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Edward James FITZGIBBON

AUTEUR DE LA THÈSE - AUTHOR OF THESIS

M. Sc. (Epidemiology)

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Department of Epidemiology and Community Medicine

FACULTÉ, ÉCOLE, DÉPARTEMENT - FACULTY, SCHOOL, DEPARTMENT

TITRE DE LA THÈSE - TITLE OF THE THESIS

A systematic Review of the Effectiveness of Palliative Radiotherapy and Survey of Family Physicians on their Awareness of the Palliative Radiotherapy Program

P. Allard

DIRECTEUR DE LA THÈSE - THESIS SUPERVISOR

CO-DIRECTEUR DE LA THÈSE - THESIS CO-SUPERVISOR

EXAMINATEURS DE LA THÈSE - THESIS EXAMINERS

L. Chambers

I. McDowell

J-M. De Koninck, Ph D

LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES

DEAN OF THE FACULTY OF GRADUATE AND POSTODORAL STUDIES

A Systematic Review of the Effectiveness of Palliative Radiotherapy and A Survey of Family Physicians on their Awareness of the Rapid Palliative Radiotherapy Program

Edward James Fitzgibbon

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Abstract.

Problem: After two years of operation a review of the Rapid Palliative Radiotherapy Program revealed that only 17 family physicians in Eastern Ontario had used the program.

Methods of Investigation: This thesis consists of: (1) A systematic literature review of the relative effectiveness of a single fraction of radiotherapy to relieve painful bone metastases and (2) A survey of family physicians to assess their awareness of the Rapid Palliative Radiotherapy Program.

Results: A single fraction of radiotherapy is of comparable effectiveness to multiple fraction radiotherapy treatment schedules in relieving painful metastatic bone disease (Odds Ratio: 1.13, 95% CI = 0.96 to 1.34). Only 18% of survey responders were aware of the RPRP.

Conclusion: Improving family physician awareness of the Rapid Palliative Radiotherapy Program is the first step to improving utilization of the program and access for patients with painful metastatic bone disease to a proven, effective analgesic treatment.

Key words: Palliative radiotherapy, systematic review, survey, family physician,

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Preamble to Thesis

Thesis Format: This thesis has been structured around two self-contained articles presented in a journal paper format (Chapters 2 and 3). Chapter 1 contains an introduction and general overview of the central issues of the thesis. Chapter 2 contains a systematic review comparing the effectiveness of a single fraction of a high dose of radiotherapy to multiple fractions of lower dose radiotherapy in treating painful metastatic bone disease. Chapter 3 reports on a survey of family physicians in Eastern Ontario on their awareness and use of the Rapid Palliative Radiotherapy Program. The final chapter serves to synthesize and interpret the thesis results and formulate appropriate conclusions.

Chapter 1: Introduction

Background: Cancer is the leading cause of premature death in Canada and is responsible for approximately 30% of all potential years of life lost. Based on current incidence rates, 38% of women and 41% of men will develop cancer at some stage during their lifetimes (1).

Given the prevalence of cancer, family physicians have a key role to play in all phases of cancer care, from prevention and screening, to the follow-up of patients with advanced cancer (2). A cross-sectional survey of family physicians on their role in cancer care reported that individual family physicians were caring for a mean of 21 cancer patients and three of these cancer patients were in an advanced or palliative phase of their illness. In addition more than 90% of the surveyed family physicians regularly provided pain management and palliative care for their patients with advanced cancer (3).

Metastatic bone disease is a major complication of advanced cancer that may be diagnosed in 23% to 84% of cancer patients. The frequency of diagnosis depends upon the site of the primary lesion and the method of detection used (4-8). Sixty-five to 75% of patients with metastatic bone disease experience pain making it the commonest cause of cancer pain (9). The pain associated with metastatic bone disease often worsens with movement and may have a devastating impact on a patient's ability to perform their activities of daily living i.e. performance status, and quality of life.

Patients with metastatic bone pain are often frail, having a mean life expectancy of less than six months (11). Thus the objective of treatment for painful metastatic bone disease is not curative, but rather to 'palliate' or ease the suffering associated with the metastatic lesions. Current treatment options include varying combinations of opioid and

non-opioid analgesic agents, bisphosphonates, radiotherapy, chemotherapy and hormonal agents, and orthopedic surgery (10). The ideal analgesic palliative intervention for this frail symptomatic patient population would be rapidly effective, well tolerated, readily accessible, and of brief duration.

Local field external beam radiotherapy is considered to be an effective well tolerated treatment for the palliation of painful metastatic bone disease. This is supported by the fact that the treatment of painful bone metastases accounts for more than 20% of all the radiotherapy treatments delivered in North America (12-14). Treatment response rates reported in three of the largest radiotherapy trials ranged from 71% to 89% for partial pain relief and 35% to 57% for complete pain relief (4;15;16). Traditionally, radiation oncologists have treated painful metastatic bone disease with five to 10 daily fractions (treatment session), each fraction consisting of a dose of radiotherapy of two or three Grey (Gy = unit of radiation), for a total radiation dose of 20Gy to 30Gy (17). However, there is a growing body of evidence that a single fraction of a larger dose (8 Gy) of radiotherapy is of comparable effectiveness to the traditional multiple fraction treatment schedules in inducing pain relief that lasts at least three months (18).

Despite this, a recent survey of patterns of practice among Canadian radiation oncologists, reported that 72% of the radiation oncologists would use a standard dose fractionation schedule of 20Gy in five fractions (4Gy per fraction) for palliative radiotherapy, with only 16% preferring an 8Gy in one fraction treatment schedule(13). Much of the controversy regarding the optimal radiotherapy treatment schedule arises from a lack of consensus among radiation oncologists regarding the definition, measurement and reporting of the treatment outcome of pain relief as well as the level

and duration of improvement after treatment (12). A one day treatment program, if of comparable effectiveness, would have obvious advantages over the traditional five day treatment schedule both for the frail patient with advanced cancer and also for an over burdened health care system.

The Rapid Palliative Radiotherapy Program (RPRP) was established in Ottawa in 1999 to provide family physicians with timely direct access for patients with advanced symptomatic cancer to a same–day radiation oncology consultation and treatment service. The rationale for the RPRP was that short courses (one or two fractions) of higher dose radiotherapy (8Gy) are an effective treatment to alleviate distressing symptoms and improve quality of life for a symptomatic patient. In addition, providing prompt access to consultation and treatment would facilitate family physician referrals and improve patient access to treatment.

A retrospective chart audit of the RPRP conducted at the Ottawa Regional Cancer Center revealed that 148 patients were treated from November 1999 to December 2001 **(Table1.1).** Painful metastatic bone disease was the primary indication for referral in 120 (81%) patients; 100 (68%) patients received a single fraction of radiotherapy and 20 patients received two fractions. Only 17 of the more than 1,000 Family physicians of Eastern Ontario had used the RPRP, referring a total of 19 patients. These figures reveal an obvious under-utilization of the program by family physicians.

The overall aims of this thesis were twofold:

1) To determine the relative effectiveness of a single fraction of a high dose of radiotherapy compared to the traditional treatment schedule of multiple fractions of lower dose radiotherapy in the treatment of painful metastatic bone disease (Chapter 2)

2) To survey family physicians in Eastern Ontario (Chapter3) to determine whether:

a) Family physicians do not perceive that a single fraction of radiotherapy is an effective palliative intervention for painful metastatic bone disease.

b) Family physicians are not aware of the Rapid Palliative Radiotherapy Program

c) Family physicians lack knowledge of the indications for palliative radiotherapy.

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Table 1.1: Indication for Referral and Type of Referring Physician to the Rapid Palliative Radiotherapy Program among 148 Referred Cases from November 1999 to December 2001

Indication for referral.	**Patients. No. (%)**
Painful metastatic bone disease.	120 (81)
*Other cancer related symptoms.	28 (19)
Total	148 (100)
Type of referring doctor.	
21 Oncologists	88 (59)
†5 PC physicians	41 (28)
17 family physicians	19 (13)
Total	148 (100)

* Includes: hemorrhage, dyspnea from obstructed bronchus, cerebral metastases
†PC = Palliative care physicians: 5 physicians who spend 100% of their practice involved in palliative care

Chapter 2: Systematic review.

Title: The Relative Effectiveness of a Single High Dose Fraction of Radiotherapy versus Multiple Low Dose Fractions of Radiotherapy for the Palliation of Painful Bone Metastases.

Structured abstract

***Background*:** Metastatic bone disease is a frequent complication of cancer and the commonest cause of cancer pain syndromes. Local external beam radiotherapy is considered to be an effective palliative treatment for painful metastatic bone disease. There is controversy regarding the optimum dose-fractionation schedule, due in part to a lack of consensus on how to measure the effectiveness of palliative radiotherapy.

***Primary Objective*:** To determine the relative effectiveness of high dose single fraction radiotherapy compared to low dose multiple fraction radiotherapy treatment schedules in the palliation of painful metastatic bone disease.

***Data sources*:** A search was carried out using electronic databases: Medline, CINAHL, Cancerlit, the Cochrane Library's Controlled clinical trial registry, and a hand search of selected journals and conference proceedings from January 1982 to April 2003.

***Selection criteria*:** Randomized clinical trials were sought comparing high dose single fraction and low dose multiple fraction schedules of local field external beam radiotherapy for the palliation of painful bone metastases.

***Data Collection and analysis*:** Two independent reviewers extracted data from selected studies. Studies were quality scored according to the Oxford scale, and allocation concealment was assessed. The possibility of publication bias was explored. The relative analgesic effectiveness of radiotherapy regimens was assessed with respect to changes in

pain intensity defined as 'Complete' or 'Partial' pain relief, and frequency of repeat radiation.

Main results: Eight studies involving 3,260 patients were included in the review. Complete pain relief was achieved in 34% of patients, with partial pain relief achieved in 62% of patients. A single fraction of radiotherapy was of comparable effectiveness to the multiple fraction schedules in achieving 'Complete' (Odds Ratio 1.13, 95% CI=0.96 to 1.34) and 'Partial' pain relief (Odds Ratio 1.15, 95% CI= 0.99 to 1.33). Patients receiving a single fraction of radiotherapy were three times more likely than those receiving multiple fractions to receive repeat radiation (Odds Ratio 3.4, 95% CI= 2.66 to 4.35).

***Conclusion*:** A single fraction of high dose radiotherapy is of comparable effectiveness to low dose multiple fraction radiotherapy schedules for the treatment of painful bone metastases. This conclusion must be tempered by recognition of the inadequate and inconsistent assessment of pain, quality of life, performance status and toxicity associated with radiotherapy across the reviewed trials. Issues regarding the speed of onset and duration of pain relief and of how to optimize patient, tumor, and site selection for the various treatment schedules have yet to be resolved. Further trials are necessary, using outcome measures that are sensitive to, and specific for, a palliative patient population and to the palliative intent of radiotherapy.

Background

Metastatic bone disease is a frequent complication of cancer. Depending upon the site of the primary lesion and the method of detection used, metastatic bone disease may be diagnosed in 23% to 84% of oncology patients(1-3). Breast, prostate, lung, thyroid, renal and multiple myeloma are the primary cancer sites that most frequently cause metastatic bone disease. Approximately 65% of patients with metastatic bone disease will develop bone pain, making it the most common cause of cancer pain (4). Bone pain syndromes are challenging to treat as they may contain features of neuropathic and/or somatic pain and are often worsened by movement with a resulting deleterious impact on a patient's mobility and quality of life (5;7).

Potential mechanisms causing bone pain include structural damage, periosteal irritation, nerve compression, muscle spasm, and the secretion of chemical mediators such as prostaglandins and cytokines, which activate both osteoclasts and nociceptors(6;7). Radiotherapy is considered to be an effective treatment for painful metastatic bone disease, although different primary tumors are not equally radiosensitive. (3;5). Non-randomized prospective studies have suggested that metastases from non-small cell lung cancer and adenocarcinoma of the kidney respond poorly regardless of the dose fractionation radiotherapy schedule used (8).

The exact mechanism by which radiotherapy alleviates metastatic bone pain is incompletely understood. The initial rapid onset of pain relief that occurs within days of receiving radiotherapy is associated with a decrease in chemical pain mediators secreted by osteclasts and tumor cells, while actual tumor shrinkage may contribute to the delayed prolonged analgesic effect of radiotherapy(4;6;9;10).

In a review of palliative radiotherapy trials, 'complete' pain relief was reported to occur in 21% to 80% of patients, with 25% to 85% achieving a 'partial' or significant reduction in pain scores (11). This wide disparity in the reported effectiveness of radiotherapy reflects the clinical heterogeneity across trials and a lack of consensus regarding the definition of the outcome of 'pain relief' and of the measurement of the effectiveness of palliative radiotherapy (12;13).

The assessment of the effectiveness of a palliative analgesic intervention such as palliative radiotherapy requires a multidimensional approach, as pain is a personal subjective sensation, the appreciation of which represents a complex multidimensional human experience with functional, emotional, social and spiritual components (14). In addition, patients with incurable disease have outcome expectations and concerns that differ from patients undergoing potentially curative therapy (15). Quality of life and improvement of mobility may be the primary goals where extension of life cannot be obtained (12). When we assess the effectiveness of palliative radiotherapy, the success of treatment in relieving pain and improving mobility should be assessed as well as the impact of the treatment on a patient's personal psycho-social characteristics (5;16).

Traditional palliative radiotherapy treatment regimens consisted of five to 10 fractions of three to five Grey (Gy) for a total radiation dose of 20 to 30 Gy (11). More recently there has been a growing body of evidence suggesting that a single fraction of a higher dose (8Gy) of radiotherapy is of comparable effectiveness to the traditional radiotherapy treatment schedules in treating painful bone metastases (17).

Two previous systematic reviews that attempted to compare a single fraction radiotherapy schedule with the traditional multiple fraction radiotherapy schedules, were

unable to calculate pooled odds ratios due to significant heterogeneity among the trials(11;18). Since then, three large, well designed trials comparing a high dose single fraction of radiotherapy versus a low dose multiple fraction radiotherapy schedule, involving 2,330 patients, have been completed (2 published, 1 awaiting publication), and provide additional evidence sufficient to reconsider attempting a meta-analysis (19-21).

