Understanding Palliative Radiotherapy Use for BC Cancer Patients at the End of Life

by

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B.Sc., Xi'an Institute of Technology, 1994
B.Sc., University of Victoria, 2007

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Abstract

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Palliative radiotherapy (PRT) is proven to be effective in palliation of symptoms for end-stage cancer patients. However, little is known about its utilization at the end of life. This research aims to examine the utilization and the practice patterns of PRT at the end of life for cancer patients in British Columbia using population-based data. The pattern observed for PRT_{1Y} dose-fractionation practice in BC are in line with published clinical guidelines and evidence from the literature, which advises "proper" use of PRT in BC as delivered to cancer patients at the end of life. However, after controlling for age, primary cancer site, and survival time, geographic access is found to be significantly associated with PRT_{1Y} utilization. Variations found in PRT_{1Y} rates by geographic access, which is operationalized by the Health Services Delivery Area (HSDA) and travel time, suggests potential underutilization of PRT_{1Y} for patients with suboptimal access.

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Acknowledgments

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1 Introduction

Radiotherapy (RT) is a well-established treatment modality in the management of many cancers with an especially important role in palliative settings often with clinically significant response rates of 60%-80%.[1] However, published data in Canada suggests that radiotherapy (RT) is vastly underutilized in the Province of Nova Scotia and Ontario especially for palliation.[2,3] Studies from Europe also confirm the underutilization of RT.[4,5]To the best of our knowledge, there is no published data yet available in BC examining the utilization of PRT for the cancer population at the end of life.

1.1 Purpose of the Proposed Research Study

The purpose of this study was to

(1) Report on the overall and site-specific rates of the PRT utilization for BC cancer patients at the last year of life.

(2) Describe the pattern of PRT utilization focusing on characterizing the technical aspects of the PRT received at the last year of life.

(3) Examine factors associated with such use of the PRT at the end of life.

1.2 Research Questions

The study answered the following research questions:

1. Among BC cancer patients who died between April 1, 2010 and March 31, 2011, what proportion of patients received at least one course of PRT during the last year, last month, and the last two weeks of life?
2. What were patient, disease and health system related factors associated with receiving PRT in the last year of life?

3. For BC cancer patients who died between April 1, 2010 and March 31, 2011, what was the pattern of PRT utilization by PRT treatment site in relation to their primary cancer site during the last year of life?
4. For BC cancer patients who died between April 1, 2010 and March 31, 2011, what were the most commonly used dose/fractionation schedules for PRT treatment in the last year of life?

1.3 Background

Despite advances in oncology, cancer is a leading cause of death in many countries with rates that will continue to escalate into the foreseeable future. In Canada, an estimated 186,400 new cases of cancer were diagnosed and more than 75,700 people died from it in 2012.[6] Health Canada estimates that nearly three quarters of the total expenditures for people with cancer are mortality related, particularly since people with cancer experience a greater chance of dying at all ages.[7] Research has found the last few months or year of a person's life are associated with an increased need for and use of health services, resulting in substantial healthcare costs.[8] In fact, cancer accounts for 30% of all deaths in Canada and for 32% of all mortality costs.[9]

The number of cancer deaths is projected to increase in the future; therefore it is increasingly important to ensure high quality End-of-Life care services are in place to meet the growing need. Unfortunately, recent evidence has shown that, all too often, people who die of cancer suffer unrelieved pain and other symptoms such as anxiety/depression, breathlessness, insomnia, nausea, constipation and/or anorexia, as well as unmet psychosocial needs.[10] Many patients who could have benefitted from palliative care either did not receive it or the care they received was inadequate. It is often

left to patients, their families and a loosely knit community of volunteer organizations to sort through the myriad of physical, psychological, spiritual and ethical choices. Quality of care toward and at the end of life is a significant issue[11] and there is an urgent need to improve care at the end of life for cancer patients and families.[12]

The key to change lies in rigorous scientific research that will provide the evidence for informed decision making by cancer care providers and policy makers. However, substantial challenges have been reported in conducting research in palliative care. Historically, palliative and end-of-life care research has been underfunded and underdeveloped across Europe and in Canada.[11,12] With increased awareness of the need for palliative/EOL care research in recent years, a steady increase in the quantity of the research has been observed; however, one literature review[13] has indicated that the majority of publications are surveys and observational studies using small scale data, e.g. observational data at the institutional level and few randomised control studies have been published. This is mainly because the heterogeneity of the palliative care population represents major challenges to research methodology including study design, informed consent (and ethical issues in general), assessment and classification of symptoms and signs, as well as practical issues in the clinic. It has been claimed that there is a need for larger, multi-centre, or population based studies in palliative care research.[13]

One of the major focuses in providing quality palliative care to advanced cancer patients lies in managing pain and relieving symptoms. This can be achieved through a number of palliative treatments including, but not limited to, surgery, chemotherapy and RT. Palliative treatments are an essential part of palliative care aiming to secure and improve a patient's quality of life at the end of life. The intention of palliative treatments

is not curative but rather to relieve pain and suffering. PRT is one of the palliative treatments that could greatly enhance the quality of life in appropriately selected patients with advanced cancer who have more than a few weeks or months to live.[1] However, researchers and policy makers have pointed to severe deficiencies in the provision of palliative care in Canada as well as the United States, United Kingdom and European Union.[10, 15-19] The majority of cancer patients suffer from pain and other symptoms in the terminal phase of their life.[14]

Anecdotally, PRT is thought to be commonly used,[20] but little population-based data are available regarding the patterns of, and factors associated with, its use. A description of PRT, used by cancer patients in the time leading up to death, can provide valuable information to radiation oncologists, cancer care providers and policy makers and help them assess whether or not terminally ill cancer patients receive adequate treatment as needed at the end of life. Knowing the pattern of PRT patients received before death offers insight into whether or not they are receiving care meant to improve the quality of life before dying.

2. Literature Review

2.1 Introduction

Currently there is neither scholarly nor non-academic literature addressing PRT utilization at the population level for BC cancer patients at the end of life. There is, however, literature that addresses areas related to this topic such as issues/challenges related to palliative care for cancer patients, understanding the role the PRT for palliation, identifying cancer site specific 'optimal' practice regarding PRT prescription and utilization patterns, and efforts made in searching for benchmarking for PRT utilization at the end of life.

This chapter summarizes the findings from the literature review on the proposed research. The purpose of this literature review was to provide a scientific base for understanding the importance of the proposed research, the existing gap in the knowledge in the research subject area, as well as the potential contribution it would make in improving palliative end of life care for cancer patients.

2.2 Methods

This review was conducted using Medline, ScienceDirect (Elsevier), PubMed electronic databases. The following Medical Subject Heading terms were used with a combination of "radiotherapy/radiation", "advanced/metastatic cancer", "end of life care", "palliative care", "palliative treatment(s)", "palliative radiation", "PRT", "PRT", "resource utilization", and "quality of end of life care". Abstracts were viewed and considered for relevancy. Rather than going through the rigours of systematizing the inclusion and exclusion criteria (performing a systematic review), in general, articles which involved discussion of RT/PRT treatment guidelines, optimal RT/PRT practice, as

well as optimal PRT rates and PRT rates for cancer patients at the end of life were included in the review. In addition, given that the practice guidelines and the standard of care evolves through time, only articles published in English in the last 20 years were considered as the most relevant evidence in terms of RT practice and were included in the review.

2.3 Results

2.3.1 Definitions of palliative care

According to Webster, [21] to *palliate* is to alleviate or lessen the severity without curing. In 1990, the World Health Organization provided a more global definition which stated that palliative care was "the active total care of patients whose disease is not responsive to curative treatment. Control of pain, other symptoms, and of psychological, social, and spiritual problems is paramount. The goal of palliative care is achievement of the best possible quality of life for patients and their families." [22] This global definition reinforces a need for symptom alleviation across the cancer trajectory. Control of pain and deleterious physical, psychological, and spiritual symptoms is paramount to holistic cancer care at each phase of the trajectory.

The definitions of palliative medicine and palliative care,[23,24] point towards a population of patients with life-limiting disease, win whom cure is not possible and life-prolonging treatment is no longer the focus of treatment. Thus, from a narrow perspective, palliative care may be understood as 'end of life' only. In fact, "palliative care" and "end-of-life care" are often used interchangeably in much literature when discussing care provided to terminally ill patients.

2.3.2 Issues regarding palliative care for cancer patients

2.3.2.1 Inadequate care patients received at the end of life

For many cancer patients, medical and surgical treatment leads to long-term remission or cure. Other patients have aggressive or metastatic cancer at the time of diagnosis or experience a recurrence later in their illness. Because of increasing cancer incidence, despite advances in cancer detection and treatment, more and more patients die of cancer each year.[25]

Very often, care for patients near the end of life falls short of the desires of patients and families. This has been well documented for patients with advanced illness and specifically for cancer. The Institute of Medicine's 1997 report, "Approaching Death: Improving Care at the End of Life", documented the pervasive under-treatment of pain and other burdensome symptoms. As well as overtreatment with curative measures that many patients do not want. In 2001, the Institute released a related report, "Improving Palliative Care for Cancer", which concluded:

> Improvements in the development and delivery of symptom control and other aspects of palliative care needed in the late stage of cancer (and other chronic diseases) have not kept pace with the medical advances that have allowed people to live longer. For at least half of those dying from cancer, death entails a spectrum of symptoms, including pain, labored breathing, distress, nausea, confusion, and other physical and psychological conditions that go untreated or undertreated and vastly diminish the quality of their remaining days. Patients, their families, and caregivers all suffer from inadequate care available to patients in pain and distress, although the magnitude of these burdens is only now being described.[26, P2]

The quality of end of life care is gaining increasing attention as a key measure of excellence in cancer care.[27,28] Several consensus statements and surveys of patients, families, and clinicians have been published affirming the value of not simply prolonging life but also enhancing the quality of the dying process.[29-32] Some of the more common themes regarding patients' wishes for end of life care include adequate pain and symptom

management, preparation for death, and control over place of death. Advanced care planning and end of life decision-making are also salient indicators for quality care.[33, 34]

2.3.2.2 Challenges in decision making about end-of-life care

For patients with a poor prognosis, because the cancer is advanced or metastatic, death is the likely short-term outcome. Making decisions about treatments, goals of care and end-of-life planning from the time of diagnosis until death is particularly challenging. Many of these decisions are highly complex, emotionally charged, and have significant impact on how patients are managed. The health care team plays a key role helping guide patients through the maze of difficult choices by providing individualized recommendations, taking into account the patient's preferences, disease state, treatment options and resources.[35]

Literature has found wide variation in patients' preferences concerning the aims of medical treatment and the balance between benefits and side effects of different treatment options when the end of life is nearing.[36] When a cure is unlikely, some patients desire aggressive treatment up to the time of death. These patients seek to gain weeks or months of additional life irrespective of treatment side effects and the possible isolation from home and family that aggressive treatment often entail. Other patients with limited life expectancy prefer care directed toward the quality rather than the quantity of life. They want to be able to bring closure to their lives with a focus on their comfort in familiar surroundings, close to family and friends. They also want control of pain and the many other difficult symptoms associated with advanced cancer and its aggressive treatment.[37] In a study among patients with metastatic cancer, patient's actual treatment choice was most strongly predicted by patients' treatment preference, and this preference

was explained by patients' attitudes toward treatment.[38] It is known that all cancer patients vary in their attitudes and preferences concerning the aims of medical treatment. In a recent study of patient's attitudes toward cancer treatment, Voogt et al found that patients who appreciate advance care planning were more inclined to strive for quality of life than other patients. Patients with a history of cancer of less than 6 months were more inclined to prefer life prolongation than patients with a longer history of cancer.[39]

Without a doubt, patients' preferences, when available, serve as a key to guide clinical decisions on how care is delivered at the end of life. Nevertheless, it is often reported that many patients, especially advanced cancer patients dying in acute care settings, are sometimes too ill to engage in discussions regarding health care decisions.[35]

On the other hand, differences in patient preferences often impose a challenge for palliative care providers, particularly when cure or remission is the hope of most patients with cancer. The well documented failure in counselling patients about their prognosis and the full range of care options, including early palliative care, leads many patients to seek more aggressive care without fully understanding its impact on the length and quality of life.[37]

Even though many are concerned that patients with advanced cancers are over treated with curative measures which offer no help to prolong a patient's life,[26] weighing limited survival advantages against worsened quality of life is difficult.[40] In fact, it is widely reported that despite limited benefits, a substantial portion of lung cancer patients prefer aggressive treatment [41,42] and most have an unrealistic expectation of treatment outcomes.[43]

In addition, significant disagreements have been observed between patients and caregivers (usually their family members) about treatment and care decisions. For example, caregivers were more concerned about patients' quality of life and more willing to discuss hospice issues than were patients; patients were more willing to stop treatment if it was no longer effective and caregivers were more likely to stop treatment if the side effects adversely affected patients' quality of life.[40]

2.3.3 Understanding the role of RT in palliative care

RT has existed for over a century. It began with the formidable discoveries of Wilhelm Roentgen (X rays, 1895) and Marie Curie (radium, 1898). The role of RT in the management of incurable malignant disease is remarkable. For over a century, RT for the treatment of cancer has been the most effective available nonsurgical tool for cancer treatment.[44]

Historically, because the radiation oncology department is a highly technical and scientific environment that has often developed in relative isolation from the rest of the hospital setting, it may seem intimidating to both patients and other health care professionals. Also, patients may have negative experiences from their communities where a friend or relative underwent radiotherapy, appeared to be very ill and then died. The RT may be perceived as the cause when the disease process is ignored, and the aims of the RT and its side effects are misunderstood.[44] To understand the role of RT in palliative care, some basic concepts about the subject need to be introduced and understood first.

2.3.3.1 General Principles of PRT

RT is the delivery of ionizing radiation into a defined volume of the body in order to eradicate (sterilize) or substantially depopulate the tumor cells within that volume, without exceeding the tolerance of normal tissues. Intrinsic to the understanding of decision making around the use of RT is the principle of the therapeutic ratio, which is the risk/benefit analysis that allows providers to weight benefit and side effects of any therapeutic intervention. An ethically based argument for the decision making process for palliative care based on the therapeutic ratio has been approved.[44] A side effect profile should be, at the minimum, compatible with achieving the palliative aims of the treatment, and responses should be defined in terms of palliative end points which the patient will notice. Palliative therapy should maximize patient clinical benefit and convenience while minimizing patient side-effects and discomfort, e.g. through minimizing number of hospital visits and length of overall treatment time to the most effective timeframe, so that precious remaining time away from home and family is not excessive.

Significant therapeutic results from PRT typically take several days to a few weeks to occur.[45] Therefore, for most patients to benefit, they must have a life expectancy of at least two to four weeks.

2.3.3.2 Concepts Related to PRT Prescription

RT dose refers to the amount of radiation absorbed by the body. The units of measurement of the radiation used in Canada and in much of the world are Système Internationale (SI) units, based on the metric system. The SI unit of absorbed radiation dose is the Gray (Gy). The Gy is the unit used in describing the amount of energy absorbed by a substance from the radiation passing through it, or the absorbed dose. One

Gy corresponds to one joule of radiation energy absorbed by one kilogram of matter. This unit was named after the English radiobiologist Louis H. Gray. One Gy is equal to 100 centiGray (cGy).

Fractionation schedules refer to the number and timing of RT sessions and the radiation dose(s) per session. Fractionation schedules for PRT are not yet entirely based upon a firm scientific footing.[46] However, in recent years, there is much evidence that suggests that shorter courses of treatment are just as effective as more protracted schedules for many PRT indications.[47-52]

Hypofractionation refers to the delivery of RT dose in a smaller number of treatments than would be used to deliver a traditional dosing scheme. The daily fraction size, therefore, is larger than the size given in standard fractionation, commonly measuring between three and eight Gy.[53] Most structures in the human body are divided into either early-responding or late-responding tissues, depending on whether they are more likely to manifest radiation damage around the time of the treatment course or months to years later, and higher total dose and larger fraction size is correlated with greater damage to later-responding tissues. Patients who are treated for symptom palliation commonly have limited survival, physical discomfort with transportation, and insufficient emotional and physical energy for prolonged treatment courses. Lower total doses of RT are required to palliate symptoms than to cure cancers, which allows for greater use of hypofractionation. Shorter courses are usually preferred in end-of-life care because most patients who are treated for symptom palliation will benefit with lower total radiotherapy doses, and will not survive to face the possibly increased risk of long-term side effects associated with hypofractionated regimens.

2.3.3.3 Indications of PRT

It is important for palliative care providers, e.g. hospice clinicians or primary care physicians, to thoroughly understand the indications of PRT so that adequate care can be provided to patients at the end of life. There are a number of well-established indications for PRT in advanced cancer.[54] These indications are summarized in Table 1. However, not all patients will benefit from PRT and it is important to consider the underlying condition and performance status of the patient before making a final decision that referral for RT is appropriate.

Table 1: Indications for PRT

Site	***Symptom***
Bone metastases:	Local pain
	Neuropathic pain
	Spinal cord compression
	Nerve root compression
Brain metastases:	Weakness
	Headache
	Cranial nerve involvement
	Confusion
Hepatic metastases:	Pain due to massive hepatomegaly
Choroidal metastases:	Visual loss
Lung cancer:	Haemoptyis
	Chest pain
	Dysphagia
	Dyspnea due to lung collapse
Rectal cancer:	Hemorrhage, pain or discharge
Bladder cancer:	Haematuria
Prostate cancer:	Haematuria
Cervical cancer:	Bleeding, pain
Ovary cancer:	Bleeding, pain

(1) Pain relief: Bone metastasis is the most common indication of PRT for advanced cancer patients due to its effectiveness of palliating severe pain.[53] Up to 75% of patients with breast, lung, and prostate cancer have been found to have bone metastases post-

mortem.[55] Other primary tumors, namely the kidney, pancreas, rectum, colon, stomach, thyroid, and ovary are also associated with bone metastases. Meta-analyses have reported an overall response rate of approximately 60% (intent-to-treat) with a complete response rate of 33% at 4 weeks.[56-58] In addition, patients whose cancer pain is not well controlled by other methods might benefit from PRT. Or, when analgesic therapies create dominant adverse effects, PRT also should be considered.[1]

(2) Nerve Root Infiltration and Soft Tissue Infiltration: RT is often helpful in situations where tumor directly infiltrates into nerves or soft tissues.[59] It is usually administered in combination with steroids or nonsteroidal anti-inflammatory drugs. Higher doses of radiation may be required for these indications than for bone pain.

