University of Alberta

Treatment Variation and Its Association with Survival in Patients Diagnosed with Stage I-III Breast Cancers in Alberta 2002-2010: A Population-Based Study

by

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Abstract

Standard treatments for patients with stage I-III breast cancers include 1) breast conserving surgery (BCS) plus adjuvant radiotherapy; 2) mastectomy; and 3) BCS alone (e.g. age > 70 in stage I for ER/PR+ status and received hormone therapy). Currently, there is a lack of information regarding frequency and variation in utilization of these treatments in Alberta and information regarding the survival outcomes achieved in the general population by treatment type and stage.

In this study, we found that rural patients were less likely to receive BCS. Stage I-III patients who received BCS plus adjuvant radiotherapy had a lower hazard of overall death and stage II or III patients had a lower hazard of breast-cancer-specific death than those who received mastectomy; additionally, stage I and II patients who received BCS alone had a higher hazard of overall and breast-cancer-specific death. These suggested an inequity of care among Alberta breast cancer patients.

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List of Abbreviations

U.S. = United States

BCS = Breast Conserving Surgery

NIH = National Institute of Health

ER/PR = Estrogen or Progesterone Receptor

EBCTCG = Early Breast Cancer Trialists' Collaborative Group

SEER = Surveillance, Epidemiology, and End Results

ICD-O = International Classification of Diseases for Oncology

Chapter 1: Introduction

Breast cancer is the most common type and the second leading cause of death of all cancers among women in Canada, U.S., and many developed countries[1,2]. In 2013, there will be an estimated 232,340 new cases of invasive breast cancer and 39,620 deaths expected to occur among U.S. women[1]. In Canada, an estimated 23,800 women will be diagnosed, and 5,000 will die in 2013[2]. In Alberta, the approximate numbers of new cases and deaths of breast cancer in 2013 are 2,100 and 400, respectively[2].

There are two types of surgical treatments for patients diagnosed with stage I-III breast cancers – breast conserving surgery (BCS) and mastectomy. BCS (also referred to as lumpectomy or segmental resection) is an operation that removes the entire tumour (but not the breast itself) along with a margin of non-cancerous breast tissue, while mastectomy (also referred to as total mastectomy or modified radical mastectomy) involves removal of the entire breast that has cancer, and the fascia or the lining over the chest muscles and historically, part of the chest wall muscles[3,4]. Patients who are treated with either BCS or mastectomy may also have some of the lymph nodes under the arm removed for biopsy. This procedure is called lymph node dissection and it may be done at the same time as the surgery or after[4].

In the current practice, there are some contraindications for stage I-III patients to receive BCS. These include 1) inability to have radiotherapy, 2) inability to remove the tumor with acceptable cosmesis (i.e poor tumor to breast size ratio) and 3) inability to obtain clear margins. The presence of diffuse suspicious calcifications is a good indicator that widespread disease is present and these patients will usually fail breast conservation. Contraindications to radiation therapy are 1) having prior radiation therapy to the chest wall or breast and 2) active connective tissue disease involving the skin (especially scleroderma and lupus) and pregnancy. Some pregnant patients are still candidates for breast conservation depending on which trimester they are in as they will often have

delivered by the time they are due for radiation. Patients with a known or suspected genetic predisposition to breast cancer may choose not to have breast conservation as they are at increased risk of a second primary cancer.

There are two other types of treatments for breast cancers, serving as a supplement to surgeries namely, neo-adjuvant and adjuvant therapies. In neo-adjuvant therapy, physicians usually use drugs before surgery to shrink the tumor and reduce the amount of tissue that needs to be removed during the surgery[5]. These drugs include neo-adjuvant chemotherapy (treatment with cytotoxic anti-neoplastic drugs that kill cancer cells), hormone therapy (therapy that treats hormone sensitive tumours (i.e. estrogen (ER) / progesterone (PR) positive)) and HER2-directed therapy such as trastuzumab (for HER2 positive tumors). Currently, neo-adjuvant treatment is used for patients who have a large tumor size compared to the size of their breast and want BCS[5].

In adjuvant therapy, physicians use radiotherapy, chemotherapy, hormone therapy or a combination of these therapies to kill any cancer cells that are left after the surgery to lower the risk of recurrence[4,5]. Current practice of radiotherapy uses external beam radiation to kill cancer cells and shrink tumors[4,5]. This therapy is usually given 5 days per week for about 3 to 6 weeks[4,5]. Hormonal therapy is used when patients have hormone sensitive tumours (i.e. estrogen (ER) / progesterone (PR) positive) and two types of hormonal or endocrine therapy are available: Tamoxifen and Aromatase Inhibitors. Tamoxifen works at the level of the hormone receptor while aromatase inhibitors block the ability of the patient to make estrogen or progesterone. This therapy is given as a pill that patients take daily for 5-10 years[5]. The detailed information on the standard care of adjuvant treatment is provided in the appendices of this thesis.

Historically, breast cancer was primarily treated by mastectomy; BCS was given to a minority of patients[3]. In the early 1990s, however, the United States (US) National Institute of Health (NIH) consensus conference developed the treatment

guideline for breast cancer patients[6,7] in which the US NIH recommended that BCS plus adjuvant radiotherapy was the primary treatment for women diagnosed with certain breast cancer characteristics. Those characteristics covered the majority of stage I and II diagnoses and some stage III diagnoses. The more recent version of the guideline, based on updated evidence, states that female patients who are diagnosed at age 70 or older in stage I cancer, with small ER/PR positive breast cancers could be treated by BCS alone without adjuvant radiotherapy[8] if they receive 5 years of hormonal therapy.

These recommendations were based on the following findings: 1) there is survival equivalence between BCS plus adjuvant radiotherapy and mastectomy[9-11,14]; 2) no additional survival benefit from post-surgical radiotherapy among patients 70 years or older who had small ER/PR positive stage I breast cancers and received BCS and hormone therapy[12-13]; and 3) better cosmetic outcome and psychosocial impacts associated with BCS plus adjuvant radiotherapy as opposed to mastectomy[15-20]. Specifically, in a systematic review conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) on the 7 trials of mastectomy versus BCS with adjuvant radiotherapy (approximately 3,100 women enrolled) that started before 1985, all of the trials showed survival equivalence between the two procedures[14]. Among female patients who were diagnosed at an age of 70 or older, had ER/PR positive status in stage I and underwent both BCS and hormone therapy, Hugh *et al.*[12-13] found that those who received adjuvant radiotherapy had similar survival as those who did not receive adjuvant radiotherapy.

As to patients' cosmetic outcome, a study from England demonstrated that 90% of women after BCS with adjuvant radiotherapy were satisfied with the cosmesis of their breasts[15,20] and another study conducted by Rose *et al.* found that 76 months post-BCS 65% and 25% of patients scored as good or excellent, respectively, in the aesthetic results for the operated breasts by their physicians[16,20]. A study conducted by Al-Ghazal *et al.*[18,20] investigated the

psychosocial impacts between BCS and mastectomy and found that the satisfaction of body image and psychosocial morbidity (anxiety, depression, sexuality and self-esteem) were better after receiving wide local excision compared to mastectomy alone or breast reconstruction after mastectomy[18,20]. Another study conducted via telephone survey of 563 women (67 years of age or older) also found that self-esteem and body image in the elderly were improved significantly after BCS as opposed to mastectomy[19,20].

Despite the fact that BCS plus adjuvant radiotherapy was recommended as the primary treatment for patients diagnosed with breast cancers, many studies have shown inconsistent results to this recommendation in actual practice. Specifically, in Canada, the proportion of stage I-II breast cancer patients diagnosed in years 2007-2009 who received BCS was 61% from 2007, with a low of 31% in Newfoundland and Labrador to a high of 74% in Quebec. The proportion of those who received adjuvant radiotherapy after BCS was 87% in 2009, with an inter-provincial range of 76% in Manitoba to 93% in Newfoundland and Labrador[3]. The proportion of patients who received BCS and adjuvant radiotherapy after the surgery in Alberta were 44% and 87%, respectively[3].

Non-standard treatment is associated with poorer patient survival and quality of life. Clinical trials[10,11] have shown that not receiving adjuvant radiotherapy increases the chance of local recurrence and reduces overall survival for patients receiving BCS. Consistent with the clinical trials, a study from SEER[25] that included more than 100,000 stage I-IIIA patients also found that those who did not receive adjuvant radiotherapy had higher overall mortality and cancer-specific mortality rates. A study conducted by Gold *et al.*[30] also documented a similar pattern among 7,791 patients from the SEER database. In a recent observational study focused on female patients aged 65 years or older[31], patients who did not receive post-surgical radiotherapy after BCS had over a two-fold increase in mortality rate than those who received post-surgical radiotherapy. These studies

provide evidence that non-standard treatment is associated with poorer patient outcomes.

As previously mentioned, BCS with adjuvant radiotherapy offers a better cosmetic outcome and quality of life as opposed to mastectomy. For those who were eligible for that treatment but instead received mastectomy, Al-Ghazal *et al.*[15] found that they were less satisfied with their body image and had higher psychosocial morbidity. Specifically, among 577 patients studied, 68% felt sexually less attractive; 69% had some degree of anxiety and 10% had symptoms of depression. For those who received BCS, the above proportions were only 18%, 39%, and 7%, respectively[15]. Another study investigated the long-term body image and mental health among elderly recipients of BCS and mastectomy[19]. They found that patients who received mastectomy had poorer body image 2 years after the treatment than patients who had BCS, and patients who preferred BCS but received mastectomy had the poorest body image, linking with severe mental health outcomes[9].

Given the large variation in the receipt of treatments among breast cancer patients in the U.S. and Canada, many studies have investigated reasons behind this phenomenon. Particularly, some evidence suggested that women under the age of 40 or above the age of 80, or who lived in rural areas or who had lower socioeconomic status were more likely to receive mastectomy than their female counterparts[3,21-27,29,32-34,38,41-44]; for adjuvant radiotherapy, some studies discovered that patients who lived in rural areas far away from the radiation facilities, or who were diagnosed at an age of 70 or older, or had medical co-morbidities tended to be less likely to receive treatment[7,21,25,28-30,34,36,38-39]. In addition to these investigations, studies from the U.S. discussed the differences by ethnicity in undertaking the different treatments and revealed that minority women were linked to a lower chance of receiving both BCS and adjuvant radiotherapy than Caucasian patients[22-29,32-36,38-43].

It remains unclear, however, how or whether these findings and recommendations were translated into clinical practice in Alberta. In practice, treatment decisions are made based on various factors, including patients' preference and health conditions[44,45], availability and accessibility of treatment resources[46], social/cultural backgrounds[47] and physicians' experience and practice styles[47]. With these influences, treatment delivered to certain patients (e.g. those with comorbidities) does not always follow the guideline recommendations. This might lead to increased disease recurrence and shortened survival to the patients. It is, therefore, of interest for clinical as well as health care utilization purposes to investigate treatments received in practice along with the factors influencing the receipt of those treatments amongst the entire patient population in Alberta.

The primary purpose of this thesis is to assess the variation of treatment and its associated survival in all patients diagnosed with stage I-III breast cancers in the province of Alberta, Canada, during the years of 2002-2010. The secondary purpose is to identify factors affecting the receipt of these treatments, with a special emphasis on identifying the geographical patterns related to the utilization of treatment among those patients.

The paper-based thesis is organized as follows.

1. Chapter 2 is a paper describing the variation in treatment patterns received by the breast cancer patients in Alberta and discusses some important factors associated with that variation;

2. Chapter 3 presents a paper that investigates the survival outcomes related to the three treatments: BCS with adjuvant radiotherapy, mastectomy and BCS alone and discusses some possible reasons causing differential outcomes to occur;

3. Chapter 4, as a conclusion, examines some strength and limitations in the study, explains some findings to supplement the discussion of the previous chapters, and points out directions for future research.

