Population-based studies in sarcoma research

By

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THESIS ABSTRACT

Many study designs are used to provide the answers needed to further the care of orthopedic oncology patients. Underlying these differing study designs, are different data sets. The data sets vary in their size and scope, from single center to population-based, and from provincial to international. They vary in their follow-up time, from years to decades. They vary in the variables included, the fidelity and precision of each variable, and the granularity of detail. This thesis explores the use of population-based studies as a source of data on orthopedic oncology patients, and provides two studies as an example.

We make use of the large administrative data collected from every soft tissue sarcoma (STS) patient in Ontario over 23 years by the Institute of Clinical Evaluative Sciences (ICES) to answer two questions only possible with population-based studies. Using this large cohort (n=8,896) we provide for the first-time answers to 1) Given the multidisciplinary treatment of sarcoma patients, how are Ontario sarcoma patients being treated in our universal healthcare system, and, have treatment strategies changed over the past 10 years? 2) What are the long-term survival outcomes of Ontario sarcoma patients? Do these outcomes differ for rural or low-income patients?

These studies have engendered international collaborations which are also described. Overall, this thesis explores research questions that are possible to address with population-based data. Through two studies, we aim to provide accurate and clinically useful information that can hopefully be used to better the outcomes of sarcoma patients, both in Ontario and internationally.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank Dr Michelle Ghert, my primary research supervisor and the most significant research influence in my life. Your support and guidance has made all of this work possible. I look forward to many future successful collaborations.

I would like to thank all the other members of my thesis committee.

Dr Hsien Seow, you made it possible to acquire ICES data. We went through many rounds of edits together, through which the papers always improved. Thank you for helping to launch my journey as a data scientist and graduate researcher.

Dr Greg Pond, we reviewed countless statistical tests and results together, many on papers not included in this thesis. Thank you for furthering my understanding of how to properly apply statistical tests and how to think about displaying the results.

Dr Jim Reilly and Dr Kiret Dhindsa, thank you for providing guidance on the application of deep neural networks and other machine learning algorithms. Neural networks will change medical research and we will continue to work together on our project predicting fracture risk from metastatic bone disease.

I would like to thank the MacOrtho program, the Clinician-Investigator Program and the Department of Surgery for their support.

I would like to thank the New Investigator Fund and the Regional Medical Associates Research Scholarship for their support.

I would like to thank the STEM fellowship at McMaster for the opportunity to mentor Jiawen Deng, Umaima Abbas, Richa Bhasin, Marisa Deodat, and Sajid Wariach. The opportunity to take the research skills acquired during my graduate studies and apply them to teaching this group was immensely rewarding and invigorating.

As always, nothing I do would be possible without the love and support of my family. They raised me into the man I am today. Even now when I am living 6 hours away in another province, they make sure my fridge is full and my mind and heart are calm and happy. Ma, Pa, Richie, love you forever.

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GLOSSARY OF ABBREVIATIONS

AJCC – American Joint Committee on Cancer

CCO - Cancer Care Ontario

CIHI Canadian Institute for Health Information

DAD - Discharge Abstracts Database

EORTC - European Organization for Research and Treatment of Cancer

ESMO - European Society of Medical Oncology

HiREB - Hamilton Integrated Research Ethics Board

ICD10 – International Classification of Diseases 10th Edition

ICES – Institute for Clinical Evaluative Sciences

IQR – Inter-quartile Range

MOHLTC - Ministry of Health and Long-Term Care

NACRS - National Ambulatory Care Reporting System

OCR - Ontario Cancer Registry

OHIP - Ontario Health Insurance Plan

OICR - Ontario Institute for Cancer Research

RECORD - REporting of studies Conducted using Observational Routinely-collected Data

RPDB - Registered Persons Database

SEER - Surveillance, Epidemiology, and End Results

STROBE - Strengthening the Reporting of Observational Studies in Epidemiology

STS – Soft Tissue Sarcoma

CHAPTER 1: BACKGROUND

This chapter will describe in detail the Epidemiology, Treatment, Outcomes and Surveillance strategies for soft-tissue sarcoma (STS) patients.

Sarcoma - Epidemiology

Sarcomas are a rare and varied group of malignancies arising from mesenchymal cells [1]. They comprise 1% of adult cancers and up to 8% of pediatric cancers [1, 2]. Data from a European population-based study has placed the prevalence of STS at around 2.4 cases per 100,000 people [3]. They noted that annual incidence has remained constant over a 20 year period [3]. An American study reported increasing incidence, posited to be due to better screening and reporting. However, their study also included Kaposi sarcoma, an aggressive disease associated with acquired immunodeficiency syndrome (AIDS) and following considerably different diagnosis, management, and prognosis than most sarcomas [4]. As per most prior sarcoma research, the studies in this thesis do not include Kaposi sarcoma, or the other diseases not representative of soft tissue sarcomas such as visceral, bone, and uterine sarcomas, gastrointestinal stromal tumors, and mesotheliomas [5]. STS is noted to increase considerably in each decade of life, from 0.9/100,000 in children younger than 10 years of age to 18.2/100,000 in adults over the age of 70 [6].

Risk Factors

While most sarcomas are sporadic and without identifiable causes, some genetic disorders involving alterations to tumor suppressing genes are associated with sarcomas [7]. A germ-line mutation in the RB1 tumor-suppressor gene that causes hereditary retinoblastoma also confers a high risk of osteosarcoma and soft-tissue sarcoma [8]. Germ-line mutations in the p53 tumor-suppressor gene that cause Li–Fraumeni syndrome also confer higher risk of childhood soft-tissue sarcomas [9].

Patients with AIDS are well known for their risk of developing Kaposi's sarcoma, but they are also at increased risk of Leiomyosarcoma following an Epstein-Barr viral infection [10]. Furthermore, patients with neurofibromatosis type 1 have a 10% lifetime risk of malignant tumors of the peripheral-nerve sheath [11]. While radiation therapy for lymphoma, testicular tumor, cervical cancer and breast cancer is associated with radiation-induced sarcoma, the benefits of radiotherapy in these patients greatly outweigh the risk of malignant transformation [12].

Sarcoma - Treatment

Over 50 subtypes of STS are defined by the World Health Organization [13]. Concordantly, histologic confirmation of sarcoma subtype and systemic staging are required before treatment is initiated. Function-preserving limb salvage surgery with reconstruction has been the standard of care for extremity sarcomas since the 1990's, following a randomized trial showing equal disease-free survival and overall survival in patients treated with amputation or limb-salvage and radiotherapy [14]. There is evidence to support the treatment of sarcoma patients in specialized multi-disciplinary centers [15, 16]. Cohort studies of several hundred patients have shown that adherence to treatment protocols can vary based on the volume of the treating center [17]. Retrospective analysis showed that treatment at non-specialized centers from 1986-1992 was associated with positive margins after surgical resection and a reduced likelihood of radiotherapy [18]. Recently, additional international studies have also called for the treatment of STS patients in large specialized centers [19, 20].

Adjuvant therapy

Radiation therapy is supported by an RCT demonstrating significantly better local control compared to surgery alone, especially in higher grade disease [21]. It can be administered either pre-operatively (50Gy) or post-operatively (66Gy). A randomized controlled trial comparing pre-op and post-

op radiation therapy in 190 patients found no difference in local control, recurrence-free survival and overall survival [22]. Analysis of adverse events from that same trial showed that post-operative radiation has higher, but not statistically different, rates of fibrosis, edema and joint stiffness than pre-operative radiation [23].

Chemotherapy as an adjuvant therapy for STS is controversial and not typically used for curative intent. Chemosensitivity varies between STS subtypes [24], and meta-analyses have failed to demonstrate a benefit in overall survival [25]. Even within a given subtype, chemosensitivity varies by tumor grade, stage, patient age and performance status [24]. The chemosensitivity of STS subtypes has also been shown to vary based on their location on the body. For example, Angiosarcoma on the face and scalp is most sensitive to paclitaxel, while angiosarcoma at other locations is most responsive to taxanes [26]. Similarly, the sensitivity of leiomyosarcoma to chemotherapeutic agents varies based on its location on the body [1].

Despite these challenges, some have described a pre-operative role for chemotherapy. If the tumor is deemed to be responsive to chemotherapy, then marginal as opposed to radical resection may be considered for difficult anatomical areas [27]. For inoperable sarcomas, chemotherapy may be used to delay disease progression or manage associated symptoms [27]. The combination of Ifosfamide and doxorubicin has been used as palliation in patients with unresectable or metastatic disease [1].

Sarcoma - Outcomes

Survival following surgery for sarcoma is strongly associated with the stage of disease at presentation and whether negative margins were obtained [28-31]. In a single center cohort study of 2084 patients, the risk of local recurrence doubled and the risk of death increased 50% with positive margins [30].

Survival estimates have been provided both by single center cohort studies and population-based studies and these estimates have generally agreed. The Journal of Clinical Oncology published a single-center study of 2123 patients treated at Memorial Sloan Kettering and reported the following broad survival outcomes, “Five-year survival rates for stages I, II, III, and IV are approximately 90, 70, 50, and 10 to 20 percent, respectively, and are further modified by the type and site of the tumor and other factors” [32].

Recently the survival rates specific for STS patients with advanced disease, either synchronous or metachronous metastasis, were observed over a 20-year period. The authors found that overall median survival improved 50% over the 20 year study period, from 12.3 months (95%CI: 9.9-14.7) from 1987-1991 to 18.0 months (95%CI: 15.3-20.7) from 2002-2006 [33]. However, an American study including patients with localized STS over a similar time period observed a non-significant improvement in 5-year survival from 79% (1982-1986) to 85% (1997-2001) [34].

SEER database studies have observed a 66% 5-year survival rate overall with a consistent inverse relation with age [6]. Five-year survival of 79% was observed for 20-29 year-olds with decreasing survival in every decade until 56% survival was observed for patients aged 70 and over [6]. This may be explained by decreased ability to tolerate more aggressive local and systemic treatment with advanced age [6].