(3) **Control of Bleeding**: RT has a long track record of controlling hemorrhage from bleeding tumors, e.g. from the lung or cervix. It has been known for some time that vaginal bleeding from cervical carcinoma may be arrested by intracavitary isotope insertion. Equally, external beam irradiation is effective either as a short palliative course, or where indicated, in a high-dose radical treatment context.[60]

(4) **Control of Ulceration**: Most disfiguring and distressing cases of superficial tumor ulceration can be helped by radiotherapy. The most common of these tumors encountered in oncological practice are breast cancer on the chest wall, fungating head and neck cancer, and both melanoma and non-melanoma skin cancer.[61]

(5) **Dyspnea:** The most common tumor causing shortness of breath is lung cancer, although metastases from other primary sites may, and frequently do produce respiratory symptoms. The mechanisms of dyspnea are not completely understood but there is much evidence to show that RT can give excellent palliation for dyspnea due to endobronchial

obstruction or extrinsic nodal compression of the bronchi.[62,63] As well, PRT can be very effective treatment for hemoptysis, cough, chest pain, superior venal caval obstruction, and dysphagia due to extrinsic esophageal compression.[64]

2.3.4 Current knowledge on PRT practice

Evaluated concepts and practical guidelines are available for specific conditions in metastatic diseases such as brain metastases, bone metastases, spinal cord compression, lung cancer, head and neck cancer, esophageal and skin cancer, and pelvic disease.[65-68] However, at times, determining the optimal treatment regimen that delivers rapid and enduring symptom relief with minimum morbidity, disruption and cost to the patient and community, remains a challenge for the radiation oncologist in the treatment of advanced cancer.[46]

There have been numerous attempts to identify the optimal dose and fractionation for RT treatment. Despite published data on optimal dose-fractionation schedule, optimal treatment approach remains controversial. In fact, clinical practice continues to show marked variation, ranging from a single fraction to 10 or even 20 fractions for the same presenting condition.[69] In Canada, two most recent surveys of Canadian patterns of practice for the treatment of bone metastases reported that various fractionation schedules are employed by radiation oncologists, ranging from a single large-dose fraction (e.g. 8 Gy) to a more prolonged course of 30 Gy/10 fractions over 2 weeks.[69,70]

With efforts into identifying optimal RT treatment over the past decades, significant clinical trial efforts have also been devoted to compare efficacy of the treatment between shorter (e.g single large-dose) and longer (e.g. multifraction regimens -five to ten fractions) palliative schedules. The rationale behind this is to maximize cost-

benefit of the treatment for patients at the end of life. If the shorter courses of treatment are just as effective as more protracted schedules and they also incur less acute toxicity with fewer trips to a treatment facility, patients will experience less discomfort and have more time to spend with their families with limited life expectancy.

There seems to be general agreement reached through many published randomized trials: one, two or a few (at the most) fractions represent the most beneficial approach to PRT, when indicated for patients with limited life expectancy.[67]

2.3.4.1 Single fraction vs. multiple fractions for bone metastases

High quality data from multiple randomized trials demonstrated the equivalence of a single fraction and multiple fractions regimen in terms of treatment of uncomplicated painful bone metastases. Two prospective randomized and retrospective trials comparing single 8 Gy fraction and multiple factions of RT treatment have shown similar response rates, even at the 1-year time interval.[69,71] The duration of response and progression rates were also demonstrated to be similar, implying that a single 8 Gy fraction is a non-inferior treatment, even for patients with a relatively favourable prognosis.[71] In terms of acute toxicities, a statistically significant lower rate was reported for a single 8 Gy fraction in the Radiation Therapy and Oncology Group (RTOG) 9714 trial compared with the regimen of 30 Gy in ten fractions (10 vs 17%). The late toxicity rates were reported similar between the two groups in this trial.[72] Other prospective randomized trials conducted in Europe[56,73] also reported no difference in quick symptom relief, the duration of pain relief or toxicity when a single dose of RT was compared to a RT schedule with multiple RT fractions.

Multiple meta-analyses on the comparison of single- versus multiple-fraction RT have been performed.[56-58] In the study by Sze et al., 12 trials including 3621 painful bone metastasis sites and 3508 patients were involved. The overall pain response rates for single versus multiple fractions were 60% versus 59% (34% vs 32% for complete response). Wu et al. reported that among the 3260 randomized patients in seven studies, complete pain response rates for single- and multiple-fraction RT were 33.4% and 32.2%, respectively. The corresponding overall response rates were 62.1% and 58.7%. There were no significant differences found in response rates between the two groups. Chow et al. included 2513 patients in16 randomized trials comparing single- and multiple-fraction RT in the systematic review and found that there was no difference between single- and multiple-fraction RT regimens in terms of response rates.

Despite substantial evidence support the efficacy of single-fraction RT in the treatment of bone metastatic disease, concerns have been raised regarding retreatment and pathologic fractures associated with delivering single fraction treatment. Some studies have found a higher rate of retreatment among patients treated with a single fraction.[56,72,104] Sze et al.[56] reported the rates of retreatment for single- and multiple-fraction RT were 21.5 and 7.4%, respectively. Chow et al.[104] found the re-irradiation rate to the same anatomic site because of recurrent pain was significantly (2.5 times) higher for the single-fraction versus multiple-fraction RT (20% vs 8%). The higher retreatment rate found for single fraction may reflect a greater need for retreatment, but because none of the trials of the fractionation of PRT has been double-blinded, the higher retreatment rate may merely reflect radiation oncologists' greater readiness to retreat after a single fraction.[74]

Another concern regarding a single fraction is the increased risk of pathological fracture. A systematic review of randomized trails has reported there is a small but significant increase in the risk of a subsequent pathologic fracture among those treated with a single fraction.[56] A recent study has shown that most patients choose fractionated treatment when they are told about the higher risk of fracture and the increased likelihood of retreatment.[75]

Early guidelines published in 1998 by the American College of Radiology for treatment of bone metastases recommended that dose-fractionation schemes of 20 Gy/5 fractions, 30 Gy/10 fractions, or 35 Gy/14 fractions be used in most clinical situations for initial treatment of metastatic bone disease. High dose schedules were only recommended in special situations. It was also recommended that patient performance status and life expectancy are the factors that must be taken into consideration when determining optimal dose-fractionation schemes.[76] Most recently in 2011, the American Society for Radiation Oncology (ASTRO) in coordination with the Third International Consensus Conference on Palliative Radiotherapy published guidelines suggested a single 8Gy fraction RT for uncomplicated bone metastases[52]

In Canada, the final practice guideline report for palliation of uncomplicated painful bone metastases was approved in 2004 by the Practice Guidelines Coordinating Committee after a systematic review and meta-analysis of existing evidence from clinical trials with the consideration of patient convenience and ease of administration of PRT, as well as input from practitioners in Ontario.[77] The meta-analysis with existing evidence did not detect a significant difference in complete or overall pain relief between single treatment and multifraction PRT for bone metastases. The approved practice guideline for

adult patients with single or multiple radiographically confirmed bone metastases of any histology corresponding to painful areas in previously non-irradiated areas without pathologic fractures or spinal cord/cauda equine compression, stated:

> "where the treatment objective is pain relief, a single 8 Gy treatment, prescribed to the appropriate target volume, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases."

This practice guideline report serves as a convenient and up-to-date source of the best available evidence on the preferred dose-fractionation of radiotherapy for the treatment of uncomplicated painful bone metastases in Canada.

One would expect that these uniform findings and existence of practice guidelines would change daily practice worldwide. Yet, this is not the case in reality. A large number of national and international surveys have been conducted during the past two decades assessing the adoption of the single faction schedule.[69,70,78-80] In Europe, North America, Australia/New Zealand, and Asia, radiation oncologists were asked to give their opinion on hypothetical case scenarios. Overall, there seem to be abundant reasons to choose single fraction as the standard. In contrast to this expectation however, the percentages of single fraction use reported by radiation oncologists in the surveys has been consistently low.

In the most recent international survey by Fairchild et al.,[69] a questionnaire including 5 hypothetical case scenarios was sent out to 6110 practitioners who were members of the American Society for Radiology Oncology (ASTRO), the Canadian Association of Radiation Oncology (CARO), and fellows of the Royal Australian and New Zealand College of Radiology (RANZCR). The respondents were asked whether they would recommend RT for patients with single or multiple fractions secondary to

breast, prostate, or lung cancer and, if so, their preferred dose fractionation. Among 962 eligible responses received, 2 - 67% of respondents recommended single fraction RT. According to this study, a single 8 Gy is now the most common choice in Europe and the UK, 20 Gy in 5 fractions in Canada and Australia/NZ, but 30 Gy in 10 fractions is still preferred by the majority in the USA and Asia.

In a few studies [81,82,46] where patient preferences were sought, results vary in different countries. In the Australian study,[46] most patients favored single fraction RT, providing long-term outcomes were not compromised. Durability of pain relief was considered more important than short-term convenience factors. In the Singaporean study,[82] 85% of patients would choose extended courses of RT (24 Gy/6) compared to a single 8 Gy. In the Canadian study,[81] 76% of patients would choose a single 8 Gy over 20 Gy/5 of palliative RT due to greater convenience.

To summarize, there is, as yet, no consensus regarding the most appropriate way of delivering RT for metastatic bone pain. The practice differs significantly among different countries and indeed, between different treatment centres within the same country. It seems clear that single fraction is appropriate treatment for the majority of patients with uncomplicated bone metastases with the exception of rare situation where very limited uncomplicated bone metastases from favorable histologies, such as breast cancer, are present without associated extraosseous metastases, a multi-fraction regimen delivering in a higher total dose may be beneficial;[83] Also, in circumstances where there is presence of a soft-tissue mass around the bone metastasis or the bone metastases is located in a weight-bearing bone, or when there is neuropathic pain associated with the bone metastases, multiple fractions may be appropriate in patients with good performance

status.[77] Consensus is still lacking on optimal PRT schedule treating complicated bone metastases.

2.3.4.2 PRT for Brain Metastases

The brain is one of the three most common sites for metastases. The exact incidence of brain metastases is unknown and reported rates vary depending on the population studied and the method of assessment.[84] It is estimated that 20-40% of cancer patients will develop metastatic cancer to the brain during the course of their illness.[85] Lung cancer is the most frequent site metastatic to brain, constituting more than 50% of the patients, followed by breast cancer (15%) and colorectal cancer (6%). Other sites, such as melanoma, renal cell, seminoma, and others, make up the reminder of the patients.[86]

Patients develop a range of symptoms caused by increased intracranial pressure or direct tumour infiltration into functioning brain tissue, e.g., severe headache, blindness, balance disturbances, and other injury to cerebral function, which left untreated is generally progressive.[84] The prognosis for patients with brain metastases is poor, with a median survival time of 1-2 months in untreated patients and 3-6 months in patients treated with whole brain radiotherapy (WBRT).[85] Twenty-five to 50% of patients with brain metastases die of progression of disease in the brain.[87]

Therapeutic options for brain metastases include WBRT, surgery, and stereotactic radiosurgery. Although there have been no randomised trials showing that WBRT offers a survival advantage over supportive care,[88,89] WBRT is the standard recommendation in clinical practice guidelines for the management of brain metastases.[85,90] Many patients with brain metastases are treated with WBRT despite shortcomings considering long

treatment time over several weeks, the associated alopecia and fatigue and the risk of neurocognitive sequel.[91] Surgical resection is another treatment option, but it is invasive and generally reserved for minority of patients with an expansive single metastasis and with a good prognosis. The literature has reported the efficacy of radiosurgery as a minimally invasive alternative to surgery to obtain local tumor control even though it is mainly used as a boost in combination with WBRT.[91] An alternative to single fraction radiosurgery is the use of hypofractionated conformal stereotactic radiotherapy (HCSRT). The use of HCSRT is considered to be more appropriate for large tumors (e.g tumor >10 cc) given that the limited local control has been reported with single fraction radiosurgery.[91]

In the most recent international practice survey on the management of brain metastases,[92] 445 individuals who were primarily practiced in Europe, Australia/New Zealand, the United States and Canada responded to the survey. Among the respondents, 93% are radiation oncologists. Most of the survey questions are based on common management issues for which optimal management using level 1evidence was lacking. The results find significant variations in the dose fractionation schedules for the use of WBRT for brain metastases, ranging from 30 Gy in 10 fractions and 20 Gy in 5 fractions to 40 Gy in 20 fractions and 37.5 Gy in 15 fractions. Internationally across the board, the most commonly used WBRT dose fractionation schemes are 20 Gy in 5 fractions in 1 week or 30 Gy in 10 fractions in 2 weeks. In the United States, 30 Gy in 10 fractions and 37.5 Gy in 15 fractions represent the most frequently used dose/fractionation schedules[89,92] while in Canada, the most commonly employed WBRT treatment is 20 Gy in 5 fractions and 30 Gy in 10 fractions.[85,92] The results from the survey also indicate

there is a lack of uniform agreement for many common management issues in patients with brain metastases. For example, only 3 of 26 survey questions generated at least 70% agreement for a favoured response.

Literature suggests there is no consensus in the optimal dose fractionation of WBRT. In a systematic review and meta-analysis, Tsao et al.[85] compared a variety of total doses, fractionation schedules, and doses per fraction which have been tested in prospective, randomized, Phase III clinical trials, primarily in patients with multiple brain metastases. None of these regimens has proven better than another in terms of survival or efficacy.

However, there seems a general agreement that selecting treatment regimens appropriate for individual patients should be facilitated by considering prognostic factors such as Karnofsky Performance Score (KPS), patient age, the presence of extracranial metastases, and the status of the primary tumor. Thus, the WBRT regimen considered to be optimal may differ for patients with different prognostic factors e.g primary tumor. Short course treatment is appropriate for patients with poor performance status, progressive systemic disease or elderly.[89]

2.3.4.3 PRT for thoracic symptoms

Lung cancer is a major public health problem with a 5 year overall survival rate of 15%.[93] There are two main types: non-small cell lung cancer comprising approximately 80% of the cases, and small cell lung cancer comprising the remaining 20%. A large proportion of patients (75–85%) with locally advanced or metastatic non-small cell lung cancer who are not suitable for radical treatment with surgery, radiotherapy, or radiochemotherapy, demonstrate symptoms related to intra-thoracic tumor growth.

Palliation for thoracic symptoms may be achieved with PRT or systemic therapy. Thoracic irradiation may be the only option for palliation among patients who relapse after first or second-line chemotherapy or who are chemotherapy-resistant or chemotherapy-intolerant.

Even though sufficient evidences in the literature show that PRT is effective in controlling symptoms, it has not been clearly established which regimens give the most benefit and least toxicity.[94] Literature suggests that in a palliative setting for patients with poor prognosis, shorter, low dose regimens are considered a better approach in treating advanced non-small cell lung cancer. In a systematic review[95] aiming to determine the safest and most effective regimen of PRT in people with advanced non-small cell lung cancer, Toy et al identified 17 dose fractionation schedules, ranging from 10 Gy in one fraction to 60 Gy in 30 fractions during six weeks, from the randomized controlled trials they reviewed. The authors concluded that RT improves control of thoracic symptoms from baseline in people with inoperable lung cancer and poor prognosis irrespective of dose/fraction schedules. However, there is no strong evidence that higher dose of RT are more or less effective for symptom control than lower dose given the heterogeneity of studies. Some studies reported higher dose is associated with greater toxicity compared with short hypofractionated regimens. Given the aim of PRT is palliation of symptoms and high dose regimens may be more time consuming than shorter, low dose regimens, the authors concluded that shorter, low dose regimens is more appropriate to be used in the palliative setting.

A number of systematic reviews[94,96] published in recent years support the use of higher dose regimens, especially for patients with good performance status. In the most

recent review done by the Cochrane Collaboration,[96] Lester et al. reviewed 14 randomized trials comparing different regimens of PRT in patients with non-small cell lung cancer. Strong evidence has been found in 4 studies [97-100] for a significant survival benefit with higher dose regimens especially for patients with good performance status. Kramer et al.[100] also showed the duration of palliative effect was significantly longer with 30 Gy in10 fractions compared to 16 Gy in 2 fractions.

Clearly higher dose PRT is associated with more visits to cancer clinics and more toxicity and thus the balance of benefit and risk needs to be carefully assesses and discussed with the patient before making treatment decisions.

In short, there is general agreement in the literature about the use of PRT dose-fractionation schedules for the treatment of non-small cell lung cancer. The majority of patients with locally advanced non-small cell lung cancer and thoracic symptoms, especially those with poor performance status should be treated with short course of PRT (such as 10 Gy in 1 fraction or 16-17 Gy in 2 fractions). Care should be taken into avoid irradiating, or to reduce the dose to the spinal cord if 17 Gy in 2 fractions is used. Selected patients with good performance status should be considered for treatment with higher dose PRT (such as 20 Gy in 5 fractions - 36 Gy in 12 fractions) if the chance of a modest improvement in survival and palliation is considered worth the additional inconvenience and toxicity.

2.3.4.4 Factors associated with reluctance of changing PRT practice

Despite much evidence that shows similar effectiveness between shorter and longer fractionation schedules in some clinical situations, many radiation oncologists

especially in the United States prefer protracted treatment schemes. Factors associated with reluctance to adopt single fraction treatments for bone metastases have been studied.

One of the major factors has to do with reservations/concerns about the measurements of outcomes reported in clinical trials. In an evaluation study of outcome measures for PRT for bone metastases, Barton et al.[46] reviewed studies where the outcomes are specifically to the PRT. The authors found there was no standardized definition of either response to radiotherapy or assessment of pain relief. This poses extreme challenges to compare outcomes by different dose-fractionation schedules from various clinical trials. In addition, pain measurement in many studies was undertaken using very simple measures, which could possibly yield inaccurate results.

Other factors that may contribute to the reluctance of radiation oncologists to change established patterns of practice include: habit, lack of knowledge of recent (i.e., post specialty certification) clinical data, or economic advantages of established fractionation regimens.[101] In some jurisdictions, there is economic incentive to giving more treatments. Several studies have shown that the choice of fractionation is influenced not only by patient-related factors but also by physician education and attitudes, treatment toxicity, resource utilization, and departmental policy.[102,103]

2.3.5 PRT utilization rates reported in the literature

It is estimated that approximately 50% of all radiotherapy is prescribed with palliative intent.[3,105,106] Yet, data on the use of PRT in routine practice at a population level is hard to find. Some publications have estimated the appropriate utilization of RT for patients with cancer. However, the estimates are based on expert opinion. For example, the Inter-society Council for Radiation Oncology estimated that approximately

50-60% of patients with cancer will need RT treatment at one point during the course of the disease. The Swedish Survey[107] of RT practice estimated overall approximately 37% of their cancer population will need RT treatment and the Dutch Delphi Panel[108] estimated an overall rate of 50%. Optimal rates of PRT utilization for cancer patients overall or for a specific cancer site are rarely reported.

In fact, there are indications that PRT is under-utilized in general cancer population as well as in palliative care setting despite its efficacy in palliation.[108,110] Huang et al.[3] reported an overall rate of 26.4% for Ontario patients who died of cancer between 1986 and 1995 received at least one course of PRT at one time within two years prior to death. They identified a subgroup of patients, from their study population, who had more optimal access (e.g. younger residents of medium or high income communities, initially diagnosed in a hospital with a cancer centre, and residing close to a cancer centre) to PRT and used it as a substitute for the ideal population with an approximation to optimal access to PRT in their study context. They concluded that the overall rate of 26.4% for the use of PRT in Ontario, which was less than one half of the ideal rate calculated based on the subgroup population, strongly suggests that PRT was underutilized in Ontario. In another study, Lavergne et al.[2] looked at patients who died of cancer between 2000 and 2005 in Nova Scotia and found 22.3% of patients received PRT treatment in the last nine months of life. Variations were observed by cancer site and previous oncology care.

These two Canadian studies have both demonstrated a variation in the use of PRT unrelated to the needs of the patients. In both provinces, the use of PRT reduced over a 10-year period, contrary to the increasing incidence of cancer. Possible reasons for

decline in PRT utilization were identified as barriers to accessing RT, including geography, age, wait times, availability of resources, distance from a cancer centre, socioeconomic factors, differing patterns of practice between the radiation oncologists, and lack of education regarding PRT among community healthcare workers and physicians, resulting in lower referral rates.[2,3,112,113]

In reviewing PRT utilization studies, challenges are well recognized in determining whether the observed rates of PRT use by cancer site are appropriate given that no benchmark is available for assessment.

With the absence of optimal PRT utilization for benchmarking in recent years, much effort has been devoted to developing approaches for estimating the need for RT. Without an accurate estimate of appropriate RT rate, attempts to forecast and meet the populations' need for RT are difficult.