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Chapter 2: Treatment variation in patients diagnosed with stage I-III breast cancer in Alberta 2002-2010: a population-based study

Introduction

Standard treatment for breast cancer has changed dramatically in the past decades. Until the early 1980s, mastectomy was the standard treatment[1]. Later reports of clinical trials showed that the overall survival between breast-conserving surgery (BCS) followed by adjuvant radiotherapy and mastectomy was equivalent[2-4]. By 1991, the National Institutes of Health (NIH) consensus conference recognized the equal outcomes of these procedures and recommended that BCS plus adjuvant radiotherapy was a valid option as primary treatment for breast cancer[5]. In the beginning of the 21st century, several studies had found that: 1) women, in general, preferred BCS plus adjuvant radiotherapy over mastectomy due to improved cosmetic results and quality of life[6] and 2) women over 70 years of age with small tumors who were ER/PR positive and received hormone therapy did not have improved survival benefits from radiotherapy after BCS[7-8]. Given all these developments, currently, there are three primary treatment options available for women diagnosed with stage I-III breast cancers: 1) BCS plus adjuvant radiotherapy; 2) mastectomy; and 3) BCS alone (patients who are over 70 years old in stage I with ER/PR positive who receive hormone therapy). Depending on the disease stage and clinical details, patients may also receive hormone therapy and/or chemotherapy before or after the surgery[9].

It remains unclear, however, how these findings and recommendations have been translated into clinical practice. In reality, treatment decisions are made based on various factors, including patients' preference[10], availability and accessibility of treatment resources[11], acceptability upon patients' health conditions[12], social/cultural environments[1], physicians' experience and practice styles[1]. Given these influences, practice patterns vary and sometimes certain groups of patients are at a higher risk of not receiving treatment consistent with guidelines.

Consequently, such patients may be at risk of poorer survival. It is, therefore, of interest for clinical as well as health care utilization purposes to investigate the treatment received along with the factors influencing the receipt of those treatments in an entire patient population.

The primary purpose of this study is to assess the variation of treatment received by all patients diagnosed with stage I-III breast cancers in the province of Alberta, Canada during the years of 2002-2010. The secondary purpose is to investigate factors affecting the treatments received, with a special emphasis on the geography of surgery related to the treatment received. As one of the most economically prominent provinces in Canada, Alberta has a population of approximately 3 million. Given its publicly-funded universal health care system, unequal access for monetary reasons to the care caused by geographical barriers should not exist. Thus, it is important to understand the issues that cause variation in care in order to modify them and improve patients' outcomes

Methods

All female residents of Alberta, Canada, over the age of 18 who were diagnosed with stage I-III breast cancer (International Classification of Diseases for Oncology [ICD-O] code c50)[13] in years 2002 to 2010 and had surgery, were identified from the Alberta Cancer Registry. Notification of cancer cases to the registry is required by law. The Alberta Cancer Registry is a population-based cancer registry and is regularly awarded the highest level of certification by the North American Association of Comprehensive Cancer Registries for the completeness and timeliness of its data collection and reporting[14].

Patients were excluded if: 1) the cancer was not the first primary diagnosis in a given breast; 2) the morphology was not consistent with a solid breast tumor, such as, sarcoma, lymphoma, and hematopoietic morphologies; or 3) the patient had another cancer diagnosed within 6 months prior to their breast cancer (which might influence treatment decisions for breast cancer).

The following demographic, clinical, and treatment information were obtained from the cancer registry: date of diagnosis; age at diagnosis; estrogen and progesterone receptor (ER/PR) status; cancer stage; type of surgery (mastectomy or BCS); geographic region of surgery; receipt of neo-adjuvant and adjuvant chemotherapy; receipt of post-operative radiotherapy; and receipt of hormone therapy. Cancer staging used the American Joint Committee on Cancer (AJCC) 5th edition[15] staging rules for years 2002 and 2003 and the 6th edition[16] for years 2004-2010. The region of surgery was categorized into five geographically-defined administrative health zones of the province. ER/PR status was missing for patients diagnosed in years 2002 and 2003 but we inferred it based on the receipt of the hormone therapy: those who received hormone therapy were classified as ER/PR positive while those who did not receive hormone therapy were classified as ER/PR negative.

Data analyses were performed in two parts. First, the proportion of breast cancer cases who received BCS by stage at diagnosis overall and for each demographic, clinical and treatment factor of interest were calculated; Chi-square tests were used to assess statistical significance of each comparison. Log-binomial regression was then used to calculate stage-specific relative risk (probability ratio) of receiving BCS for the following factors: age at diagnosis; geography of surgery; year of diagnosis; ER/PR status; and neo-adjuvant chemotherapy status. The regression provides relative risk estimates instead of the odds ratios as a measure of association. Standard large-sample statistical inference for generalized linear models was used to construct 95% confidence intervals and significance tests of parameters[17].

The second part of the analysis assessed the relationship of clinical, demographic and treatment factors with receiving radiotherapy after BCS. The same data analysis procedures as above were used for this outcome. In this analysis, hormone therapy combined with ER/PR status as a single variable and adjuvant

chemotherapy status were included in the regression model. Receipt of hormone therapy and ER/PR status were combined to create a single variable since only women who are ER/PR positive should receive hormone therapy. In this variable, patients who were diagnosed in the year of 2002 and 2003 with missing ER/PR status and received hormone therapy were classified into the category of "ER/PR positive& received hormone" and those with missing ER/PR status who did not receive hormone therapy were classified into the category of "ER/PR negative".

All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute, Cary, NC).

Results

A total of 14,952 cases were diagnosed with stage I-III breast cancer and received either BCS (44%) or mastectomy (56%) as their primary surgical treatment in Alberta in 2002-2010. Of those who received BCS, 88% of patients subsequently received adjuvant radiotherapy. The patients' demographic and clinical characteristics and their associations with receipt of BCS are shown in Table 1. The rates of BCS ranged from 17% (stage III) to 57% (stage I). In each stage, the BCS rates were higher amongst younger patients, those who received surgery in an urban area, those with ER/PR positive breast cancers and those who did not receive neo-adjuvant chemotherapy.

Table 2 shows the results of the multivariable log-binomial analysis of BCS use with the factors listed in Table 1. In all stages, younger age at diagnosis and not receiving neo-adjuvant chemotherapy were significantly associated with the receipt of BCS. Geographic variation of receipt of BCS was apparent in all disease stages but was greatest among patients with stage I and II disease. In every disease stage, BCS was most frequent in Calgary and least frequent in Central Alberta, although the geographic variation for patients with stage III disease was only evident in Central Alberta. Relative to those who received surgery in Calgary, those who received it in Central Alberta were 36%, 43%, and

38% less likely to receive BCS for stage I, II, and III disease, respectively, adjusting for age at diagnosis, year of diagnosis, ER/PR status and receipt of neo-adjuvant chemotherapy. For other areas, the chance of receiving BCS, with respect to stage I and II diagnoses, decreased by 17% to 27% in southern Alberta, 5% to 10% in Edmonton and 1% to 28% in northern Alberta compared to Calgary, after adjusting for the aforementioned factors.

Table 3 shows the relationship between breast cancer patient characteristics and receipt of radiotherapy after BCS. The percentage of patients who received radiotherapy after BCS ranged from 83% (stage III) to 89% (stage I). In each stage, the rates of adjuvant radiotherapy were lower among patients older than 80 years old, those diagnosed with ER/PR negative status without hormone therapy received; those who underwent surgeries in rural areas, and those who did not receive adjuvant chemotherapy.

Table 4 shows the results of the multivariable log-binomial regression analysis assessing stage-specific associations between the receipt of post-BCS radiotherapy and factors listed in Table 3. Age greater than 80 years old, ER/PR positive diagnosis without hormone therapy in all stages and receiving adjuvant chemotherapy in stage II and III were significantly associated with not receiving of adjuvant radiotherapy. The analysis did not reveal any significant geographical variations for the receipt of adjuvant radiotherapy at any disease stages but small differences still existed in patients with stage I and II disease.

Discussions

Overall, the proportion of patients receiving BCS among those diagnosed with stage I-III breast cancers in Alberta was 44% (57%, 36% and 17% in stage I, II and III, respectively) and among those who received BCS, 88% (89%, 86% and 83% in stage I, II and III, respectively) subsequently received adjuvant radiotherapy. In the Netherlands, a similar result was reported[19], where 48% of patients received BCS from 2003 to 2006 (63%, 41% and 19% in stage I, II and

III, respectively) and 99% of those who received BCS further underwent adjuvant radiotherapy. In Canada, the proportion receiving BCS was 61% from 2007, ranging from 31% in Newfoundland and Labrador to 74% in Quebec, and the proportion receiving adjuvant radiotherapy after BCS was 87% in 2009, with an inter-provincial range of 76% in Manitoba to 93% in Newfoundland and Labrador[20]. As reported here, the large discrepancies between and within countries on the proportions receiving BCS may suggest a variation on the practice of current standard care.

As the guideline recommended, all patients who received BCS should also receive post-surgical radiotherapy in order to reduce the risk of cancer recurrence. However, the treatment can be omitted, though controversies exist, among those who were diagnosed at an age of 70 or older, had stage I ER/PR positive cancers and received hormone therapy. In our study, we found that patients over the age of 70 and over the age of 80 had reduced chances of receiving BCS and adjuvant radiotherapy, respectively. This might be attributed to the unclear advantage of adjuvant radiotherapy for patients in those age groups when other factors such as tumor characteristics and comorbidities were taken into account. A recent population-based study[22] has found that among patients who had stage I ER/PR positive cancers at 70+ years of age and received hormone therapy and BCS, the benefits of radiotherapy was limited for low- and intermediate-grade disease but significantly high for high-grade disease in the reduction of subsequent mastectomy risk. Another study found that radiation therapy was most effective among those aged 70-79 years without comorbidity (number needed to treat [NNT] to prevent one event = 21 to 22 patients) and was least effective among those aged 80 years or older with moderate to severe morbidity (NNT = 61 to 125 patients)[23].

Neo-adjuvant chemotherapy is considered to be effective for reducing the size of tumor and increasing the number of patients who are then eligible for BCS[24]. Based on the guideline, neo-adjuvant chemotherapy is intended to shrink tumors

greater with a poor tumor to breast ratio with the intent of converting the patient from requiring mastectomy to being eligible for breast conservation. Patients who have multicentric or widely multifocal disease are unlikely to successfully convert to being eligible for BCT. Neo-adjuvant chemotherapy is also used for locally advanced disease, including inflammatory breast cancer[25]. In our study, we found that receiving neo-adjuvant chemotherapy was strongly associated with a lower chance of receiving BCS for patients diagnosed in all stages. This might be due to the indications that it was used for. It is likely that the majority of these patients had neo-adjuvant chemotherapy for locally advanced disease and not as an attempt to achieve breast conservation. Future studies should develop a better understanding on the effect of this therapy in clinical practice.

This study showed considerable geographical variation in the surgical management of stage I-III breast cancers within the publicly-funded healthcare in Alberta. Patients who received surgeries in southern, central and northern Alberta were less likely to undergo BCS than patients treated in Calgary and Edmonton but once patients received BCS, the proportions of receiving adjuvant radiotherapy were very high in all stages and did not vary largely by geography. These findings might be related to the following explanations. First, there are radiation facilities available in the urban areas while there were not in the rural areas. For rural patients who were eligible for BCS, traveling to the nearest facility regularly to receive adjuvant radiotherapy might be a concern. Note that radiotherapy is given 5 times per week up to 5 to 7 weeks and the need to commute over a long distance or find accommodations can therefore make BCS plus radiotherapy less attractive[18,26-29]. In our study, we hypothesize that rural patients who received BCS did not have any concerns on the access of adjuvant radiotherapy and those who had concerns may be selected to receive mastectomy. Further, this concern over the access of radiotherapy might be considered between the surgeons and patients before the surgery, which may explain the varying rates of BCS but not the high and consistent rates of adjuvant radiotherapy across the province. Second, some rural patients wanting breast conservation might be

willing to travel long distances to receive care in large facilities in the urban area. This might occur by patients' own choice or by referral by their physicians from smaller cancer centers to larger cancer centers for various reasons (e.g., patients have complex tumor characteristics)[29]. In our study, healthier patients from rural areas may travel to Edmonton and Calgary for care and those who were less mobile and less healthy may receive treatment from the closest care facilities. Besides our study, geographical variation in the receipt of BCS was also documented in other publicly funded health care systems, such as ones in Netherlands[19] and in Switzerland[18]. This may indicate that the publicly funded health care system does not provide equal care by regions and this, needs to be further investigated in future studies.