This mix of population-based data and cohort studies from some of the busiest international sarcoma centers converges on STS survival estimates of around 75% at 5 years and 50% at 10 years for localized disease and % at 5 years and % at 10 years for advanced disease. Given the abundance of STS subtypes, and the well-known effect of stage, grade and other variables on prognosis, the studies providing survival estimates differ in the characteristics of their included patients. Clinicians and researchers seeking to counsel patients on prognosis would be well served to place increased emphasis on studies with an appropriately representative population.

Gaps in the current literature

Given the low prevalence of STS, a 2017 study found that the average level of evidence presented at the MSTS annual meeting remains single center level III evidence [35]. Despite this, some randomized trials have contributed to the evidence supporting the optimal surgical and adjuvant treatments for STS patients. A review of trials conducted in sarcoma care found that 75% assessed chemotherapeutic interventions, 20% assessed radiation therapy, and only 5% trial assessed surgical interventions [36].

Sarcoma is a disease with multi-disciplinary treatment involving surgeons, medical oncologists and radiation oncologists. To date, no study has assessed the treatment regimens of sarcoma patients in a country with universal healthcare. For instance, we do not know if patients with localized disease are mainly treated with surgery alone or the combination of surgery and radiation, and if treatment practices are changing over time. Furthermore, we do not have population-based estimates of survival after sarcoma in Canada, nor any estimates in the 15-20 year range.

CHAPTER 2

Data Sources

Population-based studies

Canadian Institute for Health Information (CIHI) - Discharge Abstracts Database (DAD)

The CIHI-DAD contains information on demographic and administrative data for hospital admissions and day surgeries throughout Ontario. This database has been previously validated. A high degree of accuracy for demographic data and procedures was demonstrated, whereas the accuracy of coding for diagnoses was variable [37].

National Ambulatory Care Reporting System (NACRS)

Information on post-operative surveillance is found in the NACRS database which contains information on patient visits to hospital and community-based ambulatory care facilities. Encounters that are captured include day surgery, emergency department visits, and outpatient clinic visits.

Ontario Health Insurance Plan (OHIP)

The OHIP database contains all claims made by physicians and other health care providers for insured services provided to the residents in Ontario. Each record is unique for a specific service provided to a specific person on a specific day. The record contains information on the date and type of service provided, diagnosis, provider and patient identification, the associated fee code, and the total fee paid to the provider [38].

Ontario Cancer Registry (OCR)

The OCR is a population-based tumour registry initiated in 1964 and maintained by Cancer Care Ontario. The registry passively obtains data from pathology reports on all cases where there is a diagnosis of cancer, as well as patient records from designated cancer-specialty treatment centers. Any hospital admissions and day surgery cases with a diagnosis of cancer and reports of deaths from cancer from the Registrar General in Ontario are included [39]. The OCR is estimated to capture over 95% of all cancer cases [40] and has been validated in breast cancer, with the reported cause of death shown to have 95% sensitivity, 86% specificity, 86% positive predictive value, and 95% negative predictive value [41].

Registered Persons Database (RPDB)

The RPDB is a registry maintained by the Ministry of Health and Long-Term Care in Ontario. This database has demographic information on all residents of Ontario including date of birth, gender, address, and date of death (if applicable) [38]. This database is also used to derive a patient's socioeconomic status which is estimated by linking an individual's postal code data with Canadian census data on median household income levels by neighborhood of residence [42].

Overall, ICES data is quite representative of the entire Ontario population. Given the validation studies, we can trust ICES data regarding surgical procedures and the administration of adjuvangt therapies, as well as for accurately recording death.

Potential Biases

Bias is an important concept in epidemiological research and can be thought of as a systematic error that reduces the internal validity of a study [43]. Bias can lead to inaccurate reporting and over or underestimation of the association between an exposure and an outcome. In this section, I review the potential for selection and information bias in the proposed studies.

Information bias is the systematic distortion of classifying an exposure, outcome, or other relevant variables. This can be classified as non-differential if it affects all groups equally, or differential if one group is affected more than the other. They can be further classified as independent or dependent based on whether the error rate is related to the error rate of another variable [44]. The direction of bias is usually towards the null in the context of an independent non-differential misclassification. In other situations, the direction of bias is generally unpredictable [44].

The RECORD guidelines, which extend the STROBE guidelines for observational studies to administrative healthcare data, address these concerns [45, 46]. Specific threats to validity for studies using administrative data are described in the literature; misclassification of data is known to occur [47] and the concept of accuracy encompasses 5 additional subcomponents including *Completeness, Correctness, Measurement error, Internal consistency* and *Temporal consistency* [48]. However, the data provided by ICES includes information on how many variables are missing, if any, for each field. Several validation studies have been performed on ICES data and determined a specificity of at least 94% for ICES diagnoses of arrhythmia, congestive heart failure or unstable angina [49].

Specific Objectives

- To determine the population-level demographic information, treatment patterns, and survival outcomes for soft tissue sarcoma patients

- To demonstrate that ICES data can be used for meaningful analysis of Ontario sarcoma patients

Ethics Statement

All studies obtained approval from Research Ethics Board at Hamilton Health Sciences. No personal identifying information (such as patient name, OHIP number, or date of birth) were required for these studies. All patients were identified using encoded health card numbers.

CHAPTER 3

Changes in Soft-Tissue Sarcoma Treatment Patterns over time

– A population-based study in a country with universal and centralized healthcare

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Keywords: Sarcoma, outcomes, survival, population-based study
Category: Research Article

No author received direct or indirect funding for work on this manuscript. The authors disclose no potential conflicts of interest.

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Word Count: 2416
Total tables and figures: 6

Abstract

Background
The clinical care of soft-tissue sarcoma (STS) patients is largely multi-disciplinary involving clinicians from surgical disciplines, medical oncology and radiation oncology. It is not clear if treatment patents for STS have changed over time. We present population level data on changes in treatment patterns of patients diagnosed with STS of all stages in Ontario, Canada.

Methods
We performed a population-based cohort study using linked administrative databases in Ontario, Canada of patients with STS between 2006 - 2015. Patients with AJCC stage at the time of diagnosis were included. Patients were categorized into one of seven treatment arms: single modality treatment (surgery, chemotherapy or radiation therapy), bi-modality therapy, or all three treatment modalities. Survival of STS patients of different stages is displayed with the Kaplan-Meyer method.

Results
A total of 4696 patients were diagnosed with biopsy-proven sarcoma during the study period including 1915 patients with stage information available. Treatment patterns for patients with stage 1 and 2 disease were similar enough to allow for grouping. The use of radiation therapy in stage 1 and 2 patients increased by 15% over the study period. None of the 7 treatment regimens for stage 3 patients changed appreciably during the study period. We observed that the use of chemotherapy for stage 4 STS patients increased 36% during the study period. Overall patient survival was, as expected, highest in stage 1 patients and lowest in stage 4 patients.

Conclusion
This is the first population level reporting of 7 different STS treatment regimens in a country with universal and centralized healthcare. Radiation therapy for local disease control and chemotherapy for stage 4 patients have recently become more utilized. Survival from STS is highly dependent on stage at presentation. Other population-based studies from other countries are needed to establish the current international treatment patterns.

Background

Sarcomas are rare malignancies constituting less than 1% of all adult cancers, and there are over 50 soft tissue sarcoma (STS) subtypes [50]. Management of sarcoma is multidisciplinary and may involve surgery with wide-resection, neo-adjuvant or adjuvant chemotherapy, and pre-operative or post-operative radiation, in varied combinations [51].

Recently, large population-based observational studies of STS patients have become popular as they can capture more patients than controlled study designs and can provide valuable information regarding long-term outcomes [52-54]. Thus far, studies derived from population-based administrative databases, such as the Surveillance, Epidemiology, and End Results (SEER) database in the USA have provided incidence rates for specific sarcoma subtypes [55, 56] along with outcome data for up to 10 years [57]. These studies have characterized differences between pediatric and adult patients in sarcoma subtype prevalence and location of disease [6], and characterized outcome differences based on race and gender [58]. However, the treatment regimens of sarcoma patients have not been assessed at the population level [56, 59, 60].

Generally, STS is a disease treated with surgery and radiation therapy [61]. Routine use of chemotherapy is not supported as several key trials failed to show survival benefits [62, 63], however the 2014 European Society of Medical Oncology (ESMO) guidelines allow for the use of chemotherapy in STS patients, often in cases of advanced disease or for palliation [64]. Treatment regimens are usually based on clinical stage (tumour grade, size and presence of lymph node or distant metastases) and can be broadly classified into seven categories: surgery alone, radiation therapy alone, chemotherapy alone, three bimodal combinations and lastly the combination of all three modalities. The use of multi-modal therapy is generally associated with higher stages of disease. At a patient-specific level, co-morbidities, age and patient preferences also contribute to treatment decisions. To our knowledge, no other population-based studies to date have assessed

the overall treatment patterns of sarcoma patients in a country with universal and centralized healthcare.

The purpose of this study was to investigate a large population-based database of sarcoma patients collected over the past 10 years in order to determine the treatment regimens provided for STS patients of different stages, and if treatment regimens have changed over time. We also investigated overall survival based on stage of disease.

Methods

Study Design and Population

We performed a population-based cohort study using linked administrative databases in Ontario, Canada in accordance with RECORD guidelines which extend the STROBE guidelines for observational studies to administrative healthcare data [45, 46]. All patients with biopsy-confirmed diagnosis of sarcoma between January 1st 2006 – December 31st 2015 were eligible. The International Classification of Diseases, 10th Edition (ICD-10), Clinical Modification diagnosis codes for all STS subtypes was used for classification. As per prior research, we excluded diseases with considerably different diagnosis, management, and prognosis such as Kaposi's, visceral, bone, and uterine sarcomas, gastrointestinal stromal tumors, and mesotheliomas [5]. Only patients with American Joint Committee on Cancer (AJCC) stage information were used to determine stage specific treatment patterns. Please see **Appendix 1** for details of the codes and used to identify patients and their treatments.

