The Use of Palliative Radiotherapy for Bone and Brain Metastases in Ontario

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Abstract

Background: Palliative radiotherapy (PRT) plays an important role in the management of patients with bone and brain metastases; however, little is known about the use of this treatment in Ontario.

Objectives: The objectives of this thesis were to a)identify health system-related and patient-related factors associated with the use of PRT for bone and brain metastases , and b) describe temporal trends in the use of PRT for bone and brain metastases.

Methods: The Ontario Cancer Registry was used to identify patients who died of cancer between the years 1984 and 2004. Temporal trends in the use of PRT were described by year and disease site, using the Cochran-Armitage test for trend. A multivariate logistic regression was conducted to describe the relationship between health system-related and patient-related factors, and the use of PRT, while controlling for disease-related factors.

Results: Overall, 10.0% and 4.1% of patients dying of cancer received at least one course of PRT for bone metastases and brain metastases, respectively. The use of PRT for bone metastases significantly decreased from 10.4% to 9.5% (p<0.0001), while the use of PRT for brain metastases more than doubled from 2.2 to 5.1% during the same period (p<0.0001). In the multivariate analysis, age was negatively associated with the use of PRT in both cases. Patients residing in the richest communities were more likely to receive treatment. A farther distance to the nearest cancer was negatively associated with the use of PRT. The level of RT services at the

diagnosing hospital was positively associated with the use of PRT for bone metastases.

Prevailing waiting time did not significantly influence the use of PRT in either case.

Conclusions: Over the course of the study period, the use of PRT for bone metastases decreased, while the use of PRT for brain metastases increased. Access to PRT for both bone and brain metastases was influenced by factors unrelated to need.

Co-authorship

All sections of this thesis were written by Daniel Sutton with input and guidance from William Mackillop and Keyue Ding. The study design for both manuscripts was conceptualized by Daniel Sutton, William Mackillop, and Keyue Ding. Linkage of data from different databases was performed by Daniel Sutton. All statistical analyses were also performed by Daniel Sutton. SAS code for the calculation of prevailing waiting time was created by Weidong Kong and modified by Daniel Sutton. Characterization of diagnosing hospitals was done by Weidong Kong. Interpretation of results was done by Daniel Sutton, William Mackillop, and Keyue Ding.

Acknowledgement

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I would like to thank Weidong Kong, Patti Groome, Heather Stuart, Michael Brundage, and Will King for sharing their knowledge with me at various stages throughout the course of this thesis.

I would like to thank my fellow classmates for their moral and social support. It has been great getting to know all of you.

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Chapter 1 Background and Rationale

Background

Bone and brain metastases are a dreaded complication affecting many patients with end-stage cancers. These events are a major source of morbidity and can significantly decrease a patient's quality of life. The efficacy of Palliative radiotherapy (PRT) in the management of patients with bone and brain metastases has been demonst in clinical trials. A course of PRT can relieve bone pain which is associated with bone metastases [1], as well as neurologic symptoms associated with brain metastases[2,3] in the majority of patients treated. Although PRT is regarded as an effective treatment, very little is known about the accessibility of this treatment within the general cancer population.

In Ontario, evidence suggests that access to radiotherapy (RT) services is suboptimal. A variety of factors unrelated to need, such as age, socioeconomic status (SES), and distance to the nearest cancer center, influence the use of this treatment. These findings are of particular importance, as the Ontario RT system aims to provide equitable access to care. Much of the research on access to RT in Ontario, however, has focused on general use of RT. Although one Ontario study was conducted to describe factors affecting the overall use of PRT, no studies have described the accessibility of PRT services for bone and brain metastases in particular. The treatment of patients with bone and brain metastases represents a significant proportion of the total PRT workload in RT centers[4]; thus, an examination of the accessibility of PRT in these populations is warranted.

Overview of Study Design:

This analysis is a retrospective cohort study describing the use of PRT for bone and brain metastases during the years 1984 to 2004. Data gathered from prospective databases will be examined retrospectively to identify temporal trends in the use of PRT, and determine associations with health system-related and patient-related factors.

Objectives and Hypotheses

1. Examine the relationship between health system-related and patient-related factors and the use of PRT for both bone and brain metastases.
2. Describe temporal trends in the use of PRT for both bone and brain metastases.

The health system-related factors that will be examined are level of RT services at the hospital of diagnosis, distance to the nearest cancer center, and prevailing waiting time. The patient-related factors that will be examined are sex, age, and SES. I hypothesize the health system-related and patient-related factors examined will significantly influence variation in the use of PRT. My specific hypotheses are outline below in Table 1.

Table 1. Specific hypotheses surrounding associations of health system-related and patient-related factors with the use of PRT for bone and brain metastases

Health system-related and Patient-related factors	Hypothesis
Level of RT services at the diagnosing hospital	Patients diagnosed in a hospital with a RT facility will be more likely to receive PRT.
Prevailing Waiting Time	Longer prevailing waiting times will be associated with decreased use of PRT.
Distance to the nearest cancer center	A farther distance to the nearest cancer center will be associated with decreased use of PRT.
Age	Older age will be associated with decreased use of PRT.
Median household income	Patients from higher income communities will be more likely to receive PRT
Sex	Sex will not influence the use of PRT

Thesis Organization

This thesis conforms to the regulations outlined in the Queen's School of

Graduate Studies and Research "General Forms of Theses"11. The second chapter

provides a general introduction to the topics of palliative care and PRT, and summarizes

the findings of previous studies examining access to PRT. The third chapter of the thesis

is Manuscript 1 and is a study examining factors that influence the use of PRT for bone

metastases. This manuscript has been formatted for submission to the *Radiotherapy and

Oncology*. Chapter 4 of the thesis is the second manuscript, which examines factors

influencing the use of PRT for brain metastases. Manuscript II has been formatted to

meet the submission standards of *Clinical Oncology*. Chapter 5 summarizes the findings

and contains a general discussion of both manuscripts.

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Chapter 2 Literature Review

Cancer Incidence and Mortality

Despite much advancement in the detection and treatment of various malignancies, cancer remains one of the leading causes of death in the developed world. In Canada, 40% of individuals will develop cancer during their lifetime and of these, 50% will go on to die from their disease[1]. In 2008 alone, 72,700 Canadians died from cancer, and in Ontario this number was 27,400[1]. Although Canada has observed a steady decline in the overall cancer incidence rate over the past few decades, the number of new cancer cases is expected to increase in the coming years as the population continues to age. The rising number of cancer cases will lead to an increase in the overall number of cancer deaths, placing extra strain on the cancer system (Figure 1). As such, the care of cancer patients will become increasingly important in the future. Figure 2.1 and 2.2 shows the most common causes of cancer in Canada for males and females, respectively.
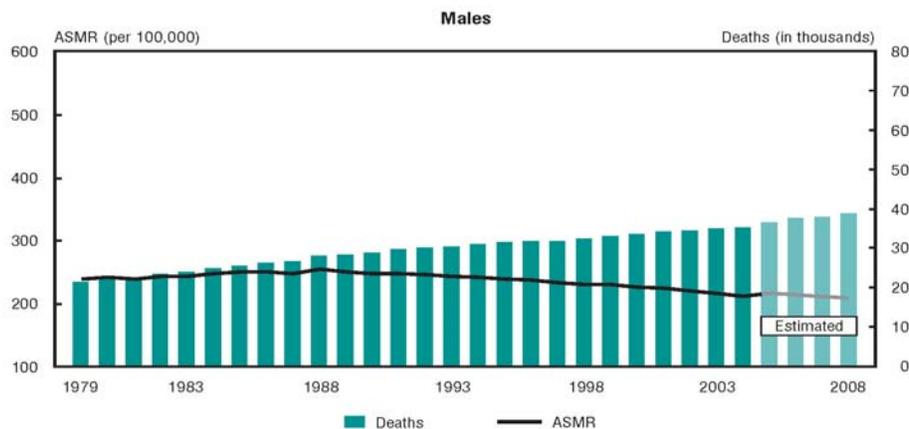
Figure 1. Changes in the age-standardize mortality rate and the absolute number of cancer deaths over time in Canada. While the age-standardized mortality has decreased over time, the absolute number of cancer deaths continues to rise because of changes in the age distribution of the population.
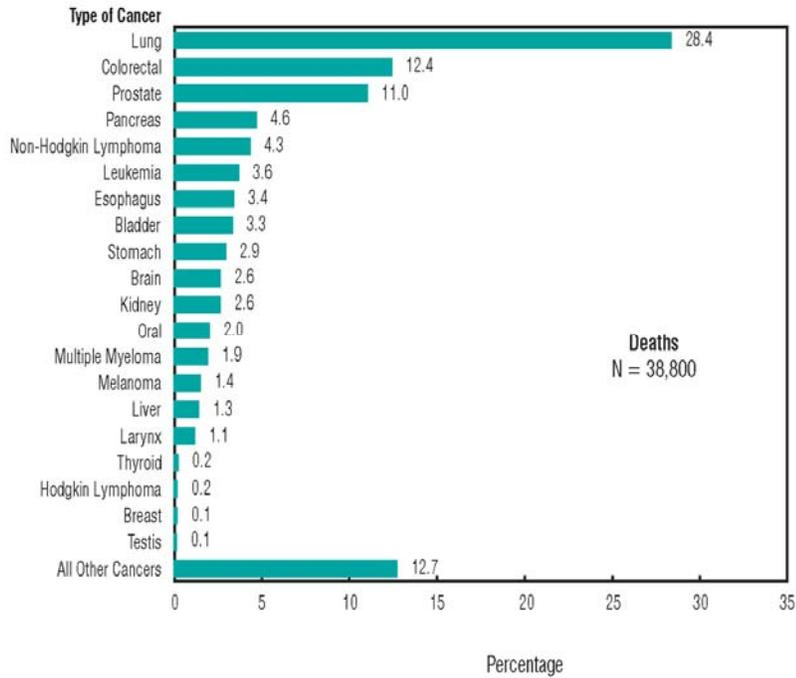
Figure 2.1. Percentage of cancer deaths by type of cancer for males. Figure adapted from Cancer Statistics, 2008.[1]
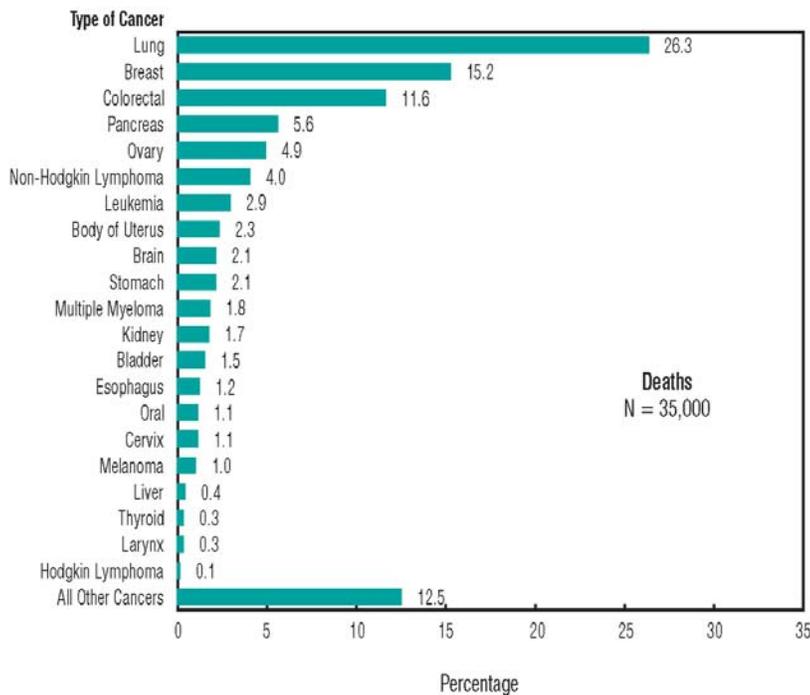
Figure 2.2. Percentage of cancer deaths by type of cancer for females. Figure adapted from Cancer Statistics, 2008.[1]

Palliative Care and Cancer

In oncology, the branch of medicine dealing with the treatment of cancer patients, an emphasis is placed on radical treatments such as surgery and radiation therapy, which seek to cure patients of their disease. Approximately 50% of all cancers in the developed world will be cured in this manner[2]. Cancer patients, however, face a variety of physical and psychological symptoms that are not necessarily addressed through the use of radical treatments. Failure to relieve these symptoms leads to unnecessary suffering. Palliative care seeks to address these issues in patients, and is recognized as an important component of comprehensive cancer care.

History of Palliative Cancer Care

The practice of palliative care has been largely influenced by the discipline of oncology. In its early stages, oncology focused mainly on curing patients, while patients dying of cancer were often times neglected by physicians. In many cases, in the absence of a cure, patients were sent to their homes to die. Concern over this began to develop in the 1950's when many began to realize that cure was not always possible, and that dying patients were suffering for want of symptom relief and attention.

In response to these concerns, Cecily Saunders, a U.K. nurse, physician, and social worker, opened the first modern hospice center, St. Christopher's Hospice, in 1967. This center was dedicated to the care of dying patients, and also was a leader in research on cancer pain control. Assessments of the hospice over time indicated improvements in the

management of pain in their patients. Eventually, the success of St. Christopher's

Hospice led to the establishment of many other hospice centers across the U.K.

By the 1980's the palliative care movement had become widespread in the U.K., and

gained increasing recognition in the medical community. Doctors had established the

Association for Palliative Medicine of Great Britain and Ireland to support the

practitioners of palliative care, the Royal College of Physicians and Surgeons established

palliative care as a medical subspecialty, requiring 7 additional years of training, and a

medical journal devoted entirely to palliative care was established. Since then, the

palliative care movement has been adopted by the international community with varying

degrees of recognition. It has been accredited as a medical specialty in Australia, New

Zealand, the U.S., and Canada, and is seeking accreditation in many other countries. The

WHO has also contributed to the palliative movement by developing a number of global

guidelines on the management of cancer pain[3].

Current view of Palliative Care

As the field of palliative care is relatively new, its scope has been subject to varying

interpretations. In some areas it is viewed as "care of the dying" or "care administered in

the last months of life". Others view the term more broadly as "symptom relief in patients

facing a life threatening illness", or "improving quality of life". The World Health

Organization (WHO) defines palliative care as: "an approach that improves the quality of

life of patients and their families facing the problems associated with life-threatening

illness, through the prevention and relief of suffering by means of early identification and

impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [3].

The WHO's definition of palliative care presents three noteworthy distinctions. First, it highlights the importance of treating all patients facing a life-threatening illness, as opposed to just dying patients. This view has come from the belief that problems that appear late in the course of the disease originate much earlier, and that it is easier to treat symptoms earlier in the course of the disease. Second, the WHO's definition includes addressing symptoms beyond pain. In addition to the physical aspects of disease, spiritual, emotional, and psychosocial symptoms are also considered. Lastly, more than just the patient, there is also consideration given to family members and caregivers. It acknowledges the need to counsel and support those who are bereaved.

Principles of Palliative Care

The principles of palliative care have been clearly laid out by the WHO[3], and are highlighted in Table 1 below.

Table 1. Principles of Palliative Care (World Health Organization)

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends to neither hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes investigations needed to better understand and manage distressing clinical complications.

Mode Delivery

Palliative care is commonly delivered by an interdisciplinary team of health professionals and support staff. This is done in an effort to prevent fragmented care and provide the most comprehensive care for the patient. Patients and family members may also be involved in the team, as their input is valued. Palliative care teams normally consist of physicians, nurses, and allied health professionals including social workers dieticians, physiotherapists, occupational therapists and pharmacists. Clergy and volunteers are also involved. Care can be provided in a variety of settings such as ambulatory clinics, hospitals, hospice units, and the home.

As the scope of palliative care is quite broad, the options that are employed in the management of issues affecting cancer patients are also wide ranging. For instance, radiotherapy and chemotherapy, which are sometimes used with curative intent, are often used to manage the physical effects of disease, such as pain. Nutritional counseling is

also important, as upwards of 87% of patients experience weight loss that can negatively impact a patients response to treatment[4]. Mental illnesses, such as depression, are common in cancer patients, and normally require psychological counseling or the administration of anti-depressants. Emotional problems are experienced by practically all patients at some level[4]. This may sometimes require support from volunteers, clergy, etc.

Ontario's Palliative Care Program

The Ontario government funds the delivery of palliative care through two provincial programs: the Ministry of Health and Long-Term Care's (MOHLTC) End-Of-Life Care Strategy and Cancer Care Ontario's (CCO) Palliative Care Program. Each program serves a distinct population. The End-Of-Life Care Strategy is targeted to all patients facing any terminal illness, while CCO's Palliative Care Program is targeted to cancer patients only[2]. Because cancer is a terminal disease in many patients, there is considerable overlap in the populations that each program serves. Patients who are terminally-ill with cancer would fall under the jurisdiction of both the End-Of-Life Care Strategy and the Palliative Care Program, the portion of overlap in Figure 3. Consequently, cancer patients make up 80-85% of patients seen by palliative care teams in Ontario[2].
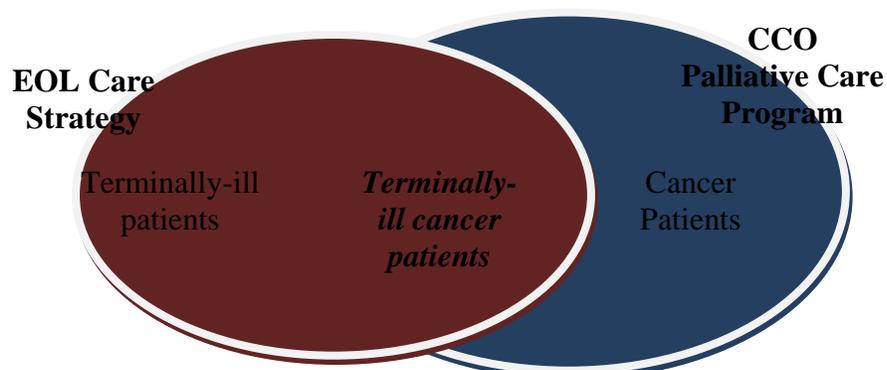
Figure 3. MOHLTC's EOL care strategy and CCO's Palliative Care Program.

Radiotherapy and Cancer Care

The discovery of X-rays and radium in the late 19th century lead to the use of

radiotherapy (RT) in the treatment of cancer. By 1902, radium had been used to cure

pharyngeal cancer, and by 1904 radium was being implanted directly into tumors, a

procedure now called brachytherapy[5]. After a subsequent period of advances and

developments, the practice of radiation oncology became recognized as a medical

specialty in some countries. In Canada, RT gained widespread acceptance, as provinces

began to fund hospitals with a supply of radium[6].

Today, RT plays a very important role in the management of cancer patients.

Approximately 50% of cancer patients will require RT at some point during the course of

their illness[7].

Principles of Radiotherapy

Radiobiology

RT is the use of ionizing radiation to destroy cancer cells. The radiation is in the form of

electromagnetic radiation (e.g. X-rays, gamma rays), charged or neutral particles (e.g.

high energy electrons or neutrons). The energy from this radiation leads to the formation

of free radicals. In this process, energy deposited into tissues results in the displacement

of electrons from biological molecules. These electrons are very reactive, and can

interact with other biological molecules, leading to the creation of more free radicals.

This can ultimately lead to cell injury or death, as these radicals possess enough energy to

create breaks in the double strand of DNA. DNA can also be damaged through the direct absorption of radiation; however, this process is less common. While normal cells are able to repair damage caused by radiation, tumor cells do not possess this ability and ultimately die.

Dose

The amount of radiation absorbed by the body is called the RT dose. It is measured in either Grays or Rads. One Gray is equivalent to the absorption of 1 Joule of energy per Kg of tissue. One Rad is equal to 10^{-2} Grays or 1 centiGray.

Fractionation

Fractionation is the administration of a total dose of RT in small packets over a specified period of time with intervals of rest in between. The rationale behind administering smaller RT doses in many fractions, as opposed to one large dose at one time has to do with the concepts of sublethal injury repair, reoxygenation, redistribution, and repopulation.

Sublethal injury sustained by normal tissue cells can normally be repaired within a few hours, but may take up to a full day. Spreading RT doses over many fractions provides normal tissues with an opportunity to repair sublethal damage. *Reoxygenation* is the process by which hypoxic (oxygen deficient) areas of the tumor become oxygenated after being exposed to RT. This increases the radiosensitivity of the tumor, as the availability of oxygen is an important component in the formation of free radicals. Thus,

fractionation leads to increased tumor oxygenation, which improves the chance that the tumor will be killed. *Redistribution* occurs when, after exposure to RT, surviving cells transition into a different phase of the cell cycle. This is important, as cells are more resistant to RT in certain phases of the cell cycle (DNA synthesis phase) than others (Gap phases). In a fractionated course of RT, redistribution causes some cells to move to a more sensitive phase of the cell cycle, leading to increased tumor radiosensitivity. *Repopulation* refers to the increased rate of proliferation in surviving cells after exposure to RT. While it is desirable that normal cells repopulate, the proliferation of tumor cells decreases the probability of cure. This issue is more concerning in tumors that initially have a high proliferation rate. Administering many fractions (hyper-fractionation) may decrease the opportunity for tumor cells to regenerate.

External Beam RT

When RT is delivered from outside the body, it is termed external beam RT. During external beam RT, a beam(s) of radiation is directed to the body to destroy the tumor and any nearby cancer cells. The radiation beam can be generated by several different types of machines that all generate high energy photons: cobalt-60 machine, linear accelerator (LINAC), neutron beam machine, orthovoltage x-ray machines, and proton beam machines. Of these, the LINAC is most frequently used in Ontario.

