.515 (1.241–1.849)	<0.0001
January to December 1999	86 (50.9%)	83 (49.1%)	Referent	–	Referent	–
January to December 2001	131 (70.4%)	55 (29.6%)	2.299 (1.491–3.569)	0.0002	2.619 (1.539–4.456)	0.0004
January to December 2004	167 (70.8%)	69 (29.2%)	2.336 (1.550–3.536)	<0.0001	3.473 (2.049–5.886)	<0.0001
January to August 2005	67 (65.7%)	35 (34.3%)	1.848 (1.117–3.091)	0.0179	2.236 (1.079–4.633)	0.0304
Gender						
Male (*n* = 395)	262 (66)	133 (34)	1.136 (0.829–1.556)	0.4270	0.604 (0.347–1.053)	0.0756
Female (*n* = 298)	189 (63)	109 (37)	Referent		Referent	
Age (years)						
Mean ± standard deviation	68.3 ± 11.2	65.6 ± 11.2	1.021 (1.007–1.035)	0.0037	1.016 (0.997–1.035)	0.1011
Median (range)	70 (31–95)	66 (33–88)				
Primary cancer site				0.0175	1.004 (0.850–1.184)	0.0555
Lung (*n* = 173)	111 (64)	62 (36)	Referent	–	Referent	–
Breast (*n* = 159)	92 (58)	67 (42)	0.767 (0.492–1.193)	0.2398	0.763 (0.392–1.487)	0.4273
Prostate (*n* = 168)	125 (74)	43 (26)	1.623 (1.022–2.597)	0.0413	2.089 (1.106–3.945)	0.0231
Others (*n* = 193)	123 (64)	70 (36)	0.981 (0.639–1.505)	0.9316	0.951 (0.559–1.620)	0.8539
Karnofsky Performance Status score						
Number patients evaluated	363 (80)	227 (94)	0.984 (0.972–0.996)	0.0076	0.982 (0.967–0.996)	0.0134
Mean ± standard deviation	62.1 ± 14.6	65.3 ± 13.5				
Median (range)	60 (10–90)	70 (30–90)				
Distance between residence and cancer centre (km)					1.198 (0.979–1.465)	0.4949
Number patients evaluated	447 (99)	227 (94)				
Continuous						
Mean ± standard deviation	45.4 ± 51.8	39.2 ± 43.9	1.003 (0.999–1.006)	0.1166		
Median (range)	26.7 (1.1–402.0)	24.0 (1.9–442.0)			–	–
Ordinal				0.1644		
Near (0 to <40 km)	291 (63.4%)	164 (36.0%)	Referent	–	Referent	–
Intermediate (<40 to >80 km)	74 (61.2%)	46 (38.3%)	0.907 (0.601–1.379)	0.6432	1.174 (0.692–1.993)	0.5525
Distant (>80 to <120 km)	37 (67.3%)	18 (32.7%)	1.158 (0.647–2.142)	0.6279	1.096 (0.522–2.300)	0.8089
Very distant (>120 km)	45 (77.6%)	13 (22.4%)	1.951 (1.050–3.864)	0.0427	1.801 (0.834–3.886)	0.1341
Dichotomous						
Near (0 to <45 km)	314 (64.0%)	177 (36.05%)	Referent	–	–	–
Distant (>45 km)	133 (67.5%)	64 (32.5%)	1.171 (0.827–1.669)	0.3763	–	–
Site of radiotherapy				<0.0001	1.392 (1.200–1.614)	<0.0001
Spine (*n* = 217)	115 (53)	102 (47)	Referent	–	Referent	–
Limbs, hips, shoulders (*n* = 210)	156 (74)	54 (26)	1.729 (1.148–2.618)	0.0092	1.875 (1.108–3.173)	0.0192
Pelvis (*n* = 174)	115 (68)	59 (34)	2.527 (1.443–4.577)	0.0016	5.626 (2.676–11.824)	<0.0001
Ribs, scapula, sternum, clavicle (*n* = 77)	57 (74)	20 (26)	2.562 (1.709–3.873)	<0.0001	3.158 (1.903–5.240)	<0.0001
Others (skull, hemi-body) (*n* = 15)	8 (53)	7 (47)	1.014 (0.352–2.984)	0.9798	0.725 (0.219–2.397)	0.5981
Year of certification of radiation oncologist				<0.0001	0.488 (0.399–0.597)	<0.0001
1970–1979 (*n* = 177)	150 (85)	27 (15)	4.074 (2.227–7.541)	<0.0001	6.356 (3.076–13.131)	<0.0001