Selection bias is a critical problem in epidemiological studies. When it happens, it distorts the results of the study and affects its accuracy and generalizability. Often, the occurrence of the selection bias is associated with the criteria of selecting studied samples (e.g. certain geographical locations or certain population characteristics). A great strength of this study is that it is population-based and included every single patient who was diagnosed with stage I-III breast cancer over an eight-year period. This allowed us to have a large generalizable sample and to perform a stage-specific analysis with complete information to understand the utilization of the two primary treatments among the patients diagnosed in Alberta. The results obtained from this study will be comprehensive, least biased and generalizable to the entire population in Alberta. This cannot be achieved by the non-population based samples in which patients were selected from certain regions and based on certain characteristics.

Although we found large geographical variation in breast cancer treatments in Alberta, this study lacked information to directly assess any further detailed factors behind this finding. The cancer registry provided important data on diagnosis and treatment, but it does not include many variables such as number of surgeons and radiation facilities available, travel distance to the nearest medical

facility and patients' education, employment and marital status in specific geographical locations. If we did have that information in our data base, then the results of our study might provide more comprehensive understanding of the treatment variation existing in this province.

In conclusion, this study identified relatively low rates of BCS but high rates of adjuvant radiotherapy after the surgery in the province, part of which might be attributed to the geographical variation in the receipt of surgery types that was also observed by the study. Thus, future researches should further investigate the issues related to the low rates of BCS and provide better understanding of the geographical variation in the receipt of the treatments. Future interventions should be guided by up-to-date knowledge from research to minimize the deviations from guideline recommendations for current standards of care.

Table 2-1 Characteristics of stage I-III breast cancer cases diagnosed in Alberta in years 2002 to 2010 who received breast conserving surgery (BCS)

	Stage I		Stage II		Stage III	
	BCS	**Total**	**BCS**	**Total**	**BCS**	**Total**
	N (%)[1]	N	N (%)[1]	N	N (%)[1]	N
Overall	4123 (57)	7296	2075 (36)	5691	333 (17)	1965
Age at Diagnosis	**P < 0.001**		**P < 0.001**		**P < 0.001**	
< 50	887 (58)	1535	659 (40)	1651	112 (18)	633
50-59	1187 (63)	1899	589 (41)	1436	102 (20)	513
60-69	1068 (58)	1857	434 (38)	1157	67 (18)	376
70-79	706 (49)	1437	249 (28)	878	27 (11)	257
≥ 80	275 (48)	568	144 (25)	569	25 (13)	186
Geography of Surgery	**P < 0.001**		**P < 0.001**		**P < 0.001**	
South	293 (50)	591	147 (30)	498	25 (17)	147
Calgary	1656 (61)	2720	913 (42)	2190	139 (18)	752
Central	180 (38)	475	112 (23)	478	17 (11)	159
Edmonton	1879 (57)	3288	833 (36)	2283	135 (17)	814
North	115 (52)	222	70 (29)	242	17 (18)	93
Year of Diagnosis	**P < 0.001**		**P < 0.001**		**P < 0.001**	
2002-2004	1287 (55)	2335	633 (36)	1777	86 (16)	528
2005-2007	1335 (57)	2347	673 (36)	1863	125 (18)	711
2008-2010	1501 (57)	2614	769 (38)	2051	122 (17)	726
ER/PR status	**P < 0.001**		**P < 0.001**		**P < 0.001**	
Positive	3786 (57)	6651	1810 (37)	4922	284 (18)	1615
Negative	337 (52)	645	265 (34)	769	49 (14)	350
Neo-adjuvant Chemotherapy	**P < 0.001**		**P < 0.001**		**P < 0.001**	
Not received	4116 (57)	7258	2008 (37)	5402	305 (20)	1547
Received	7 (18)	38	67 (23)	289	28 (7)	418

1. Percentages are column percentages in the number of total cases in each row.

Table 2-2 Adjusted[1] relative risk estimates of receiving BCS rather than mastectomy of women diagnosed with breast cancer in Alberta in years 2002 to 2010.

	Adjusted Relative Risk Estimates (95% Confidence Intervals)		
	Stage I	**Stage II**	**Stage III**
Age at Diagnosis	**P < 0.001**	**P < 0.001**	**P < 0.001**
< 50	1.0 (-)	1.0 (-)	1.0 (-)
50-59	1.08 (1.02, 1.14)	1.03 (0.95, 1.12)	1.10 (0.86, 1.39)
60-69	1.00 (0.95, 1.06)	0.95 (0.86, 1.04)	0.96 (0.72, 1.25)
70-79	0.86 (0.80, 0.92)	0.70 (0.62, 0.79)	0.52 (0.34, 0.75)
≥ 80	0.84 (0.76, 0.92)	0.63 (0.54, 0.73)	0.62 (0.40, 0.91)
Geography of Surgery	**P < 0.001**	**P < 0.001**	**P = 0.30**
Calgary	1.0 (-)	1.0 (-)	1.0 (-)
South	0.83 (0.76, 0.90)	0.73 (0.63, 0.84)	0.93 (0.62, 1.34)
Central	0.64 (0.57, 0.72)	0.57 (0.48, 0.68)	0.62 (0.37, 0.96)
Edmonton	0.95 (0.91, 0.99)	0.90 (0.84, 0.97)	0.97 (0.78, 1.19)
North	0.87 (0.76, 0.98)	0.72 (0.58, 0.87)	0.99 (0.61, 1.49)
Year of Diagnosis	**P = 0.18**	**P = 0.37**	**P = 0.93**
2002-2004	1.0 (-)	1.0 (-)	1.0 (-)
2005-2007	1.04 (0.99, 1.09)	1.03 (0.94, 1.12)	1.05 (0.82, 1.35)
2008-2010	1.04 (0.99, 1.10)	1.06 (0.98, 1.15)	1.04 (0.81, 1.33)
ER/PR status	**P = 0.003**	**P = 0.15**	**P = 0.23**
Positive	1.0 (-)	1.0 (-)	1.0 (-)
Negative	0.90 (0.83, 0.97)	0.93 (0.84, 1.03)	0.85 (0.63, 1.11)
Neo-adjuvant Chemotherapy	**P < 0.001**	**P < 0.001**	**P < 0.001**
Not Received	1.0 (-)	1.0 (-)	1.0 (-)
Received	0.32 (0.15, 0.56)	0.57 (0.46, 0.70)	0.31 (0.21, 0.45)

1. Adjusted for all variables shown in the table.

Table 2-3 Characteristics of breast cancer cases diagnosed in Alberta in years 2002 to 2010 who received radiotherapy after BCS[1].

	Stage I		Stage II		Stage III	
	Post-surgical radiation	**Received BCS**	**Post-surgical radiation**	**Received BCS**	**Post-surgical radiation**	**Received BCS**
	N (%)[2]	N	N (%)[2]	N	N (%)[2]	N
Overall	3652 (89)	4123	1792 (86)	2075	278 (83)	333
Age at Diagnosis	**P < 0.001**		**P < 0.001**		**P < 0.001**	
< 50	827 (93)	887	601 (91)	659	93 (83)	112
50-59	1109 (93)	1187	525 (89)	589	95 (93)	102
60-69	988 (93)	1068	395 (91)	434	58 (87)	67
70-79	608 (86)	706	212 (85)	249	23 (85)	27
≥ 80	120 (44)	275	59 (41)	144	9 (36)	25
Geography of Surgery	**P < 0.001**		**P < 0.001**		**P < 0.001**	
South	239 (82)	293	114 (78)	147	20 (80)	25
Calgary	1500 (91)	1656	793 (87)	913	113 (81)	139
Central	150 (83)	180	90 (80)	112	14 (82)	17
Edmonton	1665 (89)	1879	739 (89)	833	115 (85)	135
North	98 (85)	115	56 (80)	70	16 (94)	17
Year of Diagnosis	**P < 0.001**		**P < 0.001**		**P = 0.01**	
2002 - 2004	1158 (90)	1287	566 (89)	633	78 (91)	86
2005 - 2007	1159 (87)	1335	564 (84)	673	102 (82)	125
2008 - 2010	1335 (89)	1501	662 (86)	769	98 (80)	122
ER/PR Status & Hormone therapy	**P < 0.001**		**P < 0.001**		**P < 0.001**	
ER/PR positive & received hormone	2379 (93)	2565	1417 (92)	1537	215 (90)	240
ER/PR positive & no hormone	961 (79)	1221	155 (57)	273	20 (45)	44
ER/PR negative	312 (93)	337	220 (83)	265	43 (88)	49
Neo-adjuvant Chemotherapy	**P < 0.001[3]**		**P < 0.001**		**P < 0.001**	
Not received	3646 (89)	4116	1732 (86)	2008	258 (85)	305
Received	6 (86)	7	60 (90)	67	20 (71)	28
Adjuvant Chemotherapy	**P < 0.001**		**P < 0.001**		**P < 0.001**	
Not received	2984 (87)	3425	624 (75)	833	54 (56)	97
Received	668 (96)	698	1168 (94)	1242	224 (95)	236

1. Breast conserving surgery
2. The denominator for each percentage is the number of patients who received breast conserving surgery in the adjacent row for the same disease stage.
3. P-value was calculated based on the Fisher's Exact test.

Table 2-4 Adjusted[1] relative risk estimates of receiving radiotherapy after breast conserving surgery of breast cancer patients diagnosed in Alberta in years 2002 to 2010.

	Adjusted[1] Relative Risk Estimates (95% Confidence Interval)		
	Stage I	**Stage II**	**Stage III**
Age at Diagnosis	**P < 0.001**	**P < 0.001**	**P = 0.36**
< 50	1.0 (-)	1.0 (-)	1.0 (-)
50-59	1.00 (0.98, 1.02)	0.99 (0.96, 1.02)	1.02 (0.96, 1.10)
60-69	0.99 (0.97, 1.00)	1.01 (0.99, 1.04)	1.01 (0.91, 1.09)
70-79	0.94 (0.92, 0.97)	1.01 (0.95, 1.04)	1.03 (0.90, 1.11)
≥ 80	0.48 (0.42, 0.55)	0.53 (0.43, 0.64)	0.62 (0.32, 1.03)
Geography of Surgery	**P = 0.05**	**P = 0.05**	**P = 0.87**
Calgary	1.0 (-)	1.0 (-)	1.0 (-)
South	0.96 (0.92, 1.01)	0.94 (0.86, 1.00)	1.03 (0.90, 1.10)
Central	0.96 (0.91, 1.01)	0.96 (0.89, 1.01)	1.03 (0.86, 1.10)
Edmonton	0.99 (0.98, 1.01)	1.01 (0.99, 1.03)	1.03 (0.97, 1.10)
North	0.95 (0.89, 1.01)	0.93 (0.82, 1.01)	1.03 (0.83, 1.12)
Year of Diagnosis	**P = 0.03**	**P = 0.03**	**P = 0.90**
2002 - 2004	1.0 (-)	1.0 (-)	1.0 (-)
2005 - 2007	0.98 (0.96, 1.00)	0.97 (0.94, 1.00)	0.99 (0.93, 1.05)
2008 - 2010	0.99 (0.98, 1.01)	0.98 (0.95, 1.00)	0.99 (0.92, 1.05)
ER/PR Status & Hormone therapy	**P < 0.001**	**P < 0.001**	**P < 0.001**
ER/PR positive & received hormone	1.0 (-)	1.0 (-)	1.0 (-)
ER/PR positive & no hormone	0.88 (0.85, 0.90)	0.69 (0.62, 0.76)	0.62 (0.42, 0.82)
ER/PR negative	0.97 (0.94, 1.00)	0.92 (0.87, 0.97)	0.95 (0.84, 1.03)
Neo-adjuvant Chemotherapy	**P = 0.33**	**P = 0.03**	**P = 0.76**
Not received	1.0 (-)	1.0 (-)	1.0 (-)
Received	0.90 (0.66, 1.22)	1.09 (1.01, 1.14)	1.05 (0.73, 1.51)
Adjuvant Chemotherapy	**P = 0.50**	**P < 0.001**	**P < 0.001**
Not received	1.0 (-)	1.0 (-)	1.0 (-)
Received	1.01 (0.99, 1.02)	1.08 (1.04, 1.12)	1.40 (1.15, 1.89)

1. Adjusted for all variables shown in the table.

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Chapter 3: Survival differences in stage I-III breast cancer patients treated with breast conserving surgery versus mastectomy in Alberta, Canada: a population-based study

Introduction:

Core treatment modalities for breast cancer have been in place since 1990 and are based on clinical trials that evaluated breast conserving surgery (BCS) plus radiotherapy compared to mastectomy alone with respect to survival[1-3]. These trials found that 20-year survival did not differ between these two treatments. Further studies found that: 1) when given a choice, women generally prefer BCS plus radiotherapy over mastectomy[4]; and 2) women over 70 years of age who are ER/PR positive in stage I and receive hormone therapy do not have an additional survival benefit with radiotherapy post BCS[5-6]. Given the above, there are three primary treatment options for women diagnosed with stage I-III breast cancers: 1) BCS plus adjuvant radiotherapy; 2) mastectomy; and 3) BCS alone (patients who are 70 years old or older in stage I with ER/PR positive status and receive hormone therapy)[5-6]. Depending on tumor characteristics, patients may also receive hormone therapy and/or chemotherapy, prior to or after surgery[7]. In practice, treatment decisions are made based on various factors including patient preference, feasibility (e.g., it may be inconvenient for the patient to visit a radiotherapy facility due to distance), and presence of co-morbidities. It is, therefore, of clinical interest to investigate the relationship between treatments received in practice and survival following the different treatments in an unselected patient population.