In fact, two approaches have been developed and used to estimate optimal RT utilization for cancer patients – epidemiologically-based estimates (EBEST)[114] and criterion-based benchmarks (CBB).[115] EBEST estimates are based on indications derived from treatment guidelines, and epidemiological data on the proportions of cases with such indications, whereas CBB methods benchmark optimal rates to those observed in jurisdictions with characteristics that would be associated with optimal use (i.e. short waits for treatment, close proximity to a cancer clinic, multidisciplinary care). With EBEST approach, two research groups - the Radiation Oncology Research Unit (RORU) in Canada and the Collaboration for Cancer Outcomes Research and Evaluation (CCORE) in Australia have developed EBEST models of need. These estimates suggest

appropriate radiotherapy utilization rates on a site-specific basis for both initial treatment and for treatment at any point after diagnosis.

The estimates of the RT needs for various cancer sites are available based on EBEST models and CBB models. EBEST estimates (by the RORU) for the need for radiotherapy as part of the initial treatments for breast, lung, and prostate cancer have been estimated at 57, 45, and 32%.[116-118] CBB estimates for appropriate rate for radiotherapy within one year of diagnosis for patients with breast, lung and prostate cancer have been estimated as 61, 41, and 37%.[115,119,120] EBEST estimates (by the CCORE) for RT at any point after diagnosis for patients with breast, lung and prostate cancer have been estimated at 66-83, 61-76, and 60-61%, respectively.[116-118]

One should note there are substantial differences in the estimated utilization rate using different models. For example, Delaney et al.[114] estimated the optimal RT utilization for all prostate cancer incident cases to be 60% based on CCORE EBEST model while Foroudi et al.[118] estimated an ideal utilization for treating prostate cancer to be 32% based on the RORU EBEST model. Significant methodological differences need to be acknowledged when interpreting these estimates. In addition, differences in estimated utilization rate may potentially be a result of, but not limited to, population characteristics and treatment guidelines in the recommendation of an indication to when (or whether) RT should be used. Discrepancy between optimal benchmark values and actual RT utilization rates may indicate suboptimal patient care.

In a validation study of the estimate models, BC has found that their Canadian EBEST and CBB model estimates are closer to their actual RT rates than the Australian EBEST estimates, which supported the use of either the Canadian EBEST or CBB model

to obtain the appropriate RT rate. When comparing the results of the actual rates with estimated rates from Canadian EBEST model, it suggested underutilization of RT treatment for lung, breast and prostate cancer patients in BC.[116] The same conclusion of an underutilization of RT treatment for prostate cancer patients in Ontario has also been made in a study of defining the RT need for prostate cancer patients in Ontario.[120]

During our literature search, the only attempt found on estimating the needs of PRT for cancer population was done in Australia where the CCORE estimated the proportion of new cases of cancer that should receive PRT as their first course of RT at some time during the course of their illness.[105] Based on existing EBEST models developed for optimal RT utilization, Jocob et al. re-analyzed the original RT utilization tree. All branches that ended in an indication for RT were classified as either PRT or as RT with radical treatment intent. The patients were scored on the RT utilization tree only when the PRT was recommended by the guidelines as initial treatment for patients. Using this approach, the authors estimated that 14% of all new cancer cases in New South Wales should optimally receive PRT as their first RT treatment.

There are no data on PRT utilization for cancer patients at the end of life in BC.

2.4 Summary of literature

PRT has been proven effective to relieve symptoms related to advanced cancer. Treatment guidelines have been established for specific cancer site for many years, but dose-fraction schedules still vary.

Even though empirical evidence from randomized trials shows a single fraction (8Gy) of palliative radiation provides equal efficacy of pain relief as multiple fractions in the treatment of uncomplicated bone metastases, in reality multiple fraction schedules

still dominate worldwide practice. Continuing effort should be made by the international radiotherapy community towards increasing awareness and, consequently, the percentage of single fraction usage in daily practice.

The standard radiotherapeutic treatment of patients with brain metastases has been the delivery of whole brain radiation of 20 Gy in 5 fractions to 30 Gy in 10 fractions.

There is no solid evidence to conclude higher dose of radiotherapy are more or less effective for symptom control than lower doses for patients with inoperable non-small cell lung cancer. Based on the systematic review of scientific evidence of PRT treatment for advanced lung cancer, it is suggested that shorter, low dose regimens are as effective in palliation of symptoms for most patients, but that higher doses are associated with modest survival improvements among patients with good performance status.

Currently there is neither a benchmark to help assess if the actual PRT utilization is appropriate or not, nor is there a standard approach available to assess PRT needs for cancer populations at the end of life. Two approaches –EBEST and CBB have been developed to help estimate overall RT needs of the cancer population. Caution needs to be taken when comparing actual PRT rates with "optimal/benchmark" rates obtained from different methodologies.

A few Canadian studies in other provinces have reported PRT is underutilized by the end-of-life cancer population due to restricted access to resources. In BC, the access issue has also been reported in a few RT utilization studies for newly diagnosed cancer patients for specific cancer types. However, the PRT rate for overall cancer population at the end of life has never been explored in BC. In addition, the patterns of the PRT practice from the literature are mostly from clinical trials or practice surveys. The

description of PRT utilization patterns using population-based data is sparse and such data does not exist in BC.

This research will fill the knowledge gap by providing population based data on the PRT utilization for BC cancer population at the end of life. By examining the patterns of how PRT is delivered, this research will inform cancer care providers, planners and administrators about the quality of care that BC cancer patients received at the end of life. It will also help decision makers identify the subgroup of population who might potentially receive suboptimal care at the end of life and help them target this population for quality improvement. Even though it is not an intention of this research to identify optimal PRT rates or PRT dose/fraction schedules, the current research will shed light on the appropriateness of use of PRT for the BC cancer population at the end of life. It also serves as an important first step for future studies aiming to identify optimal PRT utilization by providing the actual PRT utilization rate at the population level. Lastly, this research will add province-specific data of BC to existing data available in other Canadian provinces on the subject of PRT utilization for palliation. This will increase the availability of data on provincial comparisons for future end of life research.

3. Research Methods

3.1 Introduction

This chapter describes the research methods used in this study, including research design, recruitment of study population, study setting, data source, data collection and statistical analysis. The methods described in this chapter meant to answer the following research questions:

1. Among BC cancer patients who died between April 1, 2010 and March 31, 2011, what proportion of patients received at least one course of PRT during the last year, last month, and the last two weeks of life?
2. What were patient, disease and health system related factors associated with receiving PRT in the last year of life?
3. For BC cancer patients who died between April 1, 2010 and March 31, 2011, what was the pattern of PRT utilization by PRT treatment site in relation to their primary cancer site during the last year of life?
4. For BC cancer patients who died between April 1, 2010 and March 31, 2011, what were the most commonly used dose/fractionation schedules for PRT treatment in the last year of life?

3.2 Research design and study population

This was a retrospective population based cohort study.

The study population consisted of all patients in BC who died with invasive cancer (excluding non-melanoma skin cancer) between April 1, 2010 and March 31, 2011. Only patients who were residents of BC with a valid BC health care number were included in the study. Patients with benign and in situ tumors were excluded. Our

selection criteria included all patients died with cancer regardless of their cause of death. The outcome of interest was the provision of PRT in the final year of life. This was investigated through (1) describing the PRT patterns including overall courses, dose-fractionation pattern as well as site-specific patterns at the final year of life; and (2) examining the rate of PRT utilization for the study population overall and cancer specific rate in the last year of life. Factors investigated for associations with these utilization patterns included age at death, sex, patient's primary cancer diagnosis, travel time to the closest cancer center and survival time from the last cancer diagnosis to death.

There were many reasons why the retrospective study design was chosen over other study designs, such as pre-post control study or prospective cohort study. The most commonly reported strengths of using retrospective design in an end-of-life study are: (1) it avoids reliance on the difficult task of prospectively identifying the terminally ill – the denominator is clearly defined; (2) it avoids burdening very sick participants and minimizes missing data because of poor functional status; and (3) it is a cost effective way to collect population-based data about individuals who have died.[121]

Other reasons specifically applied to this study included the use of administrative data as the data source. The population-based administrative data used was of a high quality and completeness. It was collected and stored in an electronic database, and was thus ready available, inexpensive, and convenient for analysis.

3.3 Study setting

The Province of BC, located on the Pacific coast, is Canada's westernmost province. It is also Canada's third-largest province with a population of 4.5 million people spreading over an area of 947,800 km^2.[122] Health care in BC is delivered through

five regional health authorities providing care to the population residing in their geographic regions and one Provincial Health Services Authority (PHSA) providing specialized tertiary care for the whole province.

The BC Cancer Agency (BCCA) is an agency of the PHSA and it provides a province-wide, population-based cancer control program. The BCCA is a centralized cancer care provider, and the provincial government funds all RT through salaried physicians, physicists, and therapists at all cancer centres in the province. Therefore, financial incentives that might encourage overtreatment with RT are non-existent.

The management of information on cancer patients in BC begins with the BC Cancer Registry, where, by law, all patients with a positive pathology of cancer must be registered. The BCCA provides cancer management for patients who have been diagnosed with cancer and referred by a physician.[123] The types of cancer treatment provided at the BCCA included, but are not limited to, RT, chemotherapy, surgery, appointments and consultations. Approximately 60% of the patients who were registered with the BC Cancer Registry will eventually be referred to the BCCA for treatment.[124] Surgical treatments and some chemotherapy treatments are often provided in an acute care setting outside of the BCCA. However, the only channel to receive RT treatment is through the BCCA – all patients must be referred to the BCCA first in order to receive treatment. The BCCA provides RT treatment to referred patients only through one of the cancer centres.[116] Currently, the BCCA has six cancer centres operating across the province to serve cancer patients in BC. However, at the time the data was collected for this project, there were only five cancer centres operationalized and providing services to BC residents.

The five cancer centres were distributed across the province partly on the basis of population distribution. The Outreach Clinic Program was staffed by radiation oncologists and provided consultations in outlying regions. The province is divided into 16 Health Service Delivery Areas (HSDA). Each of the five cancer centres are responsible for RT for a defined catchment area that encompasses a collection of these regions. The cancer centre for the Southern Interior (CCSI) is located in the Okanagan region, the Vancouver Cancer Centre (VCC) is located in Vancouver, the Vancouver Island Cancer Centre (VICC) is located in the Southern Vancouver Island region, the Fraser Valley Cancer Centre (FVCC) is located in the Fraser South Health region and the Abbotsford Cancer Centre (ACC) is located in the Fraser East Health region.

The provision of RT treatment is at the regional level; however, the treatment is administered under a centralized system and all the RT treatment data is stored in the BCCA Cancer Agency Information System (CAIS). For this study, the patients were first selected from the BCCA cancer registry database according to our cohort selection criteria. Anonymized unique patient identifiers were then used to link the study cohort to their RT treatment data in the CAIS for the treatment received within one year prior to death.

3.4 Data sources

The BC Cancer Registry contains registrations for all cancer diagnoses and mortalities in the province since 1969. Sources of cancer registrations included pathology reports, hospital separation records, cancer centre registrations, and death registrations. Because the Registry is a tumor-based system, the patient may have multiple records in the Registry if s/he has multiple cancer diagnoses. The Cancer Registry contained

personal and demographic information as well as diagnosis and death information on all cases of cancer diagnosed in BC. BC Cancer Registry data fields used in this study were date of birth, sex, date of death, all the diagnosis related information including diagnosis date, site of diagnosis, and patient's geographical areas of residence at diagnosis such as health regions/HSDA.

The BCCA CAIS is a centralized database managed at the BCCA. It contains records of all cancer RT treatment administered through five cancer centres in the province. All RT including PRT and non-palliative RT treatment for our study population for the period of one year prior to death were identified. Data fields used in this study included RT course start date, site of treatment, number of RT fractions per course, dose, and treatment intent.

3.5 Study subjects

Provincial residents who died (of any cause) between April 1, 2010 and March 31, 2011 were first identified from the BC Cancer Registry. Among them, only the patients who were diagnosed with invasive cancer were included in our study cohort. Patients who were diagnosed with non-melanoma skin cancer were excluded because they were unlikely to have died of their non-melanoma skin cancer. The creation of the final study cohort from the source database is illustrated in the **Appendix A**.

From resource utilization perspective, the study cohort was classified into 3 mutually exclusive groups based on the type of RT delivered in the last year of life: no RT, PRT, and Non-palliative RT.

3.6 Definitions of variables

The variables in the analysis were used in the form in which they were abstracted from the source database. Exceptions are noted below. Definition of the data elements from the source databases which were used in this study is included in the **Appendix B**.

3.6.1 PRT

A course of RT was defined as palliative if there was a palliative intent code provided by the treating radiation oncologist or if the dose of treatment was 30 Gy or less. 30 Gy was selected as a logical cut point based on the distribution of RT dose delivered for courses with a palliative intent code in our study cohort. The results of identifying cut-point dose for PRT by the distribution of RT dose for courses with a palliative intent code are attached in the **Appendix C**. This methodology of using dose<=30 Gy in conjunction with palliative intent flag has also been used in a previous study to identify palliative RT.[125]

3.6.2 PRT_{1Y} and RT_{1Y}

The proportion of the study population that had at least one course of PRT in the last year of life (PRT_{1Y}) was used to describe access to PRT. Similarly, RT_{1Y} was used in the study to describe the proportion of the study population that had at least one course of RT in the last year of life.

3.6.3 Patient's primary cancer diagnosis

The PRT utilization was reported by the patient's primary cancer diagnosis in this study. In the BC Cancer Registry, cancer diagnosis is coded using the ICD-O-3 coding standard. Patients were grouped by their primary cancer diagnosis based on the site and histology codes coded on the Registry record. The definitions of primary cancer diagnosis are provided in the **Appendix D**.

The patient's primary cancer diagnosis was assigned based on the last known primary cancer diagnosis by the date of diagnosis. When the patient is diagnosed with multiple invasive cancers on the most recent date of diagnosis, multiple records associated with cancer sites for this patient are recorded in the BC Cancer Registry. When multiple cancer diagnoses were found on the most recent date of the cancer diagnosis, the following hierarchy was used for the primary cancer diagnosis assignment based on overall cancer mortality: Lung > Breast > Colorectal > Prostate > non-colorectal gastrointestinal (GI) > Blood > Urinary > Female genital > Brain > Cancer-other.

3.6.4 Site of treatment

The RT treatment data collected in the CAIS captured the body region to which the RT treatment was delivered. In this study, the site of treatment was grouped based on treatment region codes abstracted from the source database (the CAIS). Categories used were bone, lung, soft tissues/nodes, brain, skin, head and neck (H&N), breast and "other". **Appendix E** provides the detailed mapping of the treatment region codes to the grouped site of treatment reported in our study.

3.6.5 Unit of RT treatment

To quantify the RT utilization for this study, a unit of the RT treatment was counted by a RT course rather than by an individual RT record in the radiation data in the CAIS. A course of RT treatment was constructed as follows: for all the treatment sites with exception of Skin and Bone, a course of RT treatment was constructed using RT start and end dates and RT treatment region. For the treatment site other than Skin and Bone, if the RT records had the same RT start and end date, they were considered the same RT course. If treatment sites were Skin or Bone, every RT record was counted as a

new course of treatment regardless of the RT start and end date. In addition, when 'BON2','BON3','BON4', 'SKI2','SKI3', 'SKI4','SKI5','SKI6' were coded as the treatment site on the RT record, each record was counted as multiple courses of treatment. The number of courses was indicated by the number in the code of the treatment site on the record.

Note that the number of courses was greater than the number of decedents who received RT in the last year of life because some patients received multiple courses of treatment during the study period.

3.6.6 Fractions per course

In radiation oncology, the term "fractions" refers to the number of sessions that the patient is irradiated constituting a RT course. Fractions per course was recorded on each RT record. In this study, the fractions per course were stratified by five reporting groups: 1, 2-5, 6-10, 11-15 and 16+.

3.6.7 Travel time to the closest radiation center

Travel time from a patient's residence (HSDA) to the closest cancer centre was measured using distance calculator provided by the BCAA (http://www.th.gov.bc.ca/popular-topics/distances/calculator.asp). It represented the driving time from the centre of the HSDA where the patient resided when the last primary cancer was diagnosed before they deceased to the closest cancer centre open during the study era using the postal code of two measurement points. For reporting purposes, the patient's travel time to the closest cancer centre was grouped into <=2 hours and > 2 hours for each HSDA in this study.

Appendix F is a summary table used in this study to assign travel time to each HSDA based on a patient's diagnosis date.

3.6.8 Survival time

In our study, the time from the last diagnosis of primary cancer to death was categorized into three groups: >26 months, 1.5-26 months, <1.5 months. These survival groups had been used in the previous study as a predictor of PRT utilization at the end of life.[2]

3.7 Data analysis

Categorical variables were used to analyze age at death (age<19 years, 19-44 years, 45-64 years, 65-74 years, 75-84 years, or >=85 years), last primary cancer diagnosis (Blood, Brain, Breast, Colorectal, Female Genital, Lung, Melanoma, non-colorectal GI, Prostate, Urinary, or Other), the patient's residence health authority at time of diagnosis (Fraser Health, Interior Health, Northern Health, Vancouver Coastal, or Vancouver Island), survival time from last primary cancer diagnosis (<1.5 months, 1.5-26 months, >26 months). Binary variables were used to examine sex, travel to the closest radiation centre (<=2 hours/>2 hours), ever referred to BCCA (yes/no), referred last year to BCCA (yes/no), receipt of RT (yes/no), receipt of PRT (yes/no).

Baseline characteristics were stratified by the receipt of PRT in the last year of life. The association between the receipt of PRT and various demographic and clinical factors was assessed with logistic regression modeling. Individual factors were modeled first to check for univariable association with the receipt of PRT. Variables with a significance level of <=0.05 from the univariable analyses were considered for the final multivariable model. Multivariable logistic regression was performed to identify the

factors associated with the receipt of PRT in the last year of life. The final significance level was set at an α level of 0.05. Point estimates from the multivariable model are reported as odds ratios (ORs) with the confidence interval (CI) for each OR. All statistical analyses were conducted using the SAS statistical software package (version 9.0; SAS Institute Inc., Cary. NC).

3.8 Ethics approval

This research received approval from the University of Victoria Ethics Board (ethic protocol number: 12-262).

4. Findings

4.1 Introduction

This chapter examines the findings of this study including a description of the study cohort, a profile of the PRT treatment patients received, as well as factors associated with PRT treatment in the last year of life. The PRT utilization is reported as a proportion of decedents receiving treatment in the last year of life. The profile of PRT treatment in the final year is described by site of treatment, course of the treatment, and fractions per course. Drill down analysis is performed to look at the differences in PRT utilization by primary cancer diagnosis as well as by treatment site. In addition, a logistic regression model is used to measure the strength of association when receiving PRT in the last year of life with selected predictors.

4.2 Description of the study population

13,250 provincial residents who died (of any cause) between April 1, 2010 and March 31, 2011 were identified from the BC Cancer Registry. 5 patients were excluded due to data quality. Among the rest, 945 were diagnosed with non-melanoma skin cancer. Excluding patients with non-melanoma skin cancer, the final decedent cohort included in our study consisted of 12,300 patients (**Appendix A**).

Table 2 below describes the study population through a number of factors.