Brachytherapy

In brachytherapy, a radioactive source (i.e. seed, wire, and rod) is placed within the body, in or around the area requiring treatment. The source may be placed in the body for a

short period of time, or, in some cases, left in the body indefinitely until the radioactive material is used up. The benefit of placement within the body is that it allows for small volumes to be treated with high doses of radiation. Iridium-192 and iodine 190 are the most commonly used isotopes in brachytherapy[8]

Palliative Radiotherapy

RT can be used to cure a number of different cancers such as testicular cancer, lymphomas, and cervical cancers, and is also an important adjunct to other forms of cancer therapies which seek to cure patients [9]. In situations in which cure is no longer possible, RT may be used for palliation of symptoms associated with the cancer. In this context, the treatment is termed palliative radiotherapy (PRT).

Principles of PRT

PRT seeks to reduce complications associated with advanced disease, and to improve the patient's quality of life during the final stages of their life. The practice of PRT is guided by a number of principles, some of which overlap with the principle of palliative care. These have been outlined by Mackillop[10] in Table 2 below.

Principles one, six, and seven reiterate the fact that PRT is administered within the context of a team including multidisciplinary health professionals and the patient, if they so desire. Principle five refers to the fact that the patient has a limited life span, and that risk and benefits experienced earlier on are more important than those that occur later on, seeing that the patient may not be alive to experience them. Principle eight addresses the

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Table 2 The Principles of PRT (Mackillop, 1996)

1. PRT should be part of a comprehensive program of care
2. The decision to recommend PRT should be based on a thorough assessment of the patient
3. The decision to recommend PRT should be based on objective information
4. The risk-benefit analysis should include consideration of all aspects of the patient's well being
5. The short term risks and benefits of PRT are more important than those which may or may not occur in the future
6. The decision to use PRT should be consistent with the values and preferences of the patient
7. The patient should be involved in the treatment decision to the extent that she or he wishes
8. Time is precious when life is short
    -delays in starting PRT should be as short as reasonable achievable
    -a course of PRT should be no longer than necessary to achieve its therapeutic goal
9. Palliative and curative goals should not be considered mutually exclusive
10. PRT should consume no more resources than necessary

issue of the patient's limited life span once again. As a result, it advises that time used to undergo treatment should be as short as possible. Principle three speaks to the continued need for clinical research to evaluate the most effective way to treat each patient. This principle points to the need for clinical trials to establish the best dose, fractionation, and form of PRT for patients. Principle four affirms the importance of considering all benefits to the patient, like quality of life, which has been sometimes overlooked in clinical trials[11,12]. Principle nine is in accordance with the view that palliative care can occur at any point along the patient's illness trajectory. Principle ten speaks to the balance that physicians must strike between being good stewards of publicly funded resources, while providing adequate care to each patient.

Dose and Fractionation of PRT

While curative RT is characterized by a large a total dose (60-70 Gy) spread out over many fractions (20-30) [13] , PRT involves lower doses (20-30 Gy) spread out over fewer fractions (< 10) [13] . The use of higher doses with curative RT is done to maximize the probability of cure; however, this is associated with acute side effects. In the context of PRT, acute side effects are undesirable, as this can seriously diminish the quality of life in patients with a limited lifespan; thus, low doses are administered in a less protracted manner.

Indications for PRT

Bone pain, neurologic complications, pressure symptoms associated with increasing tumor size, and hemoptysis are all indications for PRT. In addition, there are emergencies in which the absence of PRT could result in death or irreversible damage. These include spinal cord compression, superior vena cava obstruction, and life threatening lower airway obstruction or hemorrhage. In the context of metastatic cancer, the two most common indications for PRT are bone and brain metastases.

Bone Metastases

Epidemiology

Bone metastases are a common complication of end stage cancers. The incidence of bone metastases is difficult to determine with any certainty. Necropsies, and bone scintigram studies have produced variable findings. Despite the lack of accurate estimates, it is generally believed that 27% of patients who die of carcinomas will have bone

metastases[14].In most cases, bone metastases are multiple[8], and common sites include the spine, pelvis, femur, ribs, humerus, and skull[15].Patients with lung, breast, and prostate cancer account for over 80% of the incidence bone metastases[16]. Of these, prostate and breast cancer patients have the highest propensity to develop bone metastases. The frequency of bone metastases is rising as a result of the increasing frequency of cancer cases. Survival with bone metastases is dependent on the site of primary disease. Median survival after a diagnosis of bone metastases is 24 -48 months in patients with breast and prostate cancer[17,18], and 6 months for patients with lung cancer.[19]

Bone Anatomy

There are two types of bone tissue, compact bone and spongy bone. Compact bone is hard and forms the outer layer of bone; spongy bone forms the interior of bone and contains red bone marrow. Bone tissue contains four types of cells surrounded by a complex matrix of osteoprogenitor cells, osteoblasts, osteoclasts, and osteocytes. Osteoblasts are involved in bone formation, through the secretion of collagen and other organic materials. Osteocytes exchange nutrients with their environment to nourish bone. Osteoclasts degrade bone, releasing minerals back into the blood (resorption). Osteoprogenitor cells differentiate into osteoblasts. Bone is continually being remodeled in a process that involves bone formation, mediated by osteoblasts, and bone resorption, mediated by osteoclasts.
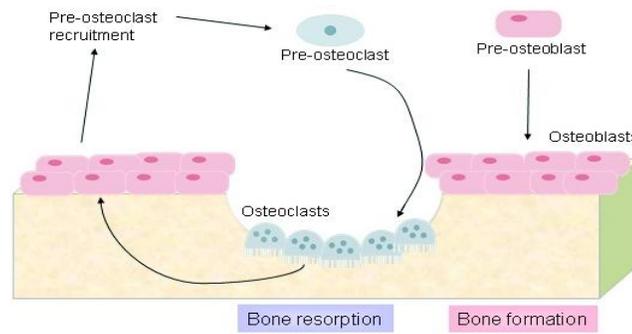
Figure 4. Process of bone remodeling

Classification of Bone metastases

Bone metastases are characterized as osteolytic or osteoblastic. Both result in changes in the normal bone remodeling process. In osteolytic metastases, bone is destroyed through the activity of osteoclasts and the formation of new bone is suppressed. Osteoblastic metastases lead to abnormal bone formation as a result of increases in the secretion of bone extra-cellular matrix proteins, and stimulation of osteoblasts. Cancers can develop into purely osteoblastic metastases, osteolytic metastases, or a mixture of both. Breast cancers are predominantly osteolytic, although approximately 20% of lesions are osteoblastic [16]. In contrast, multiple myelomas are purely ostelytic, and prostate cancers generally display osteoblastic metastases.

Consequences of Bone Metastases

Bone Pain

The most frequent consequence of bone metastases is pain[15]. It is estimated that fifty percent of all cancer pain is due to bone metastases[20]. Bone pain most frequently affects the spine and the chest, although pain in the hip, girdle and shoulder are also common[20]. The periosteum, the thick membrane covering all bones, contains many receptors and is highly sensitive to mechanical or chemical stimulation. Increasing pressure from an

expanding tumor, cytokine release, the formation of micro fractures, and pathological

fracture may all stimulate the periosteum, and produce the sensation of pain[15]. Bone pain

is generally a dull aching pain that may be interspersed with a stabbing discomfort. Pain

is often worsened by movement, and this debilitation is associated with a reduction in

quality of life[15].

Pathologic Fracture

Pathologic fractures occur in 9-29% of patients with bone metastases[21]. They are most

common with osteolytic lesions. The vertebrae and the ends of the humerus and femur

are the most frequent sites for fracture. This causes severe pain, requires immediate

medical attention, and often leads to prolonged disability[15].

Spinal Cord Compression

Spinal cord compressions occur in 2.5% to 5.0% of patients with terminal cancer[8]. The

spinal cord can become compressed by bone fragments from a vertebral fracture, or by an

expanding tumor .This damages the spinal cord by disrupting nerve signals, and can

cause paralysis of the legs and/or the arms if it is not treated immediately. Symptoms can

include pain, twitching, repetitive muscle contractions, sensory changes, and limb

weakness. The thoracic spinal region is the most common site for a spinal cord

compression.

Hypercalcemia

Hypercalcemia occurs when the blood calcium concentration elevates beyond normal levels. This can occur in patients with bone metastases as a result of the high rate of bone resoprtion. The maintenance of a hypercalcemic state involves other factors that offset normal calcium homeostatic mechanisms. The incidence is 30-40% in breast cancer patients, 20% in lung cancer patients, and less frequently in other tumors[20]. Common symptoms can include lethargy, muscle weakness, nausea, vomiting, and constipation. Severe hypercalcemia can result in a coma and death.

Management of Bone Metastases

Bone metastases are managed using a variety of treatment modalities that include: analgesics, chemotherapy and hormone therapy, bisphosphonates, surgery, and RT. In many cases, the management of bone metastases involves a combination oftreatments.

Analgesics

Opioids and non-opioid analgesics (acetaminophen and non-steroidal anti-inflammatory) drugs) play an important role in managing bone pain from bone metastases[3]. According to the WHO's three step cancer pain ladder, the management of cancer pain should progress from non-opioids to strong opioids, reflecting increasing need for pain relief. Non-steroidal anti-inflammatory drugs (NSAIDs) are used for mild to moderate pain and have been shown to reduce cancer pain by up to two times more than no treatment at all[22]. Their use is closely monitored to maintain the lowest possible dose which gives adequate pain relief but also minimizes gastrointestinal, liver, and kidney toxicities.

Opioids are stronger analgesics that are reserved for more severe cancer pain. Unlike

NSAIDs, there is no upper dosage limit, and they are associated with fewer side effects

(i.e. constipation)[23].

Chemotherapy and Hormone therapy

In some cancers, systematic treatments such as chemotherapy and hormone therapy can

be used to effectively treat bone metastases. Bone metastases from lymphoma and

myeloma respond better to chemotherapy than do bone metastases from kidney or liver

cancer. Hormone therapy is successfully used mainly in patients with hormone sensitive

breast[24] and prostate cancer[25].

Bisphosphonates

Bisphosphonates have been shown to inhibit osteoclasts activity, and induce apoptosis in

osteoclast and tumor cells. Thus, they are able to slow the process of bone resorption and

the associated elevation in blood calcium levels. A systematic review of randomized

trials demonstrated that the use of bisphosphonates reduced rates of bone fractures and

hypercalcemia[26]. The benefits of bisphosphonates are seen in patients approximately six

months after they begin treatment. Side effects of bisphosphonates include kidney

toxicity and gastrointestinal intolerance. Although they reduce the need for some

treatments (i.e. PRT), bisphosphonates are only recommended as an adjunct to other

therapeutic measures[27].

Surgery

Surgery is used in the treatment of pathologic fractures. The occurrence of a fracture is extremely painful, and surgery is performed at a time when the general condition of the patient is already poor. Hence, prophylactic surgical fixation of the bone is also indicated in patients at risk of bone fracture. Surgery may also be used in the event of spinal cord compression in a select population of patients. It may be used as an adjunct treatment in patients who have already been irradiated to the spine, or where there is spinal instability or compression of neural structures[28].

Radiotherapy

Bone pain is effectively palliated with PRT. For localized bone pain, external beam RT can provide effective relief. For patients with widespread bone pain, PRT can be administered using a wider field (half body radiation), or radiopharmaceuticals can be used. The benefits of PRT are experienced within a few weeks of treatment, and normally last for a period of three to six months[29]. PRT is recommended when opiods have failed to provide effective pain control[27], it also reduces toxicities associated with opiod use.

Efficacy of PRT for Bone Metastases

External Beam RT

The overall effectiveness of PRT for bone pain relief has been consistently demonstrated in numerous randomized controlled trials [8,11,30-35]. The majority of these trials have examined the effectiveness of external beam radiation for complete or partial pain relief [11,30,31,34,35] . McQuay et al. conducted a systematic review that synthesized the results of

twenty trials that examined the use of PRT for bone pain relief [34]. Their findings

indicated that at least 50% of patients undergoing PRT achieved complete pain relief or

partial pain relief [34]. Another review by Wu et al., reported that 60 to 80% of patients

experienced partial pain relief, and 15-40% of patients experienced complete pain

relief[36].

Hemi-body radiation

Hemi-body radiation is used in patients with delocalized pain. Treatment consists of a

wide field of radiation to the lower, mid, or upper region of the body depending on the

location of the symptoms. A major randomized trial examining the maximum tolerable

dose of hemi-body radiation showed that up to 80% of breast and 90% of prostate cancer

patients experienced improvements in pain[37]. Overall, the partial response rate was 73%

and the complete response rate was 19%. Improvements were seen in two weeks for 95%

of patients. Another trial examining the utility of hemi-body radiation with the addition

of external beam RT, showed that patients treated with the combined modality developed

fewer sites of pain[38]. The International Atomic Energy Agency trial demonstrated a

higher overall response rate. Ninety-one percent of patients achieved either complete or

partial response, and all patients responded within 3-8 days[39].

Radioisotopes

Radioisotopes are usually administered when patients present with multiple sites of bone

pain, or when systemic therapy is not effective. Strontium-89 and samarium-153, the

most commonly used radioisotopes, have been shown to be an effective adjunct to

external beam RT. A systematic review of eight studies found that radioisotopes had similar analgesic effects to external beam radiation [34]. However, Porter et al. and Quilty et al. demonstrated that increases in pain control could be achieved when radioisotopes were added to an external beam radiotherapy treatment modality [40,41]. Both authors showed that the use of radioisotopes in addition to external beam radiation resulted in fewer new sites of bone pain. Additionally, improvements in quality of life have been reported with the use of radioisotopes and external beam radiation compared to external beam radiation alone [41,42].

Fractionation and dose of PRT for Bone Metastases

While the efficacy of PRT for bone pain is well established, the ideal dose/fraction regimen remains controversial. Since the early 80's, large randomized trials have demonstrated that one single fraction of low dose RT is as effective at relieving bone pain as multiple fractions[11,43], suggesting the absence of a dose response relationship with respect to pain relief. A meta-analysis by the Cancer Care Ontario group similarly demonstrated that no difference existed[27,36].Despite the existence of this evidence, there still remains practice variation in the fractionation of PRT for bone metastases [44]. In Great Britain and the U.S. the most commonly prescribed dose/fractionation schedules are 20Gy in 5 fractions and 30Gy in 10 fractions, respectively[44,45]. In Canada, 20Gy in 5 fractions is most commonly used (72%)[46]. The reasons for the variation in practice patterns are not fully known. The fact that patients receiving single fractions are 2.5 times more likely to be retreated for subsequent episodes of pain may lead physicians to choose a multi-fractionated regimen[47]. Other reasons could include concerns about the ability of

a single fraction to prevent other serious latent bone related complications such as pathological fracture and spinal cord compression, or financial incentives for the physician working in privately funded systems.

Toxicity

Palliative radiotherapy for bone pain is well tolerated. Side-effects are related to total dose and fraction size, and depend largely on the body region that was irradiated. Pelvic irradiation may cause nausea and diarrhea resulting from bowel irritation; treatment to the cervical or thoracic spine is associated with the irritation of the throat and esophagus[48]. About one third of patients will experience pain flare-up, which can be prevented or treated with corticosteroids[29]. Wide field RT may cause myelosupression, nausea and vomiting, diarrhea, and transient increases in pain. Serious late side-effects are rarely seen due to the fact that the prognosis in patients is generally short, and treatment doses are low. However, if the patient's survival is long enough to experience them, these side effects should be considered.

Brain Metastases

Epidemiology

Brain metastases are a dreaded complication of end stage cancers. Although there are no reliable population-based measures, the incidence of brain metastases in advanced cancers is reputedly 18-24%[49,50]. Some speculate that the incidence of brain metastases is rising as a result of improvements in the management of systemic disease and better diagnostic techinques[51]. It occurs most frequently in patients with lung and breast

cancer, and these cancers account for greatest number of reported brain metastases[14].

More than 80% of patients have multiple metastases, and 50% have more than three[52,53].

Brain Anatomy

Hemispheres

The brain is divided into two cerebral hemispheres, left and right. These hemispheres are further divided into lobes: frontal, temporal, occipital, and parietal. The frontal lobes play a role in determining personality, while also housing connections for functions concerned with articulation and the process of swallowing. The temporal lobes are involved with hearing and balance, some visual functions, smell, and memory. The occipital lobes are the visual center, functioning in perception and visual recognition. The parietal lobes play a large role in speech recognition and spatial orientation. They also serve to connect the temporal and occipital lobes.

The brain is covered by the blood–brain barrier (BBB). It is composed of a continuous endothelium surrounded by a basement membrane. The endothelial cells of the brain contain tight junctions between them and lack fenestrations. The BBB restricts the free exchange of many nutrients and water-soluble compounds.

Consequences of Brain Metastases

The symptoms of brain metastases are varied, depending on where in the brain the tumor is located. Brain metastases tumors are more common in the frontal and parietal lobes than the temporal and occipital lobes. The increasing tumor size leads to increasing

intracranial pressure; thus, symptoms are generally progressive over days and weeks. The most common symptoms are mental/cognitive changes and headaches[50]. Some patients experience general weakness, vision disruptions, such as double- vision or partial blindness, and nausea or vomiting. Patients may also suffer from seizures or intratumoral hemorrhages, which are non-progressive symptoms.

Management of Brain Metastases

The treatment of brain metastases is multidisciplinary, and may involve radiotherapy, corticosteroids, surgery, and systemic therapy such as chemotherapy, and hormones.

Corticosteroids

Corticosteroids are often used at the first sign of brain metastases. They are used to help alleviate neurological symptoms due to brain metastases, and accomplishes this by reducing intracranial pressure caused by edema. There are many side effects to continued use of steroids. They include hyperglycemia, immunosuppression, psychosis, myopathy, and insomnia.

Anticonvulsants and Anticoagulants

Anticonvulsants can be used to reduce the frequency of seizures in patients who already have suffered a seizure. In patients with brain tumors, who have not yet had a seizure, anticonvulsants are sometimes used prophylactically; however, there is no evidence that this is beneficial[54]. Prophylatic therapy may reduce the effectiveness of other treatments

such as chemotherapy and corticosteroids, and could lead to other life threatening

conditions (e.g. Stevens-Johnson syndrome)[55].

Surgery

Surgery was not used in the management of brain disease until recently. It is most

commonly indicated in patients with a single metastasis to the brain. In patients with

multiple metastases, surgery is normally limited to patients with a dominant,

symptomatic lesion, and for those requiring a biopsy before the commencement of

therapy. Randomized trials have been conducted to examine whether or not surgery

conferred any advantage over whole-brain radiotherapy (WBRT) in patients with single,

operable brain metastases. Results showed that patients in the surgery plus WBRT arm

had higher rates of survival, local control, functional independence, and longer

neurologic related survival[56]. When compared to those receiving WBRT, patients who

receive surgery alone were more likely to recur locally, and distally; however, no overall

survival difference was observed.

Chemotherapy

Chemotherapy normally has a limited role in the management of brain metastases. This is

thought to be due to the inability of chemotherapeutic agents to pass the BBB, because of

their size and hydrophilicity. This may explain the increasing occurence of brain

metastases[51]. However, there is some evidence that the BBB becomes leaky in patients

with brain tumors, which suggest that chemotherapeutic agents could also penetrate the

BBB in patients with brain metastases. Some evidence indicates that response rates to

chemotherapy in the brain are similar to response rates in areas outside of the brain[57]. The fact that certain cancers are more sensitive to chemotherapy (e.g. lung, testicular, breast) explains much of the variation in the cranial response rates by disease site. Numerous randomized studies of chemotherapy alone versus chemotherapy plus WBRT have shown improvements in responses rates for the combined arm, but no difference in overall survival[57,58]. Temozolomide is a newer chemotherapeutic agent that is attractive because it has been shown to cross the intact BBB. There is some evidence that tumor response rates of temozolomide combined with WBRT are superior to WBRT alone[59].

Radiotherapy

PRT to the brain has been the standard treatment for patients with brain metastases for the past fifty years. WBRT and Stereotatic radiosurgery (SRS) are the two forms that are used. WBRT, as the name implies, is delivered to the entire brain, and is usually reserved for patients with multiple brain metastases not amenable to surgery or SRS, or with a poor functional status. SRS uses a convergent beam to deliver a single large dose of radiation to a particular target volume, which results in a greater effective dose to the tumor and less damage to surrounding tissue.

Efficacy of WBRT for Symptoms of Brain Metastases

Typically, 50-75% patients experience improvement in neurologic symptoms. Multiple studies have confirmed the efficacy of PRT with respect to relief of neurologic complications associated with brain metastases and improvements in quality of life[60-62]. In one large randomized study, Borgelt et al. assessed changes in neurologic functioning

(e.g. patient's ability to carry out normal activities) [43]. Their analysis of 1830 patients showed that neurologic improvements were experienced by 60-90% of patients post-treatment [43]. Specific neurologic symptoms have also been shown to be effectively treated with PRT. Upwards of 90% of patients with headaches, seizures, and increased intracranial pressure experience complete relief upon being treated [43]. Finally, there is evidence to indicate that median survival is increased by 3-6 months in patients undergoing WBRT; however, more research needs to be done in this area [52].

SRS for symptoms of Brain Metastases

Randomized trials have examined the additional benefit of SRS plus WBRT compared to WBRT alone[63-65]. In the Radiation Therapy Oncology Group (RTOG) trial, patients with one to three brain metastases were treated with WBRT, with the addition of SRS in one arm and no SRS in the other[63]. A benefit in overall median survival was observed only in the patients with a single metastasis. In patients with multiple metastases, the addition of SRS improved local control rates, but no survival benefit was observed.

Studies have also examined the use of SRS alone or in combination with WBRT. The rationale for this is that in a select group of patients, focused treatment can deliver better results without the late toxicity complications associated with WBRT. One randomized trial examined this issue in patients with 1-4 brain metastases[66]. They demonstrated that the addition of WBRT improved local control rates, and distant control rates; however, overall survival was not affected. These results were similar to the other retrospective studies on the topic[67-69].