The purpose of this study is to assess the relationship between the treatment received and survival in stage I-III breast cancer patients diagnosed in the province of Alberta, Canada, in 2002-2010. Alberta is a Canadian province with a population of approximately 3 million. The healthcare system is publicly funded; treatments and specialist consults related to cancer are free to patients. A

secondary purpose is to assess factors other than the treatment that are related to survival in this patient population.

Methods

Inclusion/Exclusion Criteria

All women diagnosed with stage I-III breast cancer (International Classification of Diseases for Oncology [ICD-O] code c50)[8] in Alberta, Canada, in 2002 to 2010 were identified and included in the study if the cancer was the first primary diagnosis in a given breast and the patient received either mastectomy or BCS. Cases were excluded if the histology was a hematopoetic malignancy, lymphoma or sarcoma. Patients who had another cancer within 6 months prior to their breast cancer diagnosis or who died within 30 days of their surgery were also excluded.

Data Source

In Alberta, Canada, all hospitals and physicians are required to report cancer cases to the Alberta Cancer Registry. The Alberta Cancer Registry is a population-based registry responsible for documenting information on all incident cancers and all cancer deaths in the province[9]. The information it collects includes cancer type, clinical characteristics of the tumor including histology and stage, initial treatment modalities received and start dates of each, demographics, vital status, and date and cause of death. The Alberta Cancer Registry is regularly awarded the highest level of certification by the North American Association of Comprehensive Cancer Registries for the completeness and timeliness of its data reporting[10].

All data for the study were obtained from the Alberta Cancer Registry. In addition to date of diagnosis and disease stage, data on estrogen receptor and progesterone receptor (ER/PR) status (negative if both ER and PR are negative; positive otherwise), receipt of neo-adjuvant/adjuvant chemotherapy (Yes/No), receipt of radiotherapy (Yes/No) and receipt of hormone therapy (Yes/No) were obtained. Age at diagnosis, type of surgery, geographical location where the surgery was

performed (five health zones of the province), and date and cause of death were also obtained. Surgery type is recorded in the Alberta Cancer Registry based on information abstracted directly from the surgical report. BCS was defined as either lumpectomy or segmental resection, and mastectomy included modified radical mastectomy and total mastectomy.

Statistical Analyses

Three treatment categories were defined based on the type of surgery received in combination with radiotherapy: BCS alone; BCS with adjuvant radiotherapy; and mastectomy. Descriptive statistics were calculated for each disease-stage by the treatment category to describe the cases with respect to demographic and clinical factors considered in the study. Chi-square Test was used to assess the association between the treatment received and each demographic and clinical characteristic in each stage.

Unadjusted all-cause mortality by the treatment category was assessed using Kaplan-Meier curves[11] and unadjusted breast-cancer-specific mortality by the treatment category was assessed using cumulative incidence curves. The Log-Rank Test[12] was used to assess differences in overall survival and Gray's Test[13] was used to assess differences in breast-cancer-specific mortality by the treatment category for each stage of diagnosis. The cumulative incidence analysis treats death by causes other than breast cancer as competing risks.

Cox Proportional-Hazards models[14] were used to assess the association of all-cause mortality and breast-cancer-specific mortality adjusted for age at diagnosis, surgery location/geography, ER/PR status, hormone therapy, neo-adjuvant/adjuvant chemotherapy and the treatment category. All patients were followed to the earlier of date of death or December 31, 2011. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute, Cary, NC).

Results:

There were 14,939 patients included in the study; 7,292 with stage I, 5,686 with stage II and 1,961 with stage III breast cancer. The median follow-up time was 4.2 years (range 0.1 years to 10.0 years), and the total person-years of follow-up were 66,550. By the end of follow-up, 7%, 15% and 27% of patients of stage I, II, and III breast cancer, respectively, had died.

Tables 1, 2, and 3 show the characteristics of breast cancer patients in relation to their treatment for stages I, II, and III, respectively. Consistent with treatment guidelines, only a small minority of patients received BCS without radiotherapy, 3-6% depending on the stage. The proportion of cases who received BCS plus adjuvant radiotherapy (50%, 32%, and 14% for stage I, II, and III, respectively) decreased with increasing stage. The proportion of cases who received BCS plus adjuvant radiotherapy was highest amongst younger patients, patients who received surgery in an urban area, patients with ER/PR positive breast cancer and patients who did not receive neo-adjuvant chemotherapy but received adjuvant chemotherapy and/or hormone therapy.

Figure 1 describes all-cause mortality by the treatment category for each stage. In stage I, the number of overall deaths with respect to each treatment were 257 (8.1%) for mastectomy, 180 (4.9%) for BCS plus adjuvant radiotherapy and 95 (20.2%) for BCS alone. In stage II and III, the number of overall deaths for each treatment were 608 (16.8%) and 479 (29.4%) for mastectomy, 158 (8.8%) and 40 (14.4%) for BCS plus adjuvant radiotherapy, and 76 (27.0%) and 12 (22.2%) for BCS alone, respectively. The survival probability differed ($p<0.001$) by treatment category in all stages. Specifically, the survival probability was significantly higher for those who received BCS plus adjuvant radiotherapy than those who received mastectomy or BCS alone in all stages. Additionally, the survival probability of patients who received mastectomy was higher than that of patients who received BCS alone in stages I and II, but similar in stage III ($P < 0.001$ in stage I , $P < 0.001$ in stage II and $P = 0.61$ in stage III); only 54 stage III patients received BCS alone.

Figure 2 shows the cumulative incidence of breast-cancer-specific mortality by treatment category for each stage. In stage I, the number of breast cancer deaths with respect to each treatment were 72 (2.3%) for mastectomy, 65 (1.8%) for BCS plus adjuvant radiotherapy and 19 (4.0%) for BCS alone. In stage II and III, the number of breast cancer deaths for each treatment were 326 (9.0%) and 372 (22.8%) for mastectomy, 96 (5.4%) and 31 (11.2%) for BCS plus adjuvant radiotherapy, and 28 (10.0%) and 5 (9.3%) for BCS alone, respectively. The breast-cancer-specific mortality differed significantly by treatment category in all stages ($P = 0.003$ in stage I, and $P < 0.001$ in stages II and III). Consistent with the survival curves, stage I patients who received BCS alone had appreciably higher breast-cancer-specific mortality than patients who received either of the other two treatments, while, stage II patients who received either BCS alone or mastectomy had appreciably higher breast-cancer-specific mortality than those who received BCS plus radiotherapy. Stage III patients who underwent mastectomy had significantly higher breast-cancer-specific mortality than those who received BCS plus radiotherapy.

Table 4 shows the results of Cox regression assessing the all-cause mortality by treatment category adjusted for all factors listed in Tables 1-3. In all stages, the treatment category, age at diagnosis, geography of surgery, the combination between ER/PR status and hormone therapy and adjuvant chemotherapy had strong associations with the hazard of all-cause mortality. Specifically, stage I and II patients who received mastectomy (HR = 1.24, 95% CI = (1.01, 1.50) for stage I; HR = 1.47, 95% CI = (1.22, 1.76) for stage II) or BCS alone (HR = 2.45, 95% CI = (1.87, 3.20) for stage I; HR = 1.90, 95% CI = (1.42, 2.55) for stage II) had higher mortality, compared to those who received BCS with adjuvant radiotherapy, after adjusting for the factors in Table 4. For stage III patients, mastectomy was associated with increased hazard of death (HR = 1.86, 95% CI = (1.34, 2.58)), relative to BCS plus radiotherapy. There was a suggestion of geographic variation in all-cause mortality, however the difference was

marginally or not statistically significant; stage I cases who received surgery in Central Alberta had a higher all-cause mortality than those in Calgary with a hazard ratio of 1.40 (95% CI = (1.01, 1.93)). Stage II patients who received surgery in Southern Alberta and Northern Alberta had hazard ratios of 1.25 (95% CI = (0.99, 0.57)) and 1.33 (95% CI = (0.98, 1.82)), respectively, relative to those who received surgery in Calgary.

Table 5 shows the results from Cox regression examining the breast-cancer-specific mortality by the treatment category and factors listed in Table 1-3. The adjusted breast-cancer-specific hazard of mortality for patients who received mastectomy was not statistically different from those who received BCS plus adjuvant radiotherapy in stage I (HR = 1.04, 95% CI = (0.74, 1.47)), but in stage II and III, the hazards of mortality for patients who received mastectomy were significantly higher (HR = 1.51, 95% CI = (1.19, 1.91) in stage II and HR = 1.94, 95% CI = (1.33, 2.81) in stage III). BCS alone was associated with an increased hazard of breast-cancer-specific mortality in stages I and II, relative to BCS plus radiotherapy. Also, in stage I, patients who received surgery in Central Alberta had 2.01 times (95% CI = (1.17, 3.44)) higher hazard of breast cancer death than patients who received surgery in Calgary, but in stage III, patients who received surgery in Edmonton had a slightly reduced hazard of breast cancer death (HR = 0.77, 95% CI = (0.61, 0.97)) as opposed to those treated in Calgary.

Discussions

This study found that receipt of mastectomy was associated with increased hazards of all-cause mortality among patients with stage I-III breast cancers and breast-cancer-specific mortality among patients with stage II and III breast cancers, relative to BCS plus adjuvant radiotherapy, after adjusting for several demographic, clinical and treatment factors. This finding is inconsistent with earlier clinical trials[1-3] which showed the equivalence in survival between the two treatment groups. Recently, a study conducted using the California cancer registry showed similar results to ours[15]. It found that, after adjusting for tumor grade,

proportion of nodes positive, race/ethnicity, social economic status, tumor size, age and ER/PR status, the hazard ratios between BCS plus adjuvant radiotherapy versus mastectomy were 0.72 (95% CI = (0.68, 0.76)) for all-cause mortality and 0.84 (95% CI = (0.78, 0.91)) for breast-cancer-specific mortality among patients diagnosed with stage I or II breast cancers (stage III was not included in their study). Such differences between clinical trials and large population-based studies need to be assessed and investigated further. They suggest that the selection/use of mastectomy in practice may be associated with higher risk of mortality in breast cancer patients. One possible explanation is that patients who had breast cancer with aggressive tumor/or more co-morbidities, that are not accounted for in the adjustment variables, were more likely to receive mastectomy. These might include patients who had triple negative tumors (ER negative, PR negative and her 2 negative), her-2 positive tumors, extensive lymphovascular invasion[15] or extranodal extension[15], or co-morbidities such as cerebrovascular disease[15] and chronic respiratory disease[15] or Charlson comorbidity index >=1[16].