The debate over the optimum dose-fractionation schedule of radiotherapy for the palliation of painful metastatic bone disease was highlighted in surveys of the practice patterns of radiation oncologists in the USA, Canada, Western Europe, Australia and New Zealand (22-25).Overall 11% to 42% of radiation oncologists preferred to use a single high dose fraction over multiple low dose fractions of radiotherapy for the palliation of painful metastatic bone disease. It was reported that whether a physician uses a single high dose or a multiple low dose fraction radiotherapy schedule may depend on factors other than the relative effectiveness of each treatment, such as the location where a physician trained, sources of remuneration, and local institution policy (24).

Objective: To determine whether a single high dose (8Gy or 10Gy) fraction of radiotherapy was of comparable effectiveness to multiple low dose (3Gy or 4Gy) fraction regimens of radiotherapy in treating painful metastatic bone disease, in terms of pain relief (partial or complete) achieved and frequency of repeat radiation to the same area.

Methods

Study selection.

This review included only randomized controlled trials, published or unpublished, that compared a single fraction of a higher dose of radiotherapy with multiple low dose fraction treatment schedules of local field external beam radiotherapy as treatment for painful metastatic bone disease. Single fraction radiotherapy treatment arms using a radiation dose of either 8 or 10 Gy were included, as previous studies have shown these doses to be of comparable effectiveness(26;27). The low dose multiple fraction radiotherapy treatment arms consisted of five to 10 fractions of three to five Gy, with a total radiation dose of 20Gy to 30Gy per treatment schedule. Patients treated with hemi-body radiation and radio-isotopes were not considered, as these treatment modalities are not indicated for treating isolated bone metastases.

Participants were patients of either gender, 18 years or older who had localized painful metastatic bone disease arising from any solid tumor. Patients with hematological malignancies other than multiple myeloma were excluded as hematological malignancies do not generally present with discrete bony lesions.

This review was restricted to studies reporting pain relief as the primary outcome. Pain was measured by the patients and recorded by researchers at the regularly scheduled follow-up clinical appointments using a variety of categorical assessment tools including visual analogue scales, numerical rating scales, and verbal rating scales. The duration of patient follow-up in the studies varied from three months to two years. The time of determining treatment outcome for the review was defined as the time that the maximal improvement was recorded for each particular study. All of the studies in this review

assessed only pain intensity. No other information on pain characteristics was provided, in particular, none of the reviewed studies distinguished between the different types of pain syndromes involved, such as incident, neuropathic, somatic, visceral, acute or chronic pain. In this review pain outcomes were defined as follows:(1) *Complete pain relief* i.e. pain score of zero recorded at *any time* during the follow-up period, and (2) *Partial pain relief* defined as an improvement of at least one categorical level on the pain scale used recorded at *any time* during the follow up period. Repeat radiation was defined as the patient receiving additional radiotherapy to the same site for recurring pain after completion of the initial radiotherapy treatment schedule. Secondary outcome measures assessed were duration of pain relief, duration and frequency of clinical follow-up after treatment, quality of life, patient's record of analgesic use, functional status of the patient and treatment toxicity.

Search strategy

The following electronic databases were searched: (a) Medline (1982 to April 2003); (b) Cancerlit (1982 to April 2003); (c) CINAHL (1982 to April 2003); (d) Cochrane Library Controlled Trials Register (Cochrane library 1st Quarter 2003).

The search terms 'radiotherapy' 'metastatic bone disease' and 'pain relief' were combined using the Boolean operator 'AND'. The search strategy combined MeSH terms and a free text search (**Appendix 2.A**). No language restrictions were applied. Reports in the form of abstracts and studies presented at major meetings were included as well as full journal publications. Unpublished data was sought from two authors and received from one. In addition the following journals were hand searched: (a) Journal of Pain and Symptom Management (1990-2003); (b) Pain (1990-2003); (c) International Journal of

Radiation Oncology, Biology and Physics (1992-2003); (d) Radiotherapy Oncology (1992-2003); (e) Cancer (1990-2003); (f) Clinical Oncology (1996-2003); (g) Seminars in Oncology (1993-2003).

Methodological Quality Assessment

Two reviewers [E Fitzgibbon, J Meng] independently assessed the quality of the randomized controlled trials using a modified Oxford scale (28). The Oxford scale consists of a score of 0 to 5, derived from the presence of appropriate randomization (2 points), blinding (2 points) and accounting for drop-outs and withdrawals (1 point). For this review the original scale was modified into a scale from 0 to 3 by removing the blinding criteria, as blinding is not possible in radiotherapy. Adequacy of allocation concealment was assessed for each study using the method outlined by Schulz et al (29) **(Appendix 2.B)**.

Data Extraction

References identified by the search were imported into Reference Manager (Version 9.5). The titles and abstracts of each article were reviewed. The full text of an article was obtained if it fulfilled the inclusion criteria. Each of the retrieved articles were reviewed independently by the two reviewers and assessed for inclusion in the review. Differences between reviewers were resolved by consensus; no formal rating of inter-rater agreement was calculated. A data collection form was designed for this review **(Appendix 2.C)**. It included data extraction on patient characteristics, interventions, pain relief, and other relevant outcomes. Data were independently extracted from each study that met the inclusion criteria and cross–checked by the two reviewers.

Data analysis

All comparisons were performed between treatment and control groups, thus preserving randomization. The meta-analysis was conducted following an Intention to Treat principle, whereby all of the patients initially randomized in the trials were included in the final analysis. The pain relief outcome was quantified as the difference between the percentages of treatment arms achieving (1) 'Complete' pain relief or (2) 'Partial' pain relief. Pooled Odds ratios were calculated to compare the relative effectiveness of the treatment arms. Frequency of repeat radiation was defined as the difference between the percentages of treatment arms receiving repeat radiation to the same site after completion of the assigned treatment.

Heterogeneity between studies was assessed using sub-group analyses performed on the primary pain outcome. Tests of homogeneity were performed with the Chi-square statistics for between study variations (30). The more conservative random effects meta-analyses model was used in preference to a fixed effects model in order to encompass residual variation between studies into the confidence intervals for a pooled effect (31).

The following comparisons were carried out in the meta-analysis. The relative effectiveness of a single fraction of radiotherapy was compared to the multiple fraction schedule with respect to (1) Complete pain relief and (2) Partial pain relief, using pooled Odds ratios. The frequency of repeat radiation was compared in both treatment arms.

The following secondary outcomes were assessed by a qualitative rather than a quantitative analysis: pain measurement scales used, distribution of primary tumor, loss to follow up and duration of survival, patient record of analgesic usage, quality of life, functional status and treatment toxicity.

Sensitivity analyses were carried out to check the robustness of the pooled estimates. First, the meta-analysis was repeated using both random and fixed effects models. Second, the Intention to Treat analysis was compared to an analysis including only patients who both satisfied the entry criteria and who adhered to the protocol. Third, the pooled odds-ratio was recalculated after removing the most outlying trial (i.e. the trial using 10Gy as the single fraction arm).

Publication bias arises from the fact that statistically significant results are more likely to get published than non-significant results (32). Funnel plots and the Rosenthal 'file drawer' calculation were the two methods used to detect publication bias (33;34). Funnel plots are scatter plots of the treatment effects estimated from individual studies (Horizontal axis) against a measure of the study sizes (Vertical axis). These plots illustrate the relationship between the precision in the estimation of the underlying treatment effect and the sample size of the component studies. In the absence of bias, the plot should resemble a symmetrical inverted funnel. The Rosenthal 'file drawer' calculation is based on an estimation of the number of unpublished studies with a negative result that would be required to cancel the overall treatment effect. This is based on combining the normal *z*-scores corresponding to the p-values for each included study.

Results

We identified 149 potentially relevant studies, 110 (74%) of these studies were identified by the electronic search and 39 (26%) by the hand search, suggesting that the electronic search was adequate (**Figure 2.1**). Of these studies, 18 were randomized controlled trials. Ten trials were excluded for the following reasons: one trial was written in Japanese and no translation was available (40): five trials compared only multiple dose

fractionation schedules (35-37;39;41): three trials compared only single fraction treatments with varying doses of radiation (26;38;42): one trial compared four different single fraction regimens with three different multiple dose-fractionation schedules (27).

The eight trials included in the review involved 3,260 patients **(Table 2.1).** Seven trials were published in English and one in German(19-21;43-47;). One trial had been published as an abstract and the authors sent us the unpublished manuscript (20). The single fraction arm consisted of 8Gy in seven trials and of 10Gy in one trial. The low dose multiple fraction schedules varied from a total radiotherapy dose of 20Gy in four fractions to 30Gy in 10 fractions.

Qualitative Analysis

Patient demographic characteristics including age, gender and primary tumor sites were comparable among trials for the two treatment arms (**Table 2.2**). Breast, lung and prostate tumors made up the majority of primary cancer sites in all of the trials. The frequency of follow-up, duration of survival, and number of patients lost to follow-up were incompletely recorded in all trials (**Appendix 2.D**). Proportion of patients lost to follow-up was comparable among trials ranging from 6% to 26% at one month to 70% to 82% at 12 months. The median duration of survival across trials was six months.

The use and nature of concomitant therapies were not consistently recorded in the included trials. None of the trials reported on co-morbidities. Although analgesic usage was assessed in all trials, no comparison was possible due to incomplete recording and the use of diverse non-validated scales (**Appendix 2.E**). Quality of life was assessed in only three of the trials, and each of these used a different assessment tool (21;44;46). While four of the trials reported some measure of function, none of the studies assessed

level of function concurrently with pain relief (21;43;44;46). Nausea was the only symptom of radiotherapy toxicity assessed for all trials, but the results were incompletely reported.

The primary outcome of pain relief was measured using simple one-dimensional pain intensity scales (**Table 2.3**). Seven of the trials used four to six-point categorical verbal numerical rating scales. One trial used a more complex 11 point categorical numerical rating scale (21). No information concerning type of pain mechanisms, pain interference with function or treatment site-specific pain measurement was provided in any of the studies.

1. Pain Relief

Six of the 8 trials, involving 2,833 patients, reported data on the outcome 'Complete' pain relief (**Table 2.4**). Complete pain relief was achieved in 498 of 1,416 (35%) patients who received a single fraction and 459 of 1,417 (32%) patients who received the multiple fractions of radiotherapy. Chi square statistic for heterogeneity across trials was χ^2= 4.55 df= 5 p= 0.47. The Pooled Odds ratio was 1.13 (95% CI = 0.96 to 1.34) indicating the comparable effectiveness of both treatment schedules in inducing complete pain relief.

Eight studies involving 3,260 patients, reported data on partial pain relief. Partial pain relief was achieved in 1,045 of 1,632 (64%) patients who received a single fraction and 991 of 1,628 (61%) patients who received the multiple fractions of radiotherapy (**Table 2.5**). Chi square statistic for heterogeneity across trials was χ^2= 3.99 df=7 p=0.78. The Pooled Odds ratio was 1.15 (95% CI = 0.99 to 1.33).

2. Frequency of Repeat Radiation

Data for assessing the frequency of repeat radiation was available from five studies involving 2,494 patients, of these 279 of 1,248 (22%) patients who received a single fraction and 97 of 1,246 (8%) patients who received multiple fractions of radiotherapy received repeat radiotherapy (**Table 2.6**). Chi-square statistic for heterogeneity across trials was χ^2= 6.49 df= 4 p= 0.17. Pooled odds ratio for repeat radiation to the same area at a later date was 3.23 (95% CI=2.23 to 4.70). Patients who received a single fraction of radiotherapy were three times more likely to receive further radiotherapy to the same site at a later date than patients who received the multiple fraction schedules of radiotherapy. The time to re-treatment was not recorded in most of the trials; however Steenland et al reported an average time to repeat radiation of 14 weeks post-treatment for patients in the single fraction treatment arms and 23 weeks post-treatment for the multiple does-fractionation radiotherapy treatment arms (21).

A Funnel plot of individual treatment effect sizes against study size did not reveal evidence of publication bias **(Figure 2.2).** Publication bias was also considered to be unlikely using the Rosenthal file drawer calculation, as 140 studies with negative results would need to be found to cast doubt on the results of this meta-analysis. Rosenthal has suggested that publication bias is unlikely if this number is greater than a minimum 'tolerance level' defined by the expression [5k+10] (where k =number of included studies) (33). The Rosenthal 'tolerance level' for this review was 50 studies.

Discussion

This systematic review supports the hypothesis of the comparable effectiveness of a single high dose (8Gy or 10Gy) of radiotherapy to multiple low dose fractions of external beam radiotherapy in treating painful bone metastases. However, there are a number of issues that require discussion. Synthesizing the results of a group of trials requires that we first assess the variability or heterogeneity among trails, both qualitatively and quantitatively. Two previous attempts at a meta-analysis on this topic did not proceed due to excessive clinical heterogeneity among the selected studies (5;11). To counter this, a number of strategies were used in this review to reduce potential bias from excess variability among the selected trials:

(1) The inclusion of three recent, large trials (involving 2,330 patients), of reasonable quality, consistent methodology and achieving similar effects. The addition of this data was sufficient that although there was still some clinical variability among the trials, it was reasonable to proceed to test for quantitative heterogeneity among trials. For each of the primary outcomes: complete pain relief, partial pain relief and frequency of re-irradiation, the Chi-square tests for heterogeneity were not significant that is, $p>0.05$. This suggests that for these three outcomes the results were consistent with a common effect size and permitted us to calculate a weighted overall effect for each outcome.

(2) The meta-analyses were conducted following an 'Intention to Treat' principle, as incomplete follow-up data was a problem for most of the trials reviewed. An Intention to treat analysis has been defined as one which "includes all randomized patients in the groups to which they were randomly assigned, regardless of their compliance with the entry criteria, regardless of the treatment they actually received, and regardless of

subsequent withdrawal from treatment or deviation from the trial protocol"(American Statistical Association) (48). In a meta-analysis involving large numbers of patients, following an intention to treat principle is considered to be conservative and helps to reduce bias arising from different patterns of loss to follow-up in the alternative treatment arms. However, Lewis and Machin have suggested that using an Intention to Treat analysis may increase the chance of erroneously concluding that no difference exists between the treatment arms (49). These authors suggest that the analysis could be repeated following a 'per-protocol' principle i.e. include in the analysis only those patients initially randomized, who subsequently adhered to the trial protocol. If these two analyses reach the same conclusion, then the strength of the conclusion is increased. For this systematic review, repeat meta-analyses following a per-protocol principle did not change the conclusions of the meta-analyses.