Table 2: Characteristics of study population

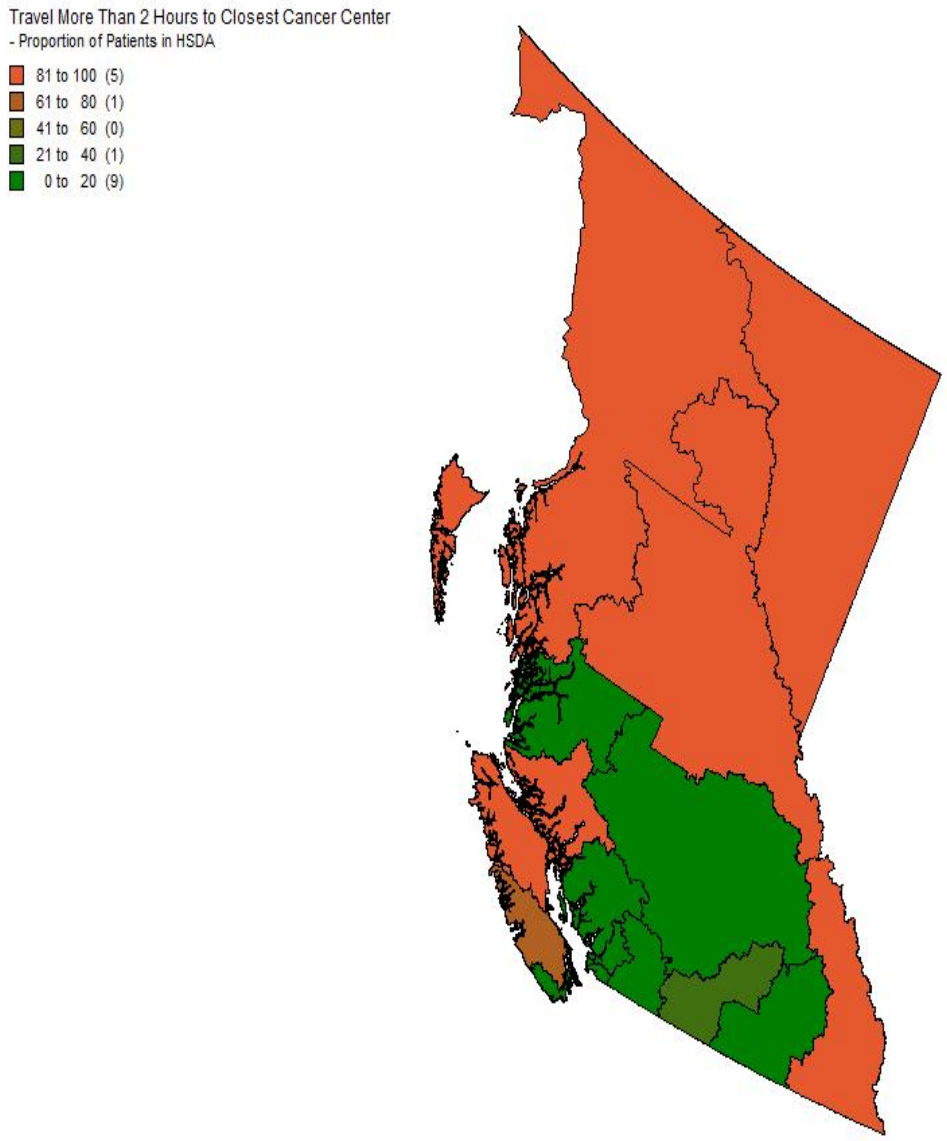
Study population	No. of Decedents	%
Age Groups		
0-18	16	0.1
19-44	226	1.8
45-64	2327	18.9
65-74	2511	20.4
75-84	3613	29.4
85+	3607	29.3
Sex		
Female	5734	46.6
Male	6566	53.4
Primary Cancer Diagnosis		
Lung	2406	19.6
Breast	1204	9.8
Colorectal	1551	12.6
Prostate	1438	11.7
Non-colorectal GI	1454	11.8
Blood	938	7.6
Urinary	656	5.3
Female Genital	623	5.1
Brain	255	2.1
Melanoma	265	2.2
Other	1510	12.3
Residence HSDA		
Central Vancouver Island	1011	8.2
East Kootenay	239	1.9
Fraser East	807	6.6
Fraser North	1346	10.9
Fraser South	1619	13.2
Kootenay Boundary	314	2.6
North Shore/Coast Garibaldi	820	6.7
North Vancouver Island	421	3.4
Northeast	124	1.0
Northern Interior	371	3.0
Northwest	171	1.4

Okanagan	**1289**	**10.5**
Richmond	**376**	**3.1**
South Vancouver Island	**1270**	**10.3**
Thompson Cariboo Shuswap	**692**	**5.6**
Vancouver	**1405**	**11.4**
Travel Time (to closest cancer center)		
<=2 hours	**9364**	**76.1**
>2 hours	**2911**	**23.7**
Survival Time (Month)		
<1.5 M	**1812**	**14.7**
1.5-26 M	**5085**	**41.3**
26 M+	**5403**	**43.9**
BCCA Referral/appointment		
Ever referred	**8415**	**68.4**
Referred last year	**3419**	**27.8**
Had appointment last year	**7010**	**57.0**

Median age of the cohort was 78 years. Almost 80% of the cohort was 65 years old or older. Males slightly outnumbered females. More than half of the study population (56.3%) resided in five major geographic regions: Fraser North (10.9%), Fraser South (13.2%), Okanagan (10.5), South Vancouver Island (10.3%), and Vancouver (11.4%).

Approximately 76.3% of study subjects lived in an area less than two hours driving distance from the closest cancer centre; the remaining 23.7% needed to travel more than two hours. The proportion of decedents who travelled more than two hours to get to the closest cancer centre varied greatly among HSDA. **Figure 1** captures the differences among HSDAs in the proportion of decedents travelling more than two hours from the closest cancer centre for RT treatment.

Figure 1: Proportion of patients in HSDA traveling more than 2 hours to the closest cancer center



The most common primary cancer diagnoses in the study cohort were: lung (19.6%), colorectal (12.6%), non-colorectal gastrointestinal (GI) (11.8%), prostate (11.7%) and breast (9.8%). About 14.7% of the study population died within 1.5 months of their last cancer diagnosis and approximately two fifths of the cohort died between 1.5 and 26 months from their last cancer diagnosis. Approximately 68.4% (8,415) of the

study population had been referred to the BCCA at least once during their course of disease for treatment. Among them, 40.6% (3,419) was referred to the BCCA during their last year of life. 31.6% of the study cohort had never been referred to the BCCA before they died. Approximately 57.0% of the study population had visited the BCCA at least once (for consultation or treatment) during their last year of life (**Table 2**).

Table 3 displays the distribution of the study cohort based on the RT classification. Of the 12,300 study subjects, 75.9% were not treated with RT during their final year of life. The remainder (24.1%) were treated with at least one RT during their final year of life, and roughly 21.7% of the study subjects were treated with "palliative" RT. The majority of these subjects had treatment fulfilling both criteria of our definition of PRT: a palliative intent code and dose<=30 Gy (19.8%). An extremely small proportion received RT dose<=30 Gy with a non-palliative intent code (0.7%) and a small proportion received dose >30 Gy with a palliative intent code (1.2%). During the study period, less than 3% of the study sample received RT that satisfied neither of the palliative criteria.

Table 3: Classifying RT received in the last year of life

RT	No. of patients	%
No RT (A)	**9,341**	**75.9**
Palliative RT (B)	**2,669**	**21.7**
B1.Palliative intent code and dose <=30Gy	2,432	19.8
B2. Nonpalliative intent code and dose <=30 Gy	90	0.7
B3. Palliative intent code and dose >30Gy	147	1.2
Nonpalliative RT (C)	**290**	**2.4**
Total*	**12,300**	**100.0**

*** Total=(A)+(B)+(C)**
(B)=B1+B2+B3

4.3 PRT_{1Y} rates

4.3.1 Overall PRT_{1Y} rate and cancer specific rates

Of the 12,300 patients in our study cohort, 2,959 (24.1%) were identified as having received RT for a total number of 4,776 courses in their final year of life – averaged at 1.6 courses per patient. The majority (91.5%) of the treatments were palliative by our definition. Note that the PRT courses counted in our analysis (4371) were the courses prescribed to the patients and 99% of courses prescribed in the last year of life were delivered. Overall, 21.7% of the study cohort received PRT treatment during the last year of life. This was counted as 9/10 (90.2%) patients among who received RT treatment in the last year of life. Not surprisingly, PRT_{1Y} rates varied from one disease group to another (**Table 4**). The rates were highest (45.7%) for lung, intermediate (20% to 30%) for GI (colorectal & non-colorectal GI), urinary, melanoma, and breast, and low (<20%) for prostate, blood, female genital, and brain.

Table 4: PRT_{1Y} utilization by primary cancer

Decedent cohort		Any RT			PRT			
		Patient #	RT_{1Y}	RT course #	Patient #	PRT_{1Y}	% RT	PRT course #
Overall	12,300	2,959	24.1	4,776	2,669	21.7	90.2	4,371
Primary Cancer Diagnosis								
Lung	2,406	1,146	47.6	1,847	1,099	45.7	95.9	1,765
Breast	1,204	252	20.9	473	236	19.6	93.7	448
Colorectal	1,551	165	10.6	224	138	8.9	83.6	195
Prostate	1,438	232	16.1	435	218	15.2	94.0	415
Non-colorectal GI	1,454	274	18.8	381	246	16.9	89.8	342
Blood	938	155	16.5	299	146	15.6	94.2	284
Urinary	656	157	23.9	235	149	22.7	94.9	224
Female Genital	623	123	19.7	186	105	16.9	85.4	150
Brain	255	94	36.9	100	45	17.6	47.9	50
Melanoma	265	61	23.0	105	56	21.1	91.8	97
Other	1,510	300	19.9	491	231	15.3	77.0	401

RT course #: Number of RT courses that decedents received during the last year of life

% RT: Proportion of decedents who receive RT courses in last year of life who received PRT

PRT course #: Number of PRT courses that decedents received during the last year of life

A broad spectrum of rates was observed in the selected cancer diagnosis subgroups (**Table 5**). The rates of PRT_{1Y} for female genital cancer were as follows: cervix, 29.6%; vulva, 25.0%; Ovary, 14.8%; and uterus, 13.8%. The rates of PRT_{1Y} for the hemopoietic diseases were as follows: multiple myeloma, 28.6%; Hodgkin's disease; 15.2%; non-Hodgkin's lymphoma, 15.9%; and leukemia, 2.3%. The rates of PRT_{1Y} for non-colorectal GI cancers were as follows: esophagus, 47.2%; stomach, 27.1%; anus and anal canal, 27.1%; liver,6.6%; pancreas, 6.6%; small intestine, 5.8% .

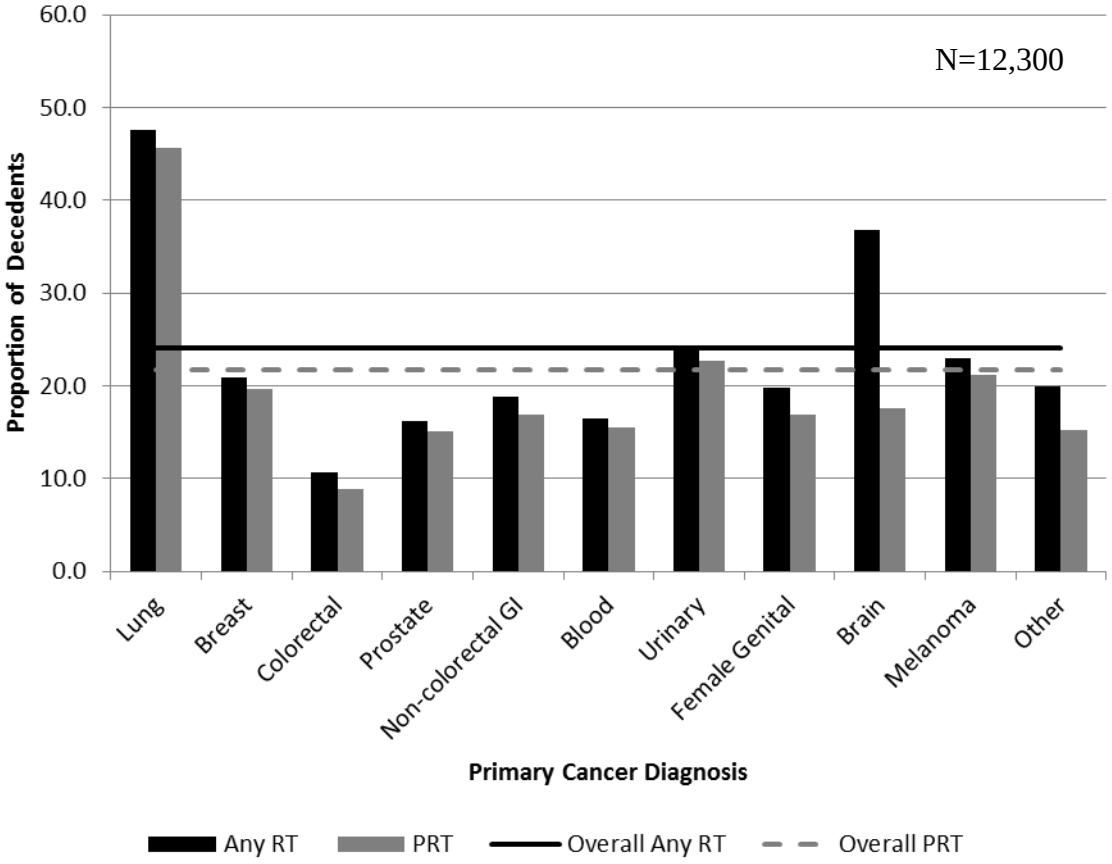
Table 5: PRT_{1Y} utilization by cancer sub-group

Decedent cohort		Any RT			PRT			
		Patient #	RT_{1Y}	RT course #	Patient #	PRT_{1Y}	% radiation	PRT course #
Blood	938	155	16.5	299	146	15.6	94.2	284
Leukemia	215	6	2.8	10	5	2.3	83.3	8
Mul. Myeloma	206	59	28.6	111	59	28.6	100.0	111
Hodg. Lymphoma	33	7	21.2	8	5	15.2	71.4	6
NonH. Lymphoma	484	83	17.1	170	77	15.9	92.8	159
Female Genital	623	123	19.7	186	105	16.9	85.4	150
Vulva	36	15	41.7	19	9	25.0	60.0	10
Vagina	11	3	27.3	6	3	27.3	100.0	6
Cervix	71	25	35.2	40	21	29.6	84.0	31
Uterus	282	45	16.0	74	39	13.8	86.7	60
Ovary	223	35	15.7	47	33	14.8	94.3	43
Non-colorectal GI	1454	274	18.8	381	246	16.9	89.8	342
Esophagus	216	115	53.2	155	102	47.2	88.7	135
Stomach	280	83	29.6	115	76	27.1	91.6	108
Small Intestine	52	3	5.8	5	3	5.8	100.0	5
Anus Anal Canal	48	18	37.5	23	13	27.1	72.2	17
Liver	259	19	7.3	34	17	6.6	89.5	30
Gallbladder	57	2	3.5	3	2	3.5	100.0	2
Pancreas	440	30	6.8	40	29	6.6	96.7	39
Intestinal Tract	30	1	3.3	1	1	3.3	100.0	1
Other Biliary Tract	72	3	4.2	5	3	4.2	100.0	5

RT course #: Number of RT courses that decedents received during the last year of life
% RT: Proportion of decedents who receive RT courses in last year of life who received
PRT course #: Number of PRT courses that decedents received during the last year of life

For most of the cancer group, the majority of the patients, when treated with RT during their last year of life, were treated with PRT with the exception of those with brain cancer. 36.9% of brain cancer decedents received RT during their last year of life. Among them, only less than a half received treatment deemed palliative by our definition in their final year of life (**Figure 2**).

Figure 2: RT_{1Y} vs. PRT_{1Y} rates by primary cancer



4.3.2 PRT_{1Y} rates by geographic access

On average, each patient in our study cohort received 1.6 PRT courses during their last year of life. The proportion of decedents who received more than one course of PRT in the final year of life, varied by HSDA; those who resided in the Richmond region were most likely to have more than one course per patient. **Table 6** provides detailed information on PRT utilization in the last year of life at the regional level, including the number of patients who received PRT, total number of PRT courses administered, and average PRT course per patient for each HSDA with a comparison of overall numbers in BC.

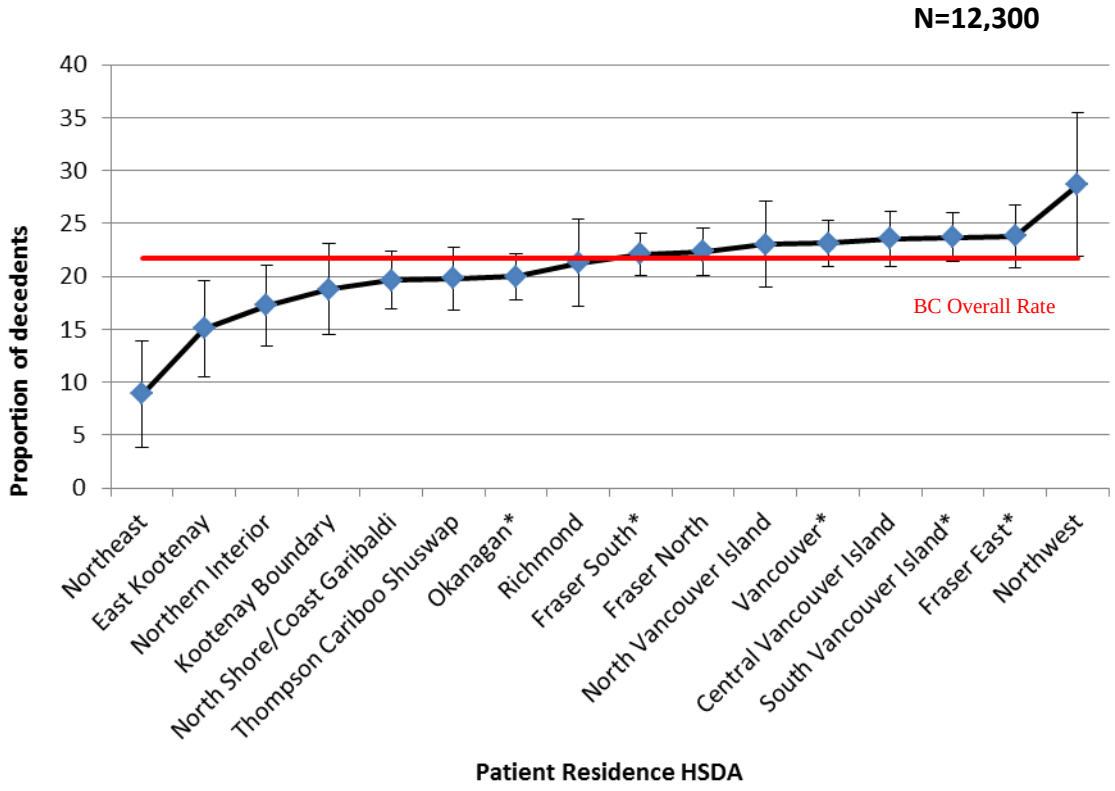
Table 6: PRT_{1Y} utilization by HSDA

Decedents Residence Region	Decedent Cohort (N)	# PT had PRT Course	PRT_{1Y}	# of PRT course	Avg. Course per Decedent
BC overall	12,300	2,669	21.7	4371	1.6
HSDA					
Central Vancouver Island	1,011	238	23.5	435	1.8
East Kootenay	239	36	15.1	55	1.5
Fraser East*	807	192	23.8	275	1.4
Fraser North	1,346	301	22.4	493	1.6
Fraser South*	1,619	358	22.1	586	1.6
Kootenay Boundary	314	59	18.8	91	1.5
North Shore/Coast Garibaldi	820	161	19.6	265	1.6
North Vancouver Island	421	97	23.0	149	1.5
Northeast	124	11	8.9	19	1.7
Northern Interior	371	64	17.3	99	1.5
Northwest	171	49	28.7	65	1.3
Okanagan*	1,289	258	20.0	422	1.6
Richmond	376	80	21.3	152	1.9
South Vancouver Island*	1,270	301	23.7	497	1.7
Thompson Cariboo Shuswap	692	137	19.8	213	1.6
Vancouver*	1,405	325	23.1	553	1.7

* indicates the region where a cancer center was located during the study era

PRT_{1Y} rates varied across geographic regions (HSDAs) in BC, ranging from 8.9% in the Northeast to 28.7% in the Northwest (Figure 3). **Figure 3** depicts the variations in the proportion of decedents in each HSDA who received PRT treatment in the last year of life. The horizontal line is the average rate for the whole province and the bars indicate the PRT_{1Y} rate with a 95% confidence interval for the HSDA. Patients living in the Northeast, East Kootenay and Northern Interior, Kootenay Boundary, North Shore/Coast Garibaldi, Thompson Cariboo Shuswap, Okanagan were less likely to receive PRT treatment than patients living in other regions during their last year of life. In general, the rates in the regions where cancer centre are located (marked with * on X-Axis) were higher than the provincial average, except for the Okanagan, which had a lower rate than the provincial average.