In patients with stage II cancer, we found that the adjusted hazard ratios of all-cause and breast-cancer-specific mortality between BCS plus adjuvant radiotherapy and mastectomy were 1.47 (95% CI = (1.22, 1.76)) and 1.5 (95% CI = (1.19, 1.91)), respectively. This might be because the stage II patients who received mastectomy had relatively larger tumor size and more positive lymph nodes than those who received BCS plus adjuvant radiotherapy. As a result, the risk of recurrence for their cancers was higher and led to reduced survival after receiving the mastectomy. Future studies are needed to further investigate this issue.

Clinical trials[1-3] have also shown that not receiving adjuvant radiotherapy after BCS increases the chance of local recurrence and reduced overall survival for early stage breast cancer patients who received BCS. Our findings are consistent with these trials in stage I and II breast cancers. In stage III breast cancer, however, our study did not find that BCS alone had different risks of all-cause

mortality or cancer-specific mortality, relative to BCS plus adjuvant radiotherapy. There were only 54 stage III patients in our study that received BCS alone, however, thus the power for this analysis was low.

In this study, we also found an increased hazard of breast-cancer-specific mortality among stage I patients treated in central Alberta (HR = 2.01, 95% CI = (1.17, 3.44)). However, this finding might be due to chance because the number of stage I patients treated in central Alberta was relatively small and had a greater variability than the regions with a large number of patients; also, the estimate of hazard ratio between mortality and geography of treatment from Cox PH model was a multiplicative effect. If the true difference between the baseline hazard and the hazard of our interest was small, the hazard ratio might still have a very large value; additionally, there were no increments of breast-cancer-specific mortality observed in stage II and III for the same region. If the HR =2.01 in stage I for the central Alberta was true, this would be very difficult to explain. Combing all these explanations, we considered that the increased hazard of breast-cancer-specific mortality in central Alberta among stage I patients was a spurious result. Future studies should be cautious about this issue and ensure the inclusion of the sufficient number of samples in each subgroup before performing any stratified analyses. Our study evaluated every single patient treated with BCS plus adjuvant radiotherapy and mastectomy in Alberta. This represented a significant difference in the studied population when compared with previous clinical trials[1-3]. In clinical trials, patients may be selected from a specific location or based on specific characteristics and the number of the patients participated in the trials are relatively small. Therefore, those patients may not be representative for the general population and the generalizability of the results might be limited. However, in our study, we benefited from the entire breast cancer patients in Alberta with a broad range of demographic characteristics and thus, our results are more representative of the real experience of breast conserving surgery and mastectomy in the breast cancer treatments in this province. Another difference between our study and clinical trials is the length of follow-up time. Breast cancer

patients have relatively long survival therefore having both a large number of patients and a long follow-up time is necessary to give us enough cases to accurately evaluate the survival difference between the two treatments. In our study, we followed every single patient who received BCS plus adjuvant radiotherapy and mastectomy for a total of 66,550.3 person-years. This time length and the size of sample could not be achieved by the previous clinical trials that established the breast cancer surgical treatments. Therefore, the results from our study might be more accurate to reflect the true survival difference between the two treatments in the practice.

While this study was population-based and included a very large number of patients, we were not able to study the impact of additional factors other than the ones available in our data set on the survival difference across the treatment groups. It is critical to understand this difference further (e.g. the influence of receiving BCS plus adjuvant radiotherapy on survival and the reasons for not receiving BCS plus adjuvant radiotherapy) and identify key factors to improve the poorer survival of patients who receive mastectomy.

Table 3-1 Characteristics of **stage I** breast cancer cases that received surgery in Alberta from 2002 to 2010

	Stage I			
	BCS alone	**BCS + adjuvant radiotherapy**	**Mastectomy**	**Total**
	N (%)[1]	N (%)[1]	N (%)[1]	N
Overall	470 (6)	3652 (50)	3170 (43)	7292
Age at Diagnosis[2]				
< 50	60 (4)	827 (54)	648 (42)	1535
50-59	78 (4)	1109 (58)	712 (37)	1899
60-69	79 (4)	988 (53)	788 (42)	1855
70-79	98 (7)	608 (42)	729 (51)	1435
≥ 80	155 (27)	120 (21)	293 (52)	568
Geography of Surgery[2]				
South	54 (9)	239 (41)	297 (50)	590
Calgary	156 (6)	1500 (55)	1063 (39)	2719
Central	30 (6)	150 (32)	295 (62)	475
Edmonton	213 (6)	1665 (51)	1408 (43)	3286
North	17 (8)	98 (44)	107 (48)	222
Year of Diagnosis				
2002 - 2004	129 (6)	1158 (50)	1047 (45)	2334
2005 - 2007	176 (8)	1159 (49)	1010 (43)	2345
2008 - 2010	165 (6)	1335 (51)	1113 (43)	2613
ER/PR status[2]				
Positive	445 (7)	3340 (50)	2862 (43)	6647
Negative	25 (4)	312 (48)	308 (48)	645
Neo-adjuvant Chemotherapy[2]				
Received	1 (3)	6 (16)	31 (82)	38
Not received	469 (6)	3646 (50)	3139 (43)	7254
Adjuvant Chemotherapy[2]				
Received	30 (2)	668 (52)	587 (46)	1285
Not received	440 (7)	2984 (50)	2583 (43)	6007
Hormone Therapy[2]				
Received	186 (4)	2379 (53)	1909 (43)	4474
Not Received	284 (10)	1273 (45)	1261 (45)	2818

1. Percentages are column percentages in the number of total cases in each row.
2. P value from Chi-square test was less than 0.001.

Table 3-2 Characteristics of **stage II** breast cancer cases that received surgery in Alberta from 2002 to 2010

	Stage II			
	BCS alone	**BCS + adjuvant radiotherapy**	**Mastectomy**	**Total**
	N (%)[1]	N (%)[1]	N (%)[1]	N
Overall	281 (5)	1792 (32)	3616 (64)	5686
Age at Diagnosis[2]				
< 50	58 (4)	601 (36)	992 (60)	1651
50-59	64 (4)	525 (37)	847 (59)	1436
60-69	38 (3)	395 (34)	722 (63)	1155
70-79	37 (4)	212 (24)	628 (72)	877
≥ 80	84 (15)	59 (10)	424 (75)	567
Geography of Surgery[2]				
South	33 (7)	114 (23)	351 (70)	498
Calgary	118 (5)	793 (36)	1276 (58)	2187
Central	22 (5)	90 (19)	365 (77)	477
Edmonton	94 (4)	739 (32)	1449 (63)	2282
North	14 (6)	56 (23)	172 (71)	242
Year of Diagnosis				
2002 - 2004	67 (4)	566 (32)	1143 (64)	1776
2005 - 2007	108 (6)	564 (30)	1189 (64)	1861
2008 - 2010	106 (5)	662 (32)	1281 (63)	2049
ER/PR status[2]				
Positive	237 (5)	1572 (32)	3109 (63)	4918
Negative	44 (6)	220 (29)	504 (66)	768
Neo-adjuvant Chemotherapy[2]				
Received	7 (2)	60 (21)	222 (77)	289
Not received	274 (5)	1732 (32)	3391 (63)	5397
Adjuvant Chemotherapy[2]				
Received	74 (2)	1168 (37)	1902 (60)	3144
Not received	207 (8)	624 (25)	1711 (67)	2542
Hormone Therapy[2]				
Received	120 (3)	1417 (34)	2594 (63)	4131
Not Received	161 (10)	375 (24)	1019 (66)	1555

1. Percentages are column percentages in the number of total cases in each row.
2. P value from Chi-square test was less than 0.001.

Table 3-3 Characteristics of **stage III** breast cancer cases that received surgery in Alberta from 2002 to 2010.

	Stage III			
	BCS alone	**BCS + adjuvant radiotherapy**	**Mastectomy**	**Total**
	N (%)[1]	N (%)[1]	N (%)[1]	**N**
Overall	54 (3)	278 (14)	1629 (83)	1961
Age at Diagnosis[2]				
< 50	19 (3)	93 (15)	520 (82)	632
50-59	7 (1)	95 (19)	411 (80)	513
60-69	9 (2)	58 (15)	308 (82)	375
70-79	4 (2)	23 (9)	230 (89)	257
≥ 80	15 (8)	9 (5)	160 (87)	184
Geography of Surgery[2]				
South	5 (3)	20 (14)	122 (83)	147
Calgary	26 (3)	113 (15)	612 (81)	751
Central	3 (2)	14 (9)	142 (89)	159
Edmonton	19 (2)	115 (14)	677 (83)	811
North	1 (1)	16 (17)	76 (82)	93
Year of Diagnosis				
2002 – 2004	8 (2)	78 (15)	442 (84)	528
2005 – 2007	23 (3)	102 (14)	585 (82)	710
2008 – 2010	23 (3)	98 (14)	602 (83)	723
ER/PR status[2]				
Positive	49 (3)	235 (15)	1328 (82)	1612
Negative	5 (1)	43 (12)	301 (86)	349
Neo-adjuvant Chemotherapy[2]				
Received	8 (2)	20 (5)	389 (93)	417
Not received	46 (3)	258 (17)	1240 (80)	1544
Adjuvant Chemotherapy[2]				
Received	12 (1)	224 (20)	860 (78)	1096
Not received	42 (5)	54 (6)	769 (89)	865
Hormone Therapy[2]				
Received	25 (2)	215 (16)	1133 (83)	1373
Not Received	29 (5)	63 (11)	496 (84)	588

1. Percentages are column percentages in the number of total cases in each row.
2. P value from Chi-square test was less than 0.001.

Table 3-4 Adjusted[1] Cox PH model assessing *all-cause* mortality by treatment category for stage I-III breast cancer patients

	Adjusted[1] Hazard Ratios (95% CI)		
	Stage I	**Stage II**	**Stage III**
Treatment Category	**P < 0.001**	**P < 0.001**	**P < 0.001**
BCS + adjuvant radiotherapy	1.0 (-)	1.0 (-)	1.0 (-)
Mastectomy	1.24 (1.01, 1.50)	1.47 (1.22, 1.76)	1.86 (1.34, 2.58)
BCS	2.45 (1.87, 3.20)	1.90 (1.42, 2.55)	0.94 (0.48, 1.83)
Age at Diagnosis	**P < 0.001**	**P < 0.001**	**P < 0.001**
< 50	1.0 (-)	1.0 (-)	1.0 (-)
50-59	1.46 (0.99, 2.16)	1.35 (1.07, 1.70)	1.02 (0.79, 1.32)
60-69	2.36 (1.61, 3.44)	1.50 (1.17, 1.92)	1.04 (0.79, 1.37)
70-79	5.22 (3.61, 7.54)	2.55 (1.95, 3.33)	1.46 (1.07, 1.99)
≥ 80	11.81 (8.01, 17.41)	4.29 (3.25, 5.67)	2.09 (1.48, 2.95)
Geography of Surgery	**P = 0.08**	**P = 0.22**	**P = 0.39**
Calgary	1.0 (-)	1.0 (-)	1.0 (-)
South	1.08 (0.79, 1.47)	1.25 (0.99, 1.57)	0.99 (0.72, 1.37)
Central	1.40 (1.01, 1.93)	1.07 (0.83, 1.36)	1.11 (0.82, 1.50)
Edmonton	1.06 (0.87, 1.29)	1.08 (0.92, 1.26)	0.86 (0.70, 1.04)
North	0.54 (0.28, 1.06)	1.33 (0.98, 1.82)	0.93 (0.61, 1.42)
Year of Diagnosis	**P = 0.87**	**P < 0.001**	**P = 0.003**
2002 – 2004	1.0 (-)	1.0 (-)	1.0 (-)
2005 – 2007	0.95 (0.77, 1.17)	0.66 (0.56, 0.78)	0.86 (0.71, 1.05)
2008 – 2010	1.00 (0.71, 1.38)	0.50 (0.39, 0.65)	0.60 (0.45, 0.81)
ER/PR Status & Hormone therapy	**P < 0.001**	**P < 0.001**	**P < 0.001**
ER/PR positive & received hormone	1.0 (-)	1.0 (-)	1.0 (-)
ER/PR positive & no hormone	1.28 (1.07, 1.54)	1.96 (1.66, 2.30)	2.22 (1.76, 2.79)
ER/PR negative	1.99 (1.44, 2.74)	2.43 (1.98, 2.97)	2.32 (1.86, 2.89)
Neo-adjuvant Chemotherapy	**P = 0.95**	**P = 0.55**	**P = 0.13**
Not received	1.0 (-)	1.0 (-)	1.0 (-)
Received	0.00 (0.00, -)	1.11 (0.78, 1.58)	0.79 (0.59, 1.07)
Adjuvant Chemotherapy	**P = 0.07**	**P < 0.001**	**P < 0.001**
Not received	1.0 (-)	1.0 (-)	1.0 (-)
Received	1.35 (0.98, 1.86)	0.71 (0.58, 0.87)	0.40 (0.30, 0.53)

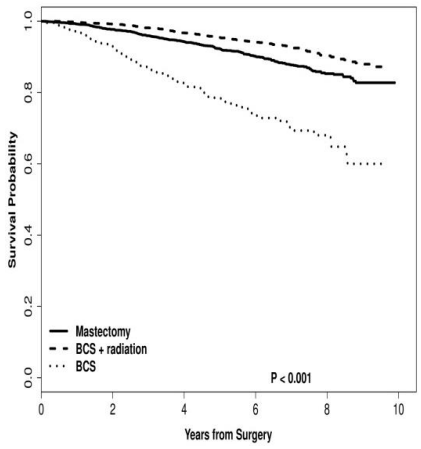
1. Adjusted for all variables shown in the table.