(3) Finally, a random effects model was applied to all meta-analyses, to incorporate residual variability between studies into a pooled effect. Similar results and conclusions were achieved by repeating the meta-analyses using a fixed effects model.

Quality scoring of the included trials in this review was of little value, as due to the nature of radiotherapy trials, blinding was not possible. Thus the maximum possible quality score was reduced from five to three. This resulted in all of the included trials having quality scores of two or three and limited the value of the scores to differentiate the trials according to quality.

No evidence of publication bias was detected in this review. One limitation of the Rosenthal calculation is that combining z scores does not directly account for the sample

sizes of the studies. However, using the funnel plot as well reduces the potential for missing significant publication bias.

Patients who received a single fraction of radiotherapy were three times more likely to receive further radiation to the same site at a later date than patients who had received the multiple fraction regimens. A longer duration of effect associated with multiple fractions is a potential explanation for this, but other factors should be considered. An alternative explanation suggested, is that due to the lower risk of cumulative toxicity, physicians may have a greater readiness to prescribe repeat radiotherapy after a single fraction of radiotherapy than after the multiple fraction regimens (19). Steenland et al also noted that physicians tended to repeat radiotherapy in patients who had received a single fraction of radiotherapy at a lower pain–score and at an earlier time, than if the patient had initially received a multiple fraction radiotherapy regimen (21). Pain relief from a first course of radiotherapy, regardless of the number of fractions used, is the major factor predicting success with subsequent courses (50;51).

The results of this review must be considered in the light of the limitations of the original trials. There was little consensus among trials regarding the time of maximal outcome assessment. No trial reported on an outcome of 'no pain relief', presupposing that radiotherapy would be effective to some degree in all patients. Inadequate reporting, loss to follow up and censuring of outcome data were prevalent among the trials. This lack of uniform methodology, and the one-dimensional assessment of the primary outcome of pain relief among the included trials imposes constraints on the extent and value of the review conclusions(11;12). All of the included trials assessed pain only in terms of pain severity. Whether palliative radiotherapy was more effective in treating

somatic or neuropathic pain could not be assessed due to the pain assessment tools used. Patients with metastatic bone disease may have more than one site of metastatic bone disease. Local external beam palliative radiotherapy can effectively relieve pain only at the actual treatment site. Thus pain controlled at one site may give place to pain at another site that would be counted as a treatment failure unless a site-specific pain assessment tool was used. In addition, none of the trials reported on changes in pain intensity over time and functional status was assessed in only four of the eight included trials.

Two recent surveys of patients' expectations of palliative radiotherapy found that chronic pain, quality of life, and level of function were the outcomes most valued by patients (12;52). Furthermore, Hearn and Higginson have suggested that palliative intervention outcomes should "reflect the specific goals of palliative care, such as improving the quality of life before death, controlling symptoms, and supporting the family" (16). Clearly the studies included in this meta-analysis did not adequately assess the full spectrum of relevant outcomes needed to determine the effectiveness of a palliative intervention. Recently, some progress towards improving outcome definition has been made with the development of an international consensus on palliative radiotherapy endpoints to better assess the effect of palliative radiotherapy for painful bone metastases. Treatment endpoints proposed include assessment of: site specific features, pain characteristics, analgesic usage, health related quality of life, and interference on the patients' level of function due to pain (13).

It is important when conducting research on a palliative intervention to acknowledge the frailty of the study population (53). Patients with painful metastatic

bone disease have a mean life expectancy of six months, are often frail and understandably have a limited tolerance for participating in clinical trials that entail frequent follow-up contacts. As a result of this, up to 40% of patients in palliative treatment trials may be lost to follow-up after three months (53). In our review loss of patients to follow-up among the trials included varied from 14% to 38% at three months after finishing their assigned treatment. This significant loss to follow-up and censoring of data represent major challenges to conducting research on palliative patients.

In summary local external beam radiotherapy delivered either by a single high dose fraction or multiple low dose fractions of radiotherapy is an effective palliative analgesic treatment for painful bone metastases. Single fraction radiotherapy regimens have practical advantages that include brevity, reduced costs and less stress for the patient. If initially effective, the single fraction can be repeated at a later date, with little risk of cumulative toxicity. Multiple dose fractionation radiotherapy schedules may confer a longer duration of pain relief, which may be important for a patient with a longer prognosis i.e. greater than six months.

At present there is a need for treatment guidelines to be developed that take into account the individual patient's expected life span, extent of metastatic bone disease, co-morbidities, medications, age, and personal preference, in order to determine the most appropriate palliative radiotherapy treatment regimen for that individual. Future trials on the effectiveness of palliative radiotherapy using patient centered outcome measures could help to better define these treatment guidelines.

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Table2.1. Characteristics of The Eight Randomized Controlled Trials Reviewed

Study	Participants	Interventions	Outcomes	Notes	Allocation concealment
BPTWP[40]	(N= 761) SF* = 383 MF† = 378	SF = 8Gy MF = 4Gy x 5 *OR* 3Gy x 10	SP‡ - 274/383 SC§ - 199/383 MP ∫ - 257/378 MC¶ - 192/378	4 protocol violations SF = 2 MF= 2	A (adequate)
Kirkbride[15]	(N=398) SF = 200 MF = 198	SF = 8Gy MF = 4Gy x 5	SP - 114/200 MP - 119/198	15 protocol violations SF = 4 MF= 11	B (unclear)
Cole[41]	(N= 29) SF = 16 MF = 13	SF = 8Gy MF = 4Gy x 6	SP - 14/16 MP - 11/13	No protocol violations	B (unclear)
Gaze[42]	(N= 280) SF = 141 MF = 139	SF = 10Gy MF = 4.5Gy x 5	SP - 108/141 SC - 50/141 MP - 99/139 MC - 47/139	15 protocol violations SF = 7 MF= 8	B (unclear)
Koswig[43]	(N= 107) SF = 52 MF = 55	SF = 8Gy MF = 3Gy x 10	SP - 41/52 SC - 16/52 MP - 45/55 MC - 18/55	No protocol violations	D (deficient)
Nilesen[44]	(N= 241) SF = 122 MF = 119	SF = 8Gy MF = 5Gy x 4	SP - 52/122 SC - 12/122 MP - 56/119 MC - 17/119	3 protocol violations SF = 2 MF = 1	A (adequate)
Price[45]	(N= 288) SF = 140 MF = 144	SF = 8Gy MF = 3Gy x10	SP - 48/140 SC - 22/140 MP- 44/148 MC-12/148	25 protocol violations SF = 11 MF = 14	A (adequate)
Steenland[14]	(N= 1171) SF = 585 MF = 586	SF = 8Gy MF = 4Gy x 6	SP -392/585 SC -175/585 MP -361/586 MC -199/586	14 protocol violations SF = 6 MF = 8	B (unclear)

*SF = single fraction arm of RCT. † MF = Multiple dose-fraction arm of RCT
‡SP = single fraction partial pain relief. §SC = Single fraction complete pain relief.
∫MP = multiple fraction partial pain relief. ¶ MC = multiple fractions complete pain relief

Table2.2. Distribution of Primary Tumor Sites Among the Eight Trials Included in the Review.

Study	Breast		Lung		Prostate		Other sites†	
	Single Fraction % *	Multiple Fractions %	Single Fraction %	Multiple Fractions %	Single Fraction %	Multiple Fractions %	Single Fraction %	Multiple Fractions %
Price[45] (n=288)	36	38	21	19	7	9	36	34
Cole[41] (n=29)	55	38	19	23	13	15	13	24
Gaze[42] (n=280)	45	43	19	22	18	14	18	21
Nielsen[44] (n=241)	35	44	38	29	13	13	14	14
BPTWP[40] (n=761)	36	36	33	36	13	10	18	18
Steenland[14] (n=1171)	38	40	24	22	25	25	13	13
Koswig[43] (n=107)	60	56	22	26	13	8	5	10
Kirkbride[15] (n=398)	41	38	27	25	18	28	14	9

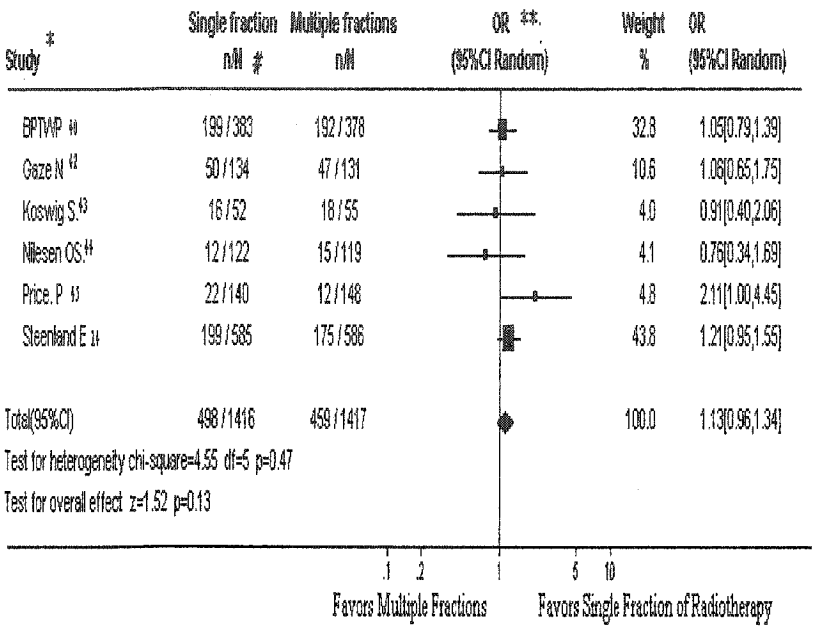
* Refers to proportion of patients randomized to each study arm.
† Other tumor sites includes: Multiple Myeloma, Renal, Colon, and Thyroid.

Table2.3. Pain Assessment in the Eight Randomized Controlled Trials Reviewed.

Study	Pain Scale	Frequency*	Follow -up	Response Definition
BPTWP[40]	4 point VRS†	2/52, 1/12, 2/12 3/12, 4/12, 5/12, 6/12,8/12, 10/12, 1year	1 year	Improve by one category
Cole[41]	5 point VRS & 10cm VAS‡	Daily x 4/52 then monthly x6/12	6 months	Improve x 1 category
Gaze[42]	5 point VRS	1/52, 3-4/52, q 2/12 x 2 years	2 years	Improve x 1 category
Koswig[43]	4 point VRS	N/A	6 months	Improve x 1 category
Nielsen[44]	5 point VRS & 10cm VAS	4/52, 8/52, 12/52, 12/52, 20/52	5 months	Improve x 1category or 50% on VAS
Price[45]	4 point VRS	Daily x 4 weeks then weekly x 3months	3 months	Improve x 1 category
Steenland[14]	11 point NRS§	Weekly x 3/12 then monthly x 2 years	2 years.	Improve x 2 points.
Kirkbride[15]	Modified McGill-Melzack -6 point NRS.	2/52, 4/52 3/12	3 months	Pain score of zero with no change in analgesic use. Or any reduction in pain score

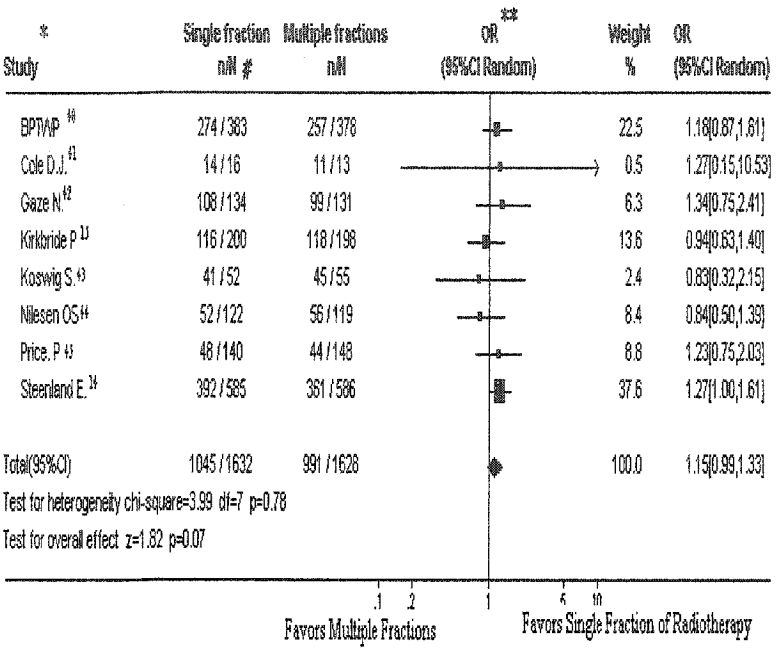
* Frequency of reporting pain assessment
†VRS= categorical Verbal Rating Scale.
‡VAS= Visual Analogue Scale.
§ NRS=categorical Numerical Rating Scale

Table 2.4: Results of the Meta-analysis of Six Trials Comparing a Single Fraction of Radiotherapy versus Multiple Dose-Fractionation Radiotherapy That Measured Complete Pain Relief As The Outcome



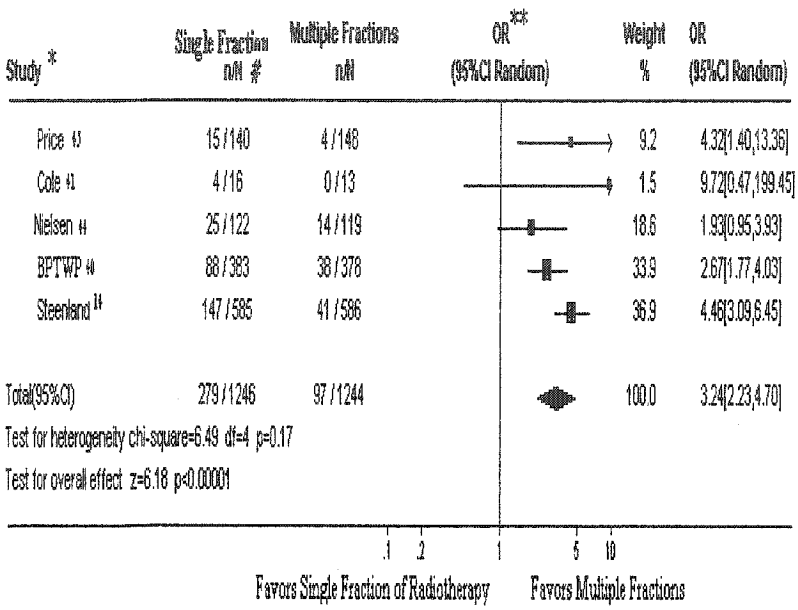
* Study = 6 Randomized Controlled Trials included in the review for the outcome ' Complete Pain Relief'
# n/N = is the number of patients achieving the outcome (n) out of the total trial population (N)
** OR = Odds ratio

Table2. 5: Results of the Meta-analysis of Eight Trials Comparing A Single Fraction of Radiotherapy versus Multiple Dose-Fractionation Radiotherapy That Measured Partial Pain Relief as the Outcome.