Table 2 — (*continued*)

	Single fraction ($n = 451$, 65.1%)	Multiple fractions ($n = 242$, 34.9%)	Univariate logistic regression		Multivariable logistic regression*	
			Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
1980–1989 ($n = 185$)	143 (77)	42 (23)	2.497 (1.417–4.405)	0.0015	3.905 (1.935–7.880)	0.0001
1990–1999 ($n = 250$)	112 (45)	138 (55)	0.595 (0.354–0.992)	0.0477	0.898 (0.479–1.683)	0.7367
2000–2006 ($n = 78$)	45 (58)	33 (42)	Referent	—	Referent	—

*$P < 0.0001$ for overall multivariable logistic regression model, after adjusting for gender, age, distance, primary cancer site, Karnofsky Performance Status, and year of certification of radiation oncologist. CI, confidence interval.

have non-differentially biased results towards a greater proportion of multiple-fraction treatments in 2005 compared with 2004. Second, there were more patients with lung cancer treated in 2005 compared with the other years, with a smaller proportion of prostate cancer patients. However, this was adjusted for in the multivariable regression model. Furthermore, information on ongoing clinical trials during each time was not collected. Clinical trials, some of which restrict patients to a given dose-fractionation schedule, may have influenced the prescription patterns of radiation oncologists during the study time periods.

Overall, single-fraction radiotherapy was used more frequently among the RRRP oncologists (65%) when compared with national patterns of practice surveys conducted before June 1999, where only 15–28% of respondents would use single-fraction radiotherapy [19,22,31]. No official departmental policy on dose-fractionation schedules for bone metastases had been established at the Odette Cancer Centre during the years of this review. Likewise, there are no financial incentives for Canadian radiation oncologists to prescribe more than one fraction of radiation, as they are not paid per fraction of radiation delivered.

To our knowledge, however, there has been only one published study [41] that has examined the change in use of single-fraction radiotherapy for bone metastases over time in a similar palliative radiation clinic. Haddad *et al.* [41] conducted a review of dose fractionations used in the treatment of bone metastases at the Palliative Radiation Oncology Program (PROP) at Princess Margaret Hospital (PMH) in Toronto, Ontario. Like RRRP, PROP provides quick access to palliative radiotherapy at a large radiation treatment centre. PROP patient profiles were comparable with those of the RRRP in terms of primary cancer site, gender, age, and skeletal sites of metastases. Overall, single-fraction radiotherapy was used with greater frequency among the 693 evaluated RRRP patients when compared with the 882 PROP patients (65% vs 32%, respectively) [41]. In both clinics, the most frequently prescribed single- and multiple-fraction treatment regimens were a single 8 Gy and 20 Gy/five fractions, respectively. In PROP, the use of single-fraction radiotherapy generally increased between 1998 and 2000, from 37 to 43%, but declined again in 2001 to 26%. As indicated in Fig. 1, the relative proportion of use of single-fraction radiotherapy was much higher in the RRRP during the same period (50.9 and 70.8% of all radiotherapy cases in 1999 and 2001, respectively).

There are no known reasons to account for the differences in use of single-fraction radiotherapy in the PROP or RRRP clinics. In 2001, a survey of radiation oncologists at PMH was conducted to investigate factors guiding the prescription and fractionation practices for bone metastases [42]. The survey found that only 28% would prescribe single-fraction radiation for bone metastases. Eighty-eight per cent and 40% reported using performance status and age, respectively, to guide their choice of dose-fractionation schedule. Less than 10% of the oncologists used the location of the lesion in the vertebrae or weight-bearing bones. A survey conducted in the UK in the 1980s found that radiation oncologists who normally prefer single-fraction radiotherapy for the palliation of bone metastases would use multiple fractions for cases involving younger age (e.g. $\leq$40 years), cervical spine metastases, neurological symptoms associated with spinal metastases, diagnoses of a single bone lesion, and lytic metastases [21]. On the other hand, oncologists who normally prefer to use multiple fractions of radiotherapy would use single-fraction radiation for cases involving older patients (i.e. $\geq$ 70 years), patients who travel further for treatment, temporary waiting lists and resource availability pressures, rib metastases and lung cancer patients [21].