Fractionation and dose of WBRT and SRS for Brain Metastases

Much like PRT for bone metastases, there remains disagreement as to the optimal

fractionation/dose schedule of WBRT for patients with brain metastases. Although there

are some who believe that a higher dose/ hyper fractionated regimen may improve

survival in patients with a favorable prognosis[53], evidence indicates that various

fractionation schedules are equivalent[60,70]. In practice, the majority of patients are treated

with a dose of 30Gy in 10 fractions over the course of two weeks. The maximum

tolerable dose for SRS as defined by the RTOG trial is dependent on the size of the

tumor. For tumors 31-40mm, 21-30mm, and <20mm the maximum tolerable doses are

15, 18 and 24 Gy, respectively.

Toxicity of WBRT and SRS for Brain Metastases

Late stage toxicity can become an issue for patients treated with WBRT who survive long

enough. WBRT is also associated with some acute toxicity. Studies have reported the

following side effects: nausea and vomiting, skin and ear toxicity, fatigue, and

headaches[59,61,71]. High doses of SRS and large target volumes are associated with

radiation necrosis

Accessibility of RT services

There exists a wealth of scientific evidence substantiating the efficacy of PRT. However,

the mere existence of this treatment within the population does not necessarily lead to

better cancer outcomes. The extent to which an effective treatment improves the health of

a population is indicated by the proportion of those who need the treatment who actually

receive it. The concept of accessibility is concerned with this very issue. Research in this

area is important, as improvements in the accessibility of PRT help to facilitate better

population health outcomes.

Concept of Accessibility

The term *accessibility* has been used to describe the relationship between the need for,

and use of a health services[72]. Need occurs when a patient develops an illness for which

there is an *available* and *acceptable* treatment. The term *available* implies that there is

adequate supply of resources so that the treatment can be administered, and the term

acceptable implies that patient is willing to use the treatment. Effectiveness could also be

added to this definition to indicate that the treatment has been proven to be efficacious

through research and experimentation.

Accessibility has also been described by Penchansky and Thomas as a measure

representing the degree of fit between the clients and the health care system. The term

accessibility can be conceptualized as being comprised of the following dimensions:

availability, spatial accessibility, affordability, accommodation, and acceptability [73].

Availability refers to the volume of health services in relation to the volume of need in the population. This dimension involves the appropriateness of the supply of health resources (e.g. physicians, health personnel, facilities) in relation to the needs of the population. *Spatial Accessibility* refers to the location of supply in relation to the location of consumers. This dimension is concerned with the distance to facilities where care is provided, travel time, and costs associated with traveling. *Accommodation* refers to the manner in which the supply resources are structured to accept clients. This dimension reflects aspects of the health care system such as a facility's hours of operation and transportation services to and from care. *Affordability* refers to the relationship between the price of services and the client's ability to pay. This involves the direct costs of treatments, as well as the indirect costs of treatments such as payments for parking or lodging during the course of treatment. *Acceptability* refers to the client's attitudes to the characteristics of the service providers and the service. This refers to factors such as the perceived invasiveness (e.g. toxicities), practicality of particular treatments (e.g. number of fractions and courses required), or expectations of treatment (e.g. will patient die, or is there a potential for cure?)

Aw*areness* is an additional dimension that has been detailed by Mackillop [72]. Awareness refers to the extent to which those who need a service are aware that it is available and that they may benefit from it. This is reflected in the level of awareness held by health professionals (e.g. referring physicians) or the patient themselves.

Measuring the accessibility of RT

Access to RT is commonly indicated by utilization rates. In this context, a utilization rate represents the proportion of patients receiving RT in a given population. Access is realized when the proportion of patients in a population who receive RT is equal to the proportion of patients who need RT treatment. When the RT utilization rate is below the proportion of those in need, access is suboptimal. Problems with any one of the *dimensions of access* can serve to decrease RT utilization. Hence, much research on access to RT examines the relationship between the dimensions of access and RT utilization rates. Discovering deficiencies in any of the dimensions is an important role for research, as these may offer a prescription for improving access to RT.

Indicators of the Dimensions of Access

The following section discusses some indicators of the dimensions of access available within population-based registries, and their potential influence on RT utilization rates.

Information on prevailing RT waiting times can be used as an indicator of the *availability of* RT resources. The existence of long prevailing RT waiting times signals an imbalance between supply and demand and could lead to implicit rationing. Implicit rationing is a process whereby physicians, in the presence of long RT waiting lists, defer the use of RT and prescribe alternative, sometimes less effective modes of treatments. This results in decreased utilization of PRT.

Travel distance to a cancer facility has been shown to be associated with inadequate *spatial accessibility* of RT services. Those living far from a cancer facility encounter potential barriers such as lack of transportation or long travel time that may act to discourage the use of PRT.

Median household income, an SES measure, has been shown to be connected with the *affordability* of PRT services [74]. Those earning a lower income may be deterred from using PRT due to implicit costs of treatment, such as the price of parking or gas, or indirect costs to family members who may transport them to treatment, such as time taken off work. Median household income is also associated with the *awareness* of RT. Patients from lower SES may not have the educational background or social networks that would inform them of the availability and benefits of PRT treatments.

Age may be associated with *awareness* of PRT. Numerous studies have shown that older patients are less likely to receive treatment with RT[74,75]. This relationship holds even after taking into account a patient's functional status. It could be that due to the lack of elderly patients in PRT efficacy trials, referring physicians may be skeptical of the effectiveness of PRT in the elderly population. This could lead to ageism among referring physicians.

The presence of a radiation oncologist at the hospital of diagnosis may indicate *awareness* of PRT services. Doctors who work in a setting with a RT facility are more likely to be aware of the indications for PRT; thus, prescribe the treatment for their

patients.

Studies on Access to RT and PRT

Access to RT services has been studied extensively in the literature. Many studies have identified many barriers to access that serve to reduce utilization of RT. Ballard-Barbash et al. demonstrated that a lack of health insurance coverage was associated with the reduced rates of RT[76]. Far distance from a RT facility, and the absence of family physicians and oncologists within the community are also all associated with decreased RT utilization rates [77-80] . Numerous studies have found that old age is associated with reduced RT utilization. Athas et al. found that patients over the age of 70 were 0.30 times less likely to receive RT after breast conserving surgery compared to those under the age of 50. Other patient-related factors such as SES, education, and race/ethnicity have been shown to influence the use of RT services [74,77,81 80].

Much less is known about the accessibility of PRT in the general cancer population. During the past decade, only five population based studies of the use of PRT have been published. These studies have demonstrated similar findings to those of the other population-based RT studies[77,78,82,83]. Distance to the nearest cancer facility, age, SES were all identified as factors influencing access to PRT. Hayman et al. described the use of PRT in patients with lung cancer. They found that patients who were hospitalized or admitted to a teaching hospital were more likely to receive RT. Further they showed that patients who were already on chemotherapy were more likely to receive treatment. Danielson et al. demonstrated the presence of a radiation oncologist in the city in which

the patient resided was associated with increased PRT rates, suggesting problems with the dimension of availability and awareness. Johnston et al. showed that, when compared to patients not receiving RT, those who received a previous course of curative RT were more likely to receive PRT, indicating potential problems with the dimension of awareness.

Although studies have been conducted in other regions, the majority of what is known about access to RT has come from the province of Ontario.

The structure of the Ontario RT system

Key elements of the Ontario RT system such as the existence of regional cancer care centers, a centralized coordinating body, and government funding have remained largely unchanged since its development in the 1950's. All RT is provided by 12 regional cancer centers located in major cities across the province (Toronto, Ottawa, Kingston, Sudbury, Thunder Bay, London, Windsor, Hamilton, and, Kitchener). These centers are home to state of the art cancer therapies and RT equipment, and employ a team of expert cancer specialists and supportive staff. Radiation Oncologists, physicians who prescribe RT, working in these centers see patients only through referrals from other physicians. There are no direct financial expenses to the patient for any consultations or RT treatments that they may receive, as this is fully covered by the Ontario Health Insurance Plan (OHIP).

The structure of the Ontario RT system affords two clear benefits. First, the centralization of RT services results in the concentration of a high level of expertise and state of the art

equipment within the regional cancer centers, which grants all Ontarians access to the highest quality of RT care. Second, the absence of direct financial barriers to treatment promotes equitable access to care, allowing patients to gain access to RT regardless of their ability to pay.

Studies on access to RT in Ontario

Despite the many advantages of the RT system in Ontario, access to this treatment is still inequitable. Studies have shown that a variety of different health system-related and patient-related factors govern the use of RT for Ontarians. Long RT waiting lists have been shown to be associated with the use of RT in Ontario[83]. One study showed that patients residing in counties with a longer prevailing waiting time were prescribed a smaller number of fractions of PRT[83].

As a result of the centralization of RT services, patients living in counties without a regional cancer center are at a disadvantage when it comes to receiving treatment. Paszat et al. showed that patients who lived greater than 325km from a RT facility were 0.31 times as.likely to receive RT as compared to those living less than 8km away , and Mackillop et al. demonstrated that rates of RT use were lowest in regions without a RT facility, indicating that traveling distance to a cancer centre may be a prohibitive factor in the use of RT [75,74].

Patient-related factors have also been identified as barriers to treatment. Paszat showed that patients over the age of 80 were 0.08 as less likely to receive RT as compared to

patients <40 yrs[74]. Tyldesly et al. demonstrated similar results, and also showed that the decline in rate of RT was not justified by a decline in functional status in the elderly[81].

An association between SES and the use of RT has consistently been demonstrated in the literature. Patients from poorer communities are less likely to receive RT treatment. One study showed that residents of the poorest communities were 0.83 times as likely to receive treatment when compared to residents of the richest communities[74].

Studies on access to PRT in Ontario

Although much is known concerning the accessibility of RT in Ontario and in other comparable centralized systems, very little is known about the use of PRT. To date, there has only been one population-based study that has examined the overall utilization of PRT in Ontario. The author's findings were consistent with those from the other population based RT studies in Ontario. Residing in a county without a RT facility or in a low income community, and advanced age were all shown to be associated with decreased utilization of PRT[83]. The authors also demonstrated that the hospital in which a patient was initially diagnosed influenced whether or not they received treatment. Overall, the PRT utilization rate was 26.4%.

In addition to these findings, surveys suggest that access to PRT in Ontario may be hindered by a lack of awareness of the indications for PRT among referring physicians. Results have shown that a large proportion of family physicians and other health professional are not aware of the indications for PRT. One survey of 345 Ontario family

physicians reported that only 40% had received formal training in palliative care, and only 10% had received training in radiation oncology[84]. Another survey of 172 Ontario family physicians similarly found that a lack of PRT knowledge and awareness of cancer center services were a barrier to PRT referral[85].

Studies on access to PRT for Brain metastases and Bone metastases in Ontario

Much like use of PRT, very little is known about the use of PRT for brain and bone metastases. To date, there has only been one population based study on the utilization of PRT for bone metastases. Kong et al. examined factors that influenced variation in the fractionation of PRT for bone metastases[86]. This question was of particular interest because evidence indicates that single short fractions are equivalent to multiple fractions in terms of pain relief. The time taken to complete a multi-fractionated course may act as a deterrent for many patients with a limited lifespan, and family physicians may be less likely to seek out PRT as a treatment option. The authors showed that long prevailing waiting times were associated with the use of fewer fractions. They also showed that a far distance from a cancer facility, as well as advanced age were associated with the use of a single fraction of PRT for bone metastases as opposed to multiple fractions.

No population based studies examining the use of PRT for brain metastases were identified.

Improving the Accessibility o RT services in Ontario

Since the mid 1990's the RT system in Ontario has undergone considerable changes that were aimed to improve access to RT services. This section discusses a few notable changes.

Opening of New Cancer Facilities

In 2003 and 2005, regional cancer centres opened in Kitchener and Mississauga, respectively, serving a combined catchment area of 1.9 million. The addition of new staff, equipment, and facilities has increased the supply of RT services in these previously underserviced areas, which may have improved the *availability* of RT services.

Reorganization of Cancer Services

Previously, Cancer Care Ontario (CCO), the Ministry of Health's sole advisor on issues relating to cancer, operated all of the regional cancer programs across Ontario. These programs were responsible for providing 75% and 40% of all RT and systemic therapies respectively [87]. The remaining portion of cancer therapies was provided by hospitals and community centres across the province; however, there was a lack or coordination between all cancer related programs. In 2001, the regional cancer programs became integrated into their host hospitals, offering more comprehensive services, and including surgical treatments that were previously outside the scope of CCO's program. The integration of these once disparate services may have increased the *awareness* of the

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benefits of RT among previously disassociated health professionals working in separate
systems.

Increases in the number of Radiotherapy Machines across Ontario

From 1996-2004 the number of LINACs at all Ontario Cancer Centres increased from 45
to 70. The yearly number of new RT courses that can be administered on one LINAC
machine ranges from 200-500 [88] . Figure5 demonstrates that the increase in the number
of RT machines (capacity) exceeded the increase in incident cases of cancer (demand),
indicating that the *availability* of PRT may have improved during that time.
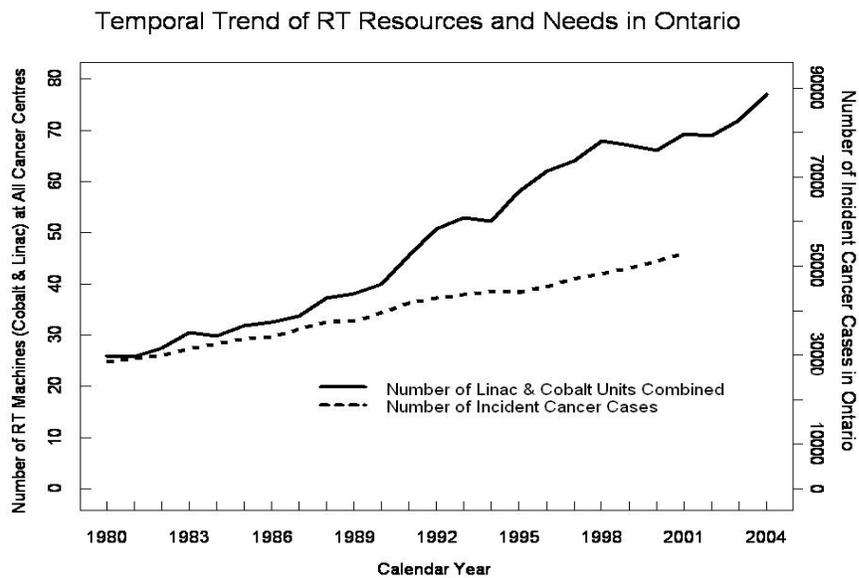
Figure 5. Increases in the number of RT machines and incident cancer cases in Ontario
over time.

Rapid Response Radiotherapy Programs

Long waiting lists are a barrier to PRT referral and PRT utilization [86]. In Ontario, the median waiting time from referral to the start of treatment is 7 weeks [89]. The period is comprised of the waiting time from referral to consultation, and waiting time from consultation to treatment. In 1996, in an effort to reduce waiting time specifically for PRT, the Toronto-Sunnybrook Regional Cancer Centre developed the Rapid Response Radiotherapy Program (RRRP). When appropriate, the RRRP allows for patients to be referred, consulted, and treated on the same day, drastically reducing the waiting time. From the 1996-2003, 3920 patients were referred to the RRRP. A plan for RT was created on the same day as consultation in eighty percent of patients, and 60% received treatment on the same day of their consultation[89]. Other Regional Cancer Centres, such as the Princess Margaret hospital, and the Hamilton and Ottawa regional cancer centers have adopted a similar program[90].

Summary of Background and Rationale

Studies of RT utilization have shown that access to RT in Ontario is inequitable. A variety of health system-related factors, such as distance to a cancer facility, and patient-related factors, such as age and SES, influence the use of RT. Very little is known, however, about the use of PRT in Ontario. While one Ontario study has examined the general use of PRT, no study has been conducted to describe the accessibility of PRT for bone and brain metastases, in particular.

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Chapter 3

Manuscript 1: The use of Palliative Radiotherapy for Bone Metastases in Ontario from 1984-2004

This manuscript conforms to the specifications for submission to the peer-reviewed journal
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Abstract

Background: Palliative radiotherapy (PRT) plays an important role in the management of patients with bone metastases; however, little is known about the use of this treatment within the general cancer population.

Purpose: To describe the use of PRT for bone metastases in Ontario, and to identify factors that are associated with receiving treatment.

Methods: The Ontario Cancer Registry was used to gather information on all cancer deaths in Ontario between the years 1984-2004. The proportion of these patients receiving at least one course of palliative radiotherapy for bone metastases within the last two years of life (rate of PRT) was described. We conducted a multivariate analysis to examine the association between health system-related, patient-related and disease-related factors, and the use of PRT for bone metastases.

Results: Between 1984 and 2004, there were 434,241 cancer deaths. Of these patients, 10.0% percent received at least one course of PRT for bone metastases within the last two years of life. We observed a decrease in the rate of PRT over the study period, which remained significant after controlling for other factors. The rate of PRT varied by factors reflecting varying need such as primary site (e.g. myeloma-32.7%, breast -25.7%, prostate-25.0%, head and neck-5.2%, stomach-2.8%, pancreatic-1.1%), and time between diagnosis and death (e.g. <1 month-1.5%, 6-12 months-9.7% 12-36 months-12.5%). However, factors unrelated to need also influenced the rate of PRT. The rate of PRT was negatively associated with age, and there was an association with SES. There was a negative association with distance to the nearest cancer center (i.e.10km-10.3%, 10-50km-9.8%, >50km 8.7%), and the level of RT services at the diagnosing hospital was positively associated with the use of PRT (i.e. affiliated with RT facility-12.0%, not affiliated with RT facility-9.8%).

Conclusions: The use of PRT for bone metastases has significantly decreased over time, and was significantly influenced by factors unrelated to need.

Keywords: Palliative; Radiotherapy, Bone Metastases; Access; Utilization

Introduction

Bone metastases are a common and serious complication of advanced cancers. The exact incidence of bone metastases is difficult to determine with accuracy. Estimates vary depending on the method of assessment that is used. Although there are no reliable population-based estimates, the incidence of bone metastases among those dying of cancer is reputedly 20-27%[1,2]. Metastatic bone disease most frequently results in bone pain, and can also lead to major skeletal events such as pathological fracture, spinal cord compression, and hypercalcemia. These consequences are a significant source of morbidity, causing immobility and neurologic deficits, and can negatively affect a patient's quality of life.

The use of palliative radiotherapy (PRT) in the management of bone metastases is well established. Numerous trials have demonstrated the efficacy of PRT for the relief of bone pain[3-9]. A recent systematic review of trials examining differing fractionation schedules, demonstrated that PRT was able to achieve partial pain relief in 58% of patients, and complete pain relief in 23% of patients[10]. Consensus statements and guidelines from numerous groups advocate the use of PRT for the palliation of pain due to bone metastases[11-13]. In Ontario, the Cancer Care Ontario Guidelines Initiative recommends a single 8 Gy treatment to relieve uncomplicated bone pain[14]. While PRT is regarded as an

effective treatment, very little is known about the *accessibility* of this treatment within the general cancer population.

The term *accessibility* has been used to describe the relationship between the need for, and use of a health services[15]. Need occurs when a patient develops an illness for which there is an available and acceptable treatment, and use refers to the utilization of that particular treatment. The concept of *accessibility* can be thought of as being comprised of six dimensions: availability, affordability, spatial accessibility, accommodation, acceptability, and awareness[15,16].

Availability refers to the supply of services, such as oncologists and health care facilities, in relation to the demand for those services (e.g. incident cases of cancer). Spatial accessibility refers to the location of the supply of health care in relation to the location of those who are in need of it.(e.g. travel distance to a health care center[17]). Affordability refers to the price of treatment and the patient's ability to pay for it, and can be indicated by such things as the level of insurance coverage within a population. Accommodation refers to the manner in which the health system is set up to accept patients. This reflects factors such as the operating hours of a health care facility or transportation services to and from care. Acceptability refers to the patient's attitudes about the suitability of the treatment provider or the treatment itself. Last, awareness refers to the extent to which those who are in need are aware that a treatment is available, and that they may benefit from it. This is reflected in the level of awareness held by health professionals (e.g. referring physicians) or patients themselves. Problems with any of these dimensions can

serve as barriers to access, ultimately leading to a reduction in service utilization rates. On a population-wide level, low rates of RT have been shown to be associated with poorer health status[18]. Further, suboptimal access may also indicate that the provision of care is inequitable. This may be at odds with the objectives of many health care systems, whose aim is to provide equitable access to treatments.

The Ontario RT system is one such system. All RT is provided by a network of large regional cancer centers located across the province. Radiation oncologists in theses centers work in large multidisciplinary groups, which promotes the provision of comprehensive and high quality care. All patients are insured through universal health coverage and thus, do not directly pay for any treatments or consultations they receive. While these aspects of the RT system minimize some potential barriers to access, evidence suggests that the accessibility of RT services in Ontario is still suboptimal. The centralization of RT facilities has lead to problems with spatial accessibility. Patients living in more remote areas, not immediately serviced by a cancer center, have been shown to have reduced access to RT[19,20]. The level of cancer service at the diagnosing hospital has been shown to influence RT rates[21], suggesting problems with the awareness of RT services. Advanced age and low SES[20,22] are also associated with lower rates of RT, which could indicate potential problems with the acceptability or awareness of RT services. Long waiting lists signal inadequacies with the availability of RT resources, and have been shown to influence the choice of fractionation[23]. Long waiting list may also decrease the utilization of RT[15].

Research on access to RT in Ontario, however, has remained focused on the general use of RT (i.e. curative, palliative). Although a previous study by our group did examine the overall use of PRT services in Ontario[24], no studies have described the accessibility of PRT for bone metastases in particular. Hence, the primary objective of this study was to describe the relationship between potential indicators of access and the use of PRT for bone metastases.