Data Sources

Data were obtained from the Institute for Clinical Evaluative Sciences (ICES). ICES holds several provincial health care administrative databases and links them together via encrypted health insurance number of Ontario residents. The person-level linking of all these databases allows for a comprehensive longitudinal follow-up of a patient's interactions with the healthcare system. Databases used include the Ontario Cancer Registry which provides the biopsy confirmed diagnostic information, the Discharge Abstract Database which contains information on hospitalizations, surgical procedures and other treatment data, and the Cancer Activity Level Reporting database which contributes information regarding chemotherapy and radiation therapy. Databases containing information on physician billings (Ontario Health Insurance Plan), emergency department visits (National Ambulatory Care Reporting System), prescription medications (Ontario Drug Benefit), and death (Registered Persons DataBase) were also linked. Using these databases, we collected demographic information including sex, age at surgery, subtype of sarcoma, place of residence, income quintile, chemotherapy and radiation therapy treatment information, vital status at time of data collection, and Charlson-Deyo Comorbidity Index [65, 66]. Physician billing codes in these databases have been validated in the measure of other conditions such as heart disease and diabetes [49, 67, 68].

Statistical Methods

Demographic data and treatment patterns are summarized using descriptive statistics. Patients were categorized by treatment received as having single modality treatment (surgery, radiation therapy, or chemotherapy), bi-modality therapy or patients who received all three treatment modalities. Treatments are included if they occurred within 1 year of diagnosis. As the

treatment patterns for patients with Stage 1 and 2 disease were quite similar, we grouped these stages together for presentation. We present changes in the treatment patterns of patients from the first five-year period of our cohort (2006-2010) to the second five-year period (2011-2015).

All statistical analyses were performed with R version 3.3.0 (www.r-project.org) [69] and Microsoft Excel 2016. Authors AB and GP had direct access to the data. Cell sizes of 5 or less are reported as '<6' as per ICES guidelines. Ethical approval was provided for this study by the Hamilton Integrated Research Ethics Board (HiREB) for observational research with encrypted and anonymized patient information (REB#: 3745-C).

Results

We identified 4696 patients with biopsy-confirmed STS diagnosis during the study period. A total of 1915 STS patients (40.8%) had AJCC stage information available. Patient characteristics of the entire cohort are summarized in **Table 1**. There is a near 1.5:1 ratio of males to females in our cohort and 68% of STSs occurred in patients 50 years of age or older. Sarcoma cases were evenly distributed among income quintiles and 13.1% of patients living in rural areas. There was a 23% increase in the number of STS cases with stage information between the first and second half of the study period. A total of 57 STS subtypes were identified within our database and the full list is available in **Appendix 1.**

Sarcoma Treatment for Stage 1 & 2 patients

Treatment patterns for patients with Stage 1 and 2 disease (localized low- to mid-grade) were alike enough to allow grouping. The combination of surgery and radiation therapy was the most common treatment regimen for Stage 1 and 2 patients and complete treatment information is presented in **Figure 1**. Of note, we observed a 15% relative increase in the use of radiation

therapy in the most recent 5 years compared to the first half of our study period. While 55% of Stage 1 and 2 patients received radiation therapy from 2006-2010, 64% received radiation therapy from 2011-2015. Pre-operative radiation therapy for STS was initiated a median of 33 days from biopsy, with surgery occurring a median of 83 days from biopsy.

Sarcoma Treatment for Stage 3 patients

Detailed treatment information for STS patients with Stage 3 disease, who generally present with high-grade, large tumors without distant metastases, is presented in **Figure** 2. Just over 40% of stage 3 STS patients were treated with the combination of surgery and radiation therapy, and all treatment patterns remained remarkably similar between each half of our study period. This group had the lowest proportion of patients receiving no treatment, at 8.9%. A total of 29% of Stage 3 patients received chemotherapy in any combination of treatments.

Sarcoma Treatment for Stage 4 patients

Detailed treatment information for STS patients with Stage 4 (metastatic) disease is presented in **Figure 3**. In contrast with the other groups, 49% of patients with Stage 4 STS received chemotherapy. Considering only the most recent 5 years, 57% of STS patients received chemotherapy, a relative increase of 36% from the use of chemotherapy in the first 5 years of the study period. Only a minority of stage 4 patients were treated with surgery and radiation (7%), the most common treatment regimen for all other stages. About 18% of Stage 4 patients did not receive surgical or systemic treatment.

Survival by Stage

Overall survival following diagnosis of Stage 1 STS was 82% at 5 years and 74% at 10 years. Stage 3 patients displayed 51% survival at 5 years and 45% at 10 years while Stage 4 patients showed only 19% survival at 5 years and 13% at 10 years. Accordingly, the median survival for Stage 4 patients is 0.96 years (IQR: 0.74 – 1.16) while it is considerably longer at 5.4 years (IQR: 3.7 – NA) for Stage 3 patients. As more than 50% of Stage 1 and 2 patients lived to the end of the follow-up period, median survival is not calculable in those groups. The Kaplan-Meyer survival curves for STS patients by stage at initial presentation are presented in **Figure 4**.

Discussion

Our paper is the first to provide data on population-level treatment regimens for local and metastatic STS in a country with universal and centralized healthcare, and the first to demonstrate how treatment patterns may be changing. The combination of surgery and radiation therapy is the mainstay of treatment for STS patients with Stage 1, 2 or 3 disease at presentation, and the use of radiation therapy in patients with Stage 1 and 2 disease increased by 15% in the last 5 years. Furthermore, the use of chemotherapy in Stage 4 patients increased by 36% over the course of our study period while remaining unchanged in patients of other stages. Our reported prevalence of the most common sarcoma subtypes and the observed 1.5:1 male to female predilection is similar to other population-based studies [6, 70, 71].

The use of chemotherapy for STS patients is controversial but has been studied for many decades. Initial trials in the 1970's and 1980's failed to demonstrate survival benefits from the use of doxorubicin alone while later trials demonstrated some advantage from the combination of doxorubicin and ifosfamide [72]. A systematic review which included 4 newer trials from 2000-2002 as well as 14 RCTs from 1977-1987 found a small but significant reduction in mortality risk

of 6% (95%CI: 2-11%) from the use of any chemotherapeutic regimen [73]. Several recent large international multi-center RCTs have been conducted with more emphasis on the selection of drugs, patients, doses and sequence: the 2012 EORTC trial compared the use of doxorubicin and ifosfamide to no chemotherapy and failed to show a difference in survival [62] and a 2014 Lancet study showed that ifosfamide and doxorubicin did not provide significant survival benefit compared to doxorubicin alone [74]. A pooled analysis of two EORTC trials failed to demonstrate a survival benefit in young patients or other subgroups [63]. While, a 2016 Lancet study did show that the combination of olaratumab with doxorubicin conferred STS patients with locally advanced or metastatic disease an additional 11.8 months of overall survival compared to doxorubicin alone [75], a 2017 Lancet study showed no benefit to tailoring the chemotherapeutic regimen to histologic subtype [76]. Despite the lack of convincing evidence of effect of chemotherapy on overall survival, we we observed the use of chemotherapy in 29% of Stage 3 and 49% of Stage 4 patients. The use of chemotherapy is likely for adjuvant or palliative purposes [1].

To our knowledge, the only other study reporting population level treatment information is a Scandinavian study published in 2001. While the authors do not report detailed treatment regimens, they state that only 4% of their STS patients received chemotherapy [77] during a time when there were no national guidelines on the use of chemotherapy for STS patients. Additional updated population-based studies from several countries are needed to replicate our findings of the popular use of chemotherapy in Stage 4 STS patients and to determine what treatment regimens constitute the current international standard in the management of advanced STS.

Our study has several strengths. Firstly, administrative records of health-care use are unaffected by recall bias, and provide large, general population samples and information on long-term follow-up. By virtue of including all sarcoma patients with stage information over a 10-year

period, our analyzed sample closely mirrors the intended population. We can therefore place more confidence in the generalizability of our results to future Ontario sarcoma patients. While STS is a heterogenous group of tumors, we excluded sarcomas most likely to not be representative of general treatment and prognostic characteristics.

Limitations

This is an observational study that does not demonstrate causation. Although AJCC stage information is available for over 40% of patients as of 2006, it was recorded in less than 2% of patients in the preceding years, limiting the long-term understanding of the effect of stage on outcomes. Reporting is likely to continue to improve with time [78], and future analyses will be able to incorporate a greater number of well-reported important variables. While the AJCC staging system has changed subtly [79], our data captures the stage according to the criteria at the time of biopsy. Likewise, the condition formerly known as Malignant Fibrous Histiocytoma is now named Undifferentiated Pleomorphic Sarcoma, but both use the same ICD10 code and we report the disease as originally labelled in the database.

While specific threats to validity for studies using administrative data are described in the literature, we expect high relative accuracy given that the diagnostic codes used to identify sarcoma patients are based strictly on biopsy and a diagnosis from a pathologist - stringent criteria with little to no room for interpretation. Thus, we expect the patients identified with ICD10 codes to truly have a diagnosis of sarcoma.

Conclusion:

This population-based cohort study presents the multi-disciplinary treatment regimens and demographic information of soft tissue sarcoma patients treated in a single-payer universal healthcare system over 10 years. The use of radiation therapy in Stage 1 and 2 patients has increased 15% and the use of chemotherapy in Stage 4 patients has increased 36% over the study period. Other population-based studies are needed to provide an international overview of treatment patterns for sarcoma patients.

Sources of Funding

This study was supported through provision of data by the Institute for Clinical Evaluative Sciences and Cancer Care Ontario (CCO) and through funding support to ICES from an annual grant by the Ministry of Health and Long-Term Care (MOHLTC) and the Ontario Institute for Cancer Research (OICR). The opinions, results and conclusions reported in this paper are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred.