* Study = 8 Randomized Controlled Trials included in the review for the outcome 'Partial Pain Relief'
# n/N = is the number of patients achieving the outcome (n) out of the total trial population (N).
** OR = Odds ratio

Table 2.6: Results of a Meta-analysis of Five Trails Comparing a Single Fraction of Radiotherapy versus Multiple Dose-Fractionation Radiotherapy that Measured Frequency of Re-Irradiation as the Outcome.

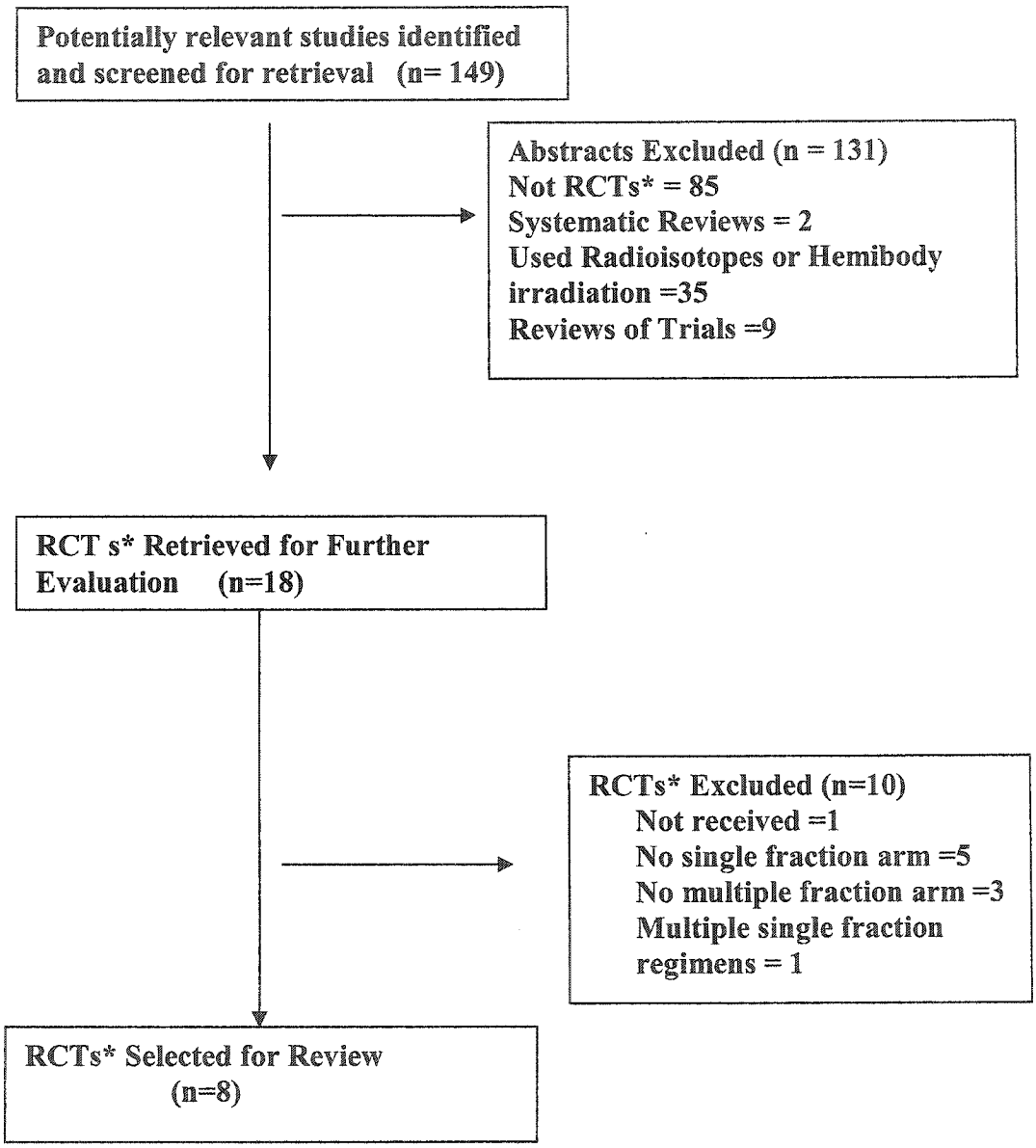


* Study = 5 Randomized Controlled Trials included in the review for the outcome Frequency of Re-Irradiation.

n/N = is the number of patients achieving the outcome (n) out of the total trial population (N)

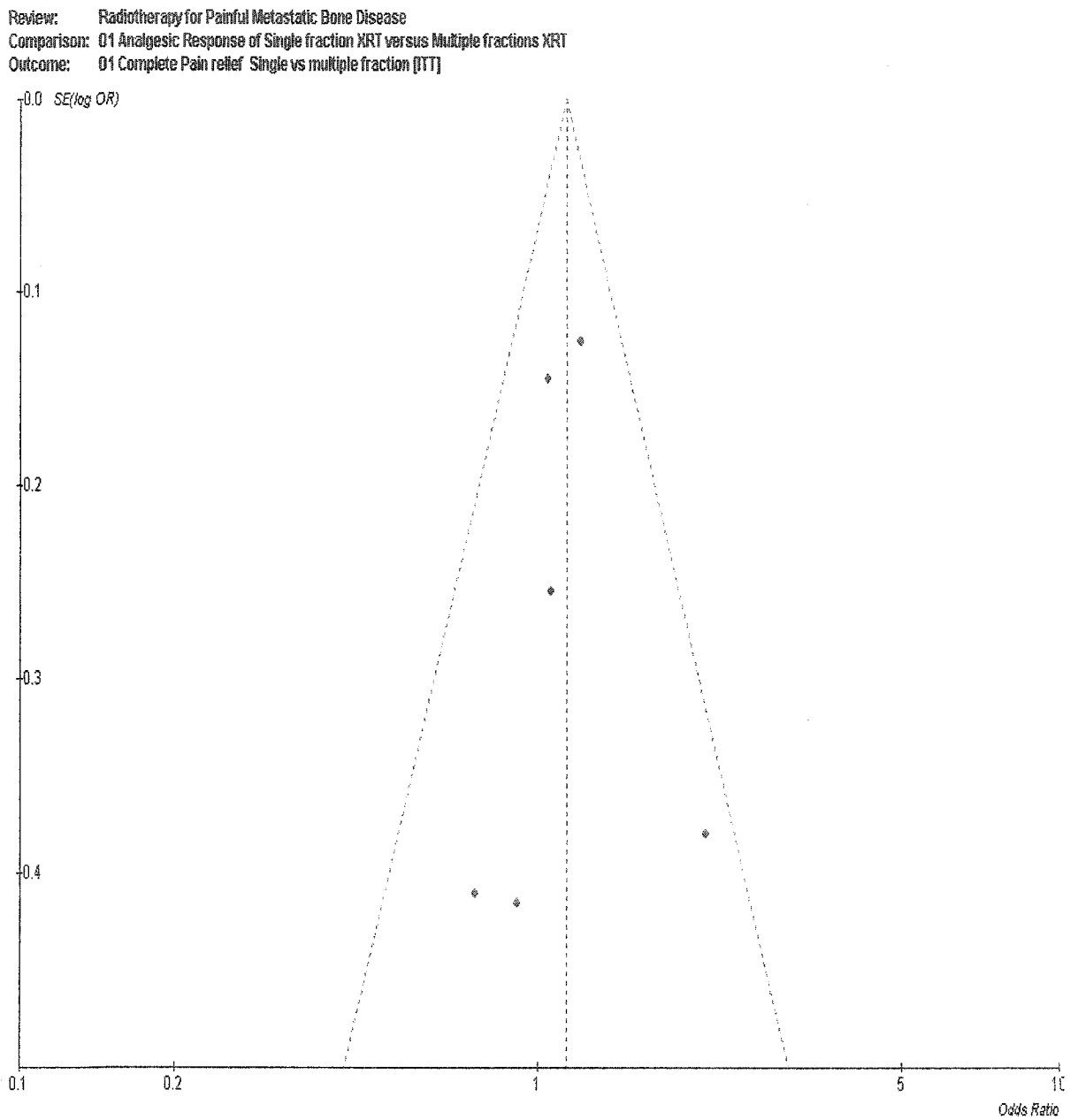
** OR = Odds ratio

Figure2.1. Results of the Search Strategy on Radiotherapy for Painful Bone Metastases



* RCTs = Randomized controlled trials.

Figure2.2. Funnel Plot Assessing for Publication Bias*



* Using the 6 Randomized Controlled Trials included in the review for the outcome 'Complete Pain Relief'

Appendix 2.A. Electronic Search Strategy for Systematic Review

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1 exp "Bone and Bones"/ or bone.mp. (83122)
2 (bone or boney or bony or osseous).mp. (45327)
3 1 or 2 (84143)
4 metastases.mp. (11231)
5 exp Neoplasm Metastasis/ or neoplasm metastasis.mp. (13931)
6 (bone metastases or bone metastasis).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (771)
7 (painful bone metastases or painful bony metastases or painful bone metastasis).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (11)
8 4 or 5 or 6 or 7 (21504)
9 (pain or painful).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (32715)
10 (pain relief or analgesia).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (6359)
11 9 or 10 (35642)
12 (radiotherapy or radiation or irradiation).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (40815)
13 exp RADIOTHERAPY/ (11497)
14 12 or 13 (43075)
15 exp Palliative Care/ or Pain, Intractable/ or exp Bone Neoplasms/ or exp Pain/ or exp Radiotherapy/ (54434)
16 palliative radiotherapy.mp. (49)
17 14 or 15 or 16 (84704)
18 randomized controlled trial.pt. (24278)
19 dt.fs. (164626)
20 tu.fs. (180670)
21 random$.tw. (34462)
22 or/1-4 (93647)
23 3 and 8 and 11 and 14 and 17 and 22 (80)

Appendix 2.B: Methodological Quality of the Eight Trials Reviewed*.

Study	Randomization Max score=2	Double-Blinding Max score=2	Withdrawals + Dropouts Max score=1	Oxford Scale Total Max =3/5	Allocation †Concealment
Price[45]	2	0	1	3	Adequate
Cole[41]	1	0	1	2	Unclear
Gaze[42]	1	0	1	2	Unclear
Nielsen[44]	2	0	1	3	Adequate
BPTWP[40]	2	0	1	3	Adequate
Steenland[14]	1	0	1	2	Unclear
Koswig[43]	1	0	1	2	Unclear
Kirkbride[15]	2	0	1	3	Adequate

* Data from the eight randomized controlled trials included in the review.

† Allocation concealment: determined by reviewing the Methods sections of the studies and determining the method used to implement the random allocation sequence of the trial was 1) Adequate i.e. described an appropriate, reliable method of protecting the assignment sequence before and until assignment of the intervention was completed. 2) Inadequate or 3) Unclear i.e. insufficient detail provided in the text to determine the adequacy of the allocation concealment [29].

Appendix 2.C: Data Extraction Form: Systematic review of Radiotherapy for Painful Bony Metastases

Study ID#

1.Study: Author:..... Year: _____

Source: _____

2.Study design:.....

3.Participants: Number → Single F ☐ / Multiple F ☐ Total N Randomized ☐

Patient Diagnostic demographics.....

4.Outcomes:

A. Pain - Scale used..... Measured By DR / PT Validated Y/N

Definition of Response: ☐

Frequency Of : Measurement ☐ Duration of Follow-up ☐

Response to XRT

Dose of XRT	PR=partial response<=50% CR= pain score=0	Study report	Intention to treat [ITT] (if different)
Single Fraction	PR CR		
Multiple Fractions	PR CR		

Proportion of Study Patients Lost to Follow up

Time	0	1 month	3 months	6 months +
Single Fraction				
Multiple fractions				

Duration of Survival

Time	1month	3months	6months	12 months +
Single Fraction				
Multiple Fractions				

B. Analgesic Use: Recorded Y N

Method: .....

Response .....

Measured by: Doctor .Patient

C. Quality of life: Measured Y N Scale Used_____

Response .....

Measured by: Doctor Patient

D. Functional scale: Y N Scale Used_____ Measured By; Dr Pt

Response.....

E. Toxicity of XRT: Recorded Y N

Describe .....

6. NOTES: .....

7.Oxford Scale score: [ ] 8. Allocation Concealment: [ ]

Appendix 2.D. Percent Loss to Follow-Up and Duration of Survival Among Trial Participants of Seven of the Trials included in the Review*.