We have previously reported on temporal trends in the fractionation of PRT for bone metastases [23], but this has not been described for the general use of this treatment. The second objective of this study was to describe temporal trends in the use of PRT for bone metastases.

Methods

Study Design

A retrospective population-based cohort study was conducted.

Study Population

The study population consisted of all Ontario residents who died of cancer between the years 1984 and 2004. Patients who died of a primary bone cancer were excluded from the cohort.

Sources of Data

The Ontario Cancer Registry (OCR) is a population-based registry that has been collecting patient demographic and vital status information on all cancer diagnoses,

except non-melanoma skin cancer, within the province since 1964. The OCR gathers its information from four major sources: hospital separation records, pathology reports, death certificates, and reports from the provincial cancer centers. Records from these sources with a mention of cancer are linked through probabilistic linkage[25]. Variables available within the registry include: date of birth, sex, date of diagnosis, primary site, total number of primaries, vital status, date of death, cause of death, residence at time of diagnosis, and diagnosing hospital. The OCR is 95% complete for all cancer sites combined[26].

Between 1984 and 2004, all RT in Ontario was provided by the Princess Margaret Hospital and eight regional cancer centers. Since 1982, these centers have kept electronic records of all RT administered in Ontario in a standard format. For every course prescribed, information on the start date of RT, total dose and number of fractions, intent of RT, and body region irradiated is provided. Information from these records was linked to the OCR database. The RT database is more than 95% complete.[23]

Statistics Canada provides socioeconomic (SES) information for the entire country at the census subdivision (i.e. municipality), and the census enumeration area code level (i.e. geographic area equivalent to one or two blocks). Area-level SES data was linked to each record in the OCR using the patient's residence at the time of diagnosis. The linkage process is described in detail elsewhere[27].

The Canadian Institute for Health Information (CIHI) receives hospital separation records from all general hospitals in Ontario. Variables available in this database include date of admission, date of discharge, and diagnosis (ICD-9).

PRT

A patient was considered to have received PRT for bone metastases if they had been treated with at least one course of PRT to a body region corresponding to a bone (e.g. femur, ribs, skull, etc.) within the last two years of life. When the pelvis was indicated by the body region code it was not possible to determine whether the region irradiated was the bony pelvis or the pelvic organ. We therefore did not include radiation to this body region in patients with pelvic cancers (e.g. prostate, rectal, bladder, etc.).

Patient-related factors

The *sex* of each patient was examined. *Age at death* was determined for each patient by subtracting the date of death from the date of birth. Values were grouped into the following categories: <40 yr, 40-49 yr, 50-59 yr, 60-69 yr, 70-79 yr, 80-89 yr, >=90 yr. *Median household income* was used to represent the SES of each patient. This variable is defined as the median household income level of the community in which the patient resided at the time of diagnosis. Values for the median household income measure were divided into quintiles.

Disease-related factors

Primary Site was determined using information from the ICD-9 coding system. *Time between diagnosis and death* was defined as the time between the date of diagnosis of the

first primary and the date of death. Values were grouped into the following categories: 0-2 months, 2-6 months, 6-12 months, 12-36 months, 36-72 months, 72-120 months, and >120 months.

Health system-related factors

Prevailing waiting time is a concept that has been previously used to describe the relationship between the supply of and demand for RT resources at a given cancer center, at a given point in time[23]. Prevailing waiting in a given county, at a given point in time was defined as the median time between the date of diagnosis and the start date of RT among residents who received adjuvant/curative RT in the preceding six months. Although each patient was not treated with PRT, we ascribed to them a prevailing waiting time value based on their county of residence on the date one year before their death. We did not include PRT because we had no measure of the date at which PRT would be indicated. Since, however, all types of RT compete for the same resources, waiting time for curative/adjuvant RT is likely to affect waiting for PRT. The distribution of prevailing waiting times was grouped into quintiles.

Level of RT service at the diagnosing hospital. We assigned each patient to a general hospital that was responsible for his or her care in and around the time of diagnosis. We were able to successfully identify the diagnosing hospital in 94.5% of patients. Hospitals were then classified into two categories:1)affiliated with RT facility 2) not affiliated with RT facility.

D*istance to the nearest cancer centre* was defined as the linear distance between a patient's residence at the time of diagnosis and the cancer centre most frequently visited by patients within that census subdivision. The linear distance was previously calculated using the Arc-Info mapping program. A more detailed account of this calculation is described elsewhere[20]. Each patient was ascribed a distance value, and then grouped into one of the following categories: <10km, 10-50km, >50km.

Death year was grouped into four time periods: 1984-1989, 1990-1994, 1995-1999, and 2000-2004.

Statistical Analysis

The *Rate of PRT* was defined as the proportion of patients who received at least one course of PRT for bone metastases within the last two years of life. We calculated the rate of PRT for bone metastases and the 95% confidence intervals for subgroups within each variable. The chi-square test was used to identify any significant associations. Arc View was used to create a map of Ontario to examine inter-county variation in the rate of PRT in the most recent time period, 2000-2004. The Cochran-Armitage test for trend was used to examine any significant temporal trends in the rate of PRT over the study period. Rates were directly age-standardized to the 2001 study population to allow for valid comparisons between counties and over time.

We conducted a multivariable logistic regression using the entire study population. All study variables were simultaneously entered into the model, and the OR and 95%

confidence interval was calculated to represent the strength and its plausible range, respectively. To examine how the association between the study variables and the use of PRT for bone metastases had changed over time, we stratified our results over four time periods: 1984-1989, 1990-1994, 1995-1999, and 2000-2004.

An alpha level of 0.05 was used to determined statistical significance. All statistical analyses were performed using SAS version 9.1 (SAS Institute, North Carolina, USA).

Results

Study Population

Column one of Table 1 and Table 2 describe the characteristics of the study population. There were 434,241 cancer deaths in Ontario during the entire study period. Eighty-two percent of cancer patients were microscopically confirmed and 18% were clinically confirmed. The number of cancer deaths per year increased from 16,394 in 1984 to 24,468 in 2004.

The median age at death for the entire cohort was 72 years. Approximately 25% of patients were over the age of 80 years. The most common causes of death were lung cancer (25.1%), colorectal cancer (10.6%), breast cancer (8.8%), prostate cancer (5.9%), and pancreatic cancer (5.0%). The median time from diagnosis to death for the entire cohort was 10 months. The majority (75%) of patients were diagnosed in a hospital not affiliated with a RT facility. Approximately a third of the study population was found in

each of the following groups: <10km, 10-50km, and >50km from the nearest cancer centre.

Fractions and Courses

Figure 1a shows the total number of treatment courses administered to patients receiving PRT for bone metastases. The majority of patients received only one treatment course (74.5%), 20.0% of patients received two courses, and 5.5% of patients received three or more courses. Figure 1b shows the number of fractions per course administered to all patients treated with PRT for bone metastases. Thirty percent of patients were treated with 1 fraction per course, 47.0% of patients were treated with 5 fractions per course, and 9.8% of patients were treated with 10 fractions per course. The mean number of fractions per course over the entire study period was five.

PRT rate in last two years

A two year interval cut-off was used because it allowed us to capture almost all patients that had received at least once course of PRT, while at the same time providing a small enough time period to allow complete follow-back for the cohort. Figure 2 shows the proportion of patients receiving at least one course of PRT for bone metastases as a function of time between last course of PRT and death. Using a 6 month cutoff the rate of PRT is 7.2%, while at one year the rate of PRT is 8.9%. Using a two year cutoff, we were able to capture 95% of patients ever treated with PRT for bone metastases, giving us a rate of 10.0%. Hence, our two year cutoff was a reasonable definition.

Patient-related factors

Table 1 shows that on univariate analysis, sex was associated with the use of PRT for bone metastases. Females were more likely to receive treatment than males, but after controlling for other factors, this association disappeared. Age was negatively associated with the use of PRT, showing a sharp decreasing trend (p<0.0001) in the univariate analysis, and in the multivariate analysis. There was a significant increasing trend in the association between median household income and the use of PRT (p=0.04). After controlling for other factors , the relationship between income and PRT remained significant. Patients in the fourth and fifth highest quintile were 1.04 and 1.11 times more likely to received treatment, respectively.

Disease-related factors

There was variation in the use of PRT by primary site. From Table 1 we see that diseases in which the incidence of bone metastases is most common had the highest rates of PRT. It should be noted that, although the absolute number of lung cancer patients receiving PRT was higher than any other disease, the rate of PRT in this group was not the highest. The rate of PRT for the other hematopoietic diseases was the following: 6.4%-non-Hodgkin'slymphoma, 4.9%-Hodgkin's lymphoma, and 1.4%-leukemia. For the gynecologic cancers, the rate of PRT was 8.7 % for endometrial cancer, 7.9% for cervix cancer, 2.2% for ovarian cancer, and 8.2% for vaginal cancer. Table 1 shows that in both univariate and multivariate analyses, time between diagnosis and death was associated with the use of PRT. The rate of PRT increased up until >120 months between diagnosis and death.

Health system-related factors

Figure 3 shows inter-county variation in the age-standardized rate of PRT for bone metastases, using the most recent time period, 2000-2004. In northern Ontario, the rate of PRT was 10.4%, while in southern Ontario the rate was 9.1%. Rates of PRT were generally higher in regions with a cancer centre, and in southeastern Ontario.

Table 2 shows that distance was negatively associated with the use of PRT in the univariate analysis, demonstrating a clear downward trend (p<0.0001). After controlling for other factors, this decreasing trend remained significant. The level of RT service at the diagnosing hospital significantly influenced the use of PRT for bone metastases. Patients diagnosed in a hospital affiliated with a RT facility were 23% more likely to receive PRT. This association remained significant after other factors were included in the model. Table 2 shows the univariate and multivariate results examining the association between prevailing waiting time and the use PRT for bone metastases. OIn the univariate analysis, prevailing waiting time was significantly associated with the use of PRT, but this association disappeared after controlling for patient-related and disease-related factors.

Temporal trends

From 1984 to 2004, 10.0% of patients received at least once course of PRT for bone metastases in the last two years of life. Figure 4 shows changes in the age-standardized rate of PRT for bone metastases over the entire study period for all diseases combined,

and for a few selected disease sites. The overall age-standardized rate of PRT decreased from 10.34% in 1984 to 9.5% in 2004, and this trend was statistically significant (p<0.0001). When temporal trends were examined by primary site, we observed increases in the use of PRT in some primary sites, and decreases in others. For instance, the use of PRT increased in patients with prostate, bladder, and colon cancer. The use of PRT significantly decreased in patients with hematopoietic malignancies, and in patients with breast, lung, multiple myeloma, and melanoma cancer.

Changes in the associations over time

Table 3 shows the results of the multivariate analysis stratified by time period. In general, the trends observed were similar in each time period examined. Patient-related factors such as sex and age, demonstrated similar associations across time period strata. The association between median household income and PRT, however, disappeared in the first and last time period. The relationship between some health system-related factors, distance and level of RT service at the diagnosing hospital, and the use of PRT were similar independent of time period. When prevailing waiting time was examined, a significant relationship emerged in the first and third time period only.

Discussion

The main finding of our study is that access to PRT for bone metastases is influenced by factors unrelated to need, and that, in general, this has not changed. Age and SES both influenced the use of PRT. Patients living farther distances from a cancer center, and those diagnosed in a hospital without a RT facility were less likely to receive treatment.

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Access to health care is said to be equitable when the level of utilization of a service is equal to the level of need for those services. The main limitation of this study is that, due to the lack of reliable population-based estimates of the frequency of bone metastases and symptoms of bone metastases within the population, we did not have an overall measure of the need for PRT. Without a measure of need for comparison, it is difficult to state whether our observed PRT rate of 10.0% represented overutilization or underutilization of PRT services for bone metastases.

We did observe variation in the use of PRT by factors related to varying need (i.e. disease-related), suggesting appropriate utilization. Diseases in which the probability of developing bone metastases was high, thus the need for PRTis presumably high, had higher rates of utilization (Table1). We also observed that the use of PRT was quite low in patients dying shortly after diagnosis. As life expectancy decreases so does the likelihood that a patient will benefit from PRT; therefore, the low utilization rate in these patients is appropriate.

There was, however, variation in the use of PRT by factors unrelated to need. We observed that age was negatively associated with the use of PRT for bone metastases, which is consistent with the findings of similar studies[20,22,24]. Although a declining functional status could potentially render the elderly less fit for treatment [28], evidence indicates that an age-related decline in the use of RT persists even after taking into account functional status[22]. In others words, when the need for RT is equivalent across

age groups, the use of RT still disproportionately favors the young. The reasons for this are not clear. Some have suggested that a decreased preference for treatment, ageism and a lack of awareness of life expectancy and available treatment in the elderly among referring physicians, may serve to limit access to PRT in the elderly[29], which would indicate potential problems with the dimensions of *acceptability* and *awareness.*

SES is another patient-related factor, that has been shown to influence the use of PRT[20,24]. We found that, overall, SES was positively associated with the use of PRT, but in the most recent time period, this relationship disappeared. This would suggest that the use of PRT for bone metastases across different SES groups has become equitable.

Variation in the use of PRT by health system-related factors also suggests suboptimal access to care. The hospital in which a patient is diagnosed should not determine whether or not they receive treatment; nevertheless, this is what we observed. A previous study by our group also demonstrated similar results[24]. In Ontario, hospitals affiliated with a RT facility form the regional cancer centers. It would seem that once a patient is initially managed in a hospital with a high level of cancer service, subsequent access to PRT is less challenging. We believe that oncologists working in these centers carry a greater level of *awareness* about PRT and its uses, which translates into greater access to treatment for patients.

Distance was another factor unrelated to need that influenced rates of PRT. In Ontario, and other centralized RT systems, far travel distance has been shown to restrict access to

RT[20,30-32].It is conceivable that patients living extremely far distances from a cancer center may be less inclined to travel to a center for a single course of PRT. This suggests problems with the dimension of *spatial accessibility*, and points to the need for better service in dispersed communities.

To assess the *availability* of PRT services, we developed an indirect measure of the pressure on a cancer center we termed prevailing waiting time. We hypothesized that, in periods of long waiting times, the use of PRT would decrease through a process called implicit rationing[15]; however, there was no relationship overall. Kong et al. reported that prevailing waiting time influenced the choice of fractionation for bone metastases. Taken together, these findings indicate that strain on a cancer center may not prevent a patient from accessing PRT, but may influence the type of treatment they receive.

We have reported elsewhere that during the same study period, the use of PRT for brain metastases more than doubled[33]. Thus, our finding, that the rate of PRT for bone metastases has decreased over time, highlights distinctly different PRT practice patterns in Ontario.

In conclusion, our analysis has shown that the use of PRT for bone metastases is influenced by patient–related and health system-related factors. We have also added to the knowledge of how PRT resources are utilized in Ontario. Our group has previously reported that the overall rate of PRT in Ontario was 26.4%[24], and we have now shown that 10.0% of cancer patients received PRT specifically for bone metastases, and that

utilization has significantly decreased over time. The opening of three new cancer centers since September of 2003, have potentially improved the accessibility of PRT services in Ontario. Once contemporary data are available, we will examine the extent to which these improvements have helped attenuate the disparities that we have observed.

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Table 1. Patient-related factors and disease-related factors associated with the use of PRT for bone metastases (period: 1984-2004)

	N (% patients)	N (% receiving PRT)	Rate of PRT (95% CI)	OR (95% CI)	p value
Total	434241 (100.0)	43244 (100.0)	9.96 (9.87, 10.05)		
Sex					
Male	231507 (53.3)	2511 (52.1)	9.72 (9.60, 9.84)	1.00 --	0.22
Female	202734 (46.7)	20733 (47.9)	10.23 (10.09, 10.36)	1.01 (0.98, 1.04)	
Age at death (years)					
<40	10256 (2.4)	1312 (3.0)	12.79 (12.15, 13.44)	1.77 (1.64, 1.91)	<0.0001
40-49	21050 (4.9)	3317 (7.7)	15.87 (15.37, 16.36)	1.80 (1.71, 1.89)	
50-59	52418 (12.1)	7626 (17.6)	14.65 (14.35, 14.95)	1.68 (1.62, 1.74)	
60-69	104704 (24.1)	12739 (29.5)	12.24 (12.04, 12.44)	1.40 (1.36, 1.45)	
70-79	137494 (31.7)	13027 (30.1)	9.51 (9.36, 9.67)	1.00 --	
80-89	88610 (20.4)	4842 (11.2)	5.47 (5.32, 5.62)	0.52 (0.50, 0.55)	
>90	19709 (4.5)	381 (0.9)	1.93 (1.74, 2.13)	0.19 (0.17, 0.22)	
Median Household Income (quintiles)					
1 (low)	77321 (17.8)	7644 (17.7)	9.89 (9.68, 10.10)	1.00 --	<0.0001
2	77494 (17.8)	7235 (16.7)	9.34 (9.13, 9.54)	0.97 (0.94, 1.01)	
3	77465 (17.8)	6983 (16.1)	9.01 (8.81, 9.22)	1.01 (0.98, 1.05)	
4	77374 (17.8)	7438 (17.2)	9.61 (9.41, 9.82)	1.04 (1.00, 1.08)	
5 (high)	77429 (17.8)	7813 (18.1)	10.09 (9.88, 10.30)	1.11 (1.06, 1.15)	
unknown	47158 (11.0)	6131 (14.2)	13.00 (12.69, 13.30)		
Primary Site					
Myeloma	7845 (1.8)	2561 (5.9)	32.65 (31.61, 33.68)	4.65 (4.39, 4.93)	<0.0001
Breast	38001 (8.8)	9754 (22.6)	25.67 (25.23, 26.11)	2.15 (2.06, 2.25)	
Prostate	25631 (5.9)	6408 (14.8)	25.02 (24.49, 25.55)	3.44 (3.29, 3.60)	
Kidney	8311 (1.9)	1588 (3.7)	19.11 (18.26, 19.95)	2.02 (1.89, 2.15)	
Melanoma	5474 (1.3)	791 (1.8)	14.47 (13.54, 15.40)	1.03 (0.94, 1.13)	
Lung	108716 (25.1)	10845 (25.1)	9.99 (9.81, 10.16)	1.00 ---	
Bladder	10429 (2.4)	807 (1.9)	7.74 (7.23, 8.25)	0.85 (0.79, 0.92)	
Head and Neck	11826 (2.7)	614 (1.4)	5.19 (4.79, 5.59)	0.37 (0.34, 0.41)	
Rectum	8698 (2.0)	431 (1.0)	4.96 (4.50, 5.41)	0.42 (0.38, 0.47)	
Hematopoietic	33176 (7.7)	1608 (3.7)	4.86 (4.62, 5.09)		
Gynecologic	19954 (4.6)	866 (2.0)	4.34 (4.06, 4.63)	0.31 (0.27, 0.34)	
Colon	37362 (8.6)	1499 (3.5)	4.01 (3.82, 4.21)	0.37 (0.35, 0.39)	
Stomach	15481 (3.6)	398 (0.9)	2.57 (2.32, 2.82)	0.24 (0.21, 0.26)	
Pancreatic	21420 (5.0)	243 (0.6)	1.14, (1.00, 1.28)	0.12 (0.10, 0.14)	
Brain	10297 (2.4)	92 (0.2)	0.89 (0.71, 1.08)	0.04 (0.03, 0.06)	
Other	72293(16.7)	4739 (11.0)	6.56 (6.37, 6.76)	0.71 (0.68, 0.73)	
Time between diagnosis and death (months)					
<1	64456 (14.8)	989 (2.3)	1.53 (1.44, 1.63)	0.19 (0.18, 0.20)	<0.0001
1-2	34813 (8.0)	1816 (4.2)	5.22 (4.98, 5.45)	0.55 (0.52, 0.58)	
>2-6	72968 (16.8)	6092 (14.1)	8.34 (8.24, 8.64)	0.84 (0.81, 0.87)	
>6-12	62152 (14.3)	6030 (13.9)	9.70 (9.47, 9.93)	0.84 (0.84, 0.91)	
>12-36	100353 (23.1)	12517 (28.9)	12.47 (12.27, 12.68)	1.00 --	
>36-72	48670 (11.2)	7889 (18.2)	16.21 (15.88, 16.54)	1.17 (1.13, 1.22)	
>72-120	26310 (6.1)	4557 (10.5)	17.32 (16.86, 17.78)	1.23 (1.17, 1.29)	
>120	24519 (5.7)	3354 (7.8)	13.68 (13.25, 14.11)	1.17 (1.09, 1.25)	

Abbreviations: N- number of cases; OR- Odds Ratio; CI- Confidence Interval

regression is controlled for health system-related factors examined; p-value for Wald statistic

Table 2. Health system-related factors associated with the use of PRT for bone metastases (period: 1984-2004)