None of the authors received any financial compensation for the preparation of this manuscript.

Supplementary Material

Contains the codes used to identify patients

Declarations

Ethics approval and consent to participate – Not applicable

Consent for publication – Not applicable

Availability of data and material – The data is under provincial protection

Competing interests – The authors declare that they have no competing interests

Funding – The authors have no sources of funding to declare

Acknowledgements – Not applicable

Tables and Figures

Table 1 – Demographic Information of soft tissue sarcoma patients

Characteristic	2006-2010		2011-2015	
Total Ontario sarcoma patients	2217		2479	
Age Group				
• <35	310	14.0%	269	10.9%
• 35-49	396	17.9%	392	15.8%
• 50-59	362	16.3%	436	17.6%
• 60-69	396	17.9%	492	19.8%
• 70-79	386	17.4%	470	19.0%
• 80+	367	16.6%	420	16.9%
Gender				
• Female	942	42.5%	1050	42.4%
• Male	1275	57.5%	1429	57.6%
Most common subtypes				
• Liposarcoma	356	16.1%	518	20.9%
• Malignant Fibrous Histiocytoma	250	11.3%	145	5.8%
• Leiomyosarcoma	240	10.8%	300	12.1%
• Giant Cell Sarcoma	91	4.1%	189	7.6%
• Fibromyxosarcoma	66	3.0%	165	6.7%
Topography (ICD Topography code)				
• Lower limb (C40.2, C49.2)	678	30.6%	809	32.6%
• Upper limb (C40.0, C40.1, C49.1)	294	13.3%	311	12.5%
• Axial	1245	56.2%	1359	54.8%
Charlson-Deyo Comorbidity Score (1-18)				
• Median	3.0		3.0	
• Mean	3.7		3.6	
Stage				
• I	264	11.9%	391	15.8%
• II	238	10.7%	295	11.9%
• III	199	9.0%	215	8.7%
• IV	158	7.1%	155	6.3%
• Not Reported	1356	61.3%	1423	57.4%
Income quintile ¥ σ				
• Lowest	401	18.1%	396	16.0%
• 2nd	415	18.7%	463	18.7%
• 3rd	417	18.8%	499	20.1%
• 4th	470	21.2%	561	22.6%
• Highest	505	22.8%	546	22.0%
Place of Residence σ				
• Urban	1917	86.5%	2195	88.5%
• Rural	298	13.4%	281	11.3%

¤ Please see **Appendix** for full list of sarcoma subtypes

¥ Based on nearest neighborhood census information

σ Proportion of missing data is 0.1% for Place of Residence and 0.3% for Income quintile, no other variable is missing data

Table 2 – Sarcoma treatment regimens by stage of disease, 2006-2015

	Stage 1&2	Stage 3	Stage 4	Stage Unknown
Total Patients	1188	414	313	2779
Surgery + Radiation therapy	33.2%	40.1%	7.0%	22.6%
Surgery	17.2%	7.0%	4.5%	13.1%
Radiation therapy	17.0%	15.0%	21.7%	9.6%
Surgery + Radiation therapy + Chemotherapy	6.3%	14.5%	8.6%	3.7%
Chemotherapy	2.4%	5.3%	16.0%	6.7%
Surgery + Chemotherapy	1.6%	1.7%	6.7%	3.6%
Chemotherapy + Radiation therapy	4.0%	7.5%	17.6%	4.3%
No treatment reported	18.3%	8.9%	17.9%	36.3%