Study		1 month %†	3 months %	6months+ %	12 months %
Price[45]	Follow up‡	74	62	n/a	n/a
	Surviving ∫	n/a	70	50	11
Cole[41]	Follow up	94	86	n/a	n/a
	Surviving	n/a	n/a	50	n/a
Gaze[42]	Follow up	82	n/a	50	n/a
	Surviving	n/a	n/a	65	26
Nielsen[44]	Follow up	86	65	56	n/a
	Surviving	n/a	80	60	30
BPTWP[40]	Follow up	89	n/a	52	30
	Surviving	95	78	68	44
Steenland[14]	Follow up	75	n/a	n/a	18
	Surviving	n/a	n/a	50	18
Kirkbride[15]	Follow up	82	70	n/a	n/a
	Surviving	n/a	79	n/a	n/a

*No data available form the eight study i.e. Koswig.

† % = the cumulative percent of the originally randomized study population

‡ Follow-up = proportion of the randomized study population still being followed up

∫Surviving = proportion of the randomized study population still surviving.

Appendix 2.E. Secondary Outcome Measures Used in The Eight Trials Included in the Review.

Study	Analgesic record	Quality of life Instrument	Performance Scale	Toxicity recorded.
BPTWP[40]	4 level categorical scale	Nil	Nil	Limited to Nausea and fatigue
Cole[41]	Only recorded at study entry	Nil	Karnofsky scale	Yes- diary of symptoms
Gaze[42]	5 level categorical scale + Visual analogue scale	Spitzer QOL scale + HAD† anxiety score	ECOG	Limited to nausea and lassitude
Nielsen[44]	MEDD* score Daily diary	Global QOL score	Karnofsky Scale	Limited to nausea and fatigue
Price[45]	4 level categorical scale	Nil	Nil	Limited to nausea
Steenland[14]	WHO analgesic ladder	Rotterdam Symptom check list (RSCL)	Karnofsky Scale	RSCL adapted to measure acute side effects
Koswig[43]	4 level categorical scale	Nil	Nil	Limited to Nausea
Kirkbride[15]	Analgesic score.	Nil	Nil	Limited to nausea

* MEDD: Morphine equivalent daily dose.
†HAD: Hospital anxiety depression scale.

Chapter 3: Survey.

Title: A Survey on the Awareness and Use of the Rapid Palliative Radiotherapy Program by Family Physicians in Eastern Ontario.

Introduction

Metastatic bone disease is a frequent cause of pain and is a major threat to the quality of life of a patient with cancer (1). Local external beam radiotherapy is considered to be an effective, rapidly acting, palliative intervention for painful bone metastases (2-5). The Ottawa Rapid Palliative Radiotherapy Program was developed in 1999, to provide family physicians prompt access to palliative radiotherapy for patients with advanced symptomatic cancer. In 2002, an audit of the program revealed that family physicians were infrequently using the program.

Literature Review

Metastatic Bone Disease

The Ottawa Regional Cancer Center provides primary oncology, screening, consultation, and treatment services to patients in Eastern Ontario. For the year 2001/2002 medical staff at the cancer center treated 18,625 cases, with 3,045 cases receiving radiotherapy (6). During the same year 2,100 patients died from cancer related causes.

Sixty to 80% of patients with advanced cancer will develop bone metastases, with breast, prostate, lung, kidney, and thyroid cancers the most likely primary cancer sites to spread to bone (2;3;7). An estimated 65% of patients with metastatic bone disease will develop bone pain making this the commonest cause of cancer pain (2-5;7;8). Bone pain may be complex and challenging to treat effectively, particularly as it is often linked with significant incident or movement related pain (7). In addition to bone pain metastatic

bone disease may also be associated with hypercalcemia, pathological fractures, spinal and or nerve root compression, and bone marrow infiltration (7;9). Consequently the development of metastatic bone disease may have a profoundly negative impact on a patient's level of function and limit both the quantity and quality of their remaining life (10).

Radiotherapy for Painful Metastatic Bone Disease

Painful metastatic bone disease is the primary indication for more than 50% of radiotherapy courses that are administered with a non-curative (i.e. palliative) intent (1;10). A review of palliative radiotherapy trials by Ratanatharathorn et al, reported that 'complete' and 'partial' pain relief was obtained in 21% to 80%, and 25% to 87% of patients with painful bone metastases respectively, irrespective of the radiation fractionation schedule used (11). 'Complete' pain relief was broadly defined as a pain score of zero, with or without a reduction in analgesic usage. 'Partial' pain relief was defined as an improvement from the baseline pre-treatment pain score by two or more levels on whatever categorical pain scale the authors used. This wide disparity in reported pain relief is likely due to heterogeneity among trials with respect to the pain measurement scales used, the fractionation schedules used, the site and extent of bone metastases, the site of the primary cancer, and the diversity in concurrent analgesic and oncological treatments (10;11).Lack of consensus regarding the definition and measurement of pain as an outcome has been identified as a key limiting factor in studies assessing the analgesic effectiveness of radiotherapy for painful bone metastases (12-14).

In an earlier review, McQuay et al reported that one month after the first radiotherapy session, 27% of patients had achieved 'complete' pain relief, and an

additional 29% of patients had achieved 'partial' or at least a 50% reduction in pain scores (15). Overall, radiotherapy produced at least 50% pain relief in an average of 49% of patients (range 28% to 81%), irrespective of the dose-fractionation schedule used. Fifty percent of the patients who achieved 'complete' pain relief took longer than four weeks to achieve it. The median duration of 'complete' pain relief was 12 weeks.

Since the publication of these two reviews, two large prospective randomized trials involving 1,569 patients have been conducted comparing the effectiveness of a single 8Gy (Gy = Grey: unit of radiation) fraction versus 20Gy in a multi-fraction treatment schedule (16;17). The conclusion reached in both trials was that more than 70% of patients achieved some degree of pain relief within three months of receiving radiotherapy, regardless of the treatment schedule used.

Radiotherapy is also considered to be an effective intervention for several other cancer related complications including: controlling tumor related hemorrhage, reducing tumor bulk, malignant spinal cord compression, cerebral metastases and malignant obstruction of the superior vena cava (4).

Rapid Palliative Radiotherapy Program

In 1996, a Canadian symposium on palliative radiotherapy concluded that "a separate palliative radiotherapy clinic, where access is rapid and patients can be assessed, planned, and treated the same day, is an excellent way of handling the special needs of palliative patients" (18). Following this report the first dedicated rapid response radiotherapy program was developed in Toronto, Ontario. The goal was to facilitate access to radiotherapy for cancer patients with an estimated life expectancy of less than six months (19). Subsequent program evaluations have demonstrated a high degree of

support from both patients and referring physicians, enabling expansion of the clinical program from one day per week to five days per week (20-22).

The Ottawa Rapid Palliative Radiotherapy Program (RPRP) was established in 1999 with the goal of providing family physicians who provide primary care for patients with advanced symptomatic cancer, rapid access to a same-day radiation oncology consultation and treatment service. Treatment consists of short courses of a high dose (8Gy) of radiotherapy i.e. one to two fractions, for cancer related symptoms. A chart audit revealed that 148 patients were treated by the RPRP from November 1999 to December 2001. Painful metastatic bone disease was the primary indication for referral in 81% of the 148 patients. Of the 148 patients, 88 patients (59%) were referred by 21 oncologists, 41 patients (28%) by 5 full-time palliative care physicians, and 19 patients (13%) by 17 family physicians. This study explores some of the factors that may explain why family physicians were not using the RPRP more frequently.

The Ottawa Model of Research Use provides a practical conceptual framework to study the complex process by which evidence-based interventions are integrated into clinical practice (23). The Ottawa model involves the systematic assessment, monitoring and evaluation of the state of six key elements prior to, during and following any research transfer effort: (1) the practice environment, (2) potential adopters, (3) the evidence based innovation, (4) strategies for transferring the evidence into practice, (5) the use of the evidence, and (6) health related and other outcomes of the intervention. According to the Ottawa framework, characteristics of family physicians, the practice environment, the Ottawa Regional Cancer Center and the RPRP would be expected to be important factors related to the under use of the radiotherapy program.

Roger's innovation decision process suggests that potential adopters of a clinical innovation go through five stages before adopting it: knowledge (awareness), persuasion (development of positive attitudes towards the innovation), decision, implementation, and confirmation (24). Thus awareness of the RPRP and perceptions on the effectiveness of palliative radiotherapy are expected to strongly influence a family physician's decision to use the RPRP.

Surveying Family Physicians

A survey was developed to gather data on awareness, perceptions of, and use of palliative radiotherapy by family physicians in Eastern Ontario. Surveys are considered to be an effective method of gathering data from large and geographically dispersed individuals (25). An adequate response rate is key to optimize sample size, to reduce bias and to maximize generalizability of the results (25-28). Unfortunately, recent survey response rates among family physicians have been low. An analysis of surveys published in 1991, found an average response rate in physician surveys of 54%, 13% lower than surveys administered to non-physician groups (28). The true situation is probably worse than this, because surveys with low response rates are less likely to be accepted for publication (26;29). Low response rates among family physicians have been linked to factors such as lack of time and lack of perceived relevance of the survey (30-32).

Field et al conducted a systematic review on the impact of Dillman's "Total Design Approach" to increase response rates among physicians (32). Although they confirmed the effectiveness of prepaid financial incentives, special contacts and personalization in enhancing response rates, the optimal type of incentive was not

established. Edwards et al reported that response rates to postal questionnaires were higher when a financial incentive was used (Odds ratio 2.02, 95% CI=1.79 to 2.27) (25). In studies conducted in the United States and United Kingdom, diverse financial incentives resulted in increases in response rates ranging from 9% to 30%, with no clear association identified between the amount of the incentive and the increase in response rate (33-35).

The value of using non-monetary incentives is unclear. In a survey of Canadian family physicians, the offer of entry in a lottery for a weekend for two at a resort resulted in a 6.4% higher response rate (36). The conflicting results from four recent postal surveys of Canadian family physicians on oncology related topics shed little light on the impact of using an incentive (37-40). In a non-randomized survey among 14,628 physicians, MacDonald et al reported a response rate of only 18% despite the offer of an incentive of a $5 donation to the World Health Organization cancer pain relief fund (38). Samant et al did not use an incentive and achieved a response rate of 39% in their survey on the palliative care educational needs of 739 family physicians (39). Gilbert et al found no difference in the response rate of 485 family physicians randomized to receive entry in a draw for a $100 book allowance, the response rate for both groups was 70% (37). Finally, in a recent randomized stratified survey of 300 family physicians, Barnes et al obtained a response rate of 61% without using an incentive (40).

Whether telephone or postal survey is the optimal method of surveying family physicians is still unresolved (32). Telephone surveys allow for open-ended questions and usually result in fewer missing data with a higher response rate (26). However telephone surveys are more expensive to conduct, and may be prone to a 'social desirability bias', where respondents may unknowingly seek to please the interviewer by giving more

socially valued answers (26;41;42). Additional research is needed to determine how effective incentives are and whether postal or telephone surveys should be preferred for physician populations.

Objectives

The primary objective of this study was to survey family physicians of Eastern Ontario in order to identify factors associated with their awareness of the RPRP and their willingness to use palliative radiotherapy. A secondary objective was to determine whether the method of survey solicitation (phone versus mail) and the offer of a non-monetary incentive ($10 phone card) had an effect on the response rate.

Methods

Survey design and sampling frame

This cross-sectional survey was conducted among a random sample of family physicians in Eastern Ontario. The sampling frame was obtained from the combination of two lists: (1) The Ottawa Regional Cancer Center list of family physicians who had referred patients for cancer treatment from 1991 to 2001, and (2) The Southam List, which is compiled from 20 sources, including the Canadian Medical Association, the provincial medical associations, and the Canadian College of Family Physicians. The Southam list is updated twice a year and published in the Canadian Medical Directory. The Canadian Medical directory records the name, gender, address, medical school attended, year of graduation, primary specialty, and qualifications of the listed doctors.

Physicians with their primary professional activity in Emergency Medicine, Internal Medicine, Surgery or Psychiatry were excluded. After exclusion of duplicate names, a list of 997 family physicians was entered on an Excel spread sheet. Each

physician was assigned a unique survey identification number. A random number generator was used to produce a list of 400 random identification numbers.

Based on the findings of a literature search on family physicians' perceptions and use of palliative radiotherapy, a survey methodologist (I Graham) two radiation oncologists (J Meng, R Samant) and a palliative care physician (E Fitzgibbon) developed a survey questionnaire(**Appendix 3.A**). The questionnaire consisted of five sections: (1) Respondent characteristics, (2) Awareness of, and perceived accessibility to oncology services at the Ottawa Regional Cancer Center, (3) Factors influencing patient referral for palliative radiotherapy, (4) Perception of the effectiveness of palliative radiotherapy, (5) Willingness to attend continuing medical education on radiation oncology.

The initial survey questionnaire was piloted with family physicians attending an oncology conference to assess the acceptability and clarity of the questions. The pilot questionnaire was then revised, resulting in a survey questionnaire of 50 questions **(Appendix 3.B).** Completion time was 10 to 15 minutes. Factors relating to awareness of the RPRP and intention to use palliative radiotherapy were categorized as: *(a) Family Physician factors*: skills (training in oncology and palliative care), attitudes (perception of the need for the RPRP and willingness to attend educational sessions on radiotherapy), knowledge on the indications for, and perceived effectiveness of radiotherapy, and practice patterns (frequency of providing palliative care and caring for patients with advanced cancer). *(b) Practice environment factors*: including structural factors (proximity to Cancer Center), social factors (perceived difficulty in accessing treatment), and patient factors (age, functional status, type of cancer and life expectancy). *(c) Palliative radiotherapy and palliative radiotherapy delivery programs:* awareness of the

RPRP, prior referral for palliative radiotherapy, and perceptions of the accessibility of radiation oncologists.

To compare response rates across diverse methods of survey administration, the following four groups were constituted: Group A: Mailed questionnaire with incentive, Group B: Mailed questionnaire without incentive, Group C: Telephone questionnaire with incentive, Group D: Telephone questionnaire without incentive. Random identification numbers were allocated in sequence to groups A to D, until each group contained the names of 100 physicians. Addresses and phone numbers were verified in current telephone books. Physicians' names with outdated addresses and/or phone numbers were deleted from the group and replaced with a new random number.