Figure 3: Regional PRT_{1Y} rates



* indicates the region where a cancer center is located

PRT_{1Y} rate was inversely related to travel time. Patients who resided within two hours to the closest cancer centre are more likely to receive PRT in the last year of life than patients who resided in an area which required more than two hours of driving. In our study cohort, 22.6% of patients in the travel time "less than 2 hours" group received PRT treatment in their final year of life. This is compared to 18.8% of patients in the "> 2 hours" travel time group (**Table 7**).

Table 7: PRT_{1Y} by travel time

Travel Time	Decedent Cohort	Receiving PRT Last Year		
		Decedent (N)	PRT_{1Y} (%)	PRT course (N)
<= 2 hours	9364	2120	22.6	3491
> 2 hours	2911	547	18.8	878

4.3.3 Factors associated with PRT_{1Y} utilization

The results from the univariable analysis (**Table 8**) showed that some patient-related factors such as age at death and time between diagnosis and death, the disease-related factors such as primary cancer diagnosis, as well as health system-related factors such as travel time were significantly related to the PRT_{1Y} utilization rate. The age group 85 and older was found to be significantly less likely to receive PRT treatment during their last year of life compared with other age groups. Patients with primary lung cancer, survival time between 1.5-26 months from diagnosis or residence in an area within 2 hours driving distance to a cancer centre were significantly more likely to receive PRT in the last year of life. Sex was not significantly related to PRT_{1Y} rate (P=0.2774).

Table 8: Number and percentage of decedents who received PRT_{1Y}

Variable	Decedent Cohort	Number of decedents who received PRT_{1Y}	PRT_{1Y}	P value (Chi-Square)
Age				
<19	16	4	25.0	
19-44	226	74	32.7	
45-64	2327	827	35.5	
65-74	2511	773	30.8	
75-84	3613	724	20.0	
85+	3607	267	7.4	<.0001
Sex				
F	5734	1269	22.1	
M	6566	1400	21.3	0.2774
Primary Cancer Site				
Blood	938	146	15.6	
Brain	255	45	17.6	
Breast	1204	236	19.6	
Colorectal	1551	138	8.9	
Female Genital	623	105	16.9	
Lung	2406	1099	45.7	
Melanoma	265	56	21.1	
Non-colorectal GI	1454	246	16.9	
Prostate	1510	231	15.3	
Urinary	1438	218	15.2	
Other	656	149	22.7	<.0001
Survival Time (Months)				
<1.5	1812	156	8.6	
1.5-26	5085	1727	34.0	
26+	5403	786	14.5	<.0001
Travel Time				
<=2 hours	9364	2120	22.6	
>2 hours	2911	547	18.8	<.0001

The factors that were found to be significantly related to PRT_{1Y} rate in the univariable analysis were age, primary cancer site, survival time and travel time (**Table 8**). These factors were analyzed using multivariable logistic regression. The variations in PRT_{1Y} for these variables are presented as shown as adjusted

odds ratios (OR) with 95% CIs after controlling for the effects of other variables (**Table 9**). All factors studied demonstrated significant independent effects in association with variation of PRT_{1Y}. After adjusting for other factors, age at diagnosis was negatively associated with receipt of palliative RT (p<0.0001). Patients aged 19-44 were approximately 6.7 times more likely to receive PRT_{1Y} than those patients older than 85 years. When compared to patients with lung cancer, patients with any other cancers had significantly smaller odds of receiving PRT_{1Y}. Colorectal cancer patients were only 0.1 times as likely to receive PRT_{1Y} as lung cancer patients. Brain cancer patients were only 0.2 times as likely to receive PRT_{1Y} as lung cancer patients. However, this is because a significant portion of RT given to brain cancer patients was labelled as "non-palliative" RT by our definition.[i] Breast cancer patients were 0.4 times as likely to receive PRT_{1Y} as lung cancer patients. Compared with patients who survived more than 26 months after their last cancer diagnosis, patients who survived between 1.5 and 26 months had double the odds of receiving PRT_{1Y}, while patients who survived less than 1.5 months after diagnosis were much less likely (0.34) to receive PRT_{1Y} treatment. The shorter travel time patients who travelled less than two hours were 1.4 times more likely to receive PRT than patients who travelled more than two hours.

[i] The percentage of brain cancer patients received any RT during the last year of life was the second highest compared to other primary cancer patients.

Table 9: Odds ratios describing likelihood of receiving PRT_{1Y}

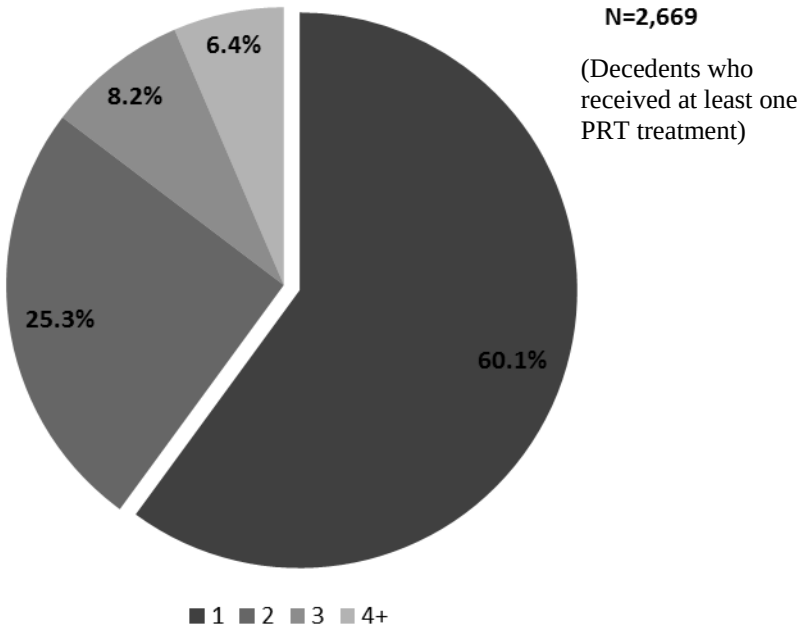
Variable	Adjusted Odds Ratio	95% CI	
Age (vs. 85+)			
<19	5.4	1.6	18.4
19-44	6.7	4.8	9.2
45-64	5.6	4.8	6.6
65-74	4.5	3.8	5.3
75-84	2.6	2.2	3.1
Primary Cancer Site (vs. Lung)			
Blood	0.2	0.2	0.3
Brain	0.2	0.1	0.2
Breast	0.4	0.3	0.5
Colorectal	0.1	0.1	0.2
Female Genital	0.3	0.2	0.3
Melanoma	0.4	0.3	0.6
Non-colorectal GI	0.2	0.2	0.2
Prostate	0.2	0.2	0.3
Urinary	0.4	0.3	0.5
Other	0.4	0.3	0.5
Survival Time, Months (vs. 26+)			
<1.5	0.3	0.3	0.4
1.5-26	2.0	1.8	2.2
Travel Time			
<=2 hours (vs. >2 hours)	1.4	1.3	1.6

4.4 PRT_{1Y} treatment characteristics

4.4.1 Number of PRT_{1Y} courses per patient

Among the decedents who received PRT treatment in the last year of life (n=2,669), the majority of them (60.1%) received one course of treatment; approximately 25.3% of the patients received two courses of treatment, 8.2% received three courses of treatment and the reminder (6.4%) received four or more courses of treatment during their last year of life (**Figure 4**).

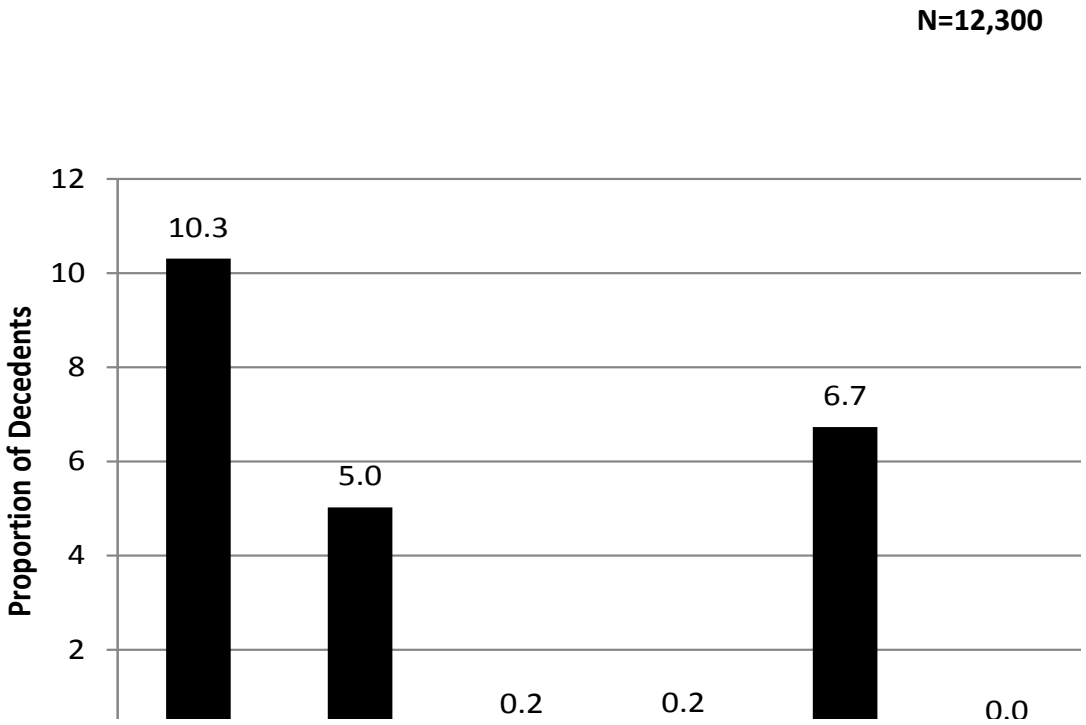
Figure 4: Distribution of PRT course per patient



4.4.2 Sites of treatment

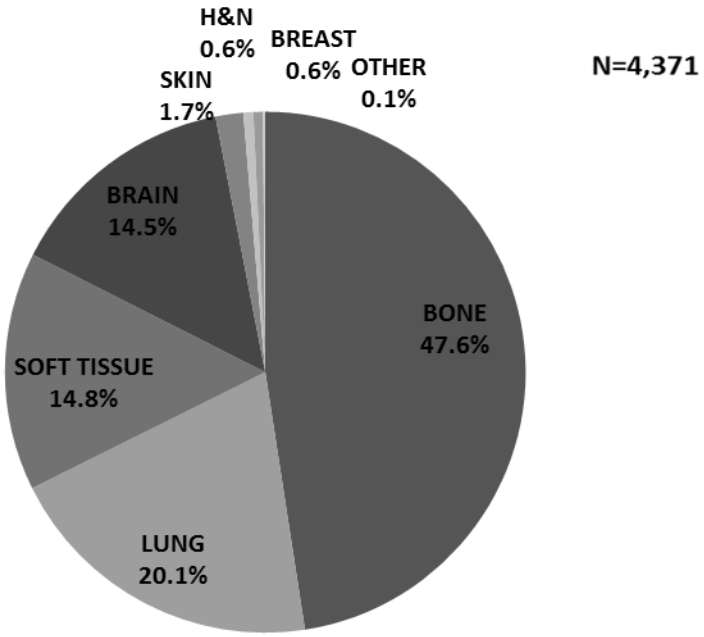
Approximately 10.3% of all decedents received PRT for bone metastases. Approximately 6.7% of the cohort received treatment to lung, 5.0% received treatment to brain and 4.4% received treatment on soft tissues/lymph nodes (**Figure 5**).

Figure 5: Proportion of decedents receiving PRT to different treatment sites



Overall, 4,371 PRT courses were delivered to a total of 2,669 decedents during their last year of life. Commonly treated sites were bone (47.6%), lung (20.1%), soft tissues (14.8%), and brain (14.5%) (**Figure 6**).

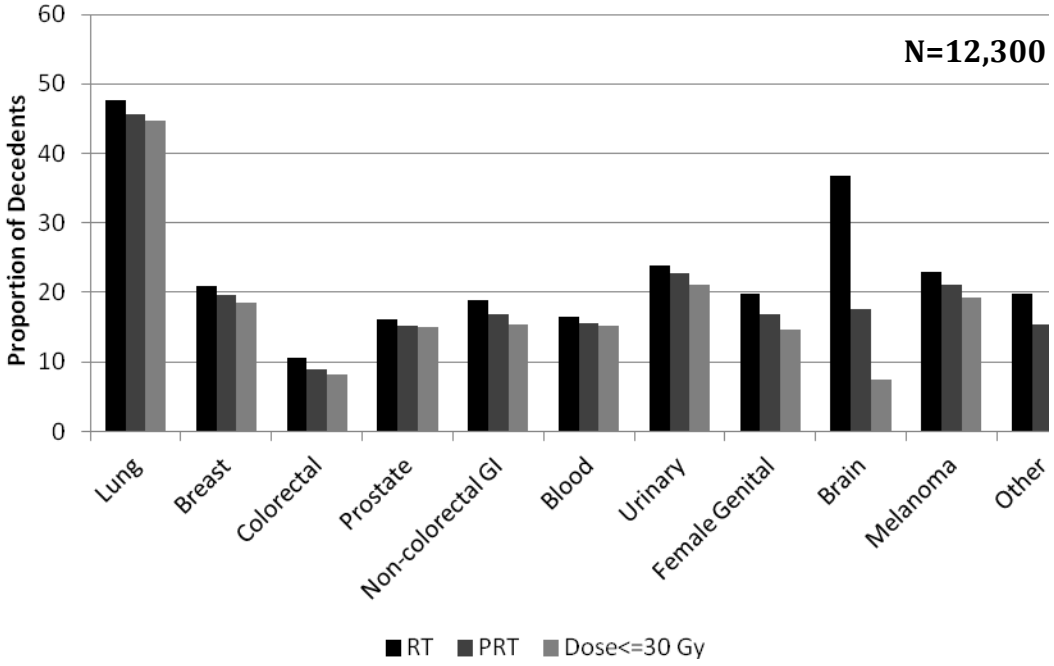
Figure 6: Distribution of PRT course by site of treatment



4.4.3 PRT Dose

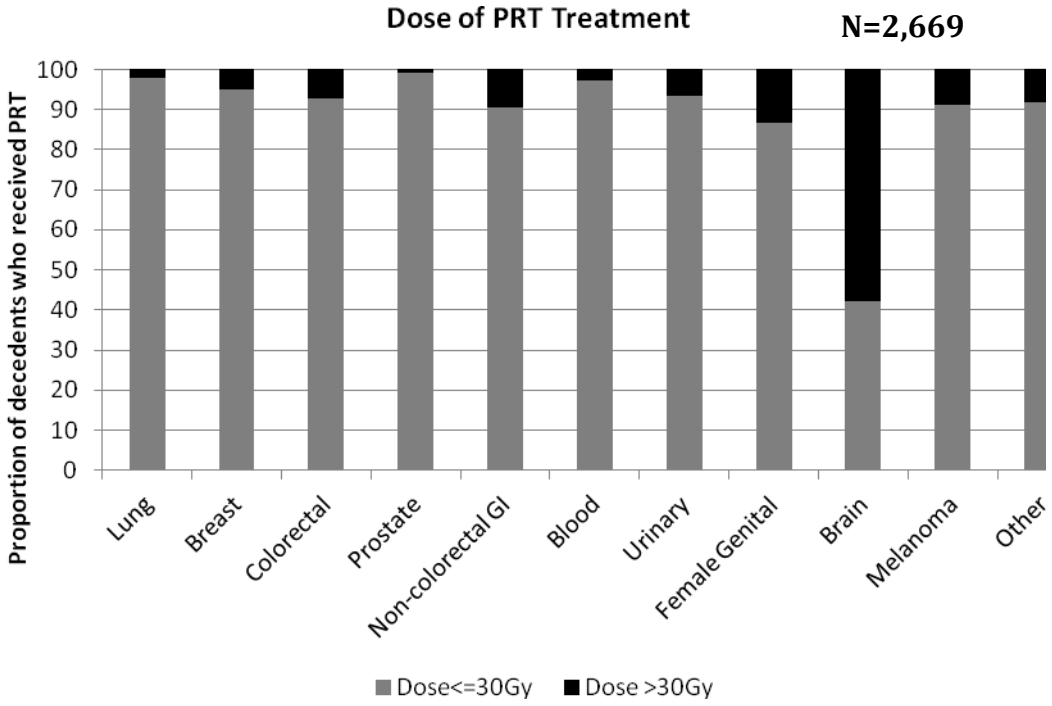
In our study, among patients who received RT treatment during their last year of life (N=2,959), the majority (85%) received an RT dose <=30 Gy during a single course of RT. The proportion of the decedents who received RT dose <=30 Gy varied across primary cancer site ranging from lung (44.8%) to brain (7.5%) (**Figure 7)**. Unlike patients with other primary cancers, of those with primary brain cancer only 1/5 patients who received RT in the final year received dose<=30 Gy.

Figure 7: Dose <= 30 Gy treatments by cancer group



The distinct pattern for the use of dose <=30 Gy for brain cancer in the last year of life is also demonstrated in **Figure 8**. Among the patients who received PRT in their last year of life, significantly more brain cancer patients (57.8%) received higher dose (dose >30 Gy) treatment. This is compared to 13.3% for female genital cancer patients and less than 10% for all other cancer types. The effect of observing significantly more brain cancer patients receiving higher dose (dose>30Gy) would be more pronounced if considering all RT.

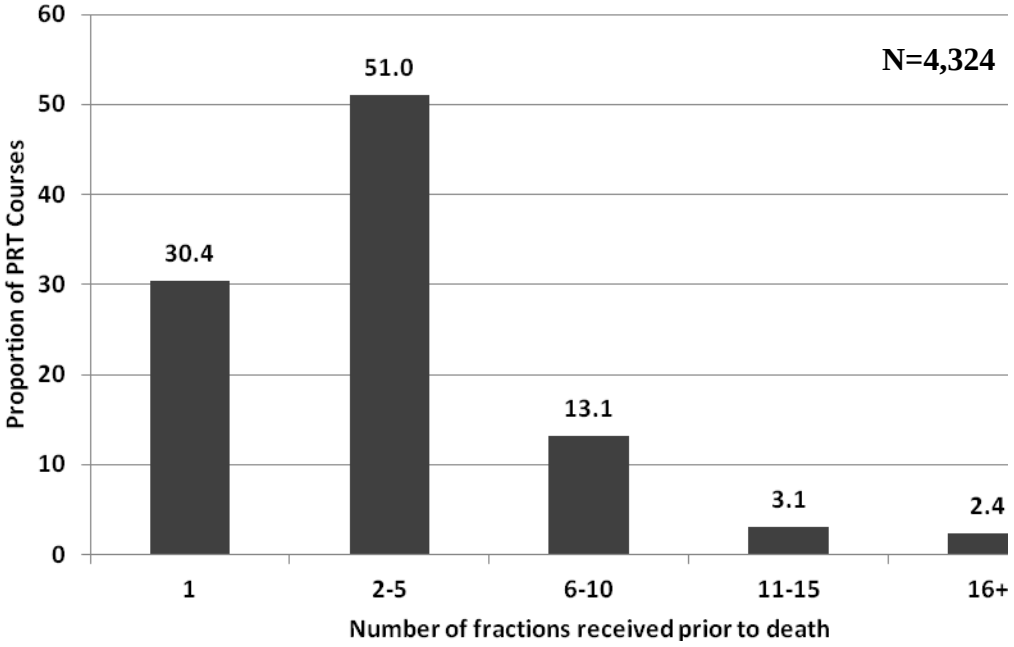
Figure 8: RT Dose <=30 Gy recipients as a proportion of PRT recipients by cancer group



4.4.4 Fractions of PRT treatment

In our study, 47 out of 4,371 PRT courses had invalid fraction number (fraction=0) recorded on the treatment record. These records were deemed as having data quality issues and were excluded from the fraction analysis. Among 4,324 PRT courses included, the most commonly delivered number of fractions given within an PRT course were 2-5 fractions per course (51.0%), 1 fraction per course (30.4%) and 6-10 fractions per course (13.1%). Ninety-four percent of all courses of PRT given during the final year of life had 10 or fewer fractions. (**Figure 9**).