Figure 1 – Treatment of Stage 1&2 STS Patients

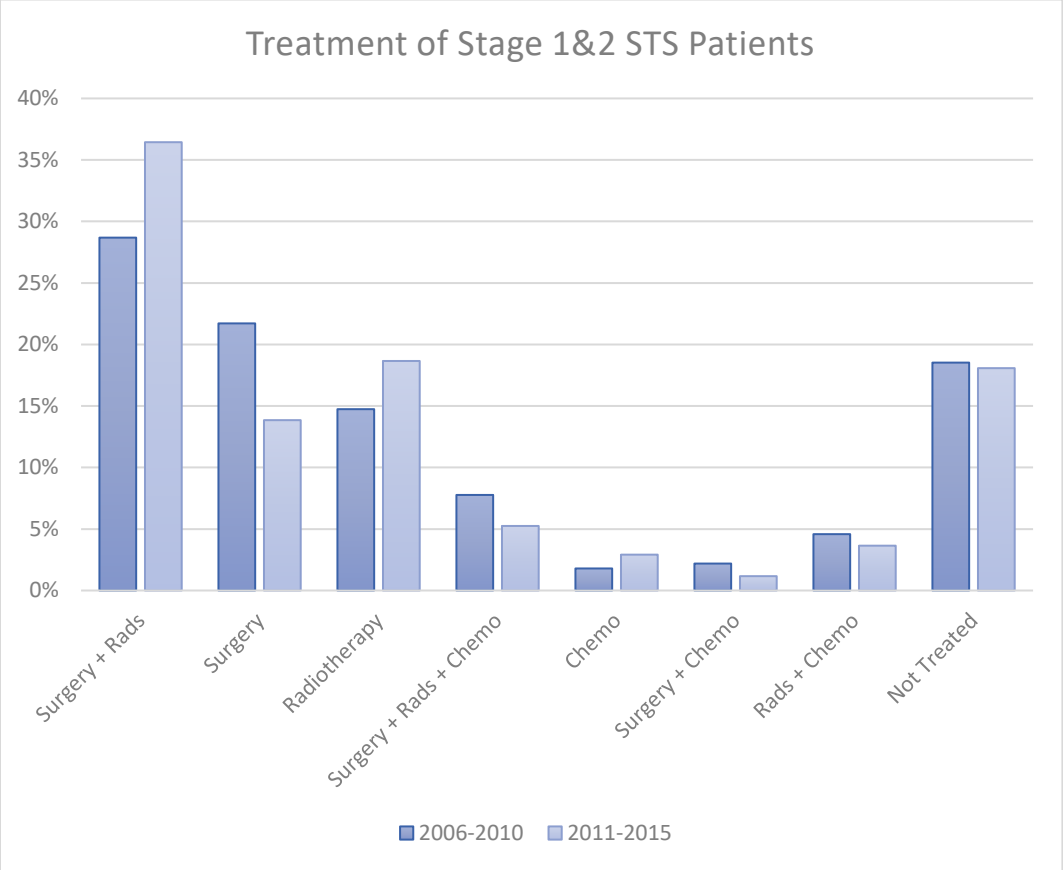


Figure 2 – Treatment of Stage 3 STS Patients

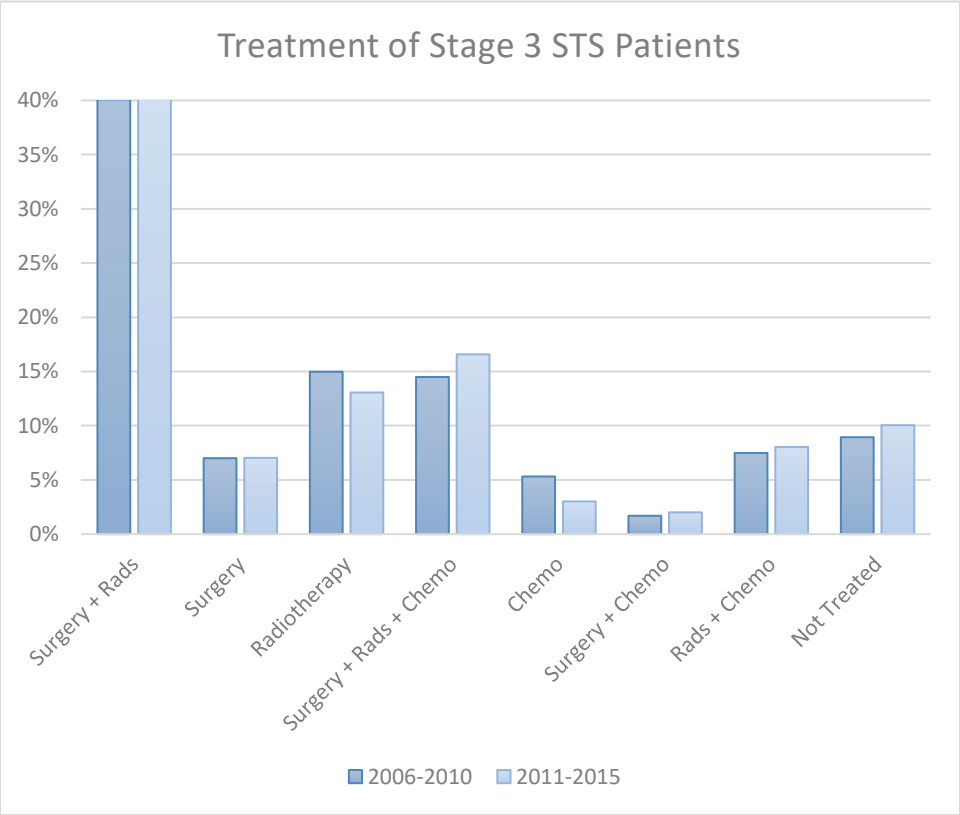


Figure 3 – Treatment of Stage 4 STS Patients

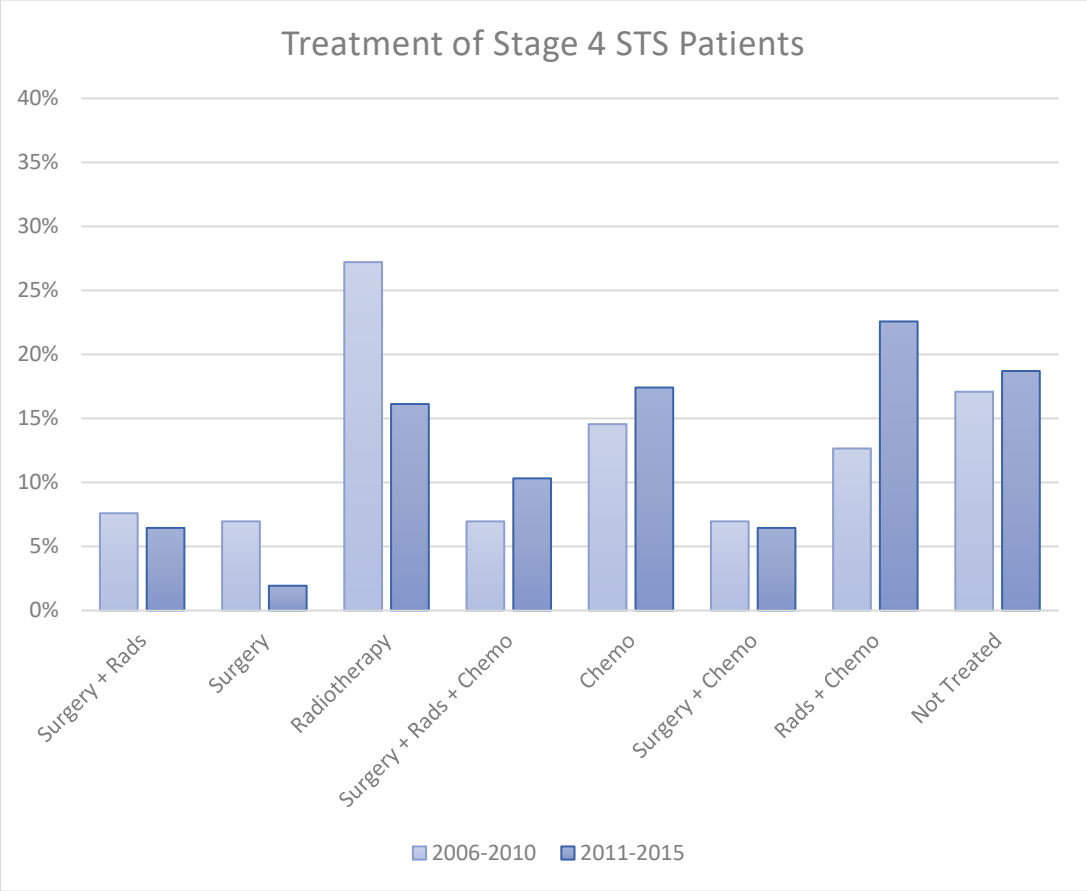
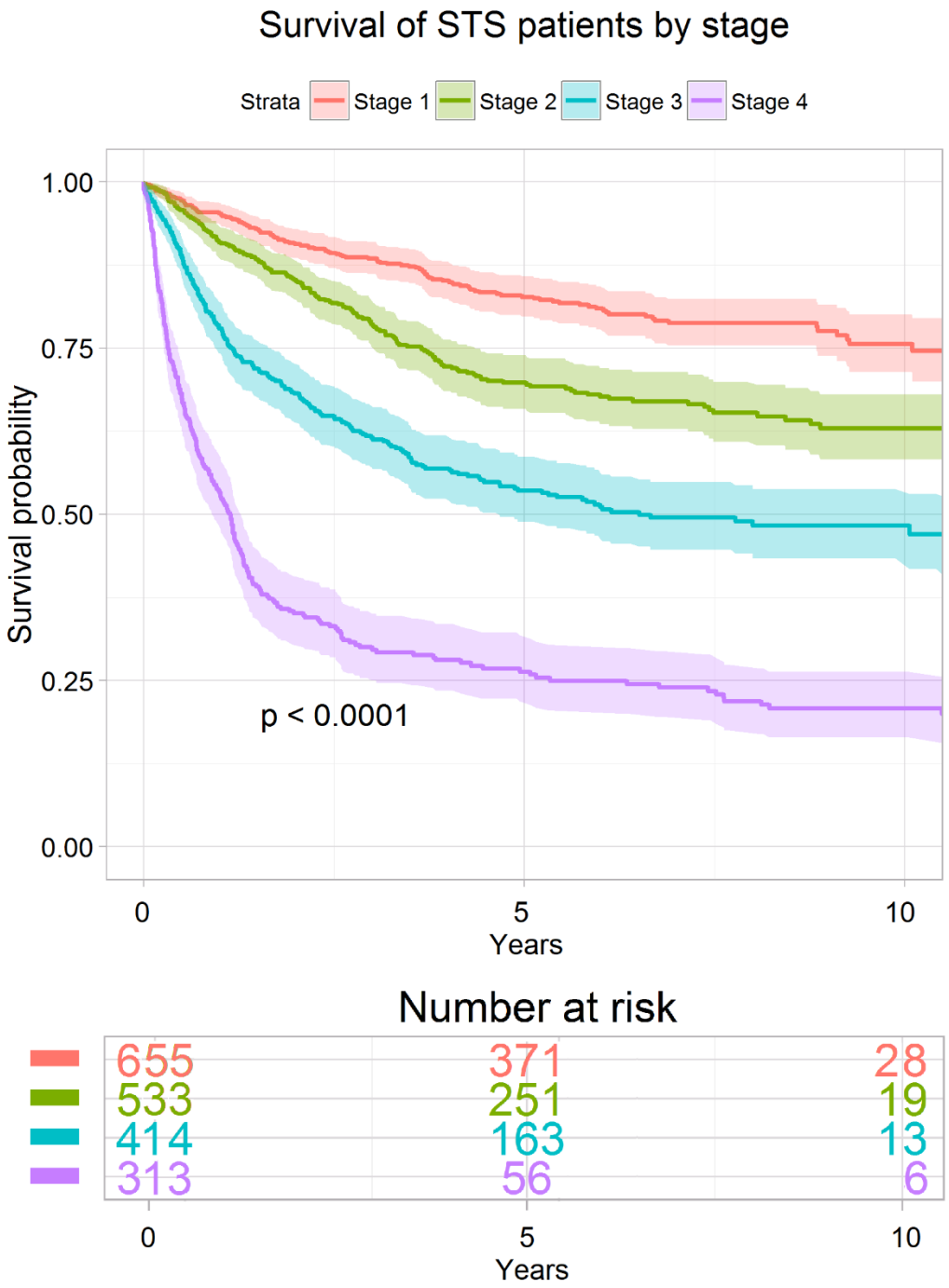


Figure 4 – Overall survival after STS diagnosis, by stage



Legend:

Significantly different survival is seen for STS patients presenting at different stages (Log Rank: p<0.0001).

Appendix 1

Table S1: Full breakdown of sarcoma subtypes

Soft Tissue Sarcoma		
Subtype	**ICD10 Code**	**N**
Malignant neoplasm	80003	1335
Sarcoma NOS	88003	1172
Leiomyosarcoma	88903	1121
Malignant Fibrous Histiocytoma	88303	961
Liposarcoma, well differentiated	88513	548
Liposarcoma NOS	88503	332
Myxoid Liposarcoma	88523	319
Giant Cell Sarcoma	88023	317
Haemangiosarcoma	91203	287
Fibromyxosarcoma	88113	266
Synovial Sarcoma	90403	231
Sarcoma, undifferentiated	88053	213
Dedifferentiated Liposarcoma	88583	182
Fibrosarcoma NOS	88103	181
Spindle Cell Sarcoma	88013	146
Chordoma	93703	146
Pleomorphic Liposarcoma	88543	132
Dermatofibrosarcoma NOS	88323	111
Embryonal rhabdomyosarcoma	89103	89
Epitheliod	88043	78
Clear cell sarcoma	90443	77
Malignant Tumor, fusiform cell	80043	66
Pleomorphic Rhabdomyosarcoma	89013	65
Kaposi Sarcoma	91403	62
Rhabdomyosarcoma NOS	89003	62
Round Cell Liposarcoma	88533	60
Neurofibrosarcoma	95403	60
Synovial Sarcoma, biphasic	90433	48
Synovial sarcoma, spindle cell	90413	38
Alveolar soft part sarcoma	95813	33
Mixed Liposarcoma	88553	22
Infantile fibrosarcoma	88143	19
Small cell sarcoma	88033	18
Malignant GCT of soft parts	91253	13
Malignant Rhabdoid Tumor	89633	12
Myxosarcoma	88403	10
Epitheliod leiomyosarcoma	88913	10
Myosarcoma	88953	9
Myxoid leiomyosarcoma	88963	6
Hystiocytic sarcoma	97553	<6
Spindle Cell Rhabdomyosarcoma	89123	<6
Lymphangiosarcoma	91703	<6
Fibroblastic Liposarcoma	91823	<6
Angiomyosarcoma	88943	<6
Mixed type rhabdomyosarcoma	89023	<6
Stromal sarcoma, NOS	89353	<6

Malignant Tynosynovial Giant Cell Tumor	92523	<6
MPNST with rhabdomyoblastic differentiation	95613	<6
Angiomyoliposarcoma	88603	<6
Myeloliposarcoma	88703	<6
Bizarre leiomyosarcoma	88930	<6
Adenosarcoma	89333	<6
Synovial sarcoma, epitheliod cell	90423	<6
Ameloblastic Fibrosarcoma	93303	<6
Gliosarcoma	94423	<6
Mast Cell Sarcoma	97403	<6
Langerhans cell Sarcoma	97563	<6

Table S2: Summary of codes used

Variable	**ICD10 Code**	**N unique**
Chemotherapy -Presence of these codes in the OHIP, as well as matching patient IDs in the ALR-Chemo database	G281 G339 G359 G381 G382 G388 Z511 Z512	3905
Surgery - Presence of these codes in the OHIP database, within 1 year of biopsy confirmed sarcoma diagnosis	Surgical codes: R037, R214, R216, R226, R246, R253, R266, R272, R293, R294, R295, R297, R330, R523, R591, R592, R641 Amputation codes: R614, R616, R620, R630, R631 Tumor excision codes: Z632, Z633, Z634 Retroperitoneal tumor: S431 Radical Soft Tissue Tumour Excision: N554, N553	5294
Radiotherapy -Presence of these codes in the OHIP database, as well as matching patient IDs in the ALR-Rads database	X310 X311 X312 X313	4289

CHAPTER 4

Survival differences for rural and low-income soft tissue sarcoma patients in a country with universal healthcare – A 23-year population-based study

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Keywords: Sarcoma, outcomes, survival, population-based study
Category: Research Article

No author received direct or indirect funding for work on this manuscript. The authors disclose no potential conflicts of interest.