The postal and telephone surveys were administered using a modification of Dillman's design for the conduct of surveys (41).The postal survey included: (1) an initial notification letter, (2) one week later a signed cover letter, questionnaire and a stamped self-addressed return envelope, (3) one week later a reminder postcard, (4) two weeks later, an additional signed cover letter and copy of the questionnaire to non-respondents. The investigators jointly signed all letters. Volunteers from the cancer foundation helped with preparing the mail outs.

Physicians allocated to the telephone survey were sent an initial notification letter, followed one week later by a letter to arrange a convenient time to complete the phone interview. A copy of the survey questionnaire was included with the letter. The research assistant used a standardized script to carry out the interview. A log of telephone contacts was kept. A maximum of four attempts were made to contact each physician.

Data management

All responses received within 12 weeks of the first mail-out were included in the analysis. Respondents were excluded from further analysis if they answered 'yes' to either of the screening questions "I do not practice family medicine" or "I do not have cancer patients in my practice". Response rates were calculated by dividing the number of completed surveys by the total number of family physicians surveyed minus the number of excluded surveys (43). Data from the completed surveys were entered on an SPSS database (version 11). Periodic random verification of the entered data was carried out by two of the investigators (E Fitzgibbon, J Meng). Additional descriptive and multivariate analyses were performed using SAS (version 8) statistical software. The Ottawa Hospital Research Ethics Board approved the survey.

Statistical analysis

Answers to survey question were either dichotomous (Yes /No) or categorical, answers were reported as frequencies and proportions. Responders were compared to non-responders using unpaired t-tests or Pearson chi-square tests as appropriate. Descriptive statistics were used to report demographic characteristics of survey responders and their practices.

Responders of Groups A and C (offered an incentive) were compared to responders of Groups B and D (not offered an incentive). No evidence of responder bias due to incentive was detected and all further analysis was conducted on the pooled data. Unpaired t-tests or Pearson chi-square tests were used to determine which factors were associated with the selected outcome variables i.e. (1) aware of the RPRP, and (2) previously referred patients for palliative radiotherapy to the cancer center. As the survey analysis was primarily exploratory no specific adjustment for multiple comparisons was

made. However a more conservative alpha (α) level of significance of (p) <0.01 was used to determine which associations would be reported.

In a secondary analysis a multivariate logistic regression model was developed to identify variables associated with a response to the survey. Demographic variables were included in the model building process if they met the pre-determined selection criteria of Wald p (z) <0.25 in univariate comparisons. Independent variables selected for the model building process were checked for numerical problems and significant correlations. The following assumptions required for multiple logistic regression analysis were verified: all observations were independent, the dichotomous outcome variable followed a binomial distribution and the relationship between the logit and the explanatory variables was linear. Model building proceeded in a stepwise manner, adding and deleting covariates based upon pre-selected entry criteria i.e. enter if the Wald statistic (p) $z < 0.25$, and removed if the (p) $z > 0.35$. The final model was examined for evidence of significant confounding by comparing the values of covariate regression coefficients in univariate models with corresponding covariate values in the final multivariate logistic regression model. In the absence of a clear rationale to identify potential interactions no interaction terms were included in the final model. Validity of the final model was assessed by calculating both the Hosmer and Lemeshow "Goodness" of fit test statistic ($\hat{C}$), and the area under the ROC curve (c)

Sample size

Sample size calculations were carried out separately for both the primary and secondary objectives. For the primary objective we calculated the number of subjects required to estimate a 50% response with a 95% confidence interval to a question with a

dichotomous answer. The required sample size was 385 subjects. For the secondary objective we based our calculation on previous studies reporting that an incentive may increase survey response rate by 9% to 30% (34-37). Sample size calculations were performed to provide a 90% power to detect a 20% or higher survey response rate among family physicians that were offered an incentive. The α error was set at *0.05* with a two-tail test of significance. Adjustments were made to the sample size to allow for a minimum expected survey response rate of 47% of 997 family physicians (37-40). Final sample size was estimated at 400 family physicians, equally split into the groups with and without incentive.

Results

Of the 400 family physicians who were contacted for the survey, 55 (14%) were excluded after their initial contact as they did not satisfy the survey eligibility criteria. Of the remaining 345 family physicians 172 (50%) responded to the survey **(Appendix3.C)**. Among responders, 99 (57%) responded after the first contact and 73 (43%) after a subsequent contact. Responders differed significantly from non-responders. Responders were more likely to practice in a non- urban setting, to have hospital admitting privileges, and to hold certification in the Canadian College of Family Physicians **(Table 3.1)**.

Of the 200 family physicians allocated to groups C and D (telephone arm), only three completed the telephone interview. All other respondents in groups C and D decided to mail in the questionnaire. As a result, comparisons between surveys administered by telephone and by mail could not be made as originally planned. Consequently the analysis was restricted to the comparison of groups surveyed with incentive (A+C) and without incentive (B+D), irrespective of the mode of survey. No

evidence of responder bias due to incentive or mode of survey was detected, thus further analysis was conducted on the pooled data.

Of the 172 responders, 148 (86%) were regularly involved in caring for patients with advanced cancer while 138 (80%) routinely provided palliative care for their patients. Sixty nine (40%) of the responders had received formal teaching in palliative care (median 2 weeks, range 1 to 104) during their medical training **(Table 3.2).** Only 10% of 172 responders had received teaching in radiation oncology. Thirty eight percent of the responders had attended post-graduate education sessions in palliative care, and six percent in radiation oncology. Most responders reported a strong need, and desire for additional education in palliative care (81%) and radiation oncology (86%). Small group workshops were the preferred continuing education format. Of the 172 survey responders, 96% considered radiotherapy to be a 'somewhat' or 'very effective' intervention in the relief of painful metastatic bone disease **(Figure 3.1).**

Of the 116 family physicians who answered the question concerning accessibility of oncologists, 60 family physicians considered radiation oncologists at the cancer center to be accessible.

Only 31 (18%) responders were aware of the existence of the RPRP **(Table 3.3).** However 99 (58%) of the responders had previously contacted a radiation oncologist at the cancer center for advice. The 31 physicians who were aware of the RPRP were more likely to have sought advice from a radiation oncologist and previously referred patients for palliative radiotherapy. Although only 15 (9%) of the responders had ever referred a patient to the RPRP, 96 (56%) responders had previously referred patients for palliative radiotherapy outside of this program at the cancer center.

The 96 family physicians who had referred patients for palliative radiotherapy differed from the remaining family physicians (**Table 3.4**). They were more often male (68% versus 41%), were more likely to have sought advice from a radiation oncologist (73% versus 29%), be aware of the referral process to the cancer center (86% versus 44%), and considered that radiation oncologists were accessible to them (60% versus 35%). In addition they regularly provided palliative care for their patients with advanced cancer (92% versus 66%), practiced outside the urban centers and had hospital admitting privileges (61% versus 39%).

Factors that family physicians reported as negatively influencing their decision to refer patients for palliative radiotherapy included, long waiting times for assessment (53% of 167) and for radiotherapy (55% of 166), and uncertainty of the benefit of radiotherapy (54% of 167). Family physicians reported that the type of cancer (80% of 172), patient preference (79% of 172) and poor functional status of the patient (67% of 172) were all factors they considered important when deciding whether to refer a patient for radiotherapy.

The response rate of family physicians offered an incentive was 61% (102/168) and 40% (70/177) among those not offered an incentive. Three factors were significantly and independently related to whether or not a family physician responded: [1] Use of an incentive (Odds ratio= 2.30, 95% CI= 1.46 to 3.63), [2] Certification in the Canadian College of Family Physicians (Odds ratio= 2.45, 95% CI=1.56 to 3.84), [3] Practice setting; a family physician practicing in a "mixed" practice i.e. containing both urban and rural areas, was associated with a higher likelihood of response (Odds ratio 3.79, 95% CI=1.32 to 10.85) (**Table 3.5**).

Discussion

The response rate (50%) to our survey appears low when compared to two recent reviews of physician response rates to surveys where average response rates of 54% and 61% respectively were reported (28;45). However the 50% response rate of our survey is a combination of the response rates achieved with and without the use of an incentive. Offering a low cost incentive ($10 phone card) was associated with a 21% higher survey response rate (61% versus 40%). No evidence of bias or difference in the quality of the survey answers was detected due to the incentive, suggesting that a low cost incentive may be a practical option to consider when planning future physician surveys.

The use of the Dillman approach was of great benefit in this survey of family physicians as 43% of survey responders replied only after a subsequent contact. It is interesting that family physicians in this survey, deliberately avoided answering the questionnaire by telephone. This raises the suggestion that postal surveys may now be a preferable method of surveying family physicians. Postal surveys do have the advantage of being answerable by the family physician whenever and wherever they have the time to do so, a fact that may be important when we consider that family physicians are now working even longer hours than before (46).

A gold standard to define an adequate survey response rate does not exist, although Gehlbach and others have suggested that response rates ranging from 40% to 80% may be acceptable providing there is a lack of non-response bias (44). In our survey, responders differed significantly from non-responders (**Table 3.1**). The former were more likely to have certification in family medicine and to practice in areas distant from the

radiation oncology center. Considering the 50% survey response rate and the possibility of non-responder bias, the estimated frequency (18%) of family physician awareness of the RPRP in this survey may be higher than the actual level of awareness among the general population of family physicians practicing in eastern Ontario. Nevertheless, awareness of the program is low enough to be a significant factor in the underutilization of the RPRP. Improving family physicians awareness of the RPRP would be a logical first step to improving utilization

The survey results indicated that 56% of responders had previously referred patients for palliative radiotherapy (**Table 3.4**). This sub-group of responders was also more likely to be aware of, and have used the RPRP. These family physicians were more likely to have regularly cared for patients with cancer, provided palliative care, had hospital admitting privileges and practiced in a rural or mixed practice setting. As such, this sub-group of responders matches the profile of the family physician that the RPRP was originally designed to assist and could logically be used to assess future family physician radiation oncology information needs and design educational programs in radiation oncology for family physicians practicing in eastern Ontario.

Grol and Grimshaw have suggested that barriers to implementing change such as using new innovations in a target population should be overcome by using multifaceted evidence based interventions (47). An initial strategy to improve awareness and subsequent utilization of the RPRP could involve using the identified sub-group of family physicians who already referred patients for palliative radiotherapy to the cancer center. A simple intervention could involve the treating radiation oncologist at the cancer center

enclosing information on the RPRP and on associated local small group education events when mailing the consultation report to the referring family physician.

Limitations in this study should be acknowledged. The survey sampling frame was a composite of two lists, in which some eligible physicians may, for various reasons, not have been registered or been incorrectly identified as family physicians. The relatively low survey completion rate was compounded by the 14% of responders who were found to be ineligible.

The association of responder bias and certification in family medicine is noteworthy: 64% of responders held certification in family medicine whereas 61% of non-responders did not have certification in family medicine. The survey response odds ratio with family medicine certification was: Odds ratio =2.45, 95% CI=1.56 to 3.84. This finding supports the results of a recent survey of family physicians in the United Kingdom that investigated their training and knowledge in palliative care and reported that certification in family medicine was associated with a two fold greater response rate (Odds ratio 2.19, 95% CI=1.34 to 3.04) (48). One suggested explanation for this, was that physicians with certification in family medicine may be more committed to attending continuing medical education events and consequently may be more confident to answer the survey. Alternatively non-responders without family medicine certification may somehow have perceived that they were not appropriate for this survey. This is an important issue that requires further study.

The complexity of the survey methodology study, which included incentive, postal and telephone interviews, has resulted in an unexpected break of the original protocol. Including a survey questionnaire with the initial notification letter in the

telephone arm of the study may have misled the majority of responders and prompted their return of the survey answers by mail.

From the perspective of the Ottawa Regional Cancer Center, this study identifies a major lack of awareness of the RPRP while also providing important information to enable the development of targeted corrective strategies to improve family physician awareness and utilization of the RPRP. In addition, the study results add to the evidence supporting the use of a low-cost incentive to improve response rates. Further study is also warranted to determine why family physicians consistently avoided the opportunity of a telephone interview.

Palliative radiotherapy is acknowledged to be an effective intervention in the treatment of many distressing cancer related symptoms, thus programs such as the RPRP that improve access to radiation oncology services for patients with advanced symptomatic cancer would if used, translate into improved quality of care for cancer patients living in eastern Ontario.

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Table3.1. Demographic Characteristics of Physicians According to Survey Response*

Variable	Responders (N= 172) No.	(%)	Non-Responders (N=173) No.	(%)	Probability value (p)†
Gender					
Female	76	(44)	62	(36)	0.16
Male	96	(56)	111	(64)	
Year of graduation					
Mean	1980		1980		Unpaired t-test
(range)	(1948 to 1998)		(1955 to 1997)		0.355
CCFP ‡					
Yes	111	(64)	68	(39)	**<0.001**
No	61	(36)	105	(61)	
Practice setting:					
Urban	110	(64)	129	(75)	
Rural	43	(25)	39	(22)	**0.006**
Mixed	19	(11)	5	(3)	
Hospital Admitting Privileges.					
Yes	89	(52)	72	(42)	0.011
No	83	(48)	101	(58)	

* Demographic data for non-respondents obtained from Canadian Medical Directory.
†Significant association = Chi-square (p) or un-paired t-test (p) < 0.01.
‡ CCFP = Certificant of the Canadian College of Family Physicians.

Table3.2. Characteristics of the 172 Physicians Responding to the Survey

Characteristic	*Possible Answers*	No.‡ (%)
Aware of the RPRP*?	Yes	31 (18)
	No	141 (82)
Previously referral to the RPRP*?	Yes	15 (9)
	No	157 (92)
Previous referral for PXRT†	Yes	96 (56)
	No	76 (44)
No. of cancer patients seen in past month:	0	6 (4)
	1-5	76 (44)
	6-10	55 (32)
	>10	35 (20)
Frequency of providing palliative care.	Never	5 (3)
	Rarely	29 (17)
	Sometimes	56 (33)
	Often	82 (47)
Previous training in palliative care	Yes	69 (40)
	No	103 (60)
Training in radiation oncology	Yes	17 (10)
	No	153 (90)
Previously obtained advice from a Radiation oncologist.	Yes	92 (53)
	No	80 (47)
Perception of accessibility to radiation oncologists.	Never tried	22 (19)
	Easy	60 (51)
	Difficult	34 (30)
PXRT† perceived as somewhat or very effective for treating painful bone metastases.	Yes	161 (95)
	No	8 (5)
The ***type of cancer*** greatly influences my decision to refer for PXRT†	Yes	133 (80)
	No	34 (20)
Poor Functional status of a patient somewhat or greatly influence my decision to refer for PXRT†	Yes	111 (70)
	No	55 (33)

* RPRP = Rapid Palliative Radiotherapy Program

† PXRT = Palliative Radiotherapy through the regular radiotherapy program.

