TEMPORAL TRENDS IN THE TREATMENT COMPLEXITY OF COLORECTAL CANCER AT BC CANCER BETWEEN 2000 AND 2012

by

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis/dissertation entitled:

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ABSTRACT

Background: Substantial advances in chemotherapy for colorectal cancer (CRC) occurred between 2000 and 2012, potentially contributing to increased treatment complexity. The objective of this study was to quantify trends in CRC treatment complexity associated with chemotherapy, a primary modality for CRC treatment.

Methods: Electronic medical records for patients with stage I-IV CRC referred between 2000 to 2012 to the six oncology centers comprising the British Columbia Cancer Agency were included in this study. Trends in treatment complexity were evaluated following a phase of care approach, which stratified all analyses by five phases: I and II (first six months of adjuvant and continued adjuvant therapy), III and IV (first six months of palliative and continued palliative therapy), and V (last six months of life). Colon and rectal patients were evaluated separately due to differences in treatment. Treatment complexity was measured using 12 metrics: count and frequency of clinic visits, chemotherapy infusion treatment (CIT) visits, and chemotherapy prescriptions, as well as mean duration, total duration, and total duration per year of visits. Metrics describing count and frequency were modelled using quasi-Poisson regression models, while metrics describing duration were modelled using generalized linear regression models with Gamma distribution and log-link. A total of 120 regression models were used to evaluate trends of CRC treatment complexity

Results: A total of 14,759 patients were included in the final analyses. Counts and frequencies of clinic visits increased in all phases for rectal cancer patients, and for all phases except phase V for colon cancer patients; CIT visits increased in phase II-V among colon and rectal cancer patients but decreased in phase I; prescriptions in phases II-IV in both tumor sites increased but did not change in phases I and V. Significantly longer visits were found in 57 of 60 visit duration models; no change was found only in total duration of clinic visits per year among rectal cancer patients in phases II-IV.

Conclusions: CRC patients initiating a phase of care in 2012 received significantly more complex treatment than patients initiating in 2000, which may have had significant implications for resource allocation and patient experience.

LAY SUMMARY

Medical advancements have rapidly increased systemic therapy options available for colorectal cancer patients. These advancements have improved patient outcomes but have also contributed to an unsustainable increase in the treatment complexity and cost of cancer care. The need to better understand how and why these increases are occurring is clear, however most studies on this topic analyze aggregated data, rather than compiling visit-level results. Existing studies also often focus on the dollar value, which does not reveal whether increased costs are driven by more frequent use or increased value. This limits comparisons across nations, or even between centers, as the monetary value of healthcare services vary between even proximate and similarly developed regions. This study aims to provide a detailed understanding of trends in the complexity of chemotherapy for colorectal cancer referred to BC Cancer between 2000 and 2012 by describing complexity in real terms such as visits and duration.

PREFACE

All the work presented henceforth, including all projects and associated methods, were approved by the University of British Columbia's Research Ethics Board [certificate # H14-02271].

An early version of the study was presented at the ASCO Annual Conference 2016 and ASCO Annual Conference 2017[1,2]. I was the lead investigator, responsible for all major areas of concept formation, data collection and analysis, as well as manuscript composition. Spinelli J was the supervisory author on this project and was involved throughout the project in concept formation, data acquisition, statistical methodology, and manuscript composition. Kennecke HF was the clinical supervisory co-author on this project and was involved throughout the project in concept formation, data acquisition, and manuscript edits. Cheung WY provided practitioner perspectives in medical oncology early in the study and was involved in concept formation and contributed to the health services research approach taken in the study.

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I would like to offer a special thanks to Dr. Winson Cheung and Dr. Hagen Kennecke, who began mentoring me in 2010 and 2011 respectively, and have given me the opportunity to participate in numerous research initiatives. It is thanks to their willingness to mentor young scientists that I, and many others, could pursue their careers in oncologic research.

Finally, I would like to acknowledge my family and friends, who give me the will and purpose to keep on keeping on. Your encouragements have been a great source of motivation, as have my sister's frequent and highly insightful commentary on the "thesis that never ends". Thanks Annie!

DEDICATION

I dedicate this dissertation to my parents, Alan Paochin Chen and Grace Shuyin Tsai, who sacrificed their careers and personal lives to immigrate to Canada so that I could be here today.

1 INTRODUCTION

1.1 RESEARCH OBJECTIVES

Objective: To quantify temporal trends in the treatment complexity of chemotherapy and clinic visits among colorectal cancer patients referred to BC Cancer.

1.2 BACKGROUND

1.2.1 Colorectal Cancer

Colorectal cancer is defined as the malignant neoplasm originating from cells of the colon or rectum[3]. Due to their many commonalities, they are often categorized together. This type of cancer is frequently curable if diagnosed and resected early in its development, and odds for recurrence can be further decreased by use of systemic therapy or radiotherapy to compliment surgical therapy. If the disease is untreated while in its earlier stages, however, the odds for patient survival are drastically reduced. In 2017, it is estimated that 26,800 Canadians were diagnosed with colorectal cancer and 9,400 Canadians died due to colorectal cancer. Currently, colorectal cancer is the most commonly diagnosed cancer in Canada (excluding non-melanoma skin cancers), and is the second leading cause of death from cancer among Canadian men and third leading cause of death from cancer among Canadian women. Prognosis following diagnosis remains suboptimal, with five-year net survival being 63% among Canadian men and 65% among Canadian women.