Figure 9: Number of fractions per PRT course



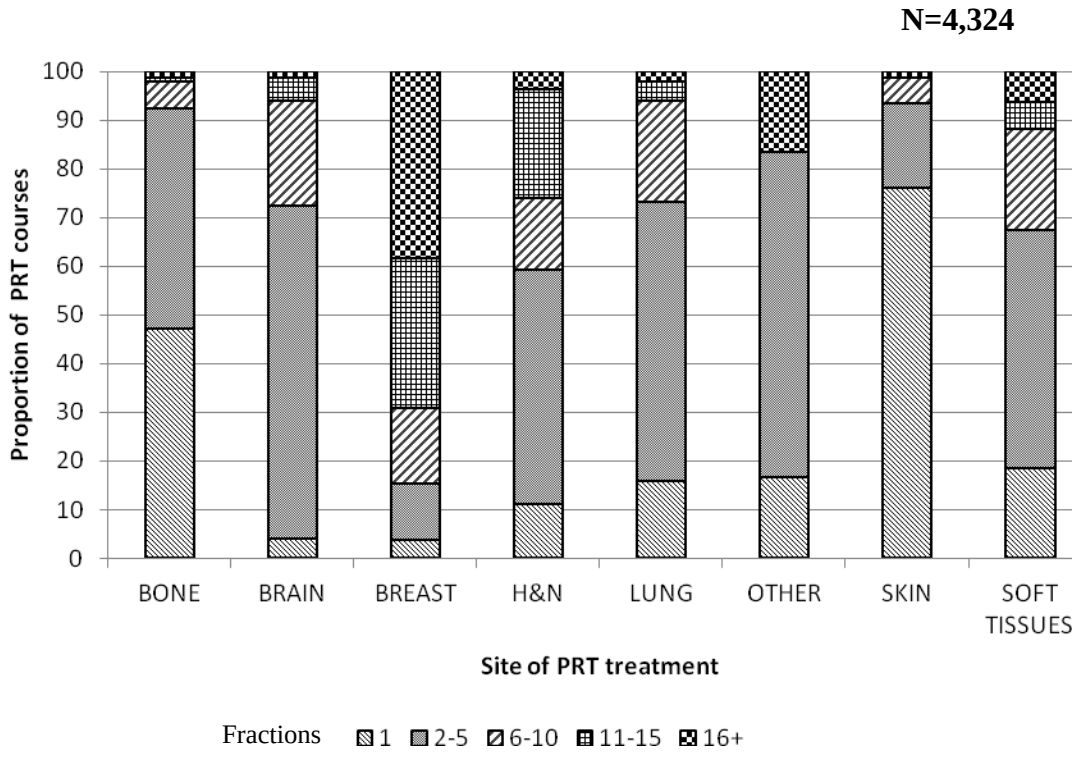
Fractionation schedules for PRT varied significantly by treatment site. The most commonly treated site during the last year of life was bone. Among 2,079 courses delivered to bone, 978 courses (47.0%) had 1 fraction and 942 courses (45.3%) had 2-5 fractions **(Table 10 & Figure 10).** These two fraction groups accounted for more than 90% of PRT treatment to the bone**.** Lung was the second commonly treated site with 876 courses in total delivered during the last year of life. The most frequently used schedule to lung was 2-5 fractions per course. This accounted for 57.5% of all PRT treatments to the site. Among 633 PRT treatments to brain, approximately 68.6% of the treatments were 2-5 fractions. The fractions greater than 2 and less than 10 accounted for more than 90% of all PRT treatment to brain. The most commonly used schedules for soft tissues and nodes were 2-5 fractions (48.7%), 6-10 (20.9%) and 1 fraction (18.6%). The majority of the treatment to skin (76%) had 1 fraction.

Table 10: PRT courses to treatment sites by number of fractions per course

Fractions per course	BONE	BRAIN	BREAST	H&N	LUNG	OTHER	SKIN	SOFT TISSUES	Number of Courses
1	978	25	*	*	138	*	57	112	1,315
2-5	942	434	*	13	504	*	13	293	2,206
6-10	113	136	*	*	181	0	*	126	568
11-15	21	30	8	6	34	0	0	33	132
16+	25	8	10	*	19	*	*	38	103
Number of courses	2,079	633	26	27	876	6	75	602	4,324

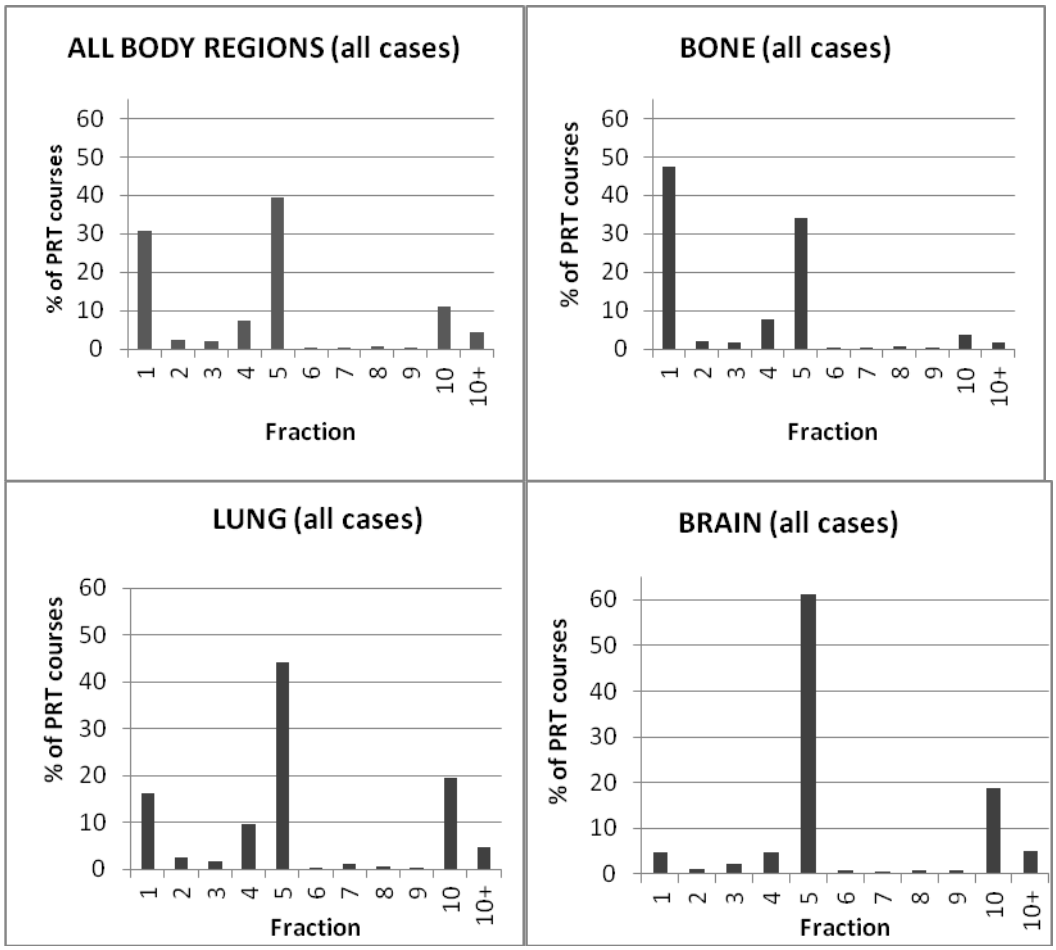
* Numbers are suppressed due to small cell size

Figure 10: Distribution of PRT courses by site of treatment and fractions



PRT treatment was delivered, on average, using 4.7 fractions per course to all body regions combined, 6.3 fractions per course to the brain, 5.7 fractions to the chest, and 3.3 fractions to bone (**Figure 11**). Overall for all body regions, the most commonly used fractionation schedules were 5 fractions (39.5%), 1 fraction (30.9%) and 10 fractions (11.1%). The most commonly used fractions for bone metastasis was 1 fraction (47.6%) and 5 fractions (34%); the most commonly used fractionation schedule for lung RT were 5 fractions (44.2%) and 10 fractions (19.4%); and the most commonly used fractionation schedule for brain RT were 5 fractions (61.1%) and 10 fractions (18.8%).

Figure 11: Frequency distribution of fractions per course by selected treatment site

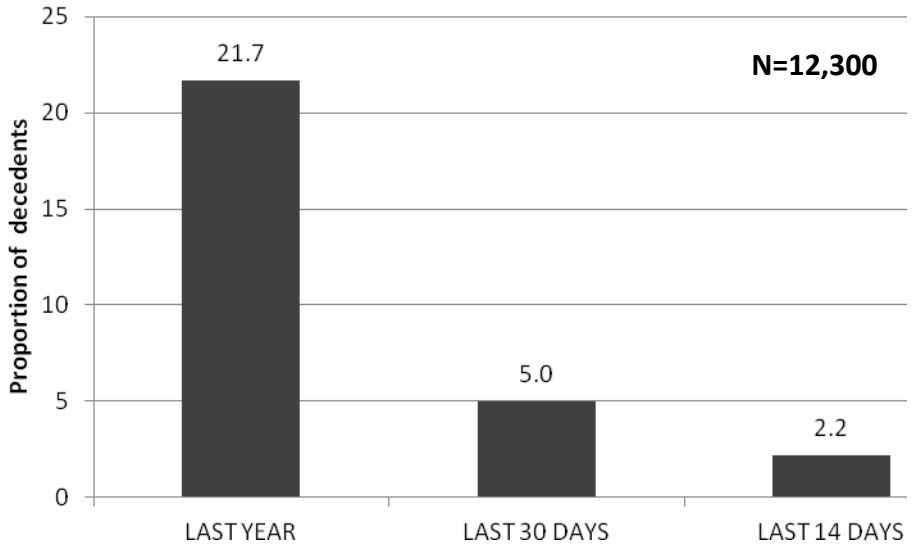


4.5 PRT utilization in the last 30 & 14 days of life

4.5.1 PRT rate in last 30 and 14 days of life

Overall in BC, 614 (5%) decedents received PRT treatment in the last month of life and 268 (2.2%) decedents received PRT in the last 14 days of life **(Figure 12).**

Figure 12: PRT rate in last 30 & 14 days of life



Lung cancer patients were more likely to receive PRT treatment than any other cancer group in the last 30 and 14 days of life. More than 1/10 (11.3%) lung cancer patients received PRT in the last 30 days and approximately 1/20 received treatment in the last two weeks of life. Significant variations had been found for the $PRT_{30\ day}$ utilization across cancer groups, ranging from lung (11.3%), urinary (5.5%), melanoma (4.9%) to colorectal (1.9%), female genital (2.4%) and prostate (3.0%). The rates dropped significantly in the last 14 days for all cancer groups, in which 2.2% of the study cohort still received PRT in their last two weeks of life **(Table 11).**

Table 11: PRT rates at last 30 & 14 days of life by primary cancer diagnosis

Primary Cancer Diagnosis	Decedent Cohort	Last 30 days				Last 14 days			
		# PT	% cohort	% RT	# PRT	# PT	% cohort	% RT	# PRT
Lung	2,406	272	11.3	24.8	357	129	5.4	11.7	160
Breast	1,204	42	3.5	17.8	54	18	1.5	7.6	20
Colorectal	1,551	30	1.9	21.7	33	16	1.0	11.6	18
Prostate	1,438	43	3.0	19.7	53	20	1.4	9.2	24
Non-colorectal GI	1,454	59	4.1	24.0	69	23	1.6	9.4	24
Blood	938	34	3.6	23.3	50	9	1.0	6.2	17
Urinary	656	36	5.5	24.2	45	11	1.7	7.4	15
Female Genital	623	15	2.4	14.3	15	5	0.8	4.8	5
Brain	255	8	3.1	17.8	9	4	1.6	8.9	4
Melanoma	265	13	4.9	23.2	16	4	1.5	7.1	4
Other	1,510	62	4.1	26.8	80	29	1.9	12.6	37
Cancer Overall	**12,300**	**614**	**5.0**	**23.0**	**781**	**268**	**2.2**	**10.0**	**328**

PT Number of decedents
% cohort: Proportion of decedents received PRT in their last 30/14 days of life
% RT: Proportion of decedents who receive RT courses in last year of life who received PRT
# PRT: Number of PRT courses that decedents received in their last 30/14 days of life

4.5.2 PRT prescribed at the last 30 &14 days of life by treatment site

Among 4,371 PRT_{1Y} courses, 18% (781) were prescribed in the last 30 days and 7.5% (328) were prescribed in the last 14 days of life. The most commonly treated site in the last 30 days was bone (402 courses) and lung (163 courses)**.** These treatments accounted for approximately 1/5 of courses prescribed to each site during the last year of life. In addition, 109 PRT courses were prescribed to brain and 95 courses were prescribed to soft tissues/nodes in the last 30 days of life. The patterns changed slightly for the last 14 days: lung was the site most likely to receive PRT treatment prescribed in the last 14 days (9.2 %), followed by bone (7.7%), breast (7.7%), and brain (7%) (**Figure**

13). The PRT treatment was prescribed in the last 30 days, on average, using 3.3 fractions per course to all body regions combined, 2.7 fractions per course to bone, 4.7 fractions per course to the brain and 3.8 fractions per course to the chest. The average number of fractions per course prescribed in the last 14 days of life was decreased for all treatment sites (**Table 12**).

Figure 13: PRT courses prescribed at last 30 & 14 days of life by treatment site

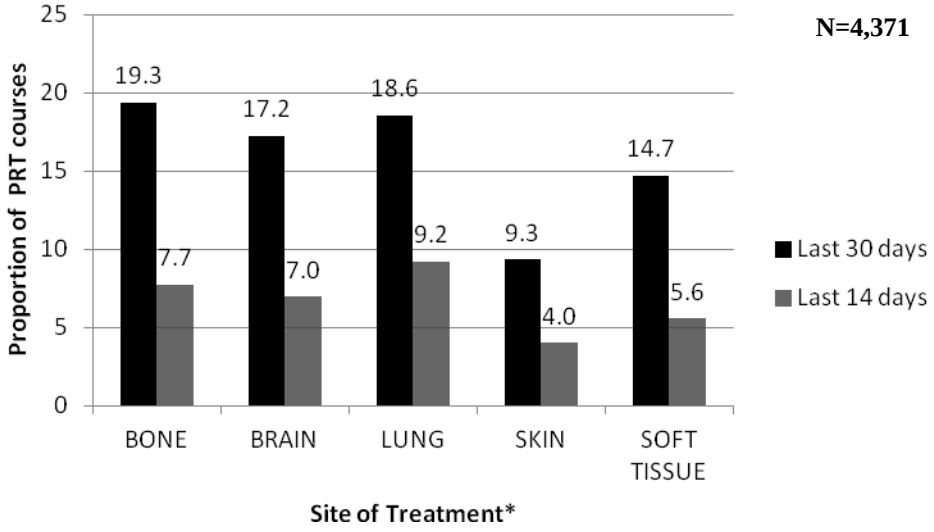


Table 12: Fractions of PRT prescribed at last 30 & 14 days of life by treatment site

Site of Treatment*	Last 30 days			Last 14 days		
	PRT Course	Fraction		PRT Course	Fraction	
		Mean	Median		Mean	Median
BONE	402	2.7	1.0	160	2.0	1.0
BRAIN	109	4.7	5.0	44	3.7	4.0
LUNG	163	3.8	4.0	81	3.2	4.0
SKIN	7	1.7	1.0	3	1.0	1.0
SOFT TISSUES	95	3.9	4.0	36	3.4	3.0
All Sites	781	3.3	4.0	328	2.7	2.0

** Breast, Head &Neck, and Other were excluded from the figure and table from reporting due to small cell size*

5. Discussion

This chapter focuses on the implications of the results, which are meant to answer the following research questions:

1. Among BC cancer patients who died between April 1, 2010 and March 31, 2011, what proportion of patients received at least one course of PRT during the last year, last month, and the last two weeks of life?
2. What were patient, disease and health system related factors associated with receiving PRT in the last year of life?
3. For BC cancer patients who died between April 1, 2010 and March 31, 2011, what was the pattern of PRT utilization by PRT treatment site in relation to their primary cancer site during the last year of life?
4. For BC cancer patients who died between April 1, 2010 and March 31, 2011, what were the most commonly used dose/fractionation schedules for PRT treatment in the last year of life?

The discuss focuses on the implications on PRT utilization rates, dose fractionation schedules, and factors associated with PRT utilization in the last year of life. Implications with respect to "aggressiveness" of PRT treatment at the terminal stage – the last 30 and 14 days of life – are also discussed to shed light on the quality of end of life care for the BC cancer population.

5.1 Implications of PRT_{1Y} rates in BC

In BC, the overall rate of PRT in the one year preceding death for patients with cancer was 21.7% but it varied widely across the province. Although several demographic factors, primary cancer sites, and survival time emerged as factors

associated with the variation, after adjusting for these variables, the effects of travel time to the closest cancer centre was strongly associated with the use of PRT in the last year of life.

Two population-based studies, conducted recently in other Canadian provinces, have reported the PRT rates at the end of life. Lavergne et al.[2] reported approximately 22.5% of patients in Nova Scotia dying from cancer received PRT in the final nine months of life. Huang et al.[3] reported the overall PRT rate at the last two years of life in Ontario for patients who die of cancer was 26.4%. The PRT_{1Y} rate in BC from our study is similar to the rate reported in Nova Scotia but lower than the rate reported in Ontario. Except for the methodological differences in how PRT is defined in our study, we believe the limitation on how our study cohort was selected contributes most to the lower rate observed in our study.

It was no surprise that we observed variations in PRT utilization by primary cancer site. Our results showed the PRT treatment in the last year of life was most commonly given to those diagnosed with primary lung cancer. This was consistent with the findings in other studies.[2,3] High PRT rates for melanoma (21.1%) in our study were expected, since radiotherapy can provide effective palliation and chemotherapy provides a less reliable response.

Significantly lower rates were observed in our study for primary breast, prostate, melanoma, and colorectal cancer when compared with other population-based studies.[2,126] One of the factors that might explain the differences, are the differences in defining the study cohort. In our study, the PRT rates were reported for patients diagnosed with cancer while the comparison studies[2,126] reported PRT rates for patients

dying from cancer. We observed similar rates for lung cancer but different rates for breast, prostate, and melanoma cancer because many lung cancer patients will die from lung cancer within a short time of diagnosis, while many breast, prostate, or melanoma cancer patients will die from their cancer many months or possibly years after diagnosis. A lower rate observed in our study for colorectal, lung, prostate and breast cancer patients receiving PRT in the last 30 days of life when compared with Guadagnolo et al. study[126] in the U.S. may be explained by the differences in physician reimbursement factors between the U.S. and Canada. In the U.S., compensation for radiation oncologists is generally on a fee-for-service basis with greater payment for increased number of PRT courses employed.