‡ = The number of physicians who answered specific questions ranged from 116 to 172.

Table3.3. Factors Related to Family Physician Awareness of the Rapid Palliative Radiotherapy Program

Factors †	Possible Answers	Unaware (n= 141) No. (%)	Aware (n= 31) No. (%)	Association* (p)
ORCC and PXRT‡				
Previously sought advice from radiation oncologist.	Yes	74 (52)	25 (81)	**0.001**
	No	67 (48)	6 (19)	
Access to radiation oncologist is considered adequate (n=116)	Yes	42 (47)	18 (69)	
	No	26 (29)	8 (31)	0.015
	Never tried	22 (24)	0 (0)	
Previous referral of patients for PXRT‡	Yes	71 (50)	25 (81)	**0.002**
	No	70 (50)	6 (19)	
Family Physician.				
PXRT‡ considered somewhat or very effective for tumor induced hemoptysis. (n=169)	Yes	51 (37)	18 (58)	0.031
	No	87 (63)	13 (42)	
Family Physician Practice				
Provides palliative care for their patients.	Often	109 (77)	29 (94)	0.039
	Rarely	32 (23)	2 (6)	

*Significant association for this survey was set at Chi-square (p) <0.01 or Fishers exact test (p)< 0.01, n=172 unless otherwise indicated.
† Three Categories of factors: (1) ORCC and PXRT, (2) Family Physician, (3) FP Practice
‡ PXRT = Palliative radiotherapy

Table3.4. Factors Related To Previous Referral of Patients for Palliative Radiotherapy*

Factors	Possible Answers	No Previous Referral No. (%)	Previous Referral No. (%)	Association (p)†
ORCC and PXRT‡				
Previously sought advice from radiation oncologist.	**Yes**	22 (29)	70 (73)	<0.001
	No	54 (71)	26 (27)	
Considers access to radiation oncologists is adequate	**Yes**	14 (35)	46 (60)	
	No	10 (25)	24 (32)	<0.001
	Never tried	16 (40)	6 (8)	
Somewhat or very familiar with the referral process to the ORCC	**Yes**	31 (44)	81 (86)	<0.001
	No	39 (56)	13 (14)	
Family Physician				
Gender	**Male**	31 (41)	65 (68)	<0.001
	Female	45 (59)	31 (32)	
Considers PXRT‡ somewhat or very effective for treating painful bony metastases	**Yes**	68 (92)	93 (99)	0.007
	No	6 (8)	1 (1)	
Family Physician Practice				
> 6 cancer patients per month	**Yes**	32 (42)	58 (60)	0.017
	No	44 (58)	38 (40)	
Regularly caring for patients with advanced cancer	**Yes**	57 (75)	91 (96)	<0.001
	No	19 (25)	4 (4)	
Regularly providing palliative care	**Yes**	50 (66)	88 (92)	<0.001
	No	26 (34)	8 (8)	
Urban practice location	**Yes**	57 (75)	53 (55)	0.007
	No	19 (25)	43 (45)	
Hospital admitting Privileges.	**Yes**	30 (40)	59 (62)	0.004
	No	46 (60)	37 (38)	

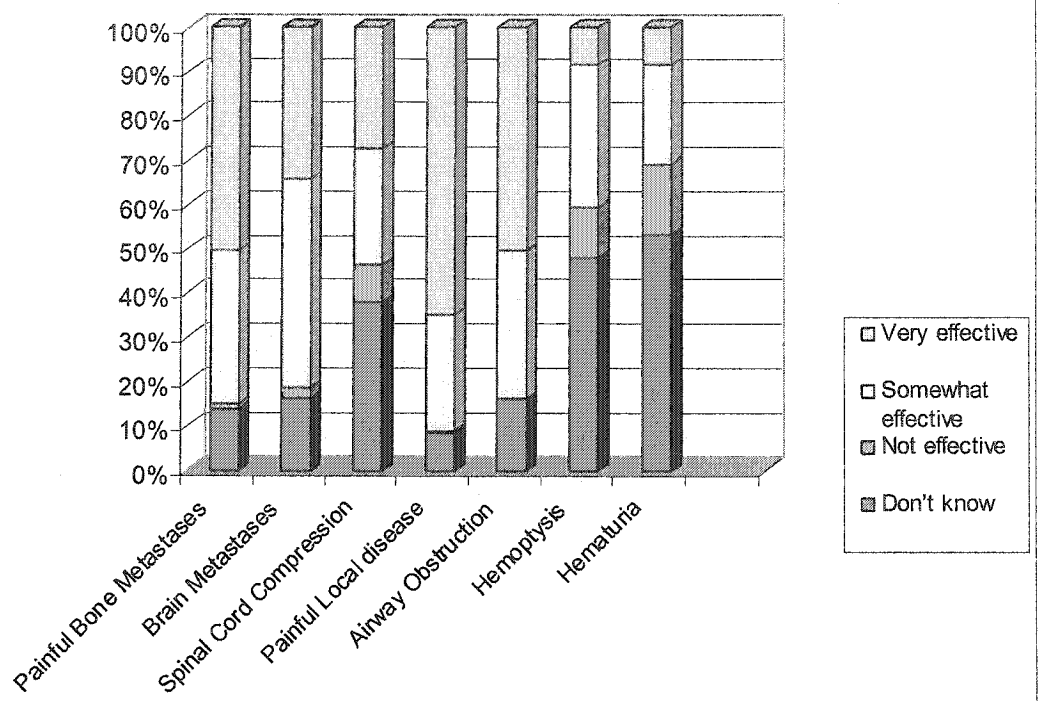
* The number of physicians who provided data on each factor varied from 116 to 172.
†Significant or interesting association for this survey was set at Chi-square (p) <0.01 or Fishers exact test F(p)< 0.01, n=172 unless otherwise indicated.
‡PXRT = Palliative Radiotherapy

Table3.5. Multiple Logistic Regression Model To Estimate the Probability of Response to the Survey Among the 345 Family Physicians Surveyed.

Variable	Regression Coefficient (β)	Standard Error	Wald χ^2	P value	Odds Ratio ∫	95% CI
Intercept*	-1.053	0.221	-----	<0.001	-----	-----
Incentive†	0.834	0.232	12.936	<0.001	2.30	1.46 to 3.63
CCFP‡	0.894	0.230	15.080	<0.001	2.45	1.56 to 3.84
Practice§						
Setting: Rural	0.412	0.272	2.294	0.129	1.51	0.87 to 2.58
Mixed	1.332	0.537	6.155	0.013	3.79	1.32 to 10.85
Tests for Model validity	1.Classification = Hosmer and Lemeshow 'Goodness of Fit' Chi square (χ^2) = 2.9238, df =6, (p) = **0.818** 2. Discrimination = Area under the ROC curve (c) = **0.698**					

*Intercept = a mathematical constant; no clinical interpretation.
† Incentive = Family physician offered an incentive with the survey.
‡CCFP = Canadian College of Family Physicians.
§Practice = primary practice setting for FP i.e. 1= urban, 2= rural, 3= mixed
∫Odds ratio =the odds of the outcome occurring for every unit increase in an individual independent variable, controlling for the other variables in the model.

Figure 3.1. Family Physicians Perception of the Effectiveness of Palliative Radiotherapy*



* The proportion of respondents who perceive radiotherapy to be "very effective', 'somewhat effective', 'not effective' or 'don't know' for each of the indications named on the X-axis. For each of these indications expert opinion suggest that radiotherapy is 'somewhat' to 'very effective' (4;9).

Appendix 3.A: Contributions of Authors.

Edward Fitzgibbon and Joanne Meng were the joint principal investigators for the survey project.

Edward Fitzgibbon conceived the project, completed the primary survey design and was part of the team who developed the questionnaire and assisted in the survey mail out. He drafted the script for the telephone interview, and reviewed all returned surveys. Finally he developed the SPSS database for the survey, extracted and entered the data from the surveys, completed and critically interpreted the statistical analysis and drafted the final manuscript.

Joanne Meng was responsible for obtaining funding for the project, was part of the team that developed the survey questionnaire and supervised the mail-out of the survey and tracking of contacts. In addition she was the expert advisor on radiotherapy for the project.

Ian Graham was part of the team that developed the survey questionnaire and was the expert advisor for the design and implementation of the survey. In addition as the thesis advisor for Edward Fitzgibbon he has critically edited the manuscript.

Rajiv Samant was part of the survey questionnaire development team, and assisted in the mail out process for the survey.

Appendix 3.B. Family Physician Survey

SURVEY OF FAMILY PHYSICIANS IN EASTERN ONTARIO ON THE ROLE OF RADIOTHERAPY IN ONCOLOGY

If you are not currently practicing family medicine or do not have any patients with cancer in your practice, please check the appropriate box.

☐ I do not practice family medicine.
☐ I do not have cancer patients in my practice.

If you checked either of the above two boxes, please return the survey in the envelope provided.

A. Background Information

1. **How many patients with cancer have you seen in your practice in the past month?**

   ☐ None
   ☐ 1-5
   ☐ 6-10
   ☐ >10

2. How often do you participate in the care of your patients with advanced and/or metastatic cancer?

   ☐ Never
   ☐ Rarely
   ☐ Sometimes
   ☐ Often

3. How often are you involved in the palliative care management of your patients?

   ☐ Never
   ☐ Rarely
   ☐ Sometimes
   ☐ Often

B. Ottawa Regional Cancer Centre Awareness

1. **Are you aware of the Ottawa Regional Cancer Centre's Community Oncology Program?**

   ☐ Yes ☐ No

2. Would you like information about the Ottawa Regional Cancer Centre's Community Oncology Program?

   ☐ Yes ☐ No

3. Have you ever obtained advice from the radiation oncologists at the Ottawa Regional Cancer Centre?

   ☐ Yes ☐ No (If **no**, skip to question C.1)

4. If **yes**, what kind of advice? *Please check all that apply.*

   ☐ How to make a referral to the Ottawa Regional Cancer Centre
   ☐ To determine suitability of a referral
   ☐ To discuss unanticipated side effects of treatment
   ☐ To discuss current plan of management

   Other, please specify: _____
   _____
   _____

5. How would you rate your ability to contact a radiation oncologist when necessary?

   ☐ Have never attempted to reach
   ☐ Very easy to reach
   ☐ Somewhat easy to reach
   ☐ Somewhat difficult to reach
   ☐ Very difficult to reach

C. Radiotherapy

1. Have you ever referred a patient for radiotherapy at the Ottawa Regional Cancer Centre?

   ☐ Yes ☐ No (If **no**, skip to question C.3)

2. If **yes**, how many patients have you referred in the past two years?

   ☐ None
   ☐ 1-5
   ☐ 6-10
   ☐ >10

3. If you were to refer a patient for consideration of palliative radiotherapy, how much would the following factors influence your decision? *Please **circle** the most appropriate response.*

	Not at All	A Little	Somewhat	A Lot
a. Type of cancer a patient has	1	2	3	4
b. Age of patient	1	2	3	4
c. Poor functional status of patient	1	2	3	4
d. Anticipated inconvenience for a patient to go to Cancer Centre	1	2	3	4
e. Uncertainty about the benefits	1	2	3	4
f. Concern about the side effects	1	2	3	4
g. Waiting time for assessment and consultation	1	2	3	4
h. Waiting time for patients to receive radiation	1	2	3	4
i. Difficulty in contacting a nurse or oncologist to discuss a patient	1	2	3	4
j. Unsure of referral process to Cancer Centre	1	2	3	4
k. Patient's preference	1	2	3	4
l. Proximity to Cancer Centre	1	2	3	4

4. Would a patient's life expectancy influence your decision to refer a patient for radiotherapy?

   ☐ Yes ☐ No (If **no**, skip to question C.6)

5. If **yes**, what would you consider the minimum life expectancy to be prior to referring a patient for radiotherapy?

   ☐ Less than 1 month
   ☐ 1 - 3 months
   ☐ 4 - 6 months
   ☐ Greater than 6 months
   ☐ Unsure

6. Are there any other factors that have influenced or might influence your decision to refer a patient for radiotherapy?

   ☐ Yes ☐ No

   a. If **yes**, please specify: _____
   _____

D. Cancer Related Symptoms

1. How effective do you consider radiotherapy for the treatment of the following cancer related symptoms? *Please circle the most appropriate response.*

	Not Effective	Somewhat Effective	Very Effective	Don't Know
a. Painful bony metastases	1	2	3	4
b. Airway obstruction due to tumor	1	2	3	4
c. Hemoptysis	1	2	3	4
d. Hematuria	1	2	3	4
e. Painful local disease	1	2	3	4
f. Brain metastases	1	2	3	4
g. Spinal cord compression	1	2	3	4

E. Rapid Palliative Radiation Therapy Program

1. Are you aware of the Rapid Palliative Radiation Therapy Program at the Ottawa Regional Cancer Centre?

   ☐ Yes ☐ No

2. Have you ever referred a patient to the Rapid Palliative Radiation Therapy Program?

   ☐ Yes ☐ No (If **no**, skip to question F.1)

The Rapid Palliative Radiation Therapy Program is a treatment and consultation service, which works in partnership with a patient's primary care physician to provide urgent access to palliative radiation to reduce cancer related symptoms in patients with incurable disease. The service is to be provided within 5 working days of a referral to the program.

3. Have you encountered a patient with cancer in your practice who would or could have benefited from this program in the past year?