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Word Count: 2287
Total tables and figures: 5

Abstract

Background
Population-based studies from the United States have reported that sarcoma patients living in rural areas or belonging to lower socioeconomic classes experience worse overall survival; however, the evidence is not clear for universal healthcare systems where financial resources should theoretically not affect access to standard of care. The purpose of this study was to determine the survival outcomes of soft-tissue sarcoma (STS) patients treated in Ontario, Canada over 23 years and determine if the patient's geographic location or income quintile are associated with survival.

Methods
We performed a population-based cohort study using linked administrative databases of patients diagnosed with STS between 1993 – 2015. The Kaplan-Meier method was used to estimate 2, 5, 10, 15 and 20-year survival stratified by age, stage and location of tumor. We estimated survival outcomes based on the patient's geographic location and income quintile. The Log-Rank test was used to detect significant differences between groups. If groups were significantly different, a Cox proportional hazards model was used to test for interaction effects with other patient variables.

Results
We identified 8,896 patients with biopsy-confirmed STS during the 23-year study period. Overall survival following STS diagnosis was 70% at 2 years, 59% at 5 years, 50% at 10 years, 43% at 15 years, and 38% at 20 years. Living in a rural location ($p=0.0024$) and belonging to the lowest income quintile ($p<0.0001$) were independently associated with lower overall survival following STS diagnosis. These findings were robust to tests of interaction with each other, age, gender, location of tumor and stage of disease.

Conclusion
This population-based cohort study of 8,896 STS patients treated in Ontario, Canada over 23 years reveals that patients living in a rural area and belonging to the lowest income quintile are at risk for decreased survival following STS diagnosis. We extend previous STS survival reporting by providing 15 and 20-year survival outcomes stratified by age, stage, and tumor location.

Background

Sarcomas are a heterogenous group of tumors comprising less than 1% of adult cancers [50]. In the study of sarcoma outcomes, population-based studies have been essential for capturing larger volumes of patients and for providing information regarding the long-term outcomes of soft tissue sarcoma (STS) patients [52-54].

Thus far, analysis of the Surveillance, Epidemiology, and End Results (SEER) database in the United States, a country where healthcare is provided by many distinct organizations, has provided population-based evidence to support the correlation of factors such as tumour size and grade with worse overall survival in sarcoma patients [57, 80-82]. Studies using SEER data have provided survival estimates for up to 10 years [54, 82, 83]. More importantly, population-based data has revealed novel associations: patients living in rural areas or belonging to lower socioeconomic classes are at risk for worse overall survival, including a 5% increased risk of sarcoma specific mortality after controlling for other significant factors such as stage, grade, tumor site, age and gender [84]. Analysis of survival outcomes over time showed that while survival improved between 1991 and 2010 for patients in both metropolitan counties and non-metropolitan counties, the survival difference between these groups was as high as 11% from 1997-2003 [85]. Registry data has also shown that patients with low socio-economic status (SES) have increased mortality following cancer diagnosis [86].

To our knowledge, no study to date has examined if these associations are present in STS patients in Canada, a country with fully subsidized and universal healthcare. The purpose of this study was to investigate a large population-based database of STS patients collected over 23 years in order to determine the overall survival of STS patients treated in Ontario, Canada. We aimed to determine if the patient's geographic location or income quintile are associated with survival.

Methods

Study Design and Population

We performed a population-based cohort study using linked administrative databases in Ontario, Canada in accordance with RECORD guidelines which extend the STROBE guidelines for observational studies to administrative healthcare data [45, 46]. Patients of all ages with a biopsy-confirmed diagnosis of STS of any body location between January 1st 1993 – December 31st 2015 were eligible. The International Classification of Diseases, 10th Edition (ICD-10), Clinical Modification diagnosis codes for all STS subtypes was used for classification. All STS subtypes have been included except for Kaposi's Sarcoma, which was excluded due to its confounding effect on survival outcomes, as per prior research [53]. Tumor location was determined by ICD-O-3 codes which were present in all cases. Details of the codes used to identify patients and their treatments are provided in **Supplementary Material**.

Data Sources

Data were obtained from the Institute for Clinical Evaluative Sciences (ICES). ICES holds several provincial health care administrative databases and links them together via encrypted health insurance number of Ontario residents. The person-level linking of all these databases allows for a comprehensive longitudinal follow-up of a patient's interactions with the healthcare system. Databases used include the Ontario Cancer Registry which provides the biopsy confirmed diagnostic information, and the Discharge Abstract Database which contains information on hospitalizations, surgical procedures and other treatment data. Databases containing information on physician billings (Ontario Health Insurance Plan), emergency department visits (National Ambulatory Care Reporting System), prescription medications (Ontario Drug Benefit), and death (Registered Persons DataBase) were also linked. Using these databases, we collected all

demographic and oncologic information available including sex, age at surgery, American Joint Committee on Cancer (AJCC) stage information, geographic location of the patient, income quintile, STS subtype, location of tumor, and vital status at time of data collection [65, 66].

Statistical Methods

Demographic data are summarized using descriptive statistics. The primary outcome of interest was overall survival time, defined as the time from biopsy-confirmed diagnosis to death. The Kaplan-Meier method was used to estimate survival after diagnosis of STS. Patients without a known death date were censored on the date of final contact with the healthcare system before study end. Given the large number of patients in our database, we were able to stratify survival outcomes by clinically useful variables such as age, stage, and extremity or axial location. The age of 50 was used to separate groups, as per published sarcoma risk models [28, 29]. We then compared the survival of patients who live in urban and rural areas. ICES classifies a census subdivision as rural if the population is less than 10,000. We compared the survival of patients across 5 income quintiles. The Log-Rank test was used to detect significant differences between groups. If groups were significantly different, a Cox proportional hazards model was used to test for interaction effects with other patient variables. All statistical analyses were performed with R version 3.3.0 (www.r-project.org) [69].

Authors AB and GP had direct access to the data. As per ICES privacy guidelines, cell sizes of 5 or less are reported as '<6', the lowest age reported is '<35' and subsequent ages are provided in 5-year bins. Less than 0.1% of data were missing from all fields except for rurality which was lacking 0.3% of data and income quintile which was lacking 0.7% of data. As such, no methods for accounting for missing data were required. Ethical approval was provided for this

study by the Hamilton Integrated Research Ethics Board (HiREB) for observational research with encrypted and anonymized patient information (REB#: 3745-C).

Results

We identified 8,896 patients with biopsy-confirmed STS during the 23-year study period. Patient characteristics are summarized in **Table 1**. There was a near 1.5:1 ratio of males to females. STS cases were evenly distributed among income quintiles and close to 90% of STS patients are from urban areas. There was an increase in the total annual reported incidence of STS cases over time, from 254 in 1993 to 509 in 2015.

Survival Outcomes

Overall survival following STS diagnosis was at 70% at 2 years, 59% at 5 years, 50% at 10 years, 43% at 15 years, and 38% at 20 years. Detailed survival information of STS patients stratified by stage, age and tumor location, is presented in **Table 2**. The lowest survival was observed in patients with Stage 4 STS: median survival was less than 1.5 years regardless of age or tumor location. Conversely, STS patients of all ages with Stage 1 extremity disease displayed survival of over 50% at 20 years, thus an estimate of median survival was not possible for these groups **[Table 2].** Survival outcomes stratified by treatment modality are presented in **Appendix 2**.

Survival Outcomes based on Patient's Geographic Location

A significant difference in survival was observed between STS patients living in urban vs. rural areas (p=0.0024) **[Figure 1]**. The median survival for STS patients in urban areas is 10.3

years (95% CI 9.4 – 11.3) while the median survival for STS patients from rural areas is 7.4 years (95% CI 6.1 – 9.1). This finding is robust to tests for an interaction effect with income quintile, age, stage, gender and location of tumor using a Cox proportional hazards model **[Table 3]**. The results of the Cox model demonstrate a decrease of 8.4% in mortality risk for urban patients.

Survival Outcomes based on Patient's Income Quintile

A significant difference in survival was observed between STS patients of different income quintiles ($p<0.0001$) **[Figure 2].** There is a difference of 5.1 years in median survival between STS patients from the highest income group (Median 12.5, 95% CI 10.7 – 14.4) compared to those in the lowest income group (Median 7.4, 95% CI 5.9 – 8.9). This finding is robust to tests for an interaction effect with geographic location, age, stage, gender and location of tumor using a Cox proportional hazards model **[Table 3]**. The results of the Cox model demonstrate a decrease of 4.9% in mortality risk for each increasing income quintile.

Sensitivity Analysis

Sensitivity analyses were performed to examine the robustness of observed results. The significant associations of rurality and income quintile with worse overall survival were also demonstrated after excluding stage from the model, after defining age as a categorical variable based on a cutpoint of 50, and investigating potential interactions between rurality and income quintile with other factors (data not shown).

Discussion

To our knowledge, this population-based study of 8,896 STS patients is the first to demonstrate different survival rates for rural and low-income patients in a country with universal

healthcare. These associations are robust to tests of interaction with each other, age, gender and site of disease. This is also the first study to provide 15 and 20-year survival estimates for STS stratified by age, stage, and location and stage of disease.