Similar to other studies,[2,3,110] we observed variations in the use of PRT treatment in the last year of life by geographic access. The geographic access was operationalized and assessed by patients' residence region (HSDA) as well as the travel time to the closest cancer centre in our study. Our results showed that PRT_{1Y} rate varied greatly by geographic region and patients travelling more than two hours to get to the closest cancer centre are less likely to receive PRT treatment in the last year of life.

Noticeably, more geographically remote regions such as Northern BC had lower PRT utilization. However, caution need to be taken when interpreting the lowest rates which presented in the North East and the East Kootenay region. These two regions are located near the border of the Canadian province of Alberta and patients from these regions are often referred to Alberta for treatment due to proximity and ease of accessibility. Therefore, the observed low rates can partially be explained by patients referred to cancer centres in Edmonton or Calgary.[109] In addition, those who reside in

areas geographically remote from a cancer centre (e.g. not in same region where the cancer centre is located) were less likely to receive PRT. This is well illustrated in Figure 3 of the results - all the rates for the regions where a cancer centre is located had a PRT rate higher than the provincial average with the exception of the Okanagan. We suspect that the lower-than-provincial-average rate in the Okanagan was related to the fact that 20-40% of patients in that region require travel of more than two hours to the closest cancer centre to receive treatment (Figure 1). Interestingly, we also found that there were some regions where PRT rates exceeded those in regions with cancer centres. For instance, the North West region had the highest PRT rate among all the regions. It is unfortunate that we were not able to audit utilization within cancer stages or to account for case mix variations among regions due to limited data. Whether this result is related to statistical chance, variation in cases (due to small sizes in regions), or other causes is unclear.

Even though Tyldesley et al.[116] attempted to create benchmarks for site specific cancers such as lung, breast, and prostate using criterion based benchmarking and epidemiologically based estimates models, it is difficult to determine whether observed rates of use overall or by cancer site in our study are appropriate given that the existing benchmarks are created for cancer incidences but not for PRT use at the end of life. However, given the variations observed on the rates related to non-patient factors (e.g. geographic access), it might suggest an underutilization of PRT for BC cancer patients at the end of life. In fact, as indicated in other studies,[2,3] the PRT treatment rates for the region with the highest rates, and that includes the largest cancer centre, might be a benchmark for optimal care in the province (Fraser East: 23.8%).

5.2 Factors associated with PRT_{1Y} utilization in BC

In this study, we were only able to examine some limited patient, disease, and access factors which were documented in the previous studies as having association with PRT utilization for cancer patients.

We observed that age was negatively associated with the utilization of PRT in the last year of life. After controlling for other factors such as sex, cancer sites, survival time, and travel time, the odds of a patient receiving PRT in their final year decreases as age increases. This is consistent with previous research[2,3,126,127] and for the palliative care program more broadly.[128] Older patients may have more severe comorbidity, worse performance status, and different preferences for treatment compared with younger patients. Unfortunately, we were not able to assess these factors due to the limited data in our study. However, given that PRT treatment is being administered for relief of symptoms and many studies have suggested there is no difference in toxicity and efficacy in the elderly,[129] even in the so-called oldest old cancer patients,[126,130] the decreased rate might suggest an underutilization of PRT at the end of life in BC.

In the previous study, survival time has been found one of the factors associated with PRT utilization at the end of life.[2] Our findings on survival between 1.5 and 26 months after the cancer diagnosis, showed that patients were twice as likely to receive PRT treatment during the last year of life compared to survival time >26 months. This may reflect indolent disease, availability of effective chemotherapy, or hormonal treatment for patients surviving longer than 26 months, and thus fewer symptoms requiring PRT. The fact that those who survived less than 1.5 months had lower odds of receiving PRT in the last year of life may not be inequitable if little potential benefit or informed patient choice is reflected.[131] Research has shown lower rates of PRT with

increasing comorbidity.[126] Those with short survival times from cancer diagnosis to death may have more comorbid conditions, as may older decedents. The lower PRT rate for patients with short survival time may also suggest physicians are reasonable at estimating prognosis.

Previous studies that aimed to define the factors associated with PRT indicated that patients with metastatic disease who have lower socioeconomic status[3,126,112] and those who live in nursing homes or rural settings are less likely to be referred for RT and thus, receive less treatment.[2,3,112] Unfortunately, our data does not currently capture information on patients' socioeconomic status or living situation, so we are not able to assess those factors as part of our analysis.

5.3 PRT_{1Y} utilization by treatment site in relation to their primary cancer site

In BC, among the patients who were treated with PRT during the last year of life, 60% of them received only one course of treatment and 25% received two courses of treatment before they died. This finding is consistent with other population-based end of life studies.[3]

Our data showed bone metastases are the most common indication for PRT: 47% of treatments prescribed in the last year of life. This result is in line with the literature in that up to 75% of patients with breast, lung, and prostate cancer have been found to have bone metastases post-mortem and bone metastasis is the most common indication of PRT for advanced cancer patients due to its effectiveness of palliating severe pain.[53,55]

Research has showed that radiotherapy improves control of thoracic symptoms from baseline in people with inoperable lung cancer and poor prognosis.[94-96,132] We expected to see other common indications of PRT in our study including lung primary or

metastases (20%), tumors in soft tissues/nodes (15%) and brain primary/metastases (14%), consistent with findings by Huang et al.[3] Most lung cancer patients who presented with locally advanced or metastatic disease are not appropriate candidates for resection, and PRT is often the optimal management for these patients, particularly those who have localised disease, or those with significant age or co-morbidities. For patients who relapsed after the first or second-line chemotherapy, or who were chemotherapy-resistant, PRT may be the only treatment option.

Brain is one of the three most common sites for metastases. The literature shows that brain metastases develop in 15-20% of all cancer patients and effective symptom relief can be achieved in approximately 70% of patients with symptomatic brain metastases.[4] This is consistent with the PRT use in our study.

5.4 Implications of PRT dose fractionation schedules in the last year of life

Low dose (dose less than 30 Gy) has been documented in the literature as a "standard" dose practice for the palliation of cancer patients at the end of life.[134] Previous research has also used it in conjunction with palliative intent flag to define PRT.[125] In our study, we found the overall majority (85%) of patients who received RT treatment during their last year of life received an RT dose <=30 Gy during a single course of RT. This is consistent with the "standard" dose practice for palliation found in the literature, suggesting that in most cases "appropriate" doses have been prescribed to BC cancer patients at the end of life. Similar patterns on the proportion of patients receiving low dose RT have also been observed across all the primary cancers except for primary brain cancer where only 1/5 of patients who received RT in their final year received low dose RT. This could be explained by the research that RT given in higher doses (e.g. between

58-60 Gy) in primary brain cancer patients has shown to significantly improve survival.[135]

We found the majority (94.5%) of the PRT courses prescribed to the study cohort were less than 10 fractions and the PRT treatments were predominantly given in 1, 5 or 10 fractions. This is similar to Swedish and British practice.[134] Shorter courses given in the last year of life exemplify common sense end-of-life care, especially because most patients treated for symptom palliation will not survive to face the possible increased risk of long-term side effects associated with hypofractionated regimens, and in most indications, shorter fractionation schedules have been shown to provide equivalent palliation of symptoms to longer fractionation schedules. A small proportion of PRT courses (5.5%), were prescribed a large number of fractions (greater than 10 fractions). We suspect that some of these would have been large volume treatments in which toxicity would otherwise have been considered prohibitive and where it was considered that high doses were required to achieve a useful palliative effect for the life of the patients.

In an analysis of fractions to the specific radiation site, the fractionation patterns were found consistent with the patterns reported in Ontario where the most commonly used fractions to the bone were 1 (the most) and 5 (the second most); to the brain were 5 (the most) and 10 (the second most); and to lung for patients with primary lung cancer were 5 (the most) and 10 (the second most).[3]

Even though the most recent international survey of pattern of practice, 20 Gy in 5 fractions was reported as the most commonly used practice for painful bone metastases in Canada,[69] our results showed that the single fraction (SF) was predominantly given in

BC for the indication of bone metastases and accounted for 47% of all the courses prescribed to the bone. This rate was higher than the rate reported in Ontario in 1999-2001 (35%),[136] in the United Kingdom in 2003 (36%)[134] and in Sweden in 2001(37%).[137] The pattern we observed in our study strongly suggested the higher compliance of practice in BC with the clinical practice guideline published in 2004 in Canada for uncomplicated bone metastases.[77]

We observed that the second most common fraction schedule to the bone was five fractions. This might reflect the treatment for spinal cord compression commonly caused by primary malignancies of myeloma, breast, lung, prostate, and kidney.[138] Previous research has showed that the SF is least likely to be used when the spine is involved.[136] Thoracic spine metastases from a breast primary are least likely to be treated with a SF (15%), compared with lung cancer metastases (42%).[111] The routine treatment prescription for spinal cord compression is 20Gy in five daily fractions delivery over one week.[140]

Our findings of the fractionation patterns to the brain were supported by literatures in that, 20Gy in 5 fractions and 30 Gy in 10 fractions were considered to be standard treatment for brain metastases patients with a favourable prognosis.[134]

There was more variation in fractionation schedules for thoracic PRT, used for palliation of lung symptoms, such as shortness of breath. Randomised trials[94,06,97] have consistently shown that low dose-shorter fractionation schedules are appropriate for patients with poor performance status, while higher dose-longer fractionation schedules are associated with modest survival improvements among patients with good performance status. Our observation of the diversity in fractionation practice for

palliation of thoracic symptoms is likely explained by considerable heterogeneity in patients' performance status at the time of RT. Evidence from the literature showed that moderate doses of RT (10 Gy /1 fraction or 16 Gy/2 fractions) are the recommended treatment of choice for patients with poor performance status (ECOG performance status score=3) and patients with a considerable amount of distant tumour burden. Patients with good performance status and no or little distant tumour burden benefit most from higher radiation doses (20 Gy/5 fractions, 36 Gy/12 fractions, 30 Gy/10 fractions).[99,97,100]

5.5 Implications on quality of care at the end of life

In our study, we found that 5% of the study cohort received PRT in the last month of life. We were unable to find any studies with which to directly compare this rate. However, we can compare our rate indirectly with a study published recently in the U.S., where 7.6% of the patients who died from malignant diseases of lung, breast, prostate, colorectal, and pancreas from 2000 to 2007 received PRT in the last month of life.[141] One must understand that the lower rate observed in our study may be partially explained by the differences in defining the study cohort as well as the reimbursement systems used in different health care systems. Despite the underutilization of PRT in end-of-life care in Guadagnolo et al.[141] study, due to the relevance of nonclinical factors found with the use of PRT in the last month of life, we would argue that the lower rate we found in our study might indicate the accuracy of physician predictions on prognosis and thus 'appropriate' palliative care, especially with respect to geographic access. Lower rates are considered appropriate, as good palliative care for a patient who lives far away is through use of medication and avoidance of a long trip that might hasten their death and negatively impact their overall Quality of Life (QOL).

On the other hand, concerns have also been raised in the medical oncology world regarding the aggressiveness of treatment at the end of life. Chemotherapy administration in the last month of life – either a new regimen within four weeks of death or any chemotherapy within two weeks of death – is considered a quality measure[142] as it reflects care that is too aggressive. There has been at least one implicit call for radiotherapy in the last one or two weeks of life as a similar quality measure[143] based on evidence from literature that palliative relief after radiation therapy commonly has its onset from 7-10 days[53,144] and there are potential risks of toxicity and inconvenience for patients. However, the issue of "aggressiveness of use" is much more subtle with RT, as the side effects of short-course treatment are relative minimal and real pain improvement can be achieved. Therefore, given the findings from other studies that the majority of physicians are overly optimistic on the prognoses[139,133] without a further analysis on both the accuracy of physician prediction of survival and the response rate for patients receiving PRT in the last two weeks of life for our study cohort, we do not have the confidence to conclude that the 2.2% of patients who received PRT in the last two weeks of life in our overall findings indicates an aggressive use of RT at the end of life.

In fact, we found of the 328 PRT courses delivered in the last two weeks of life in our study, the median fraction used was 2. This finding is consistent with the general agreement reached from many published randomized trials that one, two or a few (at the most) fractions represent the most beneficial approach to PRT, when indicated for patients with limited life expectancy.[67] This again might suggest "appropriate" palliative care were received by most BC cancer patients at the end of life.

5.6 Study strengths and limitations

The present study has the advantage of being population-based. We had information on all cancer incidences including information about radiotherapy. Given that the BC Cancer Registry captured more than 95% of cancer cases for BC residents, and the BCCA-CAIS system included data for all radiation treatment delivered in BC in the study era, the near-completeness of case ascertainment and a high level of accuracy featured in the use of administrative data has avoided the selection biases that can occur in a hospital-based analysis.

One of the major limitations of this study though, lies in the failure of confining our study cohort to those patients who died of cancer from those where incompleteness of cause of death data was not available from the CAIS at the time of the data collection. Therefore, our study cohort consisted of patients dying with instead of dying of cancer. This results in under-estimated PRT rates for cancer patients at the end of life. Furthermore, this makes the interpretation regarding prescription patterns and comparisons in the use of PRT with other studies less straightforward.

Another limitation in our study is associated with the use of administrative data. Since administrative databases are designed for administrative purposes rather than for quality improvement, some clinical factors such as symptom assessment and patient preferences for treatment at the end of life were not available from the CAIS. These missing clinical factors are recognized as important with respect to their impact on PRT utilization at the end of life. Therefore, by not assessing these important clinical factors, the interpretation of the PRT rate from our study becomes difficult.

Lastly, the practice patterns in BC may not be representative of radiation oncologists in general. Except for patient factors such as performance status, age, and

anatomical site,[111] studies have also shown that prescription patterns of radiation oncologists are influenced by country of training, location and type of practice, years of experience, professional membership affiliation as well as reimbursement.[69] Without controlling for these factors, it may be inaccurate to generalize our findings to the field as a whole.

5.7 Future research

It is out of the scope of this study to determine whether the PRT_{1Y} rate and the dose fractionation patterns observed from this study are clinically appropriate for BC cancer patients at the end of life; however, assessing the appropriateness of PRT use is the key quality improvement step for end-of-life cancer care. Therefore, this is an important issue for future study. Along these lines, it would have been helpful to know the decision process of both the physicians and patients on the choice of PRT treatment, as well as outcomes (e.g. response rates, side effects and overall QOL) associated with the PRT treatment at the end of life. These data could be collected through prospective observational studies or through qualitative research and would help to assess the appropriateness of use of PRT for advanced cancer patients at the end of life.

In addition, cancer care is regarded as patient-centred multidisciplinary care. For future research aiming to improve quality of cancer care at the end of life, it would be helpful to collect data which allows us to follow patients through their trajectory of care regardless of where the care is provided (e.g. cancer clinics, hospice, hospital, or at home). Without fully understanding the point of care provided at different settings by different care providers, it is difficult to draw conclusions on the quality of care patients received at the end of life and to improve the quality of care.

6. Conclusions

RT is known to provide needed palliation for patients with advanced cancer. Knowing the pattern of PRT delivered to cancer patients prior to death offers insight into whether or not the patients are receiving care meant to improve the quality of dying. This research aims to provide such information by answering four research questions related to the PRT utilization and patterns of delivery at 1 year prior to death for BC cancer patients.

Our findings on practice patterns of PRT treatment in the last year of life are in line with the evidence from the literature, indicating that, in general, most BC cancer patients, when treated with PRT in their last year of life, are treated "properly" with a good palliative care approach. However, given what we found a strong association between geographic access and PRT utilization in the last year of life, we believe, to a certain extent, that cancer patients in BC who had experienced access issues might have been under treated with PRT in their last year of life.

To the best of our knowledge, this population-based study is the first of its kind providing data on the use of PRT for the end of life cancer population in BC. It is our hope that this information could be used by local cancer care providers and health care administrators for cancer care planning as well as researchers conducting end of life care research. We believe that the findings from this study have shed light on the issues of suboptimal PRT treatment received by a subgroup of the BC cancer population due to restricted geographic access. Improving access to treatment might be an important next step for improving equity of care for end of life cancer patients. Most importantly, we hope our findings will help raise questions about the appropriateness of care in PRT

treatment at the end of life. The accurate assessment of appropriateness of use of PRT at the end of life is critical for improving palliative care, yet it is difficult to achieve. This requires richer data collected at the point of care as well as rigorous/robust methodology based on a sound scientific footing. Both aspects remain challenging in the current palliative/EOL care research but desire resolutions in the future.