	N (% patients)	N (% receiving PRT)	Rate of PRT (95% CI)	OR (95% CI)	p value
Total	434241 (100.0)	43244 (100.0)	9.96 (9.87, 10.05)		
Level RT service at diagnosing hospital					
No RT facility	309599 (75.3)	30108 (69.6)	9.72 (9.62, 9.83)	1.00 --	<0.0001
RT facility	101597 (24.7)	12052 (27.9)	11.86 (11.66, 12.06)	1.22 (1.19, 1.26)	
Not diagnosed in hospital			4.70 (4.30, 4.98)		
Distance to the nearest cancer centre					
<10km	124157 (32.4)	12707 (29.4)	10.23 (10.07, 10.40)	1.00 --	<0.0001
10-50km	132806 (34.6)	13019 (30.1)	9.80 (9.64, 9.96)	0.91 (0.88, 0.93)	
>50km	126449 (33.0)	11133 (25.7)	8.80 (8.65, 8.96)	0.85 (0.83, 0.88)	
*unknown	50829 (11.7)	6385 (14.8)	12.56 (12.27, 12.85)		
Prevailing waiting time (quintiles)					
1 (low)	79855 (18.4)	7626 (17.6)	9.55 (9.35, 9.75)	1.00 --	0.27
2	78868 (18.2)	7682 (17.8)	9.74 (9.53, 9.95)	0.99 (0.96, 1.03)	
3	82009 (18.9)	8175 (18.9)	9.97 (9.76, 10.17)	1.01 (0.98, 1.05)	
4	80934 (18.6)	7680 (17.8)	9.49 (9.29, 9.69)	0.97 (0.94, 1.01)	
5 (high)	79927 (18.4)	7659 (17.7)	9.58 (9.38, 9.79)	0.99 (0.95, 1.03)	
unknown	32648 (7.5)	4422 (10.2)	13.54 (13.17, 13.92)		
Year of death					
1984-1989	106174 (24.5)	11244 (26.0)	10.59 (10.40, 10.78)	1.07 (1.03, 1.10)	<0.0001
1990-1994	100153 (23.1)	10101 (23.4)	10.09 (9.90, 10.27)	1.01 (0.98, 1.05)	
1995-1999	108766 (25.1)	10910 (25.2)	10.03 (9.85, 10.21)	1.05 (1.02, 1.09)	
2000-2004	119148 (27.4)	10989 (25.4)	9.22 (9.06, 9.39)	1.00 --	

Abbreviations: N- number of cases; OR- Odds Ratio; CI- Confidence Interval

regression is controlled for patient-related and disease-related factors examined; p-value for Wald statistic

Table 3- Patient-related and health system-related factors associated with the use of PRT for bone metastases (stratified by time period)

	1984-1989 (N=106,934)	1990-1994 (N=100,153)	1995-1999 (N=108,766)	2000-2004 (N=119,148)
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Sex				
Male	1.00 --	1.00 --	1.00 --	1.00 --
Female	1.08 (1.07, 1.09)	1.00 (0.94, 1.07)	0.96 (0.90, 1.01)	0.97 (0.92, 1.02)
Age at death (years)				
<40	1.89 (1.61, 2.22)	1.73 (1.49, 2.00)	1.73 (1.49, 2.00)	1.71 (1.46, 2.02)
40-49	2.00 (1.78, 2.24)	1.65 (1.49, 1.82)	1.77 (1.61, 1.94)	1.81 (1.64, 1.99)
50-59	1.73 (1.59, 1.88)	1.67 (1.55, 1.79)	1.62 (1.51, 1.74)	1.71 (1.60, 1.83)
60-69	1.49 (1.38, 1.60)	1.41 (1.33, 1.50)	1.38 (1.30, 1.46)	1.38 (1.30, 1.46)
70-79	1.00 --	1.00	1.00	1.00
80-89	0.48 (0.43, 0.53)	0.50 (0.46, 0.54)	0.51 (0.48, 0.55)	0.57 (0.53, 0.61)
>90	0.25 (0.18, 0.34)	0.02 (0.15, 0.25)	0.16 (0.13, 0.20)	0.19 (0.16, 0.23)
Median Household Income (quintiles)				
1 (low)	1.00 --	1.00 --	1.00 --	1.00 --
2	1.02 (0.94, 1.17)	0.98 (0.91, 1.06)	0.92 (0.86, 0.99)	0.95 (0.87, 1.04)
3	1.05 (0.96, 1.14)	1.02 (0.95, 1.11)	1.01 (0.94, 1.08)	0.95 (0.87, 1.03)
4	1.07 (0.97, 1.17)	1.06 (0.98, 1.15)	1.05 (0.97, 1.12)	0.98 (0.90, 1.06)
5 (high)	1.06 (0.96, 1.16)	1.16 (1.08, 1.26)	1.16 (1.08, 1.25)	1.01 (0.92, 1.10)
Level RT service at diagnosing hospital				
No RT facility	1.00 --	1.00 --	1.00 --	1.00 --
RT facility	1.18 (1.10, 1.25)	1.23 (1.16, 1.30)	1.21 (1.15, 1.27)	1.27 (1.20, 1.33)
Distance to the nearest cancer centre				
<10km	1.00 --	1.00 --	1.00 --	1.00 --
10-50km	0.93 (0.87, 1.00)	0.96 (0.90, 1.02)	0.86 (0.81, 0.90)	0.91 (0.85, 0.96)
>50km	0.80 (0.75, 0.86)	0.86 (0.81, 0.91)	0.83 (0.78, 0.88)	0.90 (0.85, 0.95)
Prevailing waiting time (quintiles)				
1 (low)	1.00 --	1.00 --	1.00 --	1.00 --
2	0.94 (0.93, 0.94)	1.00 (0.93, 1.09)	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)
3	0.90 (0.89, 0.91)	1.07 (0.99, 1.15)	0.97 (0.91, 1.04)	1.02 (0.96, 1.10)
4	0.91 (0.90, 0.92)	1.03 (0.95, 1.11)	0.88 (0.82, 0.95)	1.00 (0.93, 1.07)
5 (high)	0.85,(0.84, 0.86)	0.99 (0.92, 1.07)	0.94 (0.88, 1.01)	1.03 (0.97, 1.11)

Abbreviations: N- number of cases, OR- Odds Ratio; CI- Confidence Interval
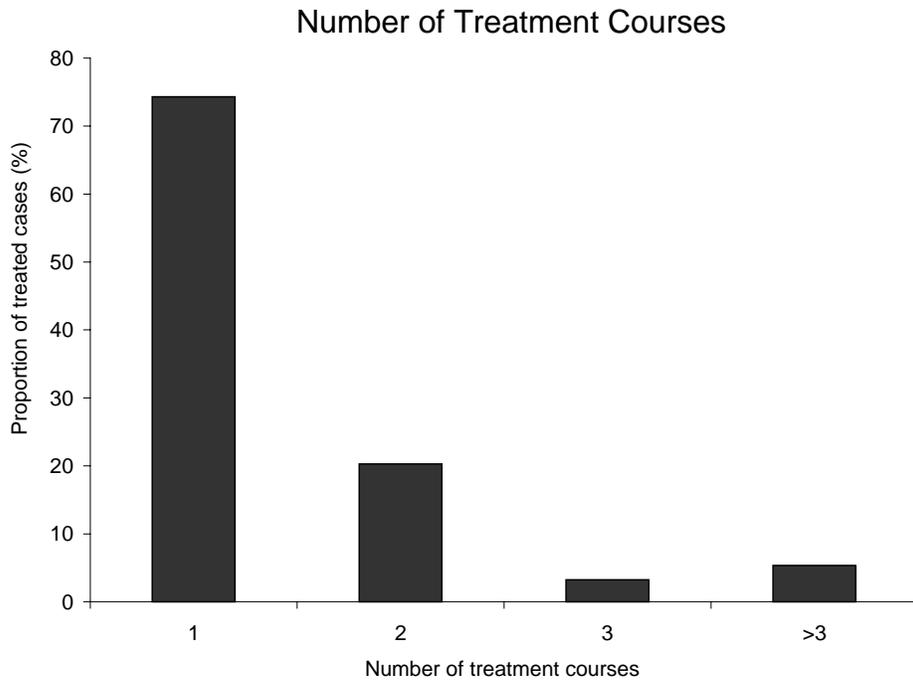*regression controlled for disease-related factors*

Number of Treatment Courses

Figure 1(a) Number of RT courses administered to patients treated between 2000 and 2004.
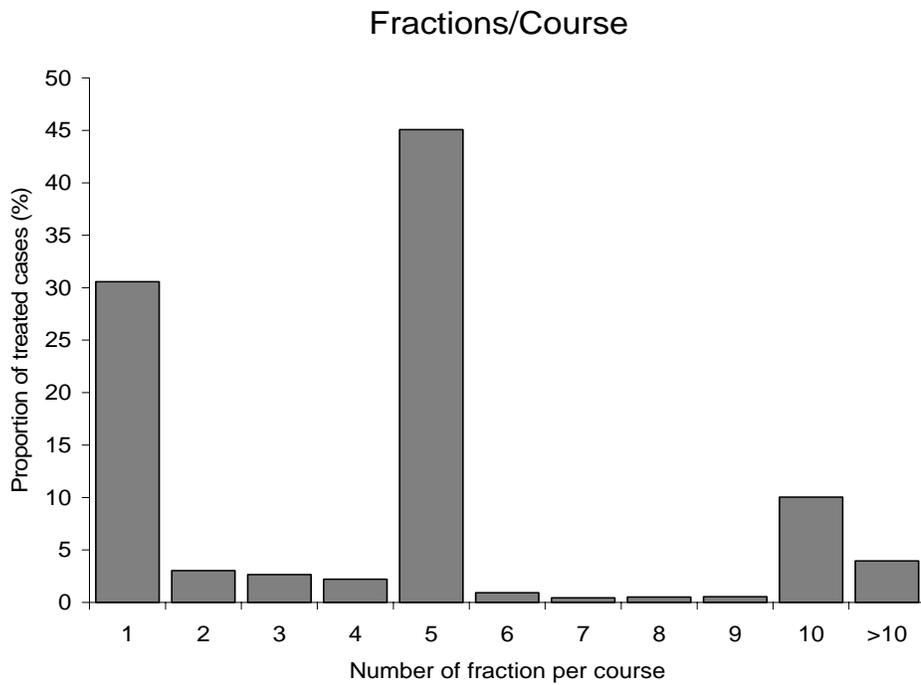
Fractions/Course

Figure 1(b) Fractions per treatment course for patients treated between 2000 and 2004.
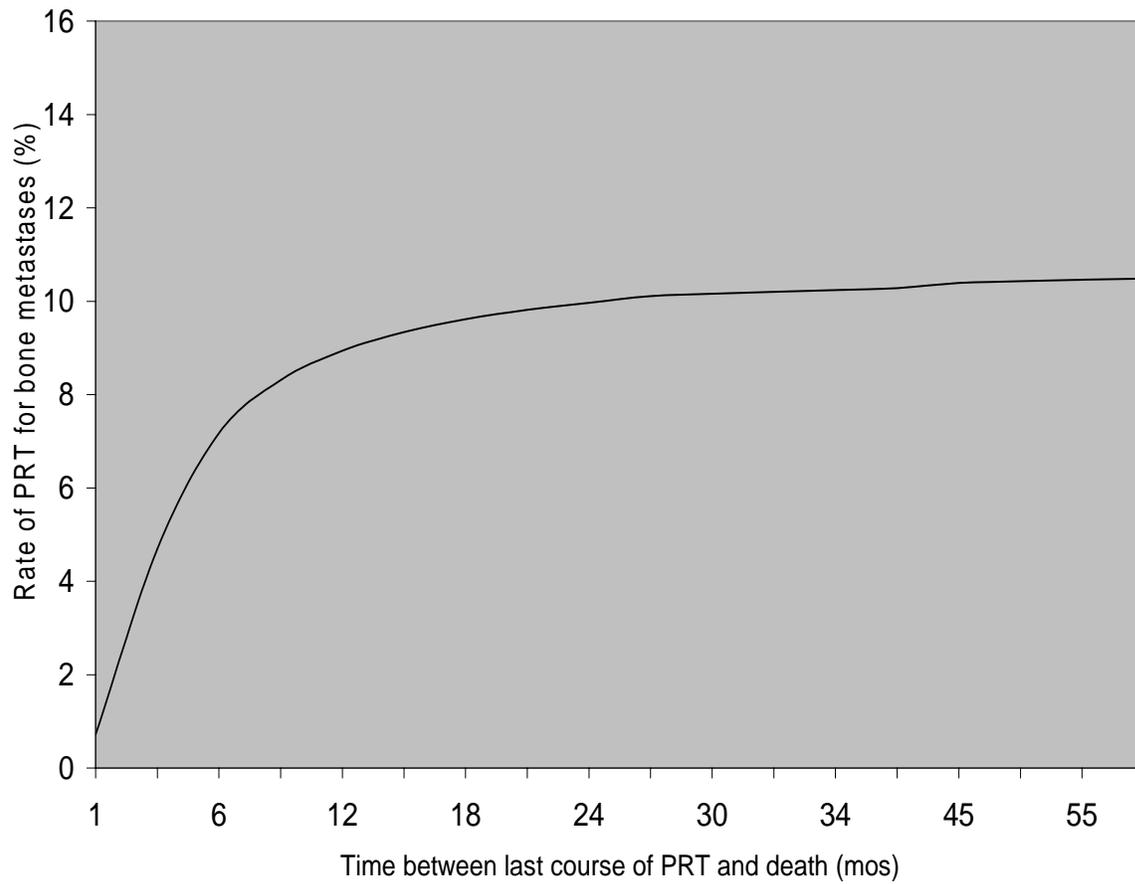
Figure 2. The rate of PRT for bone metastases as a function of time between last course of treatment and death. Beyond the 24 month period, the rate of PRT increases only slightly.
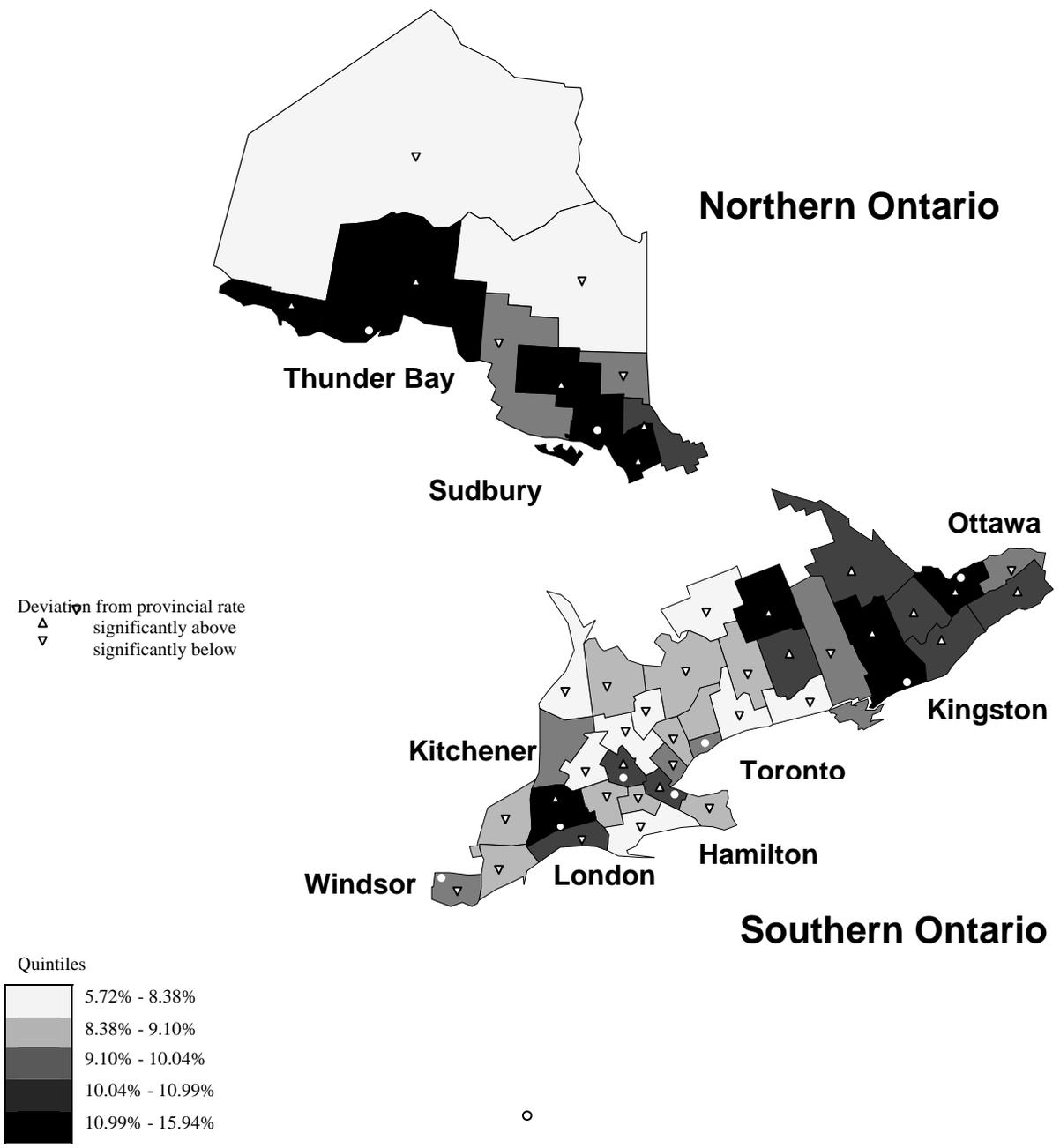
Figure 3. Inter-county variation in the age-standardized rate of PRT for bone metastases. Cities with a regional cancer center are named and their location denoted by a dot. The Kitchener Regional Cancer Center opened in 2003.
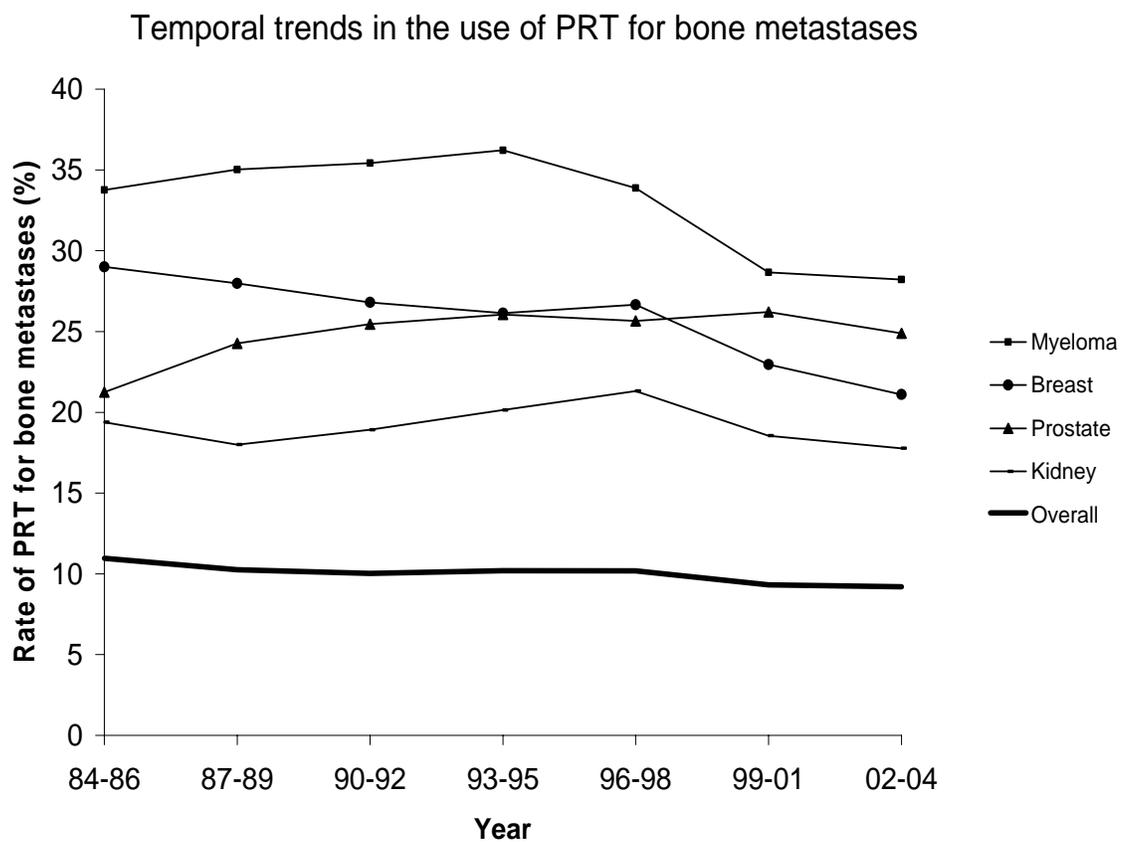
Figure 4. Changes in the age-standardized rate of PRT for bone metastases overall, and for a few selected disease sites.

Chapter 4

Manuscript 2: The use of Palliative Radiotherapy for Brain Metastases in Ontario from 1984-2004

This manuscript conforms to the specifications for submission to the peer-reviewed journal
Clinical Oncology.

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Abstract

Background: Palliative radiotherapy (PRT) plays an important role in management of patients with brain metastases; however, little is known about the use of this treatment within the general cancer population.

Purpose: The purpose of this study was to describe temporal trends in, and identify factors that influence the use of PRT for brain metastases in Ontario.

Methods: The Ontario Cancer Registry was used to gather information on all cancer deaths in Ontario between the years 1984-2004. The proportion of these patients receiving at least one course of palliative radiotherapy for brain metastases within the last two years of life (rate) was described. We conducted a multivariate analysis to examine the association between health system-related, patient-related and disease-related factors, and the use of PRT for brain metastases.

Results: Between 1984 and 2004, there were 424,758 cancer deaths. Of these patients, 4.1% received at least one course of PRT for brain metastases within the last two years of life. We observed an increase in the rate of PRT for brain metastases over the study period (i.e. 2.2% in 1984 to 5.1% in 2004), which remained significant after controlling for other factors. The rate varied by factors reflecting varying need such as primary site (e.g. melanoma-17.5%, lung -9.1%, breast-6.6.%, prostate-0.6%, pancreatic-0.2%), and time between diagnosis and death (e.g. <1 month-0.5%, >6-12 months-5.8% >12-36 months-5.5%). However, factors unrelated to need also influenced the rate of PRT. The rate was negatively associated with age, and there was an association with SES. Patients living farther from a cancer center, and who were diagnosed in a hospital without a RT facility were less likely to receive the treatment.

Conclusions: The use of PRT for brain metastases has significantly increased over time, although it is still influenced by factors unrelated to need.