Table 3-5 Adjusted[1] Cox PH model assessing *breast cancer* mortality by treatment category for stage I-III breast cancer patients

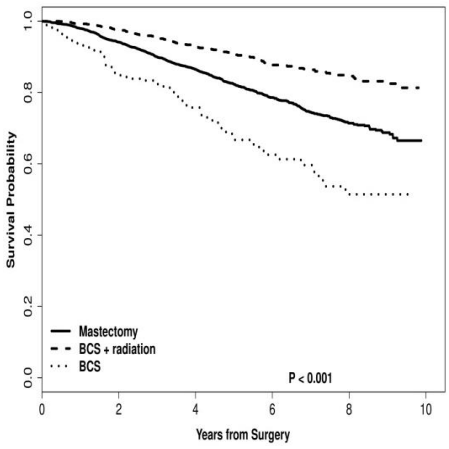
	Adjusted[1] Hazard Ratios (95% CI)		
	Stage I	**Stage II**	**Stage III**
Treatment Category	**P = 0.03**	**P = 0.002**	**P < 0.001**
BCS + adjuvant radiotherapy	1.0 (-)	1.0 (-)	1.0 (-)
Mastectomy	1.04 (0.74, 1.47)	1.51 (1.19, 1.91)	1.94 (1.33, 2.81)
BCS	2.00 (1.16, 3.46)	1.60 (1.03, 2.50)	0.58 (0.22, 1.53)
Age at Diagnosis	**P < 0.001**	**P < 0.001**	**P = 0.45**
< 50	1.0 (-)	1.0 (-)	1.0 (-)
50-59	0.63 (0.36, 1.07)	1.26 (0.97, 1.65)	0.89 (0.68, 1.18)
60-69	1.02 (0.61, 1.70)	1.30 (0.96, 1.76)	0.97 (0.72, 1.30)
70-79	2.07 (1.25, 3.44)	1.89 (1.33, 2.68)	1.19 (0.84, 1.69)
≥ 80	2.78 (1.49, 5.22)	2.46 (1.66, 3.64)	1.29 (0.85, 1.96)
Geography of surgery	**P = 0.09**	**P = 0.76**	**P = 0.26**
Calgary	1.0 (-)	1.0 (-)	1.0 (-)
South	1.37 (0.76, 2.46)	1.18 (0.85, 1.63)	0.93 (0.64, 1.35)
Central	2.01 (1.17, 3.44)	1.01 (0.72, 1.43)	0.87 (0.60, 1.25)
Edmonton	1.13 (0.78, 1.64)	1.04 (0.84, 1.29)	0.77 (0.61, 0.97)
North	0.63 (0.20, 2.03)	1.25 (0.83, 1.90)	0.84 (0.52, 1.36)
Year of Diagnosis	**P = 0.73**	**P < 0.001**	**P < 0.001**
2002 – 2004	1.0 (-)	1.0 (-)	1.0 (-)
2005 – 2007	0.86 (0.58, 1.26)	0.58 (0.46, 0.72)	0.77 (0.61, 0.96)
2008 – 2010	0.93 (0.52, 1.65)	0.37 (0.25, 0.53)	0.52 (0.38, 0.73)
ER/PR Status & Hormone therapy	**P < 0.001**	**P < 0.001**	**P < 0.001**
ER/PR positive & received hormone	1.0 (-)	1.0 (-)	1.0 (-)
ER/PR positive & no hormone	1.41 (0.98, 2.02)	2.21 (1.76, 2.78)	2.26 (1.73, 2.94)
ER/PR negative	4.10 (2.59, 6.47)	3.00 (2.32, 3.87)	2.69 (2.11, 3.42)
Neo-adjuvant Chemotherapy	**P = 0.98**	**P = 0.001**	**P = 0.57**
Not received	1.0 (-)	1.0 (-)	1.0 (-)
Received	0.00 (0.00, -)	1.96 (1.31, 2.92)	0.91 (0.65, 1.27)
Adjuvant Chemotherapy	**P = 0.01**	**P = 0.70**	**P < 0.001**
Not received	1.0 (-)	1.0 (-)	1.0 (-)
Received	1.79 (1.13, 2.82)	1.06 (0.80, 1.39)	0.43 (0.31, 0.59)

1. Adjusted for all variables shown in the table.

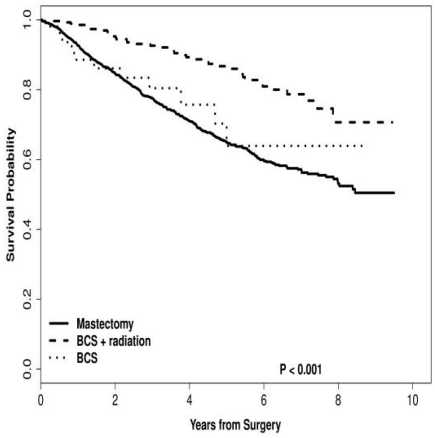
Figure 3-1 Survival probability by treatments received for stage I-III breast cancer patients (time since 30 days after surgery)



(a) Stage I

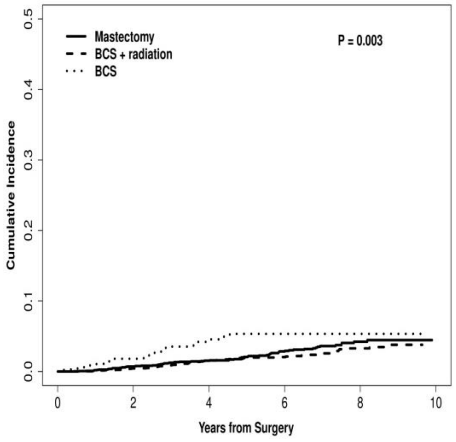


(b) Stage II

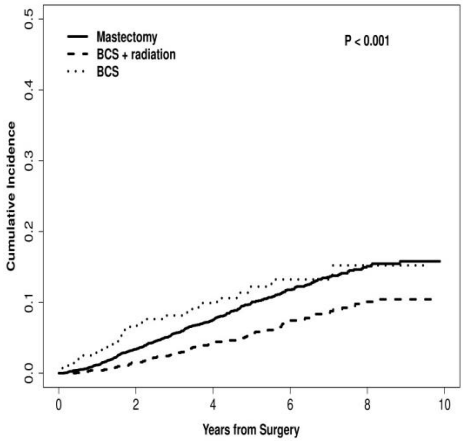


(c) Stage III

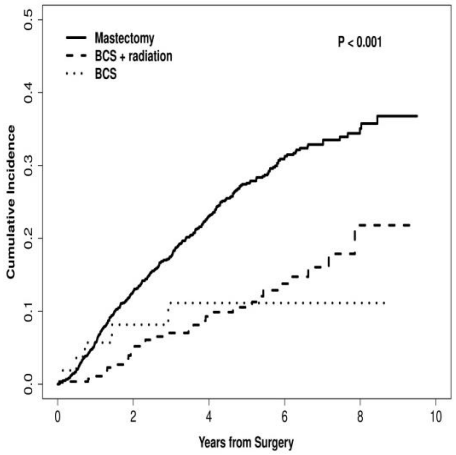
Figure 3-2 Cumulative incidence of *breast cancer* mortality by treatment received for stage I-III breast cancer patients (time since 30 days after surgery).



(a) Stage I



(b) Stage II



(c) Stage III

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Chapter 4: Discussion

Summary of Findings

Of 14,952 cases diagnosed with stage I-III breast cancers in Alberta from 2002 to 2010, 44% received BCS and 56% received mastectomy. Among those who received BCS, the proportion receiving adjuvant radiotherapy was 88%. BCS was performed on 57% of stage I patients, 36% of stage II and 17% of stage III patients. Multivariable regression identified several factors associated with lower chances of receiving BCS. These factors included age of diagnosis greater than 70 years old, surgery received in the South, Central and North areas of the province, ER/PR negative cancer, and receiving neo-adjuvant chemotherapy. Adjuvant radiotherapy was received by 87%, 86% and 84% of patients in stage I, II and III, respectively, after the surgery. For adjuvant radiotherapy after BCS, factors associated with not receiving the treatment included age of diagnosis greater than 80 years old, ER/PR positive status with hormone therapy, and not receiving adjuvant chemotherapy.

For patient outcomes, we identified that, by the end of follow-up, 7%, 15% and 27% of patients had died respectively in stage I, II and III after receiving their primary treatments. Further, we found that, in contrast to clinical trials' results, mastectomy was associated with increased hazards of all-cause death compared to BCS plus adjuvant radiotherapy amongst stage I-III patients and breast-cancer-specific death amongst stage II and III patients. As expected, BCS alone was associated with higher hazards of both all-cause and breast-cancer-specific deaths than BCS plus adjuvant radiotherapy among stage I and II patients; we did not observe this in stage III patients but we note that very few stage III patients received BCS only. In addition to these results, we also identified several factors that contributed to the hazards of patients' deaths from the multi-variable analyses. Those factors included age of diagnosis (patients who were older than 70 years old at diagnosis were more likely to die from any cause or breast cancer than those who were younger), geography of location (patients treated in Central Region were more likely to die from any cause or breast cancer than patients

treated in Calgary in the stage I cancer), interaction between ER/PR status and hormone therapy (patients with ER/PR positive cancers without hormone therapy or with ER/PR negative cancers were more likely to die than those with ER/PR positive cancers who had received hormone therapy) and adjuvant chemotherapy (stage II and III patients who received adjuvant chemotherapy were less likely to die from any cause and breast cancer than those without the therapy; stage I patients who received adjuvant chemotherapy were more likely to die from any cause or from breast cancer than those who did not receive the treatment).

Discussions

In Chapter 2 and 3, we discussed extensively how geographical locations affected patients' treatments received and their associated survival between the two primary treatments. However, we did not provide discussions on the rest of factors that also influence the selection of the therapies. In this section, we'll discuss each of them briefly.

Hormone therapy is one of the standard treatments for ER/PR positive breast cancers as it is designed specially to block the biological effects of estrogen and progesterone hormones which promote tumor growth when they bind to their respective receptors[1]. In our study, we identified a moderate proportion of patients in each stage with ER/PR positive breast cancers who did not receive hormone therapy (stage I: 26%, stage II: 9%, stage III: 7%). In further analyses, those patients had a lower chance of receiving adjuvant radiotherapy after BCS and increased risks of all-cause and breast-cancer-specific mortalities in all stages than those with ER/PR positive breast cancers that received hormone therapy. Another possible reason for not receiving adjuvant radiotherapy is the difficulty in travelling to radiation centers. However, this does not apply to hormone therapy. This may indicate a patient choice to not have any additional therapy, but needs further investigation and potentially may allow an intervention Since these patients were less likely to receive adjuvant radiotherapy after BCS, another explanation may be that some ER/PR-positive patients are subject to under

treatment, especially stage I patients. It would be useful to investigate reasons why these patients did not receive hormone therapy or adjuvant radiotherapy after BCS.