Our study has several strengths. Firstly, administrative records of health-care use are unaffected by recall bias, and provide large, general population samples and information on long-term follow-up. The ICES linking of patient information represents a very large database for this population with over 20 years of follow-up. It captures nearly 100% of all cases in the province and provides complete survival information on these patients. By virtue of including all Ontario STS patients over a 23-year period, our analyzed sample closely mirrors the intended population. We can therefore place more confidence in the generalizability of our results to future Ontario STS patients.

Our study corroborates the findings from other population-based studies that rural cancer patients and those with low SES have worse overall survival outcomes. Several studies have looked into underlying reasons for these findings. An American review of rural disparities in cancer care found that rural patients are less likely to benefit from the introduction of novel therapies which may provide survival benefits [87]. The authors note that when a cancer specialist is introduced into an area that previously did not have one, the local mortality rates can fall 5-79% depending on the type of cancer [87]. Studies have shown that patients in rural American cities without a radiation oncologist or radiation therapy facilities are less likely to receive adjuvant radiation therapy [88]. Indeed, a study of over 60,000 cancer patients over a 10-year period in Los Angeles showed that living nine or more miles away from the nearest comprehensive cancer center was associated with increased odds of initial treatment at a non-specialized facility and lower overall survival [89].

Studies of American STS patients have shown that although academic centers see patients with more advanced disease, survival outcomes are superior to patients treated in rural or community centers [15, 16]. One factor possible contributing to this differential survival is the observed difference in the post-operative surveillance regimens of STS patients treated in academic and rural centers [90]. International studies have reported that local recurrence can be up to 2.4 times higher in STS patients treated in rural centers and have called for STS treatment to be performed only in specialized academic centers [17, 19, 20]. Furthermore, a 2018 systematic review of 39 observational studies comparing survival of rural and urban cancer patients found a 5% increased risk of death for rural patients which was consistent across countries and definitions of rurality [91].

A previous study using ICES data found a significant association between patients in the lowest income quintile and decreased survival after diagnosis with breast, colon and lung cancer [92]. Our study is the first to extend the finding of worse survival outcomes for rural patients and those in the lowest income quintile to the Canadian STS population. These findings are not consistent with the theory that in universal publicly funded healthcare systems, financial status should not affect access to standard of care. Proposed solutions for increasing access to care for rural patients include telemedicine, education and screening outreach programs and virtual tumor boards, however each have their challenges [87]. For instance, although rural patients reported satisfaction with the implementation of remote supervision of chemotherapy, there were concerns related to the lack of a physician on site [87]. While virtual tumor boards have increased the likelihood that cases from rural hospitals are discussed, close to 20% of the involved physicians felt that consensus was harder to reach and technical difficulties were noticed in approximately 10% of cases [87].

Limitations

The major limitation of our study is the limited cancer specific data that ICES routinely collected. American Joint Committee on Cancer (AJCC) stage information is available for 22.7% of patients, limiting the long-term understanding of the effect of stage on outcomes. Furthermore, margin status, tumor size and grade are not recorded. Our analyses include adjustment for the variables available with the population-based data collected over 23 years, but residual confounding is likely. As collection and reporting of these variables is likely to improve with time [78], future analyses will be able to incorporate a greater number of well-reported important variables. Furthermore, the literature describes specific threats to validity for studies using administrative data such as misclassification, completeness, correctness, measurement error, internal consistency and temporal consistency of data [47, 48]. However, the data provided by ICES includes information on how many variables are missing, if any, for each field. Several validation studies have been performed which determined a specificity of at least 94% for ICES diagnoses of arrhythmia, congestive heart failure or unstable angina [49, 67, 68]. We expect high accuracy given this study's strict biopsy-dependent criteria for STS diagnosis.

Conclusion:

This population-based cohort study of 8,896 STS patients treated in Ontario, Canada over 23 years demonstrates that living in a rural area and belonging to the lowest income quintile are associated with decreased survival when controlled for each other, age, stage, tumor location and

stage of disease. We extend previous STS survival reporting by providing 15 and 20-year survival outcomes stratified by age, stage, and tumor location.

Sources of Funding

This study was supported through provision of data by the Institute for Clinical Evaluative Sciences and Cancer Care Ontario (CCO) and through funding support to ICES from an annual grant by the Ministry of Health and Long-Term Care (MOHLTC) and the Ontario Institute for Cancer Research (OICR). The opinions, results and conclusions reported in this paper are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred.

None of the authors received any financial compensation for the preparation of this manuscript.

Supplementary Material

Contains the codes used to identify patients

Declarations

Ethics approval and consent to participate – Ethics obtained, consent not applicable

Consent for publication – Not applicable

Availability of data and material – The data is under provincial protection

Competing interests – The authors declare that they have no competing interests

Funding – The authors have no sources of funding to declare

Acknowledgements – Not applicable

Tables and Figures

Table 1 – Demographic Information of entire STS cohort

Characteristic	N	%
Total Ontario Sarcoma patients 1993-2015	8896	100%
Age Group		
• <35	1198	13.5%
• 35-49	1580	17.4%
• 50-59	1474	16.6%
• 60-69	1608	18.1%
• 70-79	1686	19.0%
• 80+	1350	15.2%
Gender		
• Female	3936	44.2%
• Male	4960	55.8%
Tumor Location		
• Extremity	3983	44.8%
• Axial	4913	55.2%
Income quintile ɣ σ		
• Lowest	1609	18.1%
• 2nd	1716	19.2%
• 3rd	1754	19.7%
• 4th	1832	20.6%
• Highest	1928	21.7%
Place of residence σ		
• Urban	7675	86.5%
• Rural	1193	13.2%
Stage		
• I	682	7.7%
• II	561	6.3%
• III	436	4.9%
• IV	341	3.8%
• Not Reported	6876	77.3%

ɣ Based on nearest neighborhood census information

σ Proportion of patients not reported is 0.7% for income quintile and 0.3% for residence

Table 2 – Survival after STS diagnosis by tumor location, stage and age in years (N = 2020)

			N	2-YEAR	5-YEAR	10-YEAR	15-YEAR	20-YEAR	MEDIAN SURVIVAL IN YEARS (95% CI)
EXTREMITY	**Stage 1**	≤49	122	99%	94%	93%	93%	93%	Not reached
		≥50	216	92%	83%	75%	67%	56%	20.2 (15.0 – NC)
	Stage 2	≤49	78	92%	85%	80%	80%	NC	Not reached
		≥50	249	90%	71%	64%	42%	26%	13.8 (12.0 - NC)
	Stage 3	≤49	51	90%	75%	68%	41%	14%	13.2 (7.8 – NC)
		≥50	171	66%	52%	51%	40%	20%	11.0 (3.7 – 16.5)
	Stage 4	≤49	35	36%	32%	28%	28%	NC	1.2 (1.0 – NC)
		≥50	90	38%	30%	20%	8%	NC	1.2 (0.80 – 1.9)
AXIAL	**Stage 1**	≤49	105	92%	87%	85%	85%	NC	Not reached
		≥50	239	85%	75%	63%	42%	28%	14.5 (12.0 – NC)
	Stage 2	≤49	55	89%	85%	81%	81%	55%	Not reached
		≥50	179	74%	57%	46%	36%	36%	8.9 (5.6 – NC)
	Stage 3	≤49	43	77%	56%	50%	38%	NC	10.7 (2.7 – NC)
		≥50	171	61%	48%	39%	29%	NC	4.4 (2.8 – 6.0)
	Stage 4	≤49	57	46%	29%	29%	29%	20%	1.4 (1.2 – 2.6)
		≥50	159	30%	22%	18%	13%	4%	0.9 (0.6 – 1.2)

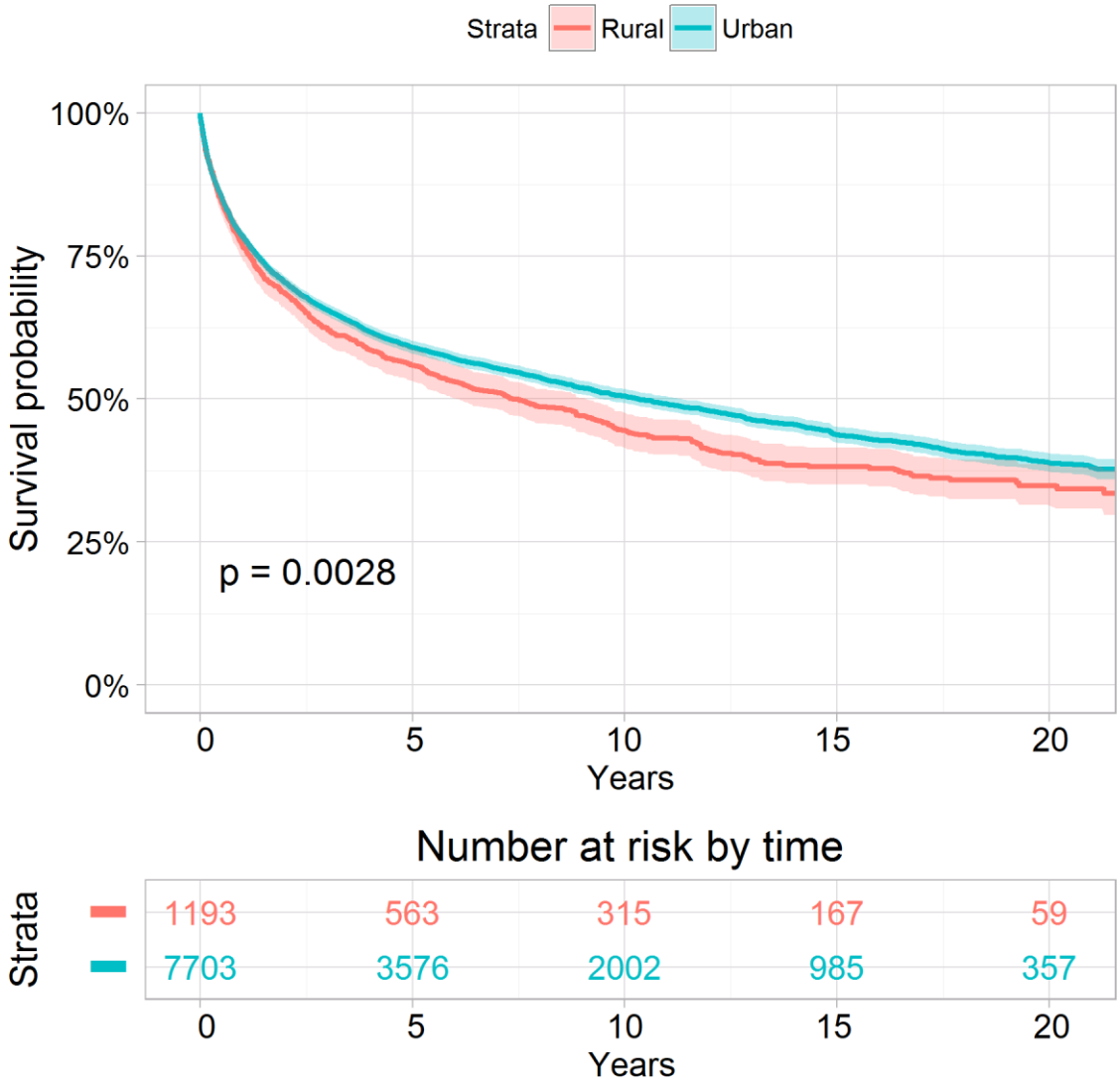
Legend: NC = Not calculable, when no patients in that category we followed for that period of time. Median survival is available for groups in which overall survival was below 50% at final follow-up.