Introduction

Brain metastases are a serious complication in patients with advanced cancers. The exact incidence of brain metastases is hard to determine with any accuracy. Epidemiologic, autopsy, and clinical studies have all produced varying findings[1,2]. Although there are no reliable population-based estimates, the incidence of brain metastases is reputedly 6.3% to 17.6% among patients who have died of carcinoma[1,3]. Of these, brain metastases occurs most frequently in lung, breast, melanoma, and kidney cancer patients[1]. Approximately two thirds of patients with brain metastases will develop neurologic symptoms during the course of their illness[4]. The most common symptoms include cognitive impairment, headaches, seizures, and vision disruptions[5].

Palliative radiotherapy (PRT) has been the standard of care for patients with brain metastases over the past 50 years. Numerous studies have demonstrated the value of PRT for the relief of symptoms and improvement in neurological functioning. The results of clinical trials indicate that upwards of 85% of patients experience some benefit after treatment[6,7]. There is also evidence to suggest that the median survival is extended by 3-4 months[6,8]. Various groups have endorsed the use of PRT for the palliation of patients with brain metastases[9,10]. Cancer Care Ontario recommends a course of 3000Gy in ten fractions, or 2000Gy in five fractions for patients with multiple brain metastases[11]. While it is generally accepted that PRT can significantly improve the quality of life for patients suffering from brain metastases, very little is known about the *accessibility* of this treatment within the general cancer population.

The term *accessibility* has been used to describe the relationship between the need for, and use of a health services[12]. Need occurs when a patient develops an illness for which there is an available and acceptable treatment, and use refers to the utilization of that particular treatment. When the level of utilization is equal to the level of need, then access is realized[12]. The concept of *access* can be thought of as being comprised of six dimensions: availability, affordability, spatial accessibility, accommodation, acceptability, and awareness[12,13].

Availability refers to the supply of services, such as oncologists and health care facilities, in relation to the demand for those services (e.g. incident cases of cancer). Spatial accessibility refers to the location of the supply of health care in relation to the location of those who are in need of those resources. A common indicator of spatial accessibility is travel distance to a health care center[14]. Affordability refers to the price of treatment and the patient's ability to pay for it, and can be indicated by such things as the level of insurance coverage within a population. Accommodation refers to the manner in which the health system is set up to accept patients. This reflects factors such as the operating hours of a health care facility or transportation services to and from care. Acceptability refers to the patient's attitudes about the suitability of the treatment provider or the treatment itself. Last, awareness refers to the extent to which those who are in need are aware that a treatment is available, and that they may benefit from it. This is reflected in the level of awareness held by health professionals (e.g. referring physicians) or the patient themselves. Problems with any of these dimensions can serve as barriers to access, ultimately leading to a reduction in health service utilization rates. On a

population-wide level, low rates of RT have been shown to be associated with poorer health status[15]. Further, suboptimal access may also indicate that the provision of care is inequitable. This may be at odds with the objectives of many health care systems, whose aim is to provide equitable access to treatments.

The Ontario health system seeks to provide equitable access to RT. All RT is provided by a network of large regional cancer centers located across the province. Radiation oncologist in theses centers work in large multidisciplinary groups, which promotes the provision of comprehensive and high quality care. All patients are insured through universal health coverage and thus, do not directly pay for any treatments or consultations they receive. While these aspects of the RT system minimize some potential barriers to access, some evidence suggests that the accessibility of RT services in Ontario is still suboptimal. The centralization of RT facilities has lead to problems with spatial accessibility. Patients living in more remote areas, not immediately serviced by a cancer center, have been shown to have reduced access to RT[16,17]. The level of cancer service at the diagnosing hospital has been shown to influence RT rates[18], suggesting problems with the awareness of RT services. Advanced age and low SES[17,19] are also associated with lower rates of RT, which could indicate potential problems with the acceptability or awareness of RT services. Long waiting lists signal inadequacies with the availability of RT resources, and have been shown to influence the choice of fractionation[20]. Long waiting list may also decrease the utilization of RT[12].

Research on access to RT in Ontario, however, has remained focused on the general use

of RT. Although a previous study by our group did examine the overall use of PRT

services in Ontario[21], no studies have described the accessibility of PRT for brain

metastases in particular. Hence, the primary objective of this study was to identify factors

that influence access to PRT for brain metastases. We also wanted to describe the

temporal trends in the use of PRT for brain metastases.

Methods

Study Design

A retrospective population-based cohort study was conducted.

Study Population

The study population consisted of all Ontario residents who died of cancer between the

years 1984 and 2004. Patients who died of primary brain cancer were excluded from the

cohort.

Sources of Data

The Ontario Cancer Registry (OCR) is a population-based registry that has been

collecting patient demographic and vital status information on all cancer diagnoses,

except non-melanoma skin cancer, within the province since 1964. The OCR gathers its

information from four major sources: hospital separation records, pathology reports,

death certificates, and reports from the provincial cancer centers. Records from these

sources with a mention of cancer are linked through probabilistic linkage[22]. Variables

available within in the registry include: date of birth, sex, date of diagnosis, primary disease site, total number of primaries, vital status, date of death, cause of death, residence at time of diagnosis, and diagnosing hospital. The OCR is 95% complete for all cancer sites combined[23].

Between 1984 and 2004, all RT in Ontario was provided by the Princess Margaret Hospital and eight regional cancer centers. Since 1982, these centers have kept electronic records of all RT administered in Ontario in a standard format. For every course prescribed, information on the start date of RT, total dose and number of fractions, intent of RT, and body region irradiated is provided. Information from these records was linked to the OCR database. The RT database is more than 95% complete.[20]

Statistics Canada provides socioeconomic (SES) information for the entire country at the census subdivision (i.e. municipality), and the census enumeration area code level (i.e. geographic area equivalent to one or two blocks). Area-level SES data was linked to each record in the OCR using the patient's residence at the time of diagnosis. The linkage process is described in detail elsewhere[24].

The Canadian Institute for Health Information (CIHI) receives hospital separation records from all general hospitals in Ontario. Variables available in this database include date of admission, date of discharge, and diagnosis (ICD-9).

PRT

A patient was considered to have received PRT for brain metastases if they had been treated with at least one course of PRT to a body region corresponding to a brain (i.e. brain, whole brain.) within the last two years of life.

Patient-related factors

The *sex* of each patient was examined. *Age at death* was determined for each patient by subtracting the date of death from the date of birth. Values were grouped into the following categories: <40 yr, 40-49 yr, 50-59 yr, 60-69 yr, 70-79 yr, 80-89 yr, >=90 yr. *Median household income* was used to represent the SES of each patient. This variable is defined as the median household income level of the community in which the patient resided at the time of diagnosis. Values for the median household income measure were divided into quintiles.

Disease-related factors

Primary Site was determined using information from the ICD-9 coding system. *Time between diagnosis and death* was defined as the time between the date of diagnosis of the first primary and the date of death. Values were grouped into the following categories: < 1 month, 1-2 months, 2-6 months, >6-12 months, >12-36 months, >36-72 months, >72-120 months, and >120 months.

Health system-related factors

Prevailing waiting time is a concept that has been previously used to describe the relationship between the supply of and demand for RT resources at a given cancer center, at a given point in time[20]. Prevailing waiting in a given county, at a given point in time was defined as the median time between the date of diagnosis and the start date of RT among residents who received adjuvant/curative RT in the preceding six months. Although each patient was not treated with PRT, we ascribed to them a prevailing waiting time value based on their county of residence on the date one year before their death. We did not include PRT because we had no measure of the date at which PRT would be indicated. Since, however, all types of RT compete for the same resources, waiting time for curative/adjuvant RT is likely to affect waiting for PRT. The distribution of prevailing waiting times was grouped into quintiles.

Level of RT service at the diagnosing hospital. We assigned each patient to a general hospital that was responsible for his or her care in and around the time of diagnosis. We were able to successfully identify the diagnosing hospital in 94.5% of patients. Hospitals were then classified into two categories: affiliated with a RT facility 2) not affiliated with a RT facility.

D*istance to the nearest cancer centre* was defined as the linear distance between a patient's residence at the time of diagnosis and the cancer centre most frequently visited by patients within that census subdivision. The linear distance was previously calculated using the Arc-Info mapping program. A more detailed account of this calculation is

described elsewhere[17]. Each patient was ascribed a distance value, and then grouped into one of the following categories: <10km, 10-50km, >50km.

Death year was grouped into four time periods: 1984-1989, 1990-1994, 1995-1999, and 2000-2004.

Statistical Analysis

The *Rate of PRT* for brain metastases was defined as the proportion of patients who received at least one course of PRT for brain metastases within the last two years of life. We calculated the rate of PRT for brain metastases and the 95% confidence interval for levels of each variable. The chi-square test was used to identify any significant associations. Arc View was used to create a map of Ontario to examine inter-county variation in the rate of PRT in the most recent time period, 2000-2004. The Cochran-Armitage test for trend was used to examine any significant temporal trends in the rate of PRT over the study time period. Rates were directly age-standardized to the 2001 study population to allow for valid comparisons between counties and over time.

We conducted a multivariable logistic regression using the entire study population. All study variables were simultaneously entered into the model, and the OR and 95% confidence interval was calculated to represent the strength and plausible range of these associations, respectively. To examine how the association between the study variables and the use of PRT for brain metastases had changed over time, we stratified our results over four time periods: 1984-1989, 1990-1994, 1995-1999, and 2000-2004.

An alpha level of 0.05 was used to determined statistical significance. All statistical

analyses were performed using SAS version 9.1 (SAS Institute, North Carolina, USA).

Results

Demographics of Study Population

Column one of Table 1 describes the characteristics of the study population. There were

424,758 cancer deaths in Ontario during the entire study period. Eighty-two percent of

cancer patients were microscopically confirmed and 18% were clinically confirmed. The

number of cancer deaths per year increased from 15,968 in 1984 to 23,800 in 2004.

The median age at death for the entire cohort was 72 years. Approximately 25% of

patients were over the age of 80 years. The most common causes of death were lung

cancer (25.3%), colorectal cancer (10.8%), breast cancer (8.9%), prostate cancer (6.1%),

and pancreatic cancer (4.9%). The median time from diagnosis to death for the entire

cohort was 10 months. The majority of patients were diagnosed in a hospital not affiliated

with a RT facility. Approximately a third of the study population was found in each of

the following groups: <10km, 10-50km, and >50km from the nearest cancer centre.

Fractions and Courses of PRT

Figure 2a shows the total number of treatment courses administered to patients receiving

PRT for brain metastases. The majority of patients received only one treatment course

(78.4%), 19.5% of patients received two courses, and 2.1% of patients received three or more courses. Figure 2b shows the number of fractions per course administered to all patients treated with PRT for brain metastases. Sixty-nine percent of patients were treated with 5 fraction per course, and 18.0% of patients were treated with 10 fractions per course.

PRT rate in last two years of life

We defined the rate of PRT in the last two years of life only. A two year interval cut-off was used because it allowed us to capture almost all patients that had received at least once course of PRT, while at the same time providing a small enough time period to allow complete follow-back for the cohort. Figure 1 shows the proportion of patients receiving at least one course of PRT for brain metastases as a function of time between last course of PRT and death. Using a 6 month cutoff the rate of PRT was 3.0%, while at one year the rate of PRT was 3.7%. Using a two year cutoff, we were able to capture 99% of patients ever treated with PRT for brain metastases, giving us a rate of 4.1%. Hence, our two year cutoff was a reasonable definition.

Patient-related factors on PRT for brain metastases

Table 1 shows that females were more likely (p< 0.0001) to receive the treatment than males in both the univariate, and multivariate analysis that controlled for other factors. In the univariate analysis, there was a sharp decreasing trend in the use of PRT for brain metastases with increasing age (p<0.0001). In the multivariate analysis, this trend remained significant. A patient over the age of 90 years was 0.04 times as likely to

receive treatment than a patient aged 70-79 years. There was an increasing trend in the use of PRT for brain metastases with increasing SES (p<0.0001). The rate in the highest quintile was 65% higher when compared to patients in the lowest income quintile. When other factors were entered into the model, SES continued to show a positive association with the use of PRT for brain metastases.

Disease-related factors on PRT for brain metastases

As expected, the rate varied by primary site. Table 1 shows that although lung cancer patients received 57% of all courses of PRT prescribed for brain metastases, the rate in this group was still second to the rate in melanoma patients. The rate of PRT for the hematopoietic malignancies was the following: 2.8%-non-Hodgkin's lymphoma, 0.7%-Hodgkin's lymphoma, 0.3%-multiple myeloma, and 0.7%-leukemia. For the gynecologic cancers, the rate of PRT was 1.5 % for endometrial cancer, 1.1% for cervix cancer, 1.3% for ovarian cancer, and 1.5% for vaginal cancer. Table 1 shows that in both univariate and multivariate analyses, the use of PRT increased with increasing time between diagnosis and death up until 12 months.

Health system-related factors on PRT for brain metastases

Figure 3 shows inter-county variation in the age-standardized rate of PRT for brain metastases, using the most recent time period, 2000-2004. In northern Ontario, the rate of PRT was 3.4%, while in southern Ontario the rate was 4.0% (p=0.01). Rates of PRT were generally higher in regions with a cancer centre, and in southeastern Ontario.

Table 2 shows that distance to the nearest cancer center was negatively associated with the use of PRT for brain metastases on univariate analysis, demonstrating a clear downward trend (p<0.0001). After controlling for other factors, this decreasing trend remained significant. The level of RT service at the diagnosing hospital was also significantly associated with the use of PRT for brain metastases. Patients diagnosed in a hospital affiliated with a RT facility had a 43% higher rate of utilization than patients diagnosed in a hospital without such a facility. This association remained significant after other factors were included in the model. Table 2 shows the univariate and multivariate results examining the association between prevailing waiting time and the use PRT for brain metastases. The effect of prevailing waiting time did not remain significant on multivariate analysis (p=0.12)

Temporal trends

Of the 424, 758 cancer deaths identified, 4.1% received at least one course of PRT for brain metastases within the last two years of life. Figure 4 shows changes in the age-standardized rate of PRT for brain metastases overall, and for selected primary sites. The overall age-standardized rate of PRT increased from 2.2% in 1984 to 5.1% in 2004 (p<0.0001). Trends in the use of PRT for brain metastases also varied by different primary sites. The rate of PRT for brain metastases increased from 3.8% to 8.8% for breast cancer patients, 5.3% to 11.2% for lung cancer patients, and 2.2% to 6.0% for kidney cancer patients.

Changes in the associations over time

Table 3 shows the results of the multivariate analysis stratified by time period. In general, the trends observed overall were similar in each time period examined. The association between patient-related factors such as sex and age were similar across time period strata. The association between income and PRT for brain metastases suggested a clear trend in the first two time periods, but not in the last two. Prevailing waiting time was a significant variable in each time period but the first, 1984-1989 (p=0.85). Unlike the results of the general multivariate analysis, distance to the nearest cancer center was not a significant factor in the period 1984-1989 and the most recent time period 2000-2004. The level of RT services at the diagnosing hospital was positively associated with the use of PRT independent of any time period examined.

Discussion

This study has shown that the use of PRT for brain metastases is significantly influenced by factors unrelated to need, and that, in general, over the past twenty years this has not changed. Older patients, and patients from a low SES community were less likely to receive treatment. Patients diagnosed in a hospital without a RT facility were also less likely to receive treatment.

Equitable access to health care services is seen when variation in utilization is reflected by variation in need. Our observations showed, to some extent, that variation in the use of PRT for brain metastases was equitable. Factors reflecting need for treatment (i.e. disease-related factors) influenced the use of PRT. The rate of PRT by various primary

sites ranged from 0. 2% in pancreatic cancer, where the incidence of brain metastases is very low, to 17.5% in melanoma, a disease with the highest propensity to develop brain metastases[25]. Time between diagnosis and death also significantly influenced rates of PRT for brain metastases, indicating appropriate variation in use. A response after treatment with PRT is normally seen after months, thus; patients with a short prognosis are not likely to benefit.

However, the use of PRT also varied by patient-related factors and health system factors which are not likely to reflect varying need for treatment. We observed a sharp decline in the use of PRT with increasing age. Although, a declining functional status may partially explain the reduced rates in patients with advanced age, it is not likely to completely explain away our observed association. Tyldesley et al. demonstrated that an age-related decline in the use of RT persisted after taking into account functional status[19]. The reasons for this disparity are not clear and may have to do with patient preference, or the lack of awareness of life expectancy and available treatment in the elderly among referring physicians[26]. This would indicate potential problems with the dimension of *awareness*.

SES was positively associated with the use of PRT, showing a 1.25 increase in the odds of receiving PRT for patients in the highest quintile as compared to patients in the lowest income quintile. Other studies have similarly shown that patients from low SES communities have reduced access to RT[17,21].Although patients from low SES communities are more likely to have comorbidities and other health problems[27], these

conditions are not a contraindication to PRT. The higher rates of PRT in patients from

high SES communities may be due to the ability of patients and family members to

advocate for specialist treatment.

Patients diagnosed in a hospital with a RT facility were more likely to receive treatment

than those diagnosed in a hospital without a facility. Huang et al. demonstrated that the

odds of PRT were 1.35 times higher for patients diagnosed in a hospital with a RT

facility[21]. It is unlikely that the need for treatment varied between these two groups. In

Ontario, hospitals with RT facilities form the regional cancer centers. We hypothesized

that physicians in these centers have a higher level of *awareness* because of their direct

access to radiation oncologists and other cancer specialists. This finding suggests that

patients who are initially managed at a cancer center have greater access to RT in the end

stages of their life.

Our overall results showed that prevailing waiting time was not associated with the use of

PRT for brain metastases. It is possible that prevailing waiting time may affect the choice

of PRT fractionation. Kong et al. examined the effect of prevailing waiting time on the

choice of PRT fractionation for bone metastases[20]. They found longer waiting times were

associated with a shorter fractionation schedule. Future research should examine the

impact on prevailing waiting on the choice of PRT fractionation for brain metastases..

Our examination of temporal trends indicates that the use of PRT for brain metastases has

increased significantly overall, and in multiple disease sites. Although there is an absence

of clear evidence, the incidence of brain metastases is believed to be rising as a result of improvements in the management of systemic disease and diagnostic procedures[2,28]. The observed doubling in the utilization rate of PRT for brain metastases over the past twenty years would suggest that incidence is indeed rising.

Although we have shown that 4.1% of cancer patients receive PRT for brain metastases, a limitation of this study is that we cannot state whether this rate is appropriate. Without reliable estimates of the frequency of brain metastases within the cancer population, we cannot establish a measure of need against which our utilization rate can be compared. Hence interpretations as to whether our observed rate represents overutilization or underutilization are difficult.

In conclusion, this study has added to the knowledge of how PRT resources are utilized in Ontario. Huang et al. have previously shown that the overall rate of PRT in Ontario was 26.4%[21], and we have shown that 4.1% of cancer patients received PRT specifically for brain metastases. We have also shown that the use of PRT for brain metastases has significantly increased over the study period, but that it is influenced by many factors unrelated to need. In September, 2003 the Kitchener Regional Cancer Center opened, and since the end of our study period, two new regional cancer centers opened in 2005 and 2007, respectively. These new centers have, among other things, increased the supply of radiation oncologists and radiotherapy machines. Future research should examine the extent to which these improvements in the capacity of the cancer system have helped attenuate the disparities that we have observed.

Conflict of Interest

The authors declare no conflicts of interest.