In the previous sections, we found that in all stages, patients who were diagnosed at an age of 70 or older were less likely to receive BCS and patients who were diagnosed at an age of 80 or older were less likely to receive adjuvant radiotherapy after breast conservation surgery. These patients had increased hazards of breast-cancer-specific deaths, as well as all-cause deaths, compared to patients who were diagnosed at an age younger than 50. The difference in treatment may be due to the results from clinical trials regarding the survival equivalence between BCS plus adjuvant radiotherapy and BCS alone for patients at an age of 70 or older and diagnosed with stage I cancer with ER/PR positive status or, the perception among elderly patients that the benefit is not worth the perceived risks (e.g., side effects) or inconveniences (e.g., distance to travel to the nearest radiation facility). For patients with advanced ages, physicians may also not have recommended radiotherapy due to minimal perceived benefit. As to their shortened survival, even the breast-cancer-specific survival, one possible explanation might be that some of the older patients did not have access to certain health care services (e.g. travel a long distance to receive radiotherapy) and support that may be more accessible by younger patients.

In addition to the age at diagnosis, we also found that ER/PR negative status was associated with a lower chance of receiving BCS and adjuvant radiotherapy in all stages of breast cancer. These patients had increased all-cause and breast-cancer-specific mortality rates than patients who had ER/PR positive breast cancers and received hormone therapy. These findings were consistent with the knowledge where ER/PR negative breast cancer is known to be a more aggressive disease and is associated with a higher rate of recurrence and poorer survival than the ER/PR positive breast cancers.[5]

Aside from age at diagnosis, ER/PR status, hormone therapy and neo-adjuvant chemotherapy, this study also identified that receiving adjuvant chemotherapy was associated with a higher chance of receiving adjuvant radiotherapy after BCS in all stages. Patients who received adjuvant chemotherapy had increased hazard of death (both all-cause and breast-cancer-specific) in stage I breast cancer and deceased hazard of death (both all-cause and breast-cancer-specific) in stage III cancer. The improved survival for stage III patients is consistent with the therapy's intent to lower the risk of recurrence and increase survival. It is unclear why adjuvant chemotherapy was associated with higher mortality rates in stage I patients but is likely that higher risk breast cancers were more likely to receive chemotherapy. Based on the guideline, stage I patients who are at higher risk for recurrence and who would be considered for chemotherapy included: 1) those who had tumors that are ER/PR negative status and 3) those who were diagnosed at an age of younger than 35. , or who were her2 positive, we hypothesize that those stage I patients who received adjuvant chemotherapy had a risk of recurrence that was higher than patients who did not receive adjuvant chemotherapy in the same stage. This may cause the stage I patients who received adjuvant chemotherapy to have a higher mortality. This observation needs further investigation.

Strengths and Limitations of the Study

One of the strengths of this study is the use of the population-based cancer registry data. We included every first-ever breast cancer case in women diagnosed in Alberta during the period of 2002-2010 with few exclusion criteria. Doing so provided us with a large generalizable sample of breast cancer patients that allowed stage-specific analyses with complete treatment and diagnosis information. The study helped us understand the utilization of the two primary treatment approaches and their associated survival outcomes among the patient population in the province. It is not possible to obtain accurate estimates of treatment effects in a non-population-based sample in which the patients are selected from specific geographical locations or based on specific characteristics.

Selection bias is a critical problem in epidemiological studies, often leaving socioeconomically-disadvantaged and/or geographically-remote people out of the studies. In Canada, especially in Alberta, there is an excellent cancer registry, and we were able to conduct a population-based health services research study without selection-bias. The information on treatment and survival are also complete and accurate as the data that comprises the Alberta Cancer Registry database are abstracted from the original data sources related to diagnosis and treatment of patients, such as surgical and pathology reports and electronic medical records maintained in cancer facilities. These are the major strengths of this study.

Another strength of this study is the long term follow-up provided by the data. This is particularly important since breast cancer patients generally have long survival. A long follow-up period is therefore required to obtain enough events to obtain precise estimates for treatment effect on survival.

The third strength of this study is the use of log-binomial regression to assess the probability of receiving BCS plus adjuvant radiotherapy or mastectomy. Using this model, we can obtain estimates of relative risk ratios directly from our data and avoid the issues associated with the use of odds ratio estimates from the highly-popular logistic regression: with the use of logistic regression and odds ratio estimates, there are often problems of overestimation of relative risks and misinterpretation of odds ratios[7]. In addition, it is easier for epidemiologists or biostatisticians to communicate with non-specialists using estimates of risk ratios than odds ratios[7].

There are some clear limitations in this study. The cancer registry does not collect information such as patients' comorbidities or socioeconomic status. According to the literature, these factors may affect the receipt of treatments. It would have been ideal if these were collected and accounted for in our analyses.

Future Research

Although this study contributes important information on the disparity of breast cancer treatments for patients diagnosed with stage I-III cancers, there are still many associated questions that remain unanswered. Those questions, as listed below, should be addressed by future investigations.

1) Impact of co-morbidities and socioeconomic status on the selection of the treatments.

As discussed above, previous studies[7-9] found that patients who had multiple co-morbidities, came from low socioeconomic areas, had low education level and/or were unemployed were more likely to receive mastectomy than BCS plus adjuvant radiotherapy in the U.S. Whether these results apply to Alberta was not addressed by this study. It is worthwhile investigating this in the future for more comprehensive understanding as some of the associations we found may be attributable to these factors.

2) More population-based studies on the effectiveness of current treatments for breast cancer patients.

Clinical trials[11-13] showed that BCS plus adjuvant radiotherapy resulted in a similar survival as mastectomy. However, in our study, BCS plus adjuvant radiotherapy showed a better overall survival for stage I-III patients and a better breast-cancer-specific survival for stage II and III patients than mastectomy. Reasons for this discrepancy are needed. Assuming the trial results are correct, our finding implies that mastectomy is offered to patients who have higher mortality, adjusting for the characteristics we controlled for in the analysis. It is unclear why and how this happens. Future population-based studies need to further our knowledge on the choice and effectiveness of the current breast cancer treatments and provide understanding of the discrepancies of the results between the clinical trials and observational studies.

3) More studies towards understanding the role physicians play in presenting treatment options and potential variation in clinician judgement in how they perceive women to be good candidates for one treatment over another.

Although treatment is ultimately the patients decision, all patients do not have the same ability to make independent decisions and all physicians do not present choices in the same way. Therefore, the role that physicians play in presenting treatment options and on how they perceive women to be good candidates for one treatment over another are key factors to understanding treatment variation. However, in this study, we cannot evaluate this perspective. Future research is needed to investigate this issue related to the understanding of the treatment variation in Alberta.

Conclusions

In summary, we identified large geographic variation in treatment patterns among patients diagnosed with stage I-III breast cancer in Alberta, Canada. In addition, we found that those who received BCS plus adjuvant radiotherapy had decreased hazards of all-cause and breast-cancer-specific deaths than those who underwent mastectomy in all stages. However, this finding was inconsistent with the clinical trials[10-13] showing the equivalent survival between these two treatment options. Future studies are needed in order to understand reasons for the discrepant results. Future interventions must be conducted towards reducing the geographic treatment variation and minimizing disparities in survival by minimizing variation of treatment patterns locally and provincially.

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Appendices

Appendix 1: Guideline recommended adjuvant treatment for breast cancers

1. Adjuvant radiation therapy for invasive (i.e. T1-T4) breast cancers[1].

Guideline recommended radiotherapy following breast cancer surgery (e.g. BCS or mastectomy) for patients with invasive breast cancer is presented in the Table 1.

Table A-1[1] Radiotherapy recommendations for invasive breast cancer following surgery

Type of breast cancer	**Surgery**	
	BCS*	**Mastectomy**
T1/T2 and node negative	• Adjuvant WBRT alone (no regional nodal RT) is recommended • Partial breast radiotherapy investigational as part of clinical trial if available, or in very select patients off trial	• No adjuvant radiotherapy recommended, even if resection margins close. Adjuvant RT can be considered when margin positive, but benefit not defined
T1/T2 and node positive	• Adjuvant WBRT recommended in all cases • Regarding regional nodal irradiation (RNI): 1. Isolated tumour cells in nodes (N0 as per TNM staging): RNI not recommended 2. SNB positive micromets without AND: RNI individualized based on risk assessment 3. SNB micromets with completion AND: RNI	• Isolated tumour cells in nodes (N0 as per TNM staging): No adjuvant radiotherapy recommended • SNB micromets without AND: Chest wall with RNI individualized, based on risk assessment • SNB micromets with completion AND: No adjuvant radiotherapy recommended • Macrometastatic nodal disease: Chest wall and RNI

	not recommended 4. Macrometastatic nodal disease: RNI recommended	recommended
T3/T4 and node negative or node positive	• Radiotherapy to breast and RNI recommended	• Radiotherapy to chest wall and RNI recommended
Treated with neoadjuvant chemotherapy	• Radiotherapy to breast recommended regardless of final pathology • Regarding RNI: 1. Clinical stage T1/T2N0: No RNI recommended 2. Clinical stage II (T1/ T2N1 or T3N0): RNI based on consultation with radiation oncologist and degree of pathologic response 3. Clinical stage III/Locally advanced breast cancer (T1-T4N2-3, T3N1): RNI recommended	• Clinical stage T1/T2N0: No adjuvant radiotherapy recommended • Clinical stage II (T1/T2N1 or T3N0): Adjuvant radiotherapy individualized based on consultation with radiation oncologist and degree of pathologic response • Clinical stage III/Locally advanced breast cancer (T1-T4N2-3, T3N1): Chest wall and RNI recommended

***** For margins <2 mm, re-excision recommended (close margins at fascia is an exception); radiotherapy boost recommended in all women <40 yrs regardless of margin; in women >40 yrs, boost individualized based on risk assessment

Glossary of Abbreviations

BCS: Breast conserving surgery

RNI: Regional node irradiation

RT: Radiotherapy

WBRT: Whole breast radiation therapy

2. Adjuvant systemic therapy for lymph node negative and lymph node positive breast cacner[2]

- Systemic therapy for recommendations for lymph node negative breast cancer

Table A-2[2] Risk categories for lymph node negative breast cancer

Risk Category	Risk Factor
Adverse Prognostic Factors	• Age < 35 years • HER2 over-expression (HER2+) • Presence of lymph/vascular invasion • Grade 3 • Hormone receptor negative disease
Lower Risk	• ≤ 2 cm, grade 1, with no other adverse prognostic factors • <0.5 cm with any other feature
Intermediate Risk	- All other combinations of factors that do not fit into either the low or high risk criteria
Higher Risk	• >1 cm with any 2 or more adverse prognostic factors • >2 cm with any 1 or more adverse prognostic factors • >3 cm +/- any adverse prognostic factor • Special consideration for HER2+ breast cancers (see page 5) • Oncotype DX® recurrence score ≥31 for ER+/LN- disease*

* Oncotype DX® testing is currently under evaluation but is not publically funded in Alberta at this time

Table A-3[2] Systemic therapy for lymph node negative breast cancer

	Hormone Receptor (+)	Hormone Receptor (-)
Lower Risk	Observation OR Endocrine Therapy	Observation
Intermediate Risk	Endocrine Therapy +/-	Chemotherapy

	Chemotherapy	
Higher Risk	Chemotherapy + Endocrine Therapy	Chemotherapy
No systemic therapy may be offered to patients in cases where: *• The tumour is less than 1 cm, or* *• The patient has other significant co-morbidities which precludes the safe administration of adjuvant systemic therapy, or* *• The patient has limited life expectancy*		

Table A-4[2] Systemic therapy for lymph node negative breast cancer (continued)

Chemotherapy options for lymph node negative breast cancer	
HER2(-) Lymph Node (-)	
Lower risk: No systemic therapy recommended Intermediate risk: CMF or AC or DC Higher risk: DC or FEC-D or AC or FEC x 6 or CMF	
HER2(+) Lymph Node(-)	
≤ 0.5 cm • ER(-): No adjuvant trastuzumab-based chemotherapy is generally recommended [special considerations may apply] • ER(+): Discuss adjuvant endocrine therapy **>0.5 cm – 1cm** • ER(-): Discuss adjuvant trastuzumab-based chemotherapy • ER(+): Discuss adjuvant endocrine therapy +/- adjuvant trastuzumab-based chemotherapy **> 1 cm** • ER(-): Discuss adjuvant trastuzumab-based chemotherapy • ER(+): Discuss adjuvant trastuzumab-based chemotherapy and adjuvant endocrine therapy	
Chemotherapy options for HER2+ / lymph node negative: • Non-Anthracycline based options – docetaxel / carboplatin / trastuzumab (DCbH x 6) or – docetaxel / cyclophosphamide / trastuzumab (DC/H x 4) • Anthracycline based options	• Non-anthracycline based regimens are preferred if there are cardiac risk factor concerns • Trastuzumab duration =1 year (17 cycles)