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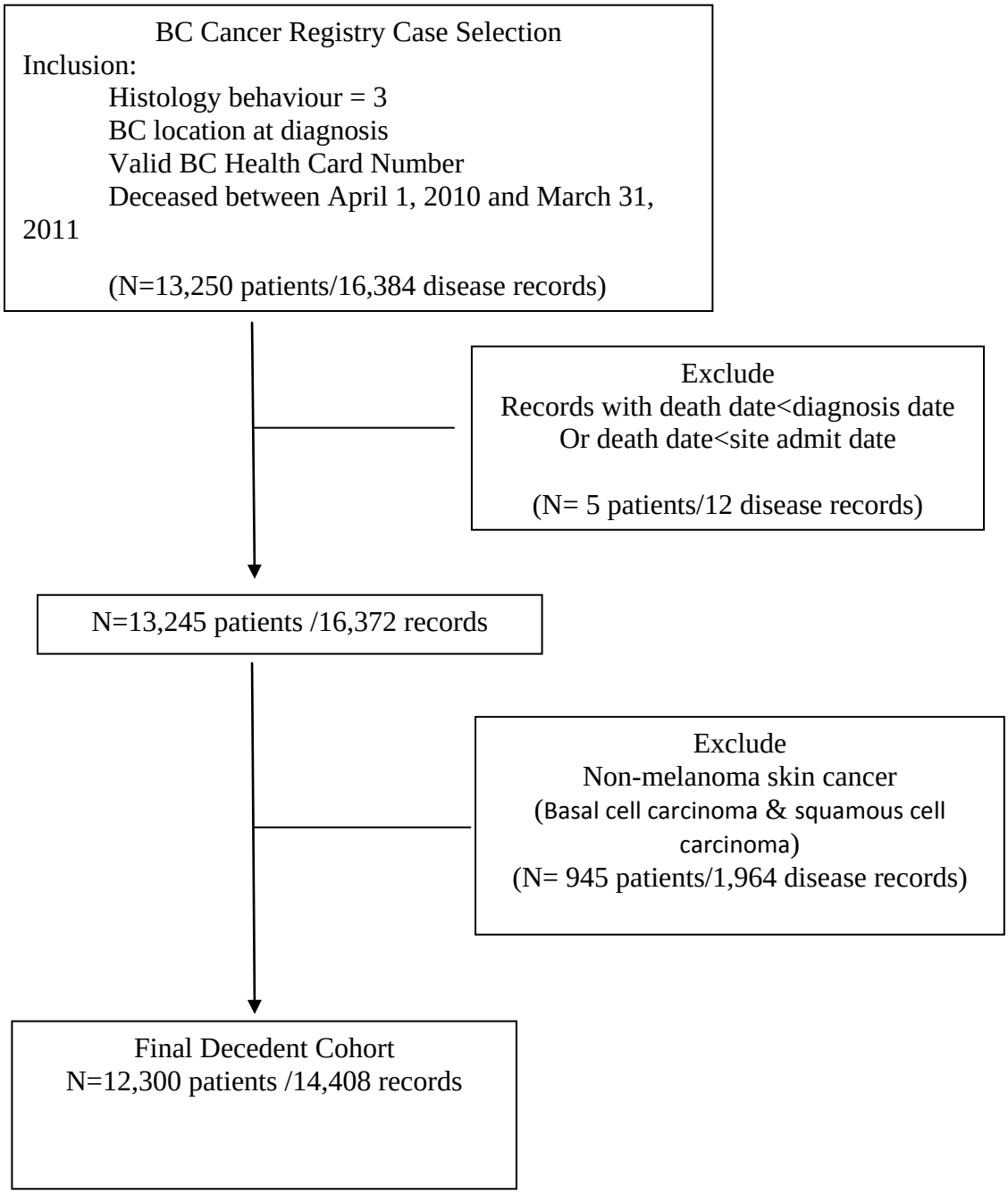
Appendix A: Creating the Study Cohort



Appendix B: Definition of Data Elements

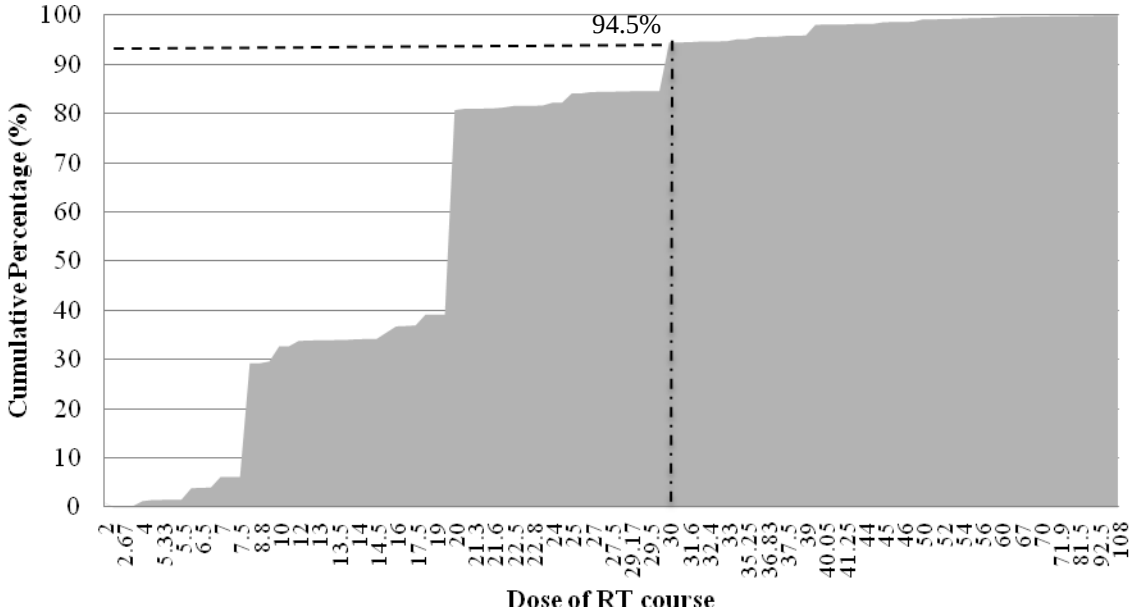
Variable Name	Data Source	Value Set	Definitions
Sex	Cancer Registry	'M'=Male 'F'=Female	Patient's gender
Birth_yr	Cancer Registry	YYYY	The year of patient's birth date
Death_date	Cancer Registry	YYYY/MM/DD	Patient's date of death
Curr_desc_hlth_auth	Cancer Registry	'01"= Interior "02"=Fraser "03"=Vancouver coastal "04"=Vancouver Island "05"=Northern	Patient's residence health authority at the time of diagnosis
Curr_hsda	Cancer Registry	Valid HSDA code	Patient's residence HSDA at the time of diagnosis
Diagnosis_date	Cancer Registry	YYYY/MM/DD	Date of diagnosis
Site_admit_date	CAIS	YYYY/MM/DD	The date the patient was admitted to a COP clinic or a cancer centre for a particular site.
Site	Cancer Registry	ICDO-3 code such as 'C53.0', 'C60.9' etc.	The ICDO-3 site code for the patient's distinct primary disease (where the diagnosis date is prior to January 1 2001 the ICDO code is converted to ICDO-3).
Hist1	Cancer Registry	Valid histology code such as 80003, 80013 etc.	The highest ICD-O3 histology code of the patient's distinct primary disease (where the diagnosis date is prior to January 1 2001 the ICDO code is converted to ICDO-3).
RT_start_date	CAIS	Valid date	The date radiation therapy treatment started.
RT_end_date	CAIS	Valid date	The date radiation therapy treatment ended
RT_treat_intent_code	CAIS	"R"=RADICAL "P"=PALLIATIVE "A"=ADJUVANT "O"=OTHER "X"=UNKNOWN	The expected result of the treatment course
RT_treat_region_code	CAIS	Valid value such as "PRO"= PROSTATE "PEL"= PELVIS	The anatomic site where the patient received radiotherapy treatment.
Dose_cgy	CAIS	Valid entries: 0000-9999	Amount radiation received

		centigrays (cGy)	
Fractions	CAIS		The total number of individual exposures to radiation that the patient received for each treatment line

Appendix C: Distribution of Dose of RT Courses with "Palliative Intent" Code

We looked at the distribution of dose among RT courses with palliative intent code. Among all the RT courses (4776) prescribed to the study cohort during the last year of life, 88.4% (4221) of the courses had a "palliative intent" code. The majority (94.5%) of them were prescribed with dose<=30 Gy (**Figure 14**).

Figure 14: Cumulative percentage for dose of RT with a palliative intent code



Appendix D: Definitions of Primary Cancer Diagnosis

Primary Cancer Site	ICD-O-3 Site	ICD-O-3 Site Description	Histology Code Exclusion
Lung	C34		excluding histology code 9590-9989, 9050-9055, 9140
	C340	Malignant neoplasm of main bronchus	
	C341	Malignant neoplasm upper lobe, bronchus or lung	
	C343	Malignant neoplasm lower lobe, bronchus or lung	
	C348	Overlapping malignant lesion of bronchus and lung	
	C349	Malignant neoplasm bronchus or lung unspecified	
Colorectal	C18-C20		
	C18	Malignant neoplasm of colon	
	C19	Malignant neoplasm of recto sigmoid junction	
	C20	Malignant neoplasm of rectum	
Prostate	C61	Malignant neoplasm of prostate	
Breast	C50		
	C500	Malignant neoplasm of nipple and areola	
	C501	Malignant neoplasm of central portion of breast	
	C502	Malignant neoplasm of upper-inner quadrant of breast	
	C503	Malignant neoplasm of lower-inner quadrant of breast	
	C504	Malignant neoplasm of upper-outer quadrant of breast	
	C505	Malignant neoplasm of lower-outer quadrant of breast	
	C506	Malignant neoplasm of axillary tail of breast	
	C508	Overlapping malignant lesion of breast	
	C509	Malignant neoplasm breast part unspecified	
Brain	C70-C72		
	C70	Malignant neoplasm of meninges	
	C71	Malignant neoplasm of brain	
	C72	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system	
Blood			
Hodgkin Lymphoma	All primary sites with histology codes 9650-9667		
Non-Hodgkin Lymphoma	All primary sites with histology codes 9590-9596, 9670-9719, 9727-9729 histology codes 9823, all sites except C42.0, C42.1, C42.4 histology codes 9827, all sites except C42.0, C42.1, C42.4		
Multiple Myeloma	All primary sites with histology codes 9731, 9732, 9734		
Leukemia	All primary sites with histology codes 9733, 9742, 9800-9801, 9805, 9820, 9826, 9831-9837, 9840, 9860-9861, 9863, 9866-9867, 9870-		

		9876, 9891, 9895-9897, 9910, 9920, 9930-9931, 9940, 9945-9946, 9948, 9963-9964 For sites C42.0, C42.1, C42.4, histology codes 9823 and 9827	
Other Digestive (excluding colorectal)	C15-C17, C21-C26		excluding histology code 9590-9989, 9050-9055, 9140
Esophagus	C15	Malignant neoplasm of oesophagus	
Stomach	C16	Malignant neoplasm of stomach	
Small intestine	C17	Malignant neoplasm of small intestine	
Anus and anal canal	C21	Malignant neoplasm of anus and anal canal	
liver	C22	Malignant neoplasm of liver and intrahepatic bile ducts	
Gallbladder	C23	Malignant neoplasm of gallbladder	
Other and unspecified parts of biliary tract	C24	Malignant neoplasm of other and unspecified parts of biliary tract	
Pancreas	C25	Malignant neoplasm of pancreas	
Intestinal tract	C26	Malignant neoplasm of other and ill-defined digestive organs	
Skin - Melanoma	Site C44 and histology codes 8720-8790		
	C44	Other malignant neoplasms of skin	
Urinary	C64-C68		excluding histology code 9590-9989, 9050-9055, 9140
Kidney	C64	Malignant neoplasm of kidney, except renal pelvis	
Kidney - renal pelvis	C65	Malignant neoplasm of renal pelvis	
Ureter	C66	Malignant neoplasm of ureter	
Bladder	C67	Malignant neoplasm of bladder	
Other and unspecified urinary organs	C68	Malignant neoplasm of other and unspecified urinary organs	
Female genital	C51-C58		
Vulva	C51	Malignant neoplasm of vulva	
Vagina	C52	Malignant neoplasm of vagina	
Cervix	C53	Malignant neoplasm of cervix uteri	
Body of Uterus	C54	Malignant neoplasm of corpus uteri	
	C55	Malignant neoplasm of uterus, part unspecified	
Ovary	C56	Malignant neoplasm of ovary	
	C57	Malignant neoplasm of other and unspecified female genital organs	
	C58	Malignant neoplasm of placenta	

Appendix E: Site of RT Treatment Mapping

Treatment Region	Site of Treatment							
	Bone	Brain	Lung	Soft tissue/ nodes	H&N	Skin	Other	Breast
ABDOMEN				x				
ADRENAL							x	
Mammary+Supraclav								x
ANKLE	x							
ANUS				x				
ARM	x							
AXILLA				x				
BACK	x							
BLADDER				x				
BODY				x				
BONE	x							
BRAIN		x						
BREAST								x
BRONCHUS			x					
BUTTOCKS	x							
CERVIX				x				
CHEST			x					
CLAVICLE	x							
COLON				x				
CERVICAL SPINE	x							
EAR				x				
ESOPHAGUS				x				
ETHMOID					x			
EYE					x			
FACE				x				
FEMUR	x							
FIBULA	x							
FINGER	x							
FLANK				x				
FOOT	x							
HAND	x							
HEAD				x				
HEART				x				
HIP	x							
HUMERUS	x							
HYPOPHARYNX					x			

Treatment Region	Site of Treatment							
	Bone	Brain	Lung	Soft tissue/ nodes	H&N	Skin	Other	Breast
ILIUM	x							
INGUINAL				x				
ISCHIUM	x							
MANDIBLE	x							
KIDNEY				x				
KNEE	x							
LARYNX					x			
LEG	x							
LIVER				x				
SPINE	x							
LUNG			x					
MAXILLA				x				
MEDIASTINUM			x					
NASOPHARYNX					x			
NECK				x				
NOSE					x			
ORAL					x			
ORBIT				x				
OROPHARYNX					x			
PANCREAS				x				
lymph nodes				x				
PAROTID					x			
SOFT PALATE					x			
PELVIS	x							
PENIS				x				
PERINEUM				x				
PHARYNX					x			
PITUITARY		x						
PLEURA			x					
PROSTATE				x				
PUBIS	x							
RADIUS	x							
RECTUM				x				
RIB	x							
SACRUM	x							
SCAPULA	x							
SUPRACLAVICULAR				x				
SCALP						x		

Treatment Region	Site of Treatment							
	Bone	Brain	Lung	Soft tissue/ nodes	H&N	Skin	Other	Breast
SHOULDER	x							
SKIN						x		
SKULL	x							
SPLEEN				x				
STERNUM	x							
STOMACH				x				
SUBMANDIBULAR GLAND				x				
THYROID				x				
TIBIA	x							
TONGUE				x				
TOE	x							
TONSIL				x				
LIP				x				
ULNA	x							
URETER				x				
UTERUS AND VAGINA				x				
VULVA				x				

Appendix F: Travel Time by HSDA

HSDA Code	Health Service Delivery Areas (16 regions)	LHA	Local Health Areas (89 regions)	Driving time from Kelowna, Vancouver, Surrey or Victoria according to BCAA (hours)	Driving time from Vancouver or Victoria (prior to May 1995) (hours)	Driving time from Vancouver, Victoria or Surrey (between May 1995 - April 1998) (hours)
5911	East Kootenay	001	Fernie	>2	>2	>2
5911	East Kootenay	002	Cranbrook	>2	>2	>2
5911	East Kootenay	003	Kimberley	>2	>2	>2
5911	East Kootenay	004	Windermere	>2	>2	>2
5911	East Kootenay	005	Creston	>2	>2	>2
5911	East Kootenay	018	Golden	>2	>2	>2
5912	Kootenay Boundary	006	Kootenay Lake	>2	>2	>2
5912	Kootenay Boundary	007	Nelson	>2	>2	>2
5912	Kootenay Boundary	009	Castlegar	>2	>2	>2
5912	Kootenay Boundary	010	Arrow Lakes	>2	>2	>2
5912	Kootenay Boundary	011	Trail	>2	>2	>2
5912	Kootenay Boundary	012	Grand Forks	>2	>2	>2
5912	Kootenay Boundary	013	Kettle Valley	≤2	>2	>2
5913	Okanagan	014	Southern Okanagan	≤2	>2	>2
5913	Okanagan	015	Penticton	≤2	>2	>2
5913	Okanagan	016	Keremeos	≤2	>2	>2
5913	Okanagan	017	Princeton	≤2	>2	>2
5913	Okanagan	021	Armstrong-Spallumcheen	≤2	>2	>2
5913	Okanagan	022	Vernon	≤2	>2	>2
5913	Okanagan	023	Central Okanagan	≤2	>2	>2
5913	Okanagan	077	Summerland	≤2	>2	>2
5913	Okanagan	078	Enderby	≤2	>2	>2
5914	Thompson Cariboo Shuswap	019	Revelstoke	>2	>2	>2
5914	Thompson Cariboo Shuswap	020	Salmon Arm	≤2	>2	>2
5914	Thompson Cariboo Shuswap	024	Kamloops	>2	>2	>2
5914	Thompson Cariboo Shuswap	025	100 Mile House	>2	>2	>2
5914	Thompson Cariboo Shuswap	026	North Thompson	>2	>2	>2
5914	Thompson Cariboo Shuswap	027	Cariboo-Chilcotin>2	>2	>2	>2
5914	Thompson Cariboo Shuswap	029	Lillooet	>2	>2	>2
5914	Thompson Cariboo Shuswap	030	South Cariboo	≤2	>2	>2
5914	Thompson Cariboo Shuswap	031	Merritt	≤2	>2	>2
5921	Fraser East	032	Hope	≤2	>2	≤2
5921	Fraser East	033	Chilliwack	≤2	≤2	≤2
5921	Fraser East	034	Abbotsford	≤2	≤2	≤2
5921	Fraser East	075	Mission	≤2	≤2	≤2
5921	Fraser East	076	Agassiz-Harrison	≤2	>2	≤2
5922	Fraser North	040	New Westminster	≤2	≤2	≤2
5922	Fraser North	041	Burnaby	≤2	≤2	≤2
5922	Fraser North	042	Maple Ridge	≤2	≤2	≤2
5922	Fraser North	043	Coquitlam	≤2	≤2	≤2
5922	Fraser South	035	Langley	≤2	≤2	≤2

HSDA Code	Health Service Delivery Areas (16 regions)	LHA	Local Health Areas (89 regions)	Driving time from Kelowna, Vancouver, Surrey or Victoria according to BCAA (hours)	Driving time from Vancouver or Victoria (prior to May 1995) (hours)	Driving time from Vancouver, Victoria or Surrey (between May 1995 - April 1998) (hours)
5922	Fraser South	037	Delta	≤2	≤2	≤2
5922	Fraser South	201	Surrey	≤2	≤2	≤2
5922	Fraser South	202	South Surrey/White Rock	≤2	≤2	≤2
5931	Richmond	038	Richmond	≤2	≤2	≤2
5932	Vancouver	161	Vancouver-City Centre	≤2	≤2	≤2
5932	Vancouver	162	Vancouver-Downtown Eastside	≤2	≤2	≤2
5932	Vancouver	163	Vancouver-North East	≤2	≤2	≤2
5932	Vancouver	164	Vancouver-Westside	≤2	≤2	≤2
5932	Vancouver	165	Vancouver-Midtown	≤2	≤2	≤2
5932	Vancouver	166	Vancouver-South	≤2	≤2	≤2
5933	North Shore/Coast Garibaldi	044	North Vancouver	≤2	≤2	≤2
5933	North Shore/Coast Garibaldi	045	West Vancouver-Bowen Island	≤2	≤2	≤2
5933	North Shore/Coast Garibaldi	046	Sunshine Coast	>2	>2	>2
5933	North Shore/Coast Garibaldi	047	Powell River	>2	>2	>2
5933	North Shore/Coast Garibaldi	048	Howe Sound	>2	>2	>2
5933	North Shore/Coast Garibaldi	049	Bella Coola Valley	>2	>2	>2
5933	North Shore/Coast Garibaldi	083	Central Coast	>2	>2	>2
5941	South Vancouver Island	061	Greater Victoria	≤2	≤2	≤2
5941	South Vancouver Island	062	Sooke	≤2	≤2	≤2
5941	South Vancouver Island	063	Saanich	≤2	≤2	≤2
5941	South Vancouver Island	064	Gulf Islands	≤2	≤2	≤2
5942	Central Vancouver Island	065	Cowichan	≤2	≤2	≤2
5942	Central Vancouver Island	066	Lake Cowichan	≤2	≤2	≤2
5942	Central Vancouver Island	067	Ladysmith	≤2	≤2	≤2
5942	Central Vancouver Island	068	Nanaimo	≤2	≤2	≤2
5942	Central Vancouver Island	069	Qualicum	>2	>2	>2
5942	Central Vancouver Island	070	Alberni	>2	>2	>2
5943	North Vancouver Island	071	Courtenay	>2	>2	>2
5943	North Vancouver Island	072	Campbell River	>2	>2	>2
5943	North Vancouver Island	084	Vancouver Island West	>2	>2	>2
5943	North Vancouver Island	085	Vancouver Island North	>2	>2	>2
5951	Northwest	050	Queen Charlotte	>2	>2	>2
5951	Northwest	051	Snow Country	>2	>2	>2
5951	Northwest	052	Prince Rupert	>2	>2	>2
5951	Northwest	053	Upper Skeena	>2	>2	>2
5951	Northwest	054	Smithers	>2	>2	>2
5951	Northwest	080	Kitimat	>2	>2	>2
5951	Northwest	087	Stikine	>2	>2	>2
5951	Northwest	088	Terrace	>2	>2	>2
5951	Northwest	092	Nisga'a	>2	>2	>2
5951	Northwest	094	Telegraph Creek	>2	>2	>2
5952	Northern Interior	028	Quesnel	>2	>2	>2
5952	Northern Interior	055	Burns Lake	>2	>2	>2

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5952	Northern Interior	056	Nechako	>2	>2	>2
5952	Northern Interior	057	Prince George	>2	>2	>2
5953	Northeast	059	Peace River South	>2	>2	>2
5953	Northeast	060	Peace River North	>2	>2	>2
5953	Northeast	081	Fort Nelson	>2	>2	>2