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Table 1. Patient-related factors and disease-related factors associated with the use of PRT for brain metastases (period: 1984-2004)

	N (% patients)	N (% receiving PRT)	Rate of PRT (95% CI)	OR (95% CI)	p value
Total	424758 (100.0)	17380 (100.0)	4.01(4.03, 4.15)		
Sex					
Male	226193 (53.2)	8492 (48.9)	3.75 (3.68, 3.83)	1.00 --	<0.0001
Female	198565 (46.8)	8888 (51.1)	4.48 (4.39, 4.57)	1.21 (1.17, 1.26)	
Age at death (years)					
<40	9275 (2.2)	631 (3.6)	6.80 (6.29, 7.32)	2.67 (2.42, 2.95)	<0.0001
40-49	19928 (4.7)	1799 (10.4)	9.03 (8.63, 9.43)	2.60 (2.44, 2.77)	
50-59	50642 (11.9)	4023 (23.1)	7.94 (8.18, 11.92)	2.33 (2.22, 2.44)	
60-69	102103 (24.0)	5956 (34.3)	5.83 (5.69, 5.98)	1.78 (1.71, 1.86)	
70-79	135288 (31.9)	4164 (24.0)	3.08 (2.99, 3.17)	1.00 --	
80-89	87861 (20.7)	794 (4.6)	0.90 (0.84, 0.97)	0.37 (0.34, 0.40)	
>90	19661 (4.6)	13 (0.1)	0.07 (0.03, 0.10)	0.04 (0.03, 0.07)	
Median Household Income (quintiles)					
1 (low)	75617 (17.8)	2512 (14.5)	9.89 (9.68, 10.10)	1.00 --	<0.0001
2	75691 (17.8)	2847 (16.4)	9.34 (9.13, 9.54)	0.97 (0.94, 1.01)	
3	75642 (17.8)	3282 (18.9)	9.01 (8.81, 9.22)	1.01 (0.98, 1.05)	
4	75659 (17.8)	3657 (21.0)	9.61 (9.41, 9.82)	1.04 (1.00, 1.08)	
5 (high)	75653 (17.8)	4153 (23.9)	10.09 (9.88, 10.30)	1.11 (1.06, 1.15)	
unknown	46496 (10.9)	929 (5.3)	13.00 (12.69, 13.30)		
Primary Site					
Myeloma	5474 (1.3)	958 (5.5)	17.50 (16.49, 18.51)	1.55 (1.42, 1.69)	<0.0001
Breast	108716 (25.6)	9897 (56.9)	9.10 (8.93, 9.27)	1.00 ---	
Prostate	38001 (8.9)	2509 (14.4)	6.60 (6.35, 6.85)	0.55 (0.52, 0.59)	
Kidney	8311 (2.0)	431 (2.5)	5.19 (4.71, 5.66)	0.51 (0.46, 0.56)	
Melanoma	37362 (8.8)	621 (3.6)	1.66 (1.53, 1.79)	0.17 (0.16, 0.19)	
Lung	41021(9.7)	620 (3.6)	1.51 (1.39, 1.63)	0.41 (0.38, 0.43)	
Bladder	8698 (2.0)	124 (0.7)	1.43 (1.18, 1.67)	0.15 (0.13, 0.18)	
Head and Neck	19954 (4.7)	265 (1.5)	1.33 (1.17, 1.49)	0.10 (0.08, 0.11)	
Rectum	9923 (2.3)	132 (0.8)	1.33 (1.10, 1.56)	0.12 (0.10, 0.14)	
Hematopoietic	10429 (2.5)	121 (0.7)	1.16 (0.95, 1.37)	0.15 (0.13, 0.18)	
Gynecologic	11826 (2.8)	113 (0.7)	0.96 (0.78, 1.13)	0.08 (0.07, 0.10)	
Colon	25631 (6.0)	156 (0.9)	0.61 (0.51, 0.70)	0.11 ((0.09, 0.12)	
Stomach	15481 (3.4)	63 (0.4)	0.44 (0.32, 0.54)	0.05 (0.04, 0.06)	
Pancreatic	8188 (1.9)	32 (0.2)	0.39 (0.26, 0.53)	0.04 (0.03, 0.06)	
Brain	21420 (5.0)	41 (0.2)	0.19 (0.13, 0.25)	0.02 (0.01, 0.03)	
Other	65107 (13.0)	4739 (11.0)	2.35 (2.22, 2.48)	0.27 (0.26, 0.29)	
Time between diagnosis and death (months)					
<1	63266 (14.9)	316 (1.8)	0.50 (0.44, 0.55)	0.12 (0.10, 0.13)	<0.0001
1-2	33826 (8.0)	1029 (5.9)	3.04 (2.86, 3.23)	0.54 (0.51, 0.58)	
>2-6	70518 (16.6)	3571 (20.5)	5.06 (4.90, 5.23)	0.83 (0.79, 0.87)	
>6-12	60252 (14.2)	3504 (20.2))	5.82 (5.63, 6.00)	0.94 (0.90, 0.98)	
>12-36	98480 (23.2)	5424 (31.2)	5.51 (5.37, 5.65)	1.00 --	
>36-72	48178 (11.3)	2080 (12.0)	4.32 (4.14, 4.50)	0.87 (0.83, 0.93)	
>72-120	25993 (6.1)	843 (4.9)	3.24(3.03, 3.46)	0.70 (0.65, 0.77)	
>120	24254 (5.7)	613 (3.5)	2.53 (2.3, 2.73)	0.66 (0.59, 0.75)	

Abbreviations: N- number of cases; OR- Odds Ratio; CI- Confidence Interval

regression is controlled for all health system-related factors; p-value for Wald statistic

Table 2. Health system-related factors associated with the use of PRT for brain metastases (period: 1984-2004)

	N (% patients)	N (% receiving PRT)	Rate of PRT (95% CI)	OR (95% CI)	p value
Total	434241 (100.0)	43244 (100.0)	9.96 (9.87, 10.05)		
Level RT service at diagnosing hospital					
No RT facility	304520 (71.7)	11650 (67.0)	3.83 (3.76, 3.89)	1.00 --	<0.0001
RT facility	97790 (23.6)	5348 (30.8)	5.47 (5.33, 5.61)	1.30 (1.26, 1.35)	
Not diagnosed in hospital	22448 (5.3)	382 (2.2)	1.70 (1.53, 1.87)		
Distance to the nearest cancer centre					
<10km	12142 (28.6)	4.48 (4.37, 4.60)	4.48 (4.37, 4.60)	1.00 --	<0.0001
10-50km	129491 (30.5)	4.54 (4.43, 4.65)	4.54 (4.43, 4.65)	0.93 (0.89, 0.97)	
>50km	123726 (29.1)	4.04 (3.93, 4.15)	4.04 (3.93, 4.15)	0.89 (0.85, 0.93)	
*unknown	50069 (11.8)	1058 (6.1)	2.11 (1.99, 2.24)		
Prevailing waiting time (quintiles)					
1 (low)	78002 (18.4)	3201 (18.4)	4.10 (3.96, 4.24)	1.00 --	0.12
2	77037(18.1)	3353 (19.3)	4.35 (4.21, 4.50)	1.06 (1.01, 1.12)	
3	79993 (18.8)	3434 (19.8)	4.29 (4.15, 4.43)	1.04 (0.99, 1.10)	
4	78971 (18.6)	3310 (19.0)	4.19 (4.05, 4.33)	1.02 (0.97, 1.08)	
5 (high)	77878 (18.3)	3412 (19.6)	4.38 (4.24, 4.52)	1.06 (1.01, 1.12)	
unknown	32877 (7.7)	670 (3.9)	2.04 (1.89, 2.19)		
Year of death					
1984-1989	103645 (24.4)	2826 (16.3)	2.73(2.63, 2.83)	0.43 (0.41, 0.46)	<0.0001
1990-1994	97997 (23.1)	97997 (23.1)	3.78 (3.66, 3.89)	0.62 (0.59, 0.64)	
1995-1999	106468 (25.1)	106468 (25.1)	4.49 (4.37, 4.62)	0.79 (0.76, 0.82)	
2000-2004	116648 (27.4)	116648 (27.4)	5.21 (5.08, 5.33)	1.00 --	

Abbreviations: N- number of cases; OR- Odds Ratio; CI- Confidence Interval

regression is controlled for patient-related and disease-related factors examined; p-value for Wald statistic

Table 3 - Association between health system-related and patient-related factors and the use of PRT for brain metastases stratified by time period

	1984-1989 (N=103,645)	1990-1994 (N=97,997)	1995-1999 (N=106,468)	2000-2004 (N=116,648)
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Sex				
Male	1.00 --	1.00 --	1.00 --	1.00 --
Female	1.17 (1.06, 1.30)	1.28 (1.18, 1.38)	1.20 (1.12, 1.28)	1.23 (1.16. 1.31)
Age at death (years)				
<40	2.74 (2.13, 3.52)	2.55 (2.08, 3.12)	2.50 (2.07, 3.02)	2.93 (2.44, 3.51)
40-49	2.62 (2.20, 3.12)	2.63 (2.30, 3.01)	2.60 (2.31, 2.93)	2.64 (2.37, 2.94)
50-59	2.17 (1.89, 2.48)	2.26 (2.03, 2.51)	2.35 (2.15, 2.57)	2.49 (2.30, 2.70)
60-69	1.70 (1.50, 1.92)	1.74 (1.59, 1.91)	1.67 (1.54, 1.81)	1.96 (1.82, 2.10)
70-79	1.00 --	1.00 --	1.00 --	1.00 --
80-89	0.27 (0.20, 0.36)	0.30 (0.24, 0.37)	0.33 (0.28,0.38)	0.44 (0.39, 0.50)
>90	<0.00 (<0.00->999.9)	0.02 (0.00, 0.13)	0.04 (0.02, 0.12)	0.05 (0.02, 0.10)
Median Household Income (quintiles)				
1 (low)	1.00 --	1.00 --	1.00 --	1.00 --
2	1.08 (0.93, 1.25)	1.05 (0.93, 1.18)	1.15 (1.04, 1.27)	1.19 (1.09, 0.31)
3	1.10 (0.94, 1.28)	1.08 (0.97, 1.22)	1.15 (1.04, 1.28)	1.16 (1.05, 1.27)
4	1.26 (1.08, 1.46)	1.20 (1.07, 1.34)	1.18 (1.07, 1.31)	1.24 (1.16, 1.36)
5 (high)	1.30 (1.12, 1.51)	1.22 (1.08, 1.37)	1.31 (1.18, 1.45)	1.28 (1.16, 1.41)
Distance to the nearest cancer centre				
<10km	1.00 --	1.00 --	1.00 --	1.00 --
10-50km	0.97 (0.87, 1.09)	0.92 (0.84, 1.00)	0.91 (0.84, 0.98)	0.95 (0.88,1.02)
>50km	0.96 (0.85, 1.08)	0.90 (0.83, 0.99)	0.89 (0.82, 0.97) 97)	0.93 (0.86, 1.00)
Level of RT service at diagnosing hospital				
No RT facility	1.00 --	1.00 --	1.00 --	1.00 --
RT facility	1.51 (1.36, 1.66)	1.43 (1.33, 1.55)	1.21 (1.13, 1.31)	1.23 (1.16, 1.31)
Prevailing waiting time (quintiles)				
1 (low)	1.00 --	1.00 --	1.00 --	1.00 --
2	0.98 (0.84, 1.13)	0.92 (0.82, 1.03)	1.18 (1.07, 1.30)	1.11 (1.16, 1.31)
3	1.05 (0.90, 1.22)	0.95 (0.86, 1.06)	1.00 (0.91, 1.11)	1.18 (1.08, 1.29)
4	1.02 (0.88, 1.18)	0.82 (0.73, 0.92)	1.13 (1.02, 1.25)	1.12 (1.02, 1.23)
5 (high)	1.05 (0.90, 1.21)	0.94 (0.84, 1.05)	1.20 (1.09, 1.33)	1.06 (0.97, 1.16)

*Abbreviations: N- number of cases; OR- Odds Ratio; CI- Confidence Interval; *regression is controlled for all variables examined*
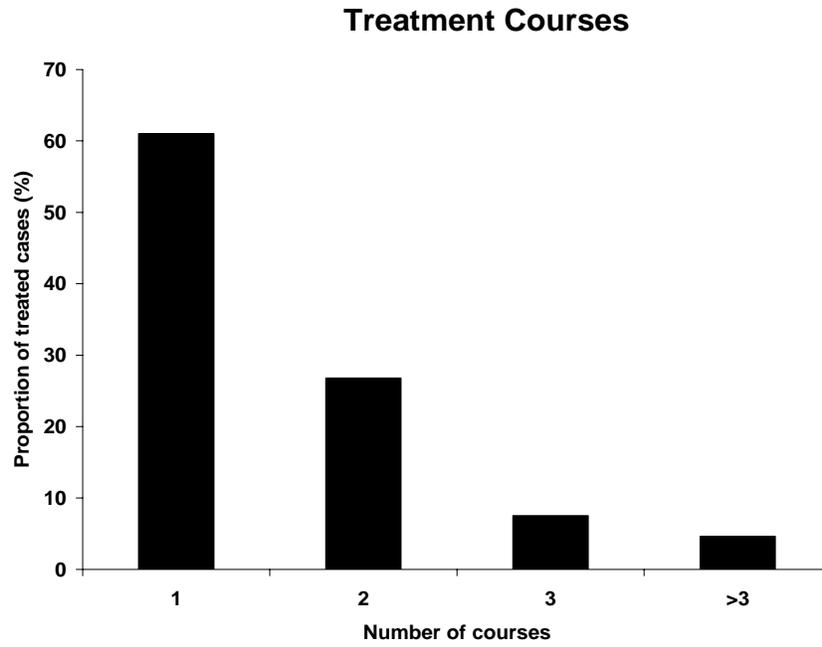
Treatment Courses

Figure 1(a) Courses per treatment for patients treated between 1984 and 2004
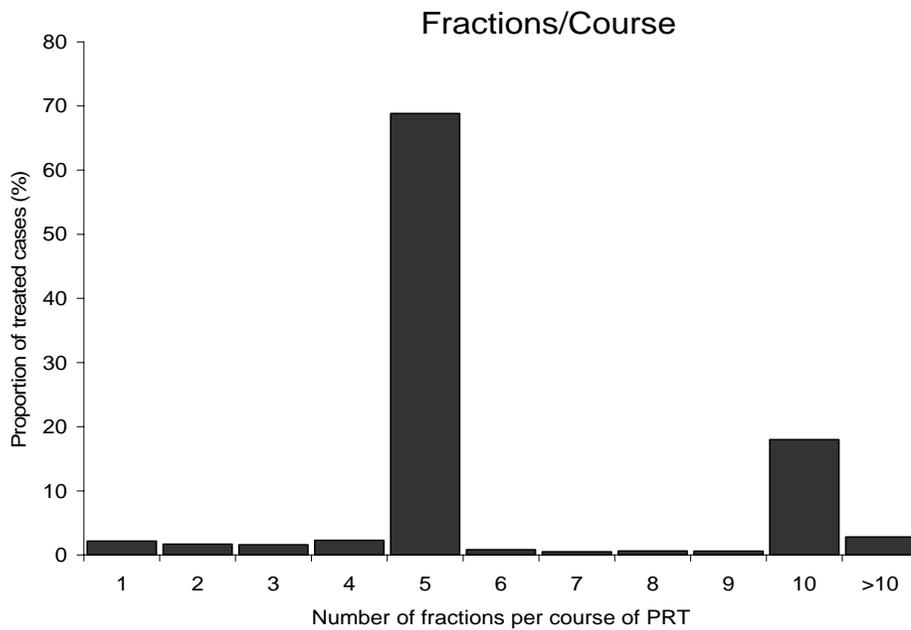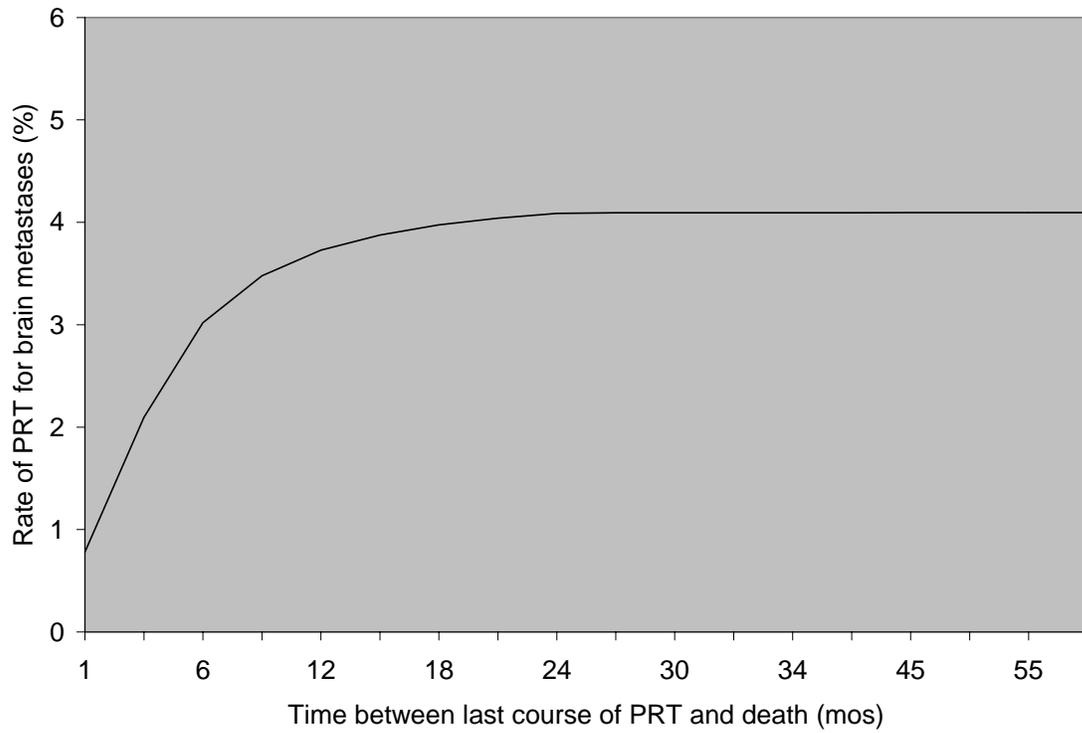
Fractions/Course

Figure 1(b) Fractions per treatment course for patients treated between 1984 and 2004

The rate of PRT for brain metastases as a function of time between last course of treatment and death. Beyond the 24 month period, the rate of PRT increases only slightly.
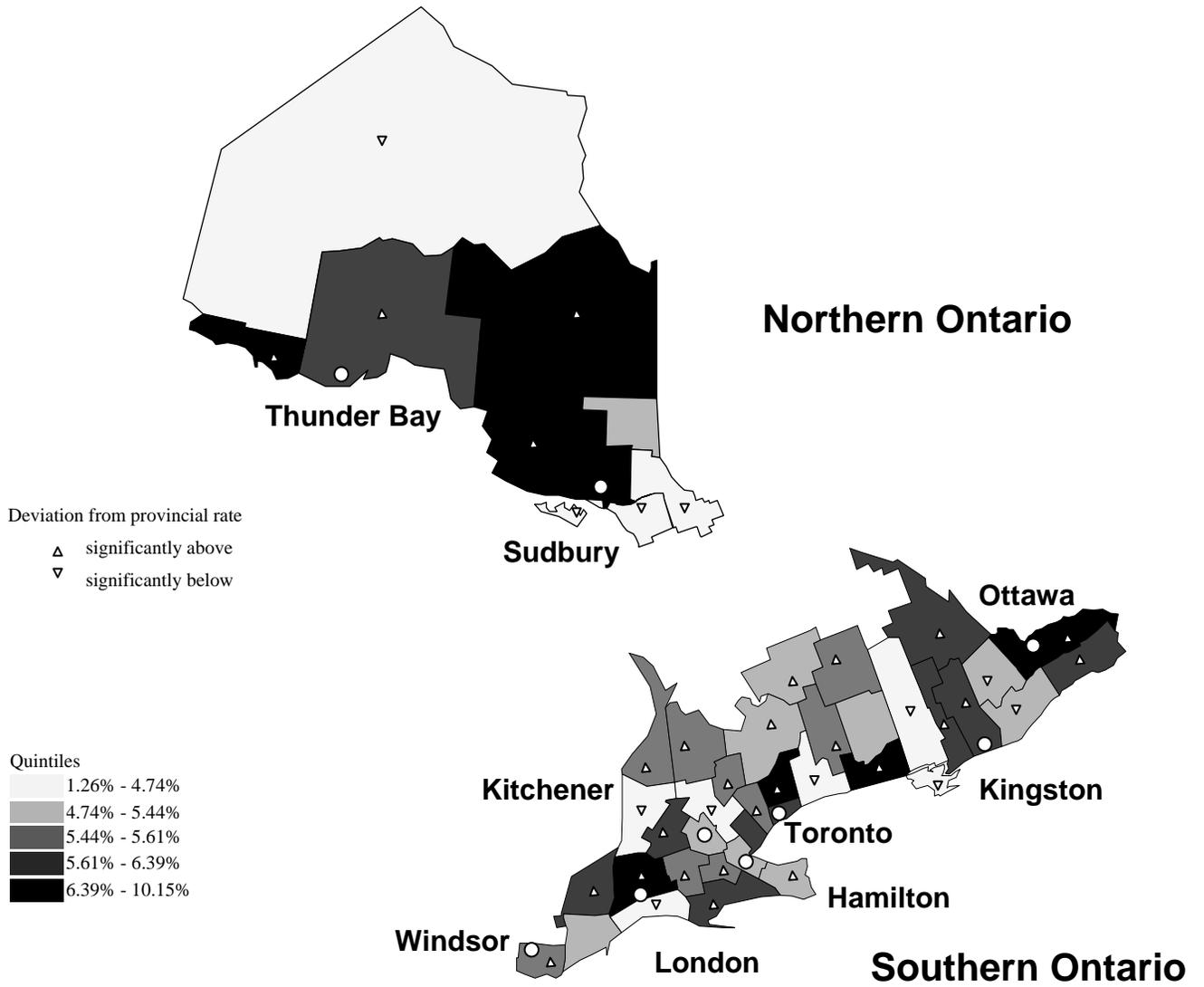
Northern Ontario

Thunder Bay

Deviation from provincial rate

△ significantly above

▽ significantly below

Sudbury

Ottawa

Quintiles

1.26% - 4.74%
4.74% - 5.44%
5.44% - 5.61%
5.61% - 6.39%
6.39% - 10.15%

Kitchener

Toronto

Kingston

Hamilton

Windsor

London

Southern Ontario

Figure 3 Inter-county variation in the age-standardized rate of PRT for brain metastases. Counties with a cancer center are denoted by a circle. The Kitchener Regional Cancer Center opened in 2003.
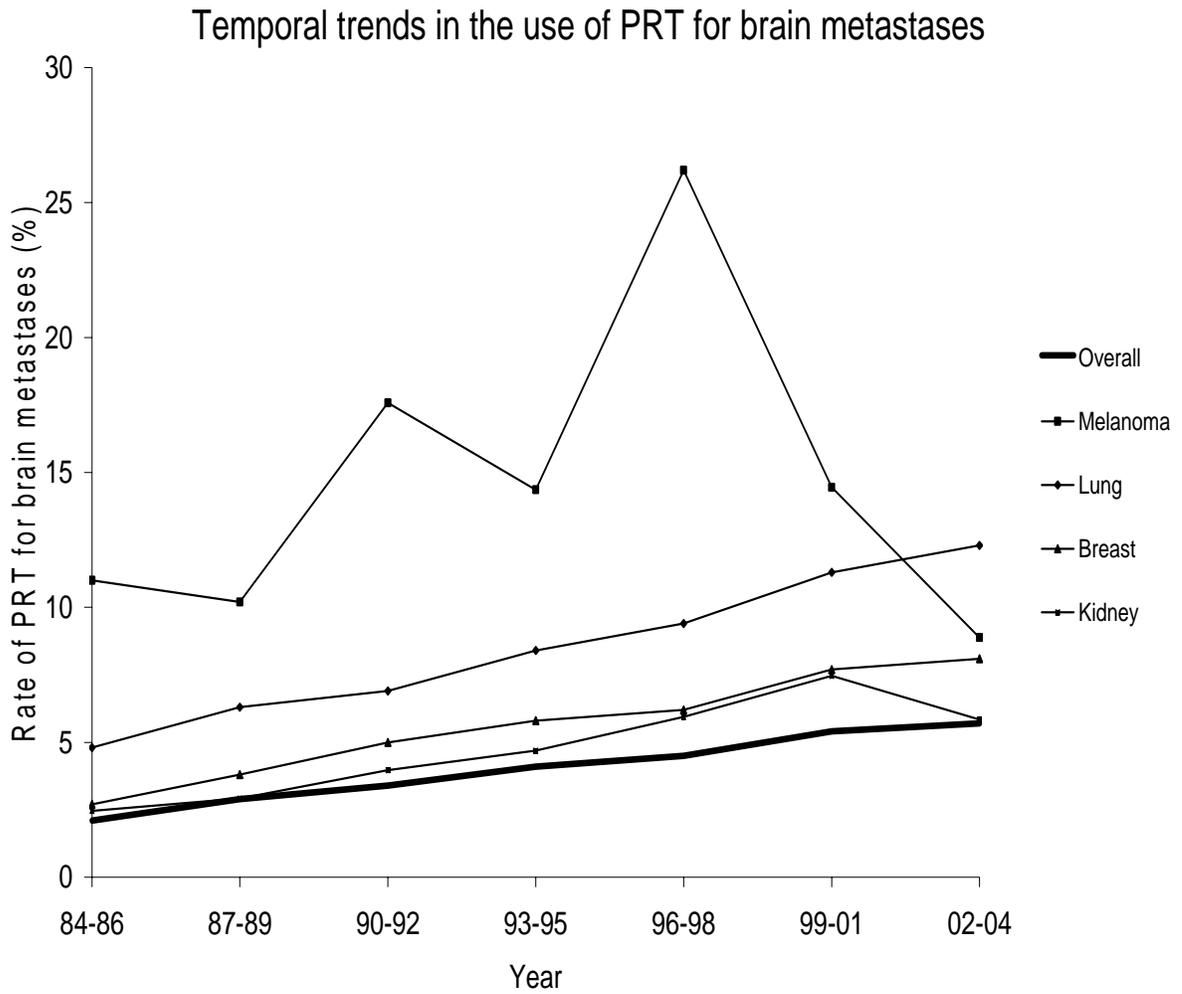
Temporal trends in the use of PRT for brain metastases

Figure 4 Changes in the age-standardized rate of PRT for brain metastases overall, and for a few selected disease sites.