– AC x 4, or FEC x 6, followed by sequential trastuzumab, or FEC-DH	

- *Systemic therapy for recommendations for lymph node positive breast cancer*

Table A-5[2] Systemic therapy for lymph node positive breast cancer

	Hormone Receptor (+)	**Hormone Receptor (-)**
HER2 (-)	Chemotherapy + Endocrine Therapy	Chemotherapy
HER2 (+)	Chemotherapy + Trastuzumab + Endocrine Therapy	Chemotherapy + Trastuzumab
No systemic therapy may be offered to patients in cases where: *• The patient has other significant co-morbidities which precludes the safe administration of adjuvant systemic therapy or* *• The patient has limited life expectancy*		

Table A-6[2] Systemic therapy for lymph node positive breast cancer (continued)

Lymph Node Positive Guidelines	
Chemotherapy: • A taxane containing therapeutic regimen is the preferred treatment option in cases of LN+ breast cancer wherever medically appropriate **HER2+ Chemotherapeutic Regimens:** • Concurrent trastuzumab therapy (generally given with taxanes) is preferred to sequential trastuzumab therapy • One year of trastuzumab therapy (17 cycles) is currently recommended	
HER2(+)	**Preferred:** • FEC-DH* or DCbH X 6 * timing of trastuzumab addition (in relation to preceding anthracycline exposure) is at the discretion of the treating physician, in cases where concern about potentiating cardiotoxicity risk exists

	Other Evidence-Based Options: • AC x 4 → (q3 weekly docetaxel or q1 weekly paclitaxel) x 4 and trastuzumab • Any standard adjuvant breast cancer chemotherapy → sequential trastuzumab (as per HERA trial) **Special Considerations:** • If cardiac risk or concern, consider using a non-anthracycline chemotherapy regimen
HER2(-)	**Preferred:** • FEC–D • TAC (with G-CSF support) **Other Evidence-Based Options:** • AC – P (weekly) • DC x 4 • FEC x 6 **Special Considerations:** • if any cardiac risk or concern, consider using a non-anthracycline chemotherapy regimen

Table A-7[2] Systemic therapy for lymph node positive breast cancer (continued)

Endocrine Therapy (for Hormone Receptor Positive Disease only)	
Patient Group	
Pre-Menopausal	**Tamoxifen x 5 years** • In pre-menopausal patients who develop amenorrhea post-chemotherapy: – No clinical trial information is currently available to guide us in the use of AIs in this population as these types of patients were not included in the postmenopausal adjuvant AI trials – Standard hormonal assays and/or monitoring algorithms are currently inadequate or unavailable to ensure that these types of patients are truly postmenopausal while on AIs • In select patients, up to 10 years of tamoxifen therapy may be considered

	• Patients who have had bilateral oophorectomy should be considered to be post-menopausal and treated accordingly • Pending clinical trial confirmation, treatment with ovarian suppression alone with GnRH agonists is not generally indicated in the adjuvant setting, however, may be considered an adjuvant treatment option for pre-menopausal patients who have had hormone receptor positive breast cancer, and are eligible for adjuvant chemotherapy but either: a) decline chemotherapy b) or where chemotherapy is contraindicated c) or have a contraindication to adjuvant tamoxifen
Post-Menopausal	**Options:** • Tamoxifen x 2-3 years → AI x 3-2 years (non-steroidal AI preferred) (total=5 years adjuvant endocrine therapy) **Alternate Options:** • Upfront AI x 5 years (non-steroidal AI preferred) • Tamoxifen x 5 years (if an AI is contraindicated; up to 10 years may be considered for some patients) • In cases of AI intolerance, an alternate AI may be used or the patient can be switched back to tamoxifen (provided that there is no contraindication to do so)
Extended Adjuvant Endocrine Therapy	• For patients with early stage, hormone receptor positive tumours who have completed 5 years of adjuvant tamoxifen [either LN(+) or high risk LN(-)] • Consider AI x 3-5 years after completing 5 years of tamoxifen
	• At this time, no evidence exists for the standard use of fulvestrant in the adjuvant setting

Glossary of Abbreviations

AC: adriamycin + cyclophosphamide

AI: aromatase inhibitors

C: cyclophosphamide

Cb: carboplatin

CMF: cyclophosphamide (oral) +methotrexate + 5-FU

D: docetaxel

DC: docetaxel + cyclophosphamide

DCbH: docetaxel + carboplatin + trastuzumab

DC/H: docetaxel + cyclophosphamide + trastuzumab

FEC: 5-FU + epirubicin + cyclophosphamide

FEC-D: FEC x 3→ D x 3

H: trastuzumab (Herceptin ®)

P: paclitaxel

TAC: docetaxel + adriamycin + cyclophosphamide

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Appendix 2: Copy Method and Log-binomial Regression

In the log-binomial regression, one models the probability of the binomial event (Y=1) as:

$$P(Y = 1| X_1, X_2, \ldots, X_k) = e^{Xb}$$

where $Xb=b_0+b_1X_1+b_2X_2+\ldots+b_kX_k$. Then $\exp(b_1)$ = relative risk (RR) or prevalence ratio (PR) for a 1 unit increase in X_1, adjusted for the other covariates. Since $P(Y=1| X_1, X_2, \ldots, X_k)$ is a probability (ranging from 0 to 1), the log-binomial model has a restriction on the set of parameters b such that $Xb \leq 0$. For many situations (e.g. having continuous covariates), the maximum likelihood estimators (MLE) will be on the boundary of this restricted parameter space. When using standard software packages (e.g. SAS, STATA, R and SPSS), the model might fail to converge because the maximum likelihood solution occurs on the boundary of the parameter space (which means the derivative of the likelihood at its maximum may not be 0).

Deddens *et al.*[1,2] developed a method to modify the data set in order to get approximate MLEs by using the standard software packages. This method, named COPY method, involves modifying data set that contains c copies of the original data and one copy of the original data with the values of the interested events interchanged (1's changed to 0's and 0's changed to 1's) to get approximate MLEs when the log-binomial regression does not converge. The advantage of this method is that when giving a specific quantity of c, the solution of maximum likelihood is no longer on the boundary, and, as c becomes large, the MLE estimates for this modified data set approach the MLEs for the original data set. The larger c is, the better the approximation, but the slower the method executes. The number c should be at least 100. In Deddens *et al.*[1,2], c=1000 was used. Lumley *et al.*[3] pointed out that this method equivalent to creating a new data set which includes one copy of the original data set (with weight 999) and one copy of the original data set with the interested event values interchanged (with weight 1), and then performing a weighted log-binomial regression. This weighted log-

binomial approach has the advantage that it can be computed faster than the COPY method to obtain the MLEs.

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Appendix 3: Difference between risk and rate in survival analysis[1]

1. Difference on the basic concept

In epidemiology, risk is defined as a probability of developing an event of interest among the studied population over a specified period of time whereas rate measures the frequency of the event of interest among the population at risk over a specific time period.

Mathematically, risk can be estimated by the number of the event divided with the initial population who was included in the study and it has a range from 0 to 1. Rate was calculated as the number of events divided by the total person-time among the population at risk over the specified time period. The range of rate can be spanned from 0 to infinity according to the unit of time (e.g. per 100,000 population).

The concept of risk and rate represent two different perspectives to describe the occurrence of the event of interest. Risk is often considered as the chance of developing the event whereas rate is reflected as the rapidity or frequency for the occurrence of the event. Risk does not include the dimension of time but rate does. It is up to the types of research questions to determine their applications in practice.

2. Difference in the setting of survival analysis

In survival analysis, a measure of the time-to-event process that corresponds to the concept of rate is hazard rate. It is described as the "instantaneous rate" for the event of interest (i.e. when the person-time at the denominator approaches to 0) at a specific time among those who survived up to that time point. Cumulative incidence, on the other hand, represents the risk measure for the event of interest. It quantifies a proportion of subjects who experienced the event of interest in a defined time period.

In survival analysis, a subject who did not experience the event of interest up to a specific time is considered that subject survived up to that time point and was at risk of developing the event. When a study has only one type of event (i.e. the event of interest), the cumulative incidence was determined solely by the hazard rate of that event. If a particular event has a high hazard rate, the cumulative incidence for that event is also high.

When a study has more than one type of events and these events are dependent, competing risk events are present. This type of events will preclude the occurrence of the event of interest or change the probability associated with the event of interest. Therefore, survival to a certain time point will depend not only on the hazard rate of event of interest but also on the hazard rates of competing risk events. These hazard rates are also referred to as cause-specific hazard rates, in which they were depicted as the "instantaneous rates" due to their respective causes (e.g. event of interest or competing risk events) at a given time among those who experienced neither the event of interest nor the competing risk events up to that time point. Thus, in the presence of competing risk events, the cumulative incidence will depend on the cause-specific hazard rate for the event of interest as well as the cause-specific hazard rates for the competing risk events. Since those who experienced events before a given time can no longer develop any further events of interest, they will be excluded from the risk set of the subjects for the event of interest.

3. Risk and rate regression models

The most common type regression model used for finding the relationship between a covariate and the occurrence of events (in terms of hazard rate) is Cox Proportional Hazards (PH) model. When the competing risk events are present, Cox PH model can be constructed for the cause-specific hazard rate for the event of interest. The standard form of Cox PH model to the cause-specific hazards is

$$\lambda_j(t, X) = \lambda_{j0}(t)e^{(X'\beta)}$$

where X is a vector of covariates, $\lambda_{j0}(t)$ is the baseline hazard rate for a specific event of j and $e^{(X'\beta)}$ measures a relative change of hazard rates for a specific event of j when there is one unit increase/decrease in an underlying covariate. At different time points, $\lambda_{j0}(t)$ changes accordingly; but for $e^{(X'\beta)}$, it remains as a constant regardless how time will change.

In the measurement of cause-specific hazards, Cox PH model treats the competing risk events as censored observations. This is because once subjects who experienced the competing risk events will no longer be able to develop the event of interest, thus, these subjects, like censored individuals, terminate the at-risk status of developing the event of interest. This technique provides valid statistical inference on the cause-specific hazard rate for the event of interest.

Fine and Gray[2] proposed a regression approach that models the hazard-rate-like quantity for the cumulative incidence of the event of interest when the competing risk events are present. They defined a "subdistribution hazard" by:

$$\lambda_j^*(t) = \lim_{\Delta t \to 0} P(T \in [t, t+\Delta t] \text{ and } J = j | T \geq t \text{ or } (T < t \text{ and } J \neq j)\}/\Delta t$$

where T is time to the first failure which measured from time 0 and J is the event indicator. This hazard is actually not a proper hazard function as its cumulative distribution can never be 1 when t increases, thus, the interpretation of this subdistribution hazard as *rate* is not appropriate.

Similar to the Cox PH model, Fine and Gray's subdistribution proportional hazards model is defined as

$$\lambda_j^*(t, X) = \lambda_{j0}^*(t) e^{(X'\beta)}$$

where $\lambda_{j0}^*(t)$ is the baseline subdistribution hazard for event j and $e^{(X'\beta)}$ measures relative changes on the subditribution hazards associated with covariates.

Unlike the cause-specific hazard where its risk set contains only individuals who did not experience any events to time t, the subdistribution hazard includes

subjects who did not experience any events but also those who had competing-risk events to time t even if those subjects cannot develop the event of interest any further. Fine and Gray noted that the risk set associated with the subdistribution hazard is "unnatural", however, we can think of those individuals as an observed "placeholder" for the proportion of the population that cannot have the event of interest.

References

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2. Fine, J. P. and Gray, R. J.. 1999. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association.* 94(446) pp. 496-509.