   ☐ Yes ☐ No

a. If **yes**, how many? _____ patients

F. Type of Practice

1. In which setting do you do most of your work as a family doctor/general practitioner?

   ☐ Urban
   ☐ Rural
   ☐ Mixed

2. Do you have admitting privileges at a hospital?

   ☐ Yes ☐ No

3. What percentage of your practice makes up each of these age groups? *Please check the most appropriate response for each age group.*

	0-20%	21-40%	41-60%	61-80%	81+%
Children 0-18 years	☐	☐	☐	☐	☐
Adults 19-39 years	☐	☐	☐	☐	☐
Adults 40-64 years	☐	☐	☐	☐	☐
Seniors 65 years and older	☐	☐	☐	☐	☐

G. Respondent Profile

1. Are you?

   ☐ Male ☐ Female

2. In what year did you graduate from medical school? _____

3. Are you a certificant of the College of Family Physicians of Canada?

   ☐ Yes ☐ No

4. Please indicate the number of years in family medicine/general practice: _____years

5. During your medical training, did you receive any formal training (e.g., lectures, mentorships or traineeships) in palliative care?

   ☐ Yes ☐ No

   a. If **yes**, please indicate the number of weeks: _____weeks

      Please indicate format:_____

6. Did you receive any formal training in radiation oncology during your medical training?

   ☐ Yes ☐ No

   a. If **yes**, please indicate the number of weeks: _____weeks

      Please indicate format: _____

7. Following completion of your medical training, have you received additional training in the following areas? *Please check all that apply.*

   ☐ Palliative care
   ☐ Radiotherapy and its use in oncology

H. Continuing Medical Education

1. Please answer the following. *Please **circle** the most appropriate response for each statement.*

	Strongly Agree	**Agree**	**Neither Agree nor Disagree**	**Disagree**	**Strongly Disagree**
a. I would benefit from more education in palliative care	1	2	3	4	5
b. I would benefit from more education in radiotherapy and use in oncology	1	2	3	4	5

2. Would you be willing to attend continuing medical education on radiotherapy and its use in oncology?

   ☐ Yes ☐ No

   a. If **yes**, please rank your top three choices of preferred learning style, in order of preference:

      Written material _____
      Small group tutorials/workshops _____
      Online CME _____
      Local hospital rounds _____
      Traineeships _____
      Other (i.e. audio/video tapes) Please specify: _____

      _____

      _____

Please feel free to make additional comments in the space provided below:

_____

_____

If you would like more information about this survey or radiotherapy services at the Ottawa Regional Cancer Centre, please indicate your name and contact information in the space provided below:

Name: _____

Address: _____

City/Province: _____

Postal Code: _____

Telephone : _____

Fax #: _____

Email Address: _____

Appendix3.C. Results of the Survey of Family Physicians in Eastern Ontario

Group	A Mailed with Incentive No	B Mailed without Incentive No	Total Mailed A+ B No (%)
Number randomized	100	100	200
Replies	71	49	120 (60)
Ineligible: Not a Family physician	10*	10*	20 (10)
: No Cancer patients	4	2	6 (3)
Blank forms	2	2	
Completed surveys	55	35	90 (45%)
Total number of eligible surveys†	86	88	174 (87%)
	55/86	35/88	90/174
Response Rate	**63.9%**	**40.9%**	**51.7%**

* (A) includes 2 moved and 1retired (B) includes 3 moved and 1 retired.
† eligible= total number of replies – ineligible surveys

Group	C Phoned with Incentive No	D Phoned Without Incentive No	Total Phoned C+D No (%)
Number Randomized	100	100	200 (100)
Contacted by phone*	97	97	194 (97)
Completed phone interview	2	1	3 (1)
Mailed in forms	**63**	**45**	**108 (54)**
Declined to complete survey	32	51	91 (45)
Ineligible:			
Not a Family Physician	14†	8†	22 (11)
No cancer patients	4	3	7 (3)
Total number of eligible‡ surveys	82	89	171 (86)
Completed surveys	47	35	82 (41)
	47/82	35/89	(82/171)
Response rate	**57.3%**	**39.3%**	**47.9%**

* Both groups C+D include 3 family physicians that after 4 attempts we were still unable to contact .
† (C) Includes 1 moved 2 maternity 1 retired, (D) 2 moved 2 sabbatical 1 maternity
‡ eligible= total number of replies – ineligible surveys

Response rate with Incentive = (A) +(C) = 102/168 = **60.7%**
Response rate without Incentive = (B) +(D) = 70/177 = **39.5%**
Total ineligible surveys = 55/400 (13.75%)
Total eligible FPS surveyed = 345/ 400 (86.25%)
Overall survey response rate = **172 / 345 (49.85%)**

Chapter 4: Conclusion

The primary objective of this thesis was to examine possible reasons why family physicians in Eastern Ontario were under-utilizing a family physician focused palliative radiotherapy program i.e. the Rapid Palliative Radiotherapy Program (RPRP). The RPRP was developed on two major principles: (1) That a short (one or two fractions) course of high dose (8Gy or 10Gy) radiotherapy is an effective palliative intervention for patients with advanced symptomatic cancer, and (2) Promoting direct family physician referral of patients with symptomatic advanced cancer for palliative radiotherapy would facilitate patient access to treatment and by alleviating symptoms improve patient quality of life. This thesis is composed of two studies that examine aspects of the RPRP: (1) A systematic review to assess the comparative effectiveness of a short course of radiotherapy to the traditional low dose multiple fraction radiotherapy treatment regimens for treating painful metastatic bone disease, and (2) A survey of the family physicians of eastern Ontario to assess their awareness, perceptions, and knowledge of palliative radiotherapy and of the RPRP.

The results of the systematic review suggest that in the treatment of painful metastatic bone disease, a single high dose fraction of radiotherapy is of comparable effectiveness to the more traditional multiple low dose radiotherapy treatment schedules in achieving 'Complete' pain relief (Odds Ratio 1.13, 95% CI=0.96 to 1.34) and 'Partial' pain relief (Odds Ratio 1.15, 95% CI= 0.99 to 1.33).Overall radiotherapy was effective in inducing 'complete' pain relief in 32% (multiple fraction) to 35% (single fraction) of patients and 'partial pain relief in 61% (multiple fraction) to 64% (single fraction) of patients with painful metastatic bone disease. In addition patients treated with a single

high dose fraction of radiotherapy were three times more likely than those treated with multiple low dose fractions, to receive further radiotherapy to the same site at a later date (Odds Ratio 3.4, 95% CI= 2.66 to 4.35).

However the systematic review highlighted significant limitations in the original studies. Treatment outcomes used in the reviewed radiotherapy trials (e.g. pain, performance status and quality of life) were inadequately assessed and incompletely reported across the trials. This resulted in a general reporting of 'pain relief', with no adjustment for known confounding factors such as the types of pain mechanisms involved, use of co-analgesics, or type and extent of the primary tumor. The lack of consensus among the studies regarding the frequency and duration of follow-up after treatment meant that clinically important outcomes such as the timing of onset, and duration of pain relief after treatment could not be estimated. Despite these limitations the results of the systematic review support the principle of the RPRP in using high dose single fraction radiotherapy as a palliative intervention. The recently published consensus guidelines for conducting trials using palliative radiotherapy will, if adopted, reduce many of these limitations in future trials.

From the perspective of both the palliative patient and health care services a practical next step would be the development of treatment guidelines to define which patients would benefit most from either a single high dose or multiple low dose fractions of palliative radiotherapy. Treatment guidelines should be individualized to take into account the individual patient's disease, expected life span, personal characteristics and preference. For the frail symptomatic patient with an estimated prognosis of less than 3 months, a single fraction of radiotherapy would have practical advantages in terms of

time, physical and financial burden over the more demanding multiple fraction treatment regimen.

The information collected by the randomized cross-sectional survey of family physicians of Eastern Ontario will be crucial to the future development of the RPRP. The survey response rate of 50% was somewhat low but nevertheless the survey results confirmed the major role that family physicians play as primary care physicians for cancer patients in the community. More than 80% of family physicians regularly provide palliative care for their patients with advanced symptomatic cancer. Despite this, only 18% of family physicians were aware of the existence of the RPRP. In addition, although 52% of family physicians had previously referred patients to the cancer center for palliative radiotherapy, only 9% had ever referred patients to the RPRP. It is likely that this lack of awareness of the RPRP by family physicians is a major factor in explaining their underutilization of the program. Two factors were identified that were associated with increased family physician awareness of the RPRP i.e. if the family physician had previously: (1) contacted a radiation oncologist for advice (Chi- square, $p<0.001$), and (2): referred patients for palliative radiotherapy at the cancer center (Chi-square, $p=0.002$). Both of these factors were also significantly (i.e. $p<0.01$) associated with the family physicians who had actually used the RPRP. This suggests that physicians who were more familiar with the cancer center were more likely to be aware of the RPRP.

Other factors that were originally hypothesized to explain why family physicians were underutilizing the RPRP included family physicians' lacking knowledge regarding radiation oncology, not perceiving radiotherapy to be an effective intervention, and perceiving that the cancer center and radiation oncologists were not easily accessible to

them. The results of this survey did reveal a major deficiency in the level of family physician education in radiation oncology. Only 10% of responding physicians had receiving *any* formal training in radiation oncology during their medical training, while only 6% of respondents had received any additional training since completing their formal medical training. However family physicians were aware of this deficiency and were open to correcting it, with more than 86% perceiving a need for, and indicating their willingness to attend education sessions in radiation oncology. Despite this lack of formal education 96% of family physicians were aware of the effectiveness of radiotherapy in treating painful metastatic bone disease. This suggests that the lack of formal education in radiation oncology was not a major factor hindering family physicians from referring patients to the RPRP.

With regards to accessibility issues, the results are not as clear: 55% of family physicians report that waiting time for patients to receive radiotherapy was a factor that influenced their decision to refer patients for radiotherapy and 54% rated their ability to contact a radiation oncologist as 'somewhat' or 'very easy' to reach. These results suggest that family physician access to radiation oncology services could be improved however this does not explain why family physicians were not aware of the RPRP.

With only 18% of family physicians being aware of the RPRP the interventions originally used by the cancer center to inform family physicians of the establishment of the RPRP were clearly ineffective and need to be reviewed. These interventions consisted of: (1) mailing information pamphlets to all of the secondary health care institutions in eastern Ontario, who would distribute them to their affiliated family physicians, and (2) information sessions delivered by health care professionals from the cancer center at the

local medical advisory council meetings of four of the secondary health care institutions in eastern Ontario.

The probability of success of any intervention to increase awareness of the RPRP would be greatly improved if it were delivered to a receptive audience. Our survey has identified a subgroup of family physicians who if they were aware of the program would be more likely to use the RPRP i.e. the 56% of responders who had previously referred patients for palliative radiotherapy at the cancer center (Table 3.4, Page 73). The family physicians in this group were more likely to regularly care for patients with cancer and provide palliative care, have hospital admitting privileges, and practice in a rural or mixed practice setting. In addition they were more likely to have previously contacted the cancer center for both advice and patient referrals. Family physicians in this group are widely dispersed throughout eastern Ontario and many would be considered as local experts or peer champions in providing care for patients with advanced cancer. As such they serve as a local resource in cancer expertise and knowledge to other health care providers in their areas and could aid in increasing awareness of the RPRP throughout their own practice regions.

Given the failure of the original advertising interventions, it is crucial that as part of an ongoing audit process of the RPRP, a repeat survey of family physicians be carried out after a suitable period to determine the success of any new intervention. The format of survey to be used i.e. follow-up of the cohort of family physicians originally surveyed or a cross-sectional survey of a new randomized sample of family physicians in eastern Ontario would depend on the primary purpose of the survey. The value of a cohort follow-up study would be in measuring the effect of any interventions used to improve

family physician awareness and utilization of the RPRP on the cohort of family physicians who responded to the initial survey. The major disadvantage of a cohort study is the potential for bias being introduced by the smaller number of responders limiting the generalizability of the results. A cross sectional study of a new randomized sample of family physicians, although more expensive and time consuming to conduct, would have an advantage of greater statistical power, due to a larger sample size, facilitating the collection of data on the prevalence of awareness, knowledge and use of the RPRP.

From the perspective of survey methodology the results of this survey have demonstrated the value of using a small non monetary incentive to increase the response rate of family physicians. This and the issue of family physicians demonstrating a preference to respond by mail rather than by telephone have practical implications that warrant further study.

In summary the results of this thesis provides evidence supporting the comparable effectiveness of a single high dose fraction of radiotherapy in palliating painful metastatic bone disease. However the survey results suggest that a major factor explaining why family physicians were underutilizing the RPRP was that they were not aware of the program. The survey also confirms the crucial role that family physicians are playing in providing ongoing primary care for patients with advanced symptomatic cancer throughout eastern Ontario. Interventions are urgently needed to improve both the level of family physician awareness of the RPRP and level of medical education in radiation oncology. The results of this thesis will enable the development and delivery of a focused plan to improve family physician knowledge, awareness, and use of the Rapid Palliative Radiotherapy Program. (Proposed strategies -Appendix 4.A)

Appendix 4.A: Strategies to Improve Family physician awareness of the Rapid Palliative Radiotherapy Program.

1. Enclose a pamphlet and plasticized contact information card with each consultation letter sent back to the family physician for each patient referred to the cancer center for radiotherapy.

2. Acknowledging family physicians education format preferences (table below), design and develop a tutorial/workshop on palliative radiotherapy and the rapid palliative Radiotherapy Program. This workshop could be delivered at various health care facilities throughout Eastern Ontario.

3. The information delivered in the workshop could be summarized into an education pamphlet and circulated to all of the family physicians in the region

Family Physicians first preference choices of learning style (N=168)

Rank	No	(%)	Format
1	67	(40)	Small group tutorials / workshop format.
2	50	(30)	Written material.
3	17	(10)	Audio /video tapes.
4	15	(9)	Online CME
5	12	(7)	Local hospital rounds
6	7	(4)	Traineeships

Factors associated with willingness to attend Continuing Medical Education.

1. Rural practice location $[\chi^2 (p) = 0.0487]$
2. Frequently care for palliative patients $[\chi^2 (p) = 0.0130]$

Factors NOT associated with willingness to attend Continuing Medical Education.

1. Admitting privileges.
1. Frequency of caring for cancer patients
2. Level of knowledge
3. Gender
4. Certification in Canadian College of Family Physicians.