Chapter 5

General Discussion

Overall findings

This work describes the accessibility of PRT services for bone metastases and brain metastases in Ontario. The main findings of this thesis are that the use of PRT for bone and brain metastases is influenced by a variety of factors unrelated to need, suggesting that access to PRT in Ontario may be inequitable. The results also highlighted distinct temporal trends in the use of PRT for bone and brain metastases. A significant decline in the use of PRT for bone metastases was observed over the study period, while the use of PRT for brain metastases more than doubled. These general findings are discussed further below.

Our measure of spatial accessibility was distance to the nearest cancer center. Although this factor should not define varying need for care, the use of PRT decreased with increasing distance to a cancer center, indicating that spatial accessibility may be a barrier to treatment. This is consistent with other studies of RT utilization in Ontario. Paszat et al. found that the odds of receiving RT for breast cancer patients living farther than 325km was 0.31 when compared to patients < 8km from the nearest cancer center[1]. Huang et al. showed that patients living in a county with a RT facility were more likely to receive PRT[2]. However, our analysis of the most recent time period indicated that distance was only a factor in patients treated for bone metastases. Patients living far distances from a cancer center may be deterred from seeking treatment due to travel time, and expenses. This barrier may be of greater importance in patients with bone metastases,

as their disease can be managed through other methods that may mitigate the need for PRT.

The level of RT services at the diagnosing hospital most likely indicates varying levels of *awareness* of the indications of PRT. As was hypothesized, rates of PRT use were high in patients diagnosed at a hospital with a RT facility in both manuscripts. Varying need is not likely to explain these observations. Huang et al. also showed that patients diagnosed in a hospital with a RT facility were more likely to receive PRT (OR=1.35)[2]. Together these findings suggest that the level of *awareness* may serve as a barrier to PRT. Hospitals with a RT facility are staffed with radiation oncologists who meet regularly with other physicians charged with the care of cancer patients. Radiation oncologists are able to educate other physicians about the uses of PRT, leading to a greater level of awareness. We may have used the hospital in which the patients died as opposed to the hospital of diagnosis, but if done this way, we would not have been able to establish a clear temporal sequence. It would not be possible to determine whether patients who are dying of cancer were admitted to a hospital with a RT facility because they were dying, or because they specifically needed PRT. An analysis of our study population showed that, of patients who died in a hospital, the majority (83%) died in the same hospital that the diagnosis of cancer was made.

We used variable prevailing waiting time to assess the *availability* of PRT services in a particular county, and at a particular point in time. We would expect that in times of long waiting time, physicians would be less inclined to refer patients for PRT. Our overall

analysis showed that prevailing waiting time was not significantly associated with the use of PRT for either bone or brain metastases. When the results were stratified by time period, we saw that prevailing waiting did influence the use of PRT for bone metastases in the first and third time period. It is conceivable that when faced with long waiting lists, physicians and patients may decide to use other methods to manage symptoms of pain, rather than wait for PRT. If these methods effectively manage pain symptoms, the need for PRT would be reduced. Prevailing waiting time was also associated with the use of PRT for brain metastases in the third and most recent time period; however, no clear trend was shown. The findings suggest that longer prevailing waiting times are associated with an increased likelihood of receiving PRT for brain metastases. These findings are not intuitive, and require further analysis of the data. The creation of the Rapid Palliative Radiotherapy Program may have reduced the impact of long waiting times on the opportunity to received PRT. In centers with these programs, patients needing PRT can be consulted and treated on the same day of treatment, effectively improving access to PRT, even when wait times for RT are long. These programs, however, were not wide spread during the study period, and are not likely to explain our findings. Toronto-Sunnybrook established the first program in 1996, and Ottawa followed suit in 1999.

The need for PRT may vary by age, as functional status normally declines with increasing age. However, this is unlikely to fully explain the sharp decrease in the rate of PRT in the elderly that we observed. Tyldesley et al. showed that the rate of decrease in RT utilization surpassed the rate of functional decline in the elderly, indicating that age independently influenced RT utilization rates[3]. The observed age-related decline could

indicate problems with the dimension of *awareness.* Tyldesley et al. demonstrated that

the greatest contributor to the reduced rates of RT in the elderly was low rates of referrals

to a cancer center[3]. It could be that physicians are not aware that PRT is useful in elderly

populations. There are a significantly low proportion of elderly patients in the PRT

efficacy trials, which makes the generalizability of results to this population diffcult[4].It

could also be that physicians may underestimate the life expectancy of elderly patients.

When compared to patients treated for bone metastases, the effect of age in patients

treated for brain metastases appear stronger. For instance, the OR comparing a 70-79 year

old patient to a >90 year old patient was 0.19 for bone metastases, and 0.04 for brain

metastases. The efficacy of PRT has been less studied in patients with brain metastases,

than in patients with bone metastases. Hence, clinicians may be unsure about the relative

worth of PRT for this indication in the elderly. Perceptions about an elderly patient's

chance of survival with bone metastases as compared brain metastases may also explain

the sharper decline in the use of PRT for brain metastases.

Numerous studies have shown that community level SES is related to the use of RT[1,2,5,6].

.We too found an association with SES and PRT for both brain and bone metastases.

However, in the case of PRT for brain metastases, there was a stronger association that

persisted in each time period. In contrast, the association between SES and the use of

PRT for bone metastases showed only a weak trend (p=0.04), which completely

disappeared when the results were stratified by time period. The majority of patients with

bone metastases suffer from debilitating bone pain which unambiguously warrants

medical attention, while patients with brain metastases may suffer from less overt

symptoms. For patients with brain metastases the level of awareness held by the patient themselves or their family member may improve access to care. Patients and family members from high SES communities may be more knowledgeable about the availability of treatment options, and may be better able to articulate their desire for treatment. This could explain the higher rates of PRT among patients from high SES backgrounds.

This work also examined temporal trends in the use of PRT. In face of an increasing number of cancer deaths, we would expect that PRT utilization would have increased over time. The use of PRT for bone metastases, however, declined, suggesting that the need for PRT may have been mitigated by the availability of alternative treatments, such as bisphosphonates and chemotherapy. In contrast, we observed a doubling of the rate of PRT for brain metastases (p<0.0001). This may be explained by the suspected increase in the incidence of brain metastases as a result of improvement in the management of systemic disease and diagnostic techniques[7,8]. The findings of this thesis would lend support for the view that the frequency of brain metastases is indeed rising.

Strengths and Limitations

While other studies have focused on the general use of PRT, this thesis is the first Ontario study to specifically examine the use of PRT for both bone and brain metastases within the general cancer population. This study also derives information from the OCR database and RT information from the Regional Radiotherapy Centers. The OCR database has been shown to be a reliable and complete source of information, capturing 95% of all incident cancer cases in Ontario. Radiotherapy records from the regional

radiotherapy centers have kept complete records on all RT that has been prescribed in Ontario since 1984. As such, the results of both studies are highly generalizable to the Ontario population.

The main limitation of this study is that none of the databases used provide information about the symptoms of bone or brain metastases. As a result, it was not possible to identify a population of patients dying of cancer that would have needed PRT. Instead, we used all patients dying of cancer to form the denominator of our study population. A limitation to this method is that our observed PRT rate of 10% for bone metastases and 4.0% for brain metastases tells us nothing about the appropriateness of utilization of PRT in patients with these indications. We cannot determine if a smaller or greater proportion of patients are treated than needed. From these values, we are only able to conclude that a greater proportion of patients receive treatment for bone metastases as compared to brain metastases, which we would expect because of differences in the relative incidences for each indication[9]. To indicate how appropriate the use of PRT is within the population, we would need to be able to measure the number of patients with symptoms for PRT. A prospective design would have allowed us to capture more detailed information on each patient, and to identify those specific patients that would have developed indications for PRT. However, this type of study would have been very costly and would have required a very long follow-up period., thus, we used retrospective design, which was cheaper and less time intensive.

Despite the drawback of using this method, our observed rates still provide information about the use of PRT among patients dying of cancer, which can be of use to RT program planners for forecasting utilization of PRT services.

Although our study population consisted of all patients who died of cancer, we took a few steps to refine our population to only those patients that would need PRT. In manuscript I, patients with bone primaries were removed, and in manuscript II patients with brain primaries were removed because these patients do not develop bone or brain metastases, respectively. Patients who die very shortly after diagnosis (<1 month) could have similarly been removed because they would have had less opportunity to receive PRT. However, this group of patients represented 2.3% of patients receiving PRT for bone metastases and 1.8% of patients receiving PRT for brain metastases. Hence, a significant proportion of patients in this group did require PRT, and removing them would have significantly altered the overall PRT rate. Further it was not possible to distinguish between those who needed and who did not need PRT, so rather than completely removing this group we chose to keep them in the denominator.

In manuscript I, we also removed patients with pelvic cancer from the numerator if they had received radiation to the pelvis areas because we were not able to determine if they had been radiated to the pelvic area or the bony pelvis. Patients with pelvic cancers do not normally metastases to the bony pelvis, and so not including them in the numerator was necessary in order to not bias the results. The total number of patients that were

removed in this manner was 5155. With the exclusion of these patients from the

numerator, the rate of PRT decreased by only a small amount, from 11.1% to 9.96%.

We controlled for two factors associated with varying need for PRT (i.e. primary site, and

time between diagnosis and death); but because no indicator was readily available within

our database, we did not control for other potential need-related factors such as,

functional status and comorbidities. It is possible that not controlling for these factors

may have biased some of the estimates that we observed. For instance, functional status

generally declines with increasing age, and a declining functional status may preclude a

patient from PRT as a treatment option, so it is possible that the negative age-association

may be due to a declining functional status. While the potential for confounding due to

this factor is likely, evidence would suggest that even after functional status is accounted

for, the age-association would remain significant[3].   The SES results may have also been

biased because functional status was not accounted for. Patients from a low SES

background are more likely to have comorbidities, and it is possible that they may have

greater functional decline due to these comorbidities. The effect of not accounting for

functional status would be to make the rate of PRT in low SES patients lower than what it

truly is; hence we may have artificially observed a greater difference between low and

high SES patients. Future research could examine the impact of these covariates on our

observed SES association. It is unlikely that functional status and comorbidities would be

related to any of the other factors that we examined, so the fact that we did not measure

functional status is unlikely to bias these results.

The values for distance to the nearest cancer center, median household income, level of RT service at the diagnosing hospital, and prevailing waiting time were unknown in a significant proportion of patients (table 1 and 2 from manuscript II and II). Although there would be no reason to believe that patients with unknown values were systematically different from the general population, rates of PRT for this group were significantly higher in manuscript I, and lower in manuscript II, suggesting that patients comprising the unknown category were in fact different. The mean age of patients with unknown values (79 years) was higher than the average age of the population (70 years) which may explain why rates in this group were generally lower in manuscript II, as the use of PRT is low in the elderly. In manuscript I, however, rates of PRT in patients with unknown values were generally higher, the reasons for which are not clear. This is a potential limitation to our findings, and a further analysis of the data is required to explain these observations.

Because we did not have access to individual household income measures, we used the median household income level of the community in which the case resided. The use of this aggregate measure to represent individual SES theoretically leads to increased random measurement error with respect to the individual's true SES, and may have attenuated the observed SES result. A study examining the relationship between income and 18 different health outcomes, found that the results from individual household income and community household income were not significantly different for 16 of the 18 outcomes[10]. In urban areas, while some poorer people live in rich areas and vice versa, in general, neighborhoods are stratified by the costs of housing, and because most people

live where they can afford, the income level of a community can be a valid proxy for

individual level income. As such, variation between neighborhood incomes will be

greater than within neighborhood income variation. In rural areas, this assumption may

not hold because neighborhoods are not systematically stratified by income level. In these

areas, it is more likely that two persons with the same enumeration area code could have

very different income levels. The consequence of this is an increase in random

measurement error, leading to an attenuation of the effect estimate. If the exact individual

income levels were recorded we would see a greater association between income and

PRT. Mustard et al. also examined differences between community and individual SES in

rural settings. The results of their study were similar, to a lesser extent, to those found in

the urban setting. With respect to this thesis, the possibility for random error in the

measurement of SES does exists, and could potentially be greater in the rural areas of

Ontario. However, the results of Mustard's study would suggest that the effect estimate is

not significantly attenuated. In a worst case scenario, the SES disparity would be greater

that what was observed.

The grouping of income values into quintiles was based on the study population and not

the general Ontario population. In general, cancer patients are normally from a low SES

background. Patients that we have defined as being high SES using the study population,

may actually belong to a lower SES group by Ontario standards. If we were trying to

make generalizations to the Ontario population about our SES results they would not be

completely correct. Defining income quintiles based on the study population, however, is

a valid way of examining the impact of income on receiving PRT in patients dying of

cancer. The results clearly show that the use of PRT associated with income. It should be noted, however, that because the spread of income distribution in the general Ontario population is much wider, we probably would have seen a stronger association between income groups if income quintiles were defined using the Ontario population.

Distance to the nearest cancer center is another geographic indicator that may be subject to greater bias in rural areas. Distance was calculated using the patients' enumeration area code at the time of diagnosis. In urban areas, the enumeration area code is a smaller unit resulting in less variation between residents of the same enumeration area code. In rural areas, the enumeration area code covers a wider geographic area, and so there is likely to be more variation between residents of the same enumeration area code with respect to distances to the nearest cancer center. The measurement of distance for residents of rural areas would be more prone to misclassification error, which in all likelihood would be random, decreasing observed effect estimate to the null value.

Values for the distance variable were categorized into groups that were similar to tertiles. We did not examine distance as a continuous variable because we were not sure if the relationship with PRT was linear. We instead chose an objective way of grouping patients into distance categories, using tertiles. There is the potential that with using such big categories, some information was lost and that we could have found a stronger association if smaller categories were used.

Due to limitations of the dataset, the geographic residence of the case could only be

determined at the time of diagnosis. Thus, geographically dependent variables, such as

SES and distance from the nearest cancer center, were derived using the patient's

residence at the time of diagnosis. It is possible that patients could have relocated after

their diagnosis; thus, introducing random measurement error into the study. For instance,

some patients who were classified as living 10-50km away from the nearest cancer center

may have relocated to a residence that was <10km to the nearest cancer centre or vice

versa. Seeing that the occurrence of misclassification would be random, the observed

distance OR estimate may have been less than the true estimate. On the other hand, an

individual's SES is likely to have remained stable after diagnosis, and would not be as

affected by relocation. As such, this measure was unlikely to be biased by

misclassification error.

We decided to ascribe to each patient the prevailing waiting time one year before their

death because there was no measure within the database of when exactly a patient would

have developed an indication for PRT. Ideally, we wanted to ascribe to each patient a

prevailing waiting time at a time just before they would have needed PRT. Using the time

period one year before death may have introduce bias into the study because some

patients may have been treated prior to this point and some patients may have been

treated after this point. As such, it may be difficult to draw strong conclusions about the

temporal sequence between prevailing waiting times and the use of PRT. However, figure

2 in both manuscripts I and II shows that at one year before death, the rate of PRT does

not change substantively. In other words, the majority of patients to ever have been

treated required PRT at least one year before death; thus, the temporal sequence is clear for these patients. In patients treated prior to one year before death, the potential for bias is small. It is unlikely that prevailing waiting times will fluctuate greatly over shorter periods of time (e.g. 1-2 years), and so the waiting time value at 1 year was most likely similar to the waiting time value at 6 months, 18 months, when these patients were treated. We do acknowledge the possibility that in a small proportion of patients the waiting time value may have not reflected the true waiting time environment, and so this could have lead to misclassification bias. This error would have been random, leading to a decrease in the size of the effect estimates.

Another potential limitation to our findings was that the logistic regression analysis did not account for the clustering of our observations. Each patient observation was not fully independent, they were clustered in counties, and it is possible that the rate of PRT varied independently between counties. Not accounting for this clustering would have artificially increased the standard error estimates, making patients seem more different than they actually are. Multi-level logistic regression, with county as the higher order level, could be used in the future to account for the clustering of observations.

Future Research

In 2003, a new regional cancer center opened in Kitchener, and since the end of the study period in 2004, two additional regional cancer centers opened in Mississauga and Oshawa. Because there is significant lag time between the acquisition and processing of OCR data, at the time of this project, complete data was only available up until the end of

2004. Therefore, it was not possible to look at the impact of these centers on the accessibility of PRT services. The opening of these centers undoubtedly increased the number of radiation oncologists and RT machines available in previously underserviced areas; thus, it is possible that the accessibility of PRT services may have improved. Future studies should examine the degree to which the accessibility of PRT services has changed when contemporary data become available.

There is also a need to define the appropriate rate of PRT so that interpretations can be made as to the suitability of rates observed in utilization studies. For reasons previously mentioned, this has proven to be difficult in the context of PRT. The criterion benchmark approach is one method that has been used to overcome these drawbacks[11], and can also be used in the future to define a benchmark rate of PRT that can be used for comparison.

This work has identified potential targets that can be used as starting points for interventions aimed at improving PRT rates. For instance, the absence of a RT facility at the patient's hospital of diagnosis is associated with reduced rates of PRT, indicating potential problems with the dimension of *awareness.* This would suggest that improving *awareness* in these hospitals would result in improved rates of PRT. However, no study has been conducted to determine the best method of accomplishing this, or whether or not this is even the case. Hence there is a need to create interventions that seek to improve utilization of PRT, as well as evaluate their effectiveness at improving access to RT. The findings of this thesis provide numerous ideas that can be used to guide the creation of interventions designed to improve access to PRT.

There needs to be an objective measure of need against which the utilization rates can be compared. The criterion benchmark approach can be useful in this regard, but is not ideal. There is a need for consistent reporting of the occurrence and symptoms of bone and brain metastases, as well as other indications for PRT. This can be accomplished through the creation of a population-based registry that monitors the occurrence of these events. This would allow researchers using administrative databases to provide a clearer picture of how patients with advanced cancer are managed. We would be able to easily refine the denominator of our population to include only those patients with symptoms of bone or brain metastases, allowing clearer interpretations regarding the appropriateness of PRT utilization rates. Retrospective analyses could also be conducted to evaluate the effectiveness of treatments within the population at large, outside of the clinical trial setting.

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APPENDIX- Ethics Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

August 1, 2008

This Ethics Application was subject to:

☐ Full Board Review
Meeting Date:
☒ Expedited Review

Mr. Daniel Sutton
Department of Community Health and Epidemiology
Cancer Research Institute
Queen's University

Dear Mr. Sutton,

Study Title: Palliative Radiotherapy Utilization in Ontario
**Co-Investigators:** Dr. W. Mackillop, Dr. K. Ding

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following list of ethics requirements you must fulfill over the course of your study:

➤ **Reporting of Amendments:** If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. (see http://www.queensu.ca/vpr/reb.htm).

➤ **Reporting of Serious Adverse Events:** Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

➤ **Reporting of Complaints:** Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

➤ **Annual Renewal:** Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,
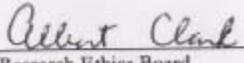
Albert Clark
_____
Chair, Research Ethics Board
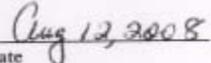
Aug 12, 2008
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Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD- COPY TO HOSPITAL(S) /P&T (If appropriate) - FILE COPY

Study Code: EPID-270-08

➤ Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

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