Table 3 – Cox Proportional Hazards model to test for interaction effects of geographic location and income quintile with each other, gender, age, stage, and location of tumor on overall survival following STS diagnosis (N = 8896)

Factor	HR (95%CI)	P-value
Place of Residence: Urban vs Rural	**0.916 (0.844 – 0.988)**	**0.025**
Income Quintile	**0.951 (0.930 – 0.972)**	**<0.0001**
Gender: Male vs Female	1.08 (1.02 – 1.15)	0.030
Age	1.10 (1.08 – 1.12)	<0.0001
Stage 1	0.35 (0.29 – 0.41)	<0.0001
Stage 2	0.64 (0.55 – 0.74)	<0.0001
Stage 3	1.12 (0.98 – 1.28)	0.11
Stage 4	2.29 (2.02 – 2.59)	<0.0001
Tumor Location: Extremity vs Axial	0.55 (0.52 – 0.59)	<0.0001

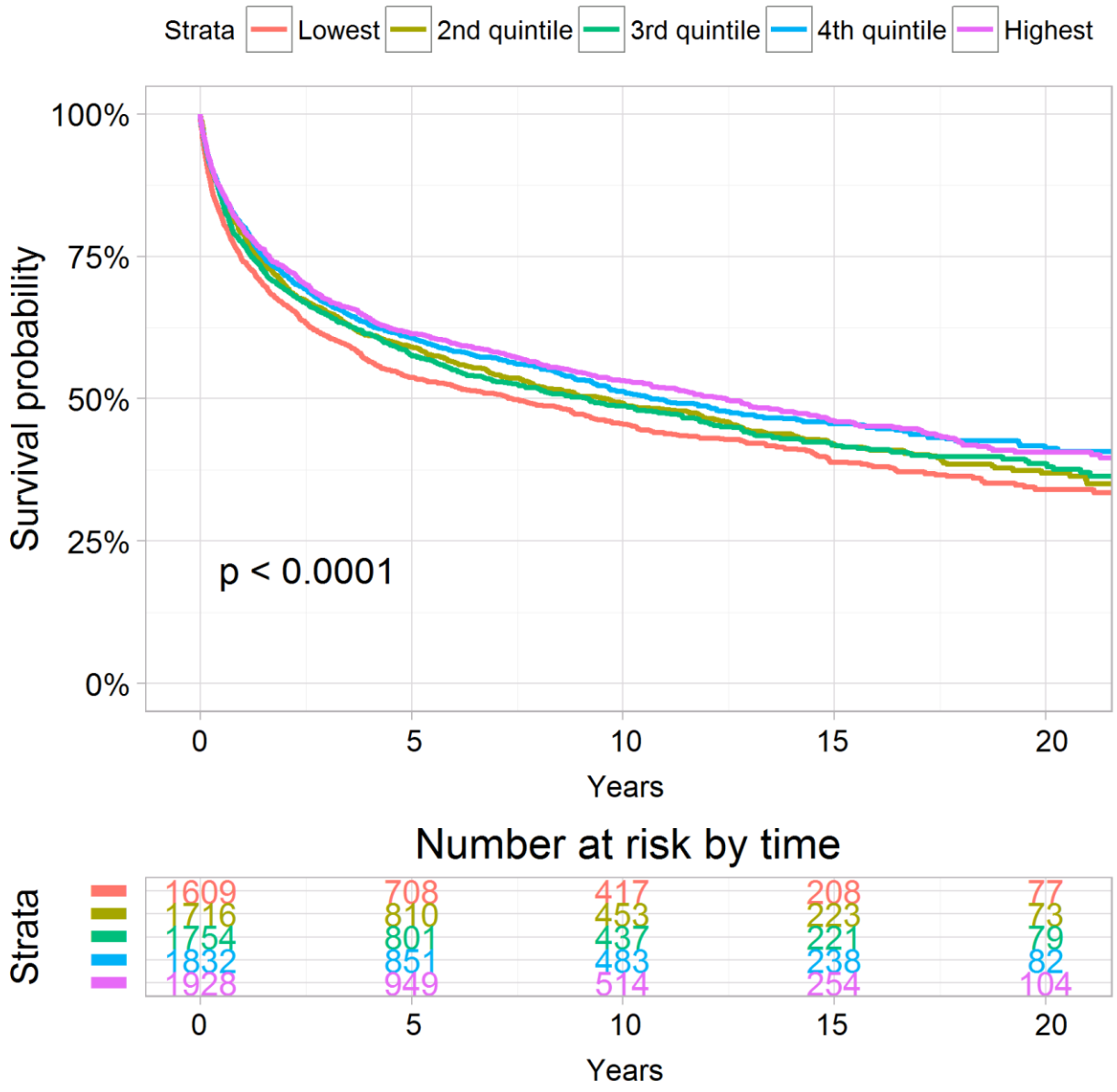
Legend: Age is modelled as a continuous variable where "1" represents patients < 35 and increasing integers represent subsequent 10-year bins of patient age. Stage is modelled as a categorical variable and the referent group is patients with unknown stage.

Figure 1 –Overall survival after STS diagnosis, by patient's geographic location



Legend: Significantly different survival is seen for STS patients who live in urban areas compared to rural areas (Log Rank: p=0.0028). This finding is robust to tests for an interaction effect with income quintile, age, gender and location of tumor. 95% confidence intervals are provided.

Figure 2 – Overall survival after STS diagnosis, by income quintile



Legend: A significant difference in survival outcomes is observed for STS patients of different quintiles (Log Rank: p<0.0001). This finding is robust to tests for an interaction effect with geographic location, age, gender and location of tumor. Due to overlap between higher income quintiles, 95% confidence intervals are not provided.

Appendix 2

Table S1 – Survival outcomes by treatment regimen

	Soft Tissue Sarcoma Survival %			
	2 year	**5 year**	**10 year**	**15 year**
All patients	70.0%	58.5%	49.6%	42.9%
Surgery Alone	85.5%	78.0%	69.8%	63.3%
Chemotherapy alone	56.2%	36.6%	30.8%	27.6%
Radiation therapy alone	56.0%	44.6%	35.2%	25.5%
Surgery + Chemotherapy	76.9%	56.0%	45.2%	37.6%
Surgery + Radiation therapy	87.4%	79.3%	70.7%	53.1%
Chemotherapy + Radiation therapy	55.6%	37.3%	24.6%	15.3%
Surgery + Chemotherapy + Radiation therapy	77.5%	50.9%	34.6%	18.5%

CHAPTER 5: DISCUSSION AND CONCLUSION

Thesis Summary

This thesis has explored the use of population-based data to answer hereto unaddressed questions in sarcoma research. We characterize the treatment regimens of STS patients treated in a universal healthcare system and report changes over time. We report survival outcomes stratified by clinically important variables. While controlling for gender, age, stage, and location of tumor, we show that STS patients living in rural locations or belonging to the lowest income quintile have lower overall survival.

Clinical Implications

Regarding STS treatment regimens in a country with universal healthcare, we are the first to provide population-based treatment information. We are the first to demonstrate at 15% relative increase in the use of radiation therapy for localized soft tissue sarcoma (stage 1&2). We are also the first to demonstrate a 36% increase in the use of chemotherapy for stage 4 STS patients.

Regarding outcomes, we further the literature by providing population-based 15 and 20-year survival estimates stratified by age, stage and tumor location. Where possible, our 5 and 10-year survival estimates can be considered alongside other published estimates.

Our demonstration of decreased overall survival for patients living in rural locations or belonging to the lowest income quintile are novel for Canadian STS patients, and surprising given the universal nature of our healthcare system.

Methodological Implications

These studies are the first to use Canadian population-based data to investigate sarcoma patients. Furthermore, this work directly led to international collaborations on two different projects.

We published a joint study with colleagues from Rutgers who use the SEER database [DOI: 10.1002/jor.24387]. We compared the incidence, demographics, and survival of all rhabdomyosarcoma subtypes across the SEER and ICES databases. This is the first paper published in sarcoma research to use population-level data from two countries.

Conclusion

In this thesis, we use population-level data to determine that STS patients with localized disease are increasingly being treated with radiation, while the use of chemotherapy is increasing in Stage 4 patients. We provide survival outcomes stratified by age, stage, tumor location. We demonstrate for the first time that rurality and low income are associated with This work led to the first international collaborations culminating in the first published manuscript in sarcoma literature using population-based data from two countries.

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