The results of the multivariable logistic regression model suggested that the increased use of single-fraction radiotherapy over time in the RRRP remained after adjusting for gender, age, KPS, primary cancer site, distance travelled from residence to centre, site of radiation, and year of certification of radiation oncologist. Although the administration of a single fraction was hypothesised to be more likely for patients who travelled further distances from their residence to the centre, after adjusting for all other covariates, distance was not a significant factor in the dose-fractionation regimen prescribed. The results also suggest that the experience of the radiation oncologist has a quantitatively greater influence on the use of single fractions than the year of treatment (odds ratios of 6.356 and 3.905 for oncologists certified in the 1970s and 1980s, respectively, compared with 2.619 and 3.473 for treatments in 1999 and 2001, respectively). It is not expected that there is a cohort effect, where more experienced oncologists who are trained in earlier years may be more likely to give single-fraction radiotherapy or be more likely to base clinical practice on empirical evidence. More experienced oncologists trained in earlier years may be more confident in knowing and applying the results of empirical evidence to clinical practice. However, the observed differences in the prescription patterns between oncologists warrant further investigation. It is difficult to confidently ascertain whether the increased use of single-fraction radiotherapy over time in the RRRP was due to the effect of empirical evidence and recommendations in the literature or due to other factors, such as personal preferences of the radiation oncologists, patient preferences, or other patient and tumour-related characteristics not examined here.

This study was limited by factors beyond the control of the researchers and resources of the study. Because one course of palliative radiation was randomly selected for patients, some cases may have been overlooked. It is difficult to know whether previous courses of radiotherapy confounded the use of single or multiple fractions for all subsequent treatments for bone metastases. Similar to the PMH review [41], estimates of patient survival and life expectancy by the treating radiation oncologist were not consistently available in patient records and were not included as potential covariates in the dose-fractionation prescription. Data on waiting times from referral to radiotherapy consultation were not collected in this study. It is hypothesised that this variable could influence the use of single or multiple fractions across time, depending on the pressure of radiation waiting times within the radiotherapy department as well as within the RRRP clinic. In the PMH review, waiting times for radiation were not found to influence the use of single or multiple fractions [41]. Also, specific tumour characteristics were not recorded, such as the lesion type (lytic, blastic, or mixed), the date of diagnosis of the primary cancer site and bone metastases, the number of bony lesions, or other sites of metastases and the extent of disease, as these data were inconsistently available in electronic patient records. Furthermore, data on the field size of radiation delivered were not collected in this study, which could have influenced the oncologist's decision for dose-fractionation choice. These disease-related factors may have influenced the dose-fractionation prescription patterns. Lastly, data on radiation oncologist sub-specialties were not collected in this study.

Conclusions

Overall, 60% of courses of palliative radiotherapy for bone metastases in our programme were prescribed as single fractions. The results of this study suggest that practice significantly changed in the RRRP after the publication of influential RCTs and recommendations for treatment. There was an increase in the prescription of single-fraction radiotherapy for painful bone metastases over time in the RRRP. The most significant changes followed the publication of the two large RCTs and two meta-analyses confirming equivalence in pain relief between single and multiple fractions in 1999 and 2004, respectively. Potential contributing factors to dose-fractionation schedules included the site of bone metastases and physician-related factors. An obligation exists to use the most cost-effective treatment plan that provides equivalent outcomes [30] in order to provide the best medical care and to optimise resources in both publicly and privately funded regions of the world. Recently, increased use of single-fraction radiotherapy in the treatment of bone metastases has been shown to reduce overall radiotherapy workload in the UK by 6% [34]. Reductions in radiation workload allow for an increased availability of radiation resources, which has the potential to reduce radiation waiting times for patients who have the potential for cure, where the time of access to radiation is essential to prevent tumour growth and metastasis [43]. Patients may also benefit from the use of single-fraction radiation, being spared additional travelling and treatment time. Many studies have already promoted and advocated the use of single-fraction radiation [5,44–46]. We also advocate the use of single-fraction radiation, but acknowledge the need for an individual case-based management for complicated bone metastases. Further research in the management of patients with complicated bone metastases is needed to determine when the use of multiple fractions is most appropriate, such as the controversy in the dose fractionation used for neuropathic pain or spinal cord compression.

Acknowledgements. This study was supported by the Michael and Karen Goldstein Cancer Research Fund and the Odette Cancer Centre Radiation Program Fund. The study sponsors had no involvement in the study design, data collection, statistical analysis, interpretation of results, writing of the manuscript, or decisions to submit for publication. This work was presented in part at the 16th Annual Provincial Conference on Palliative and End-of-Life Care, April 2006, Toronto, Ontario, Canada.

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Received 5 September 2007; received in revised form 19 December 2007; accepted 20 December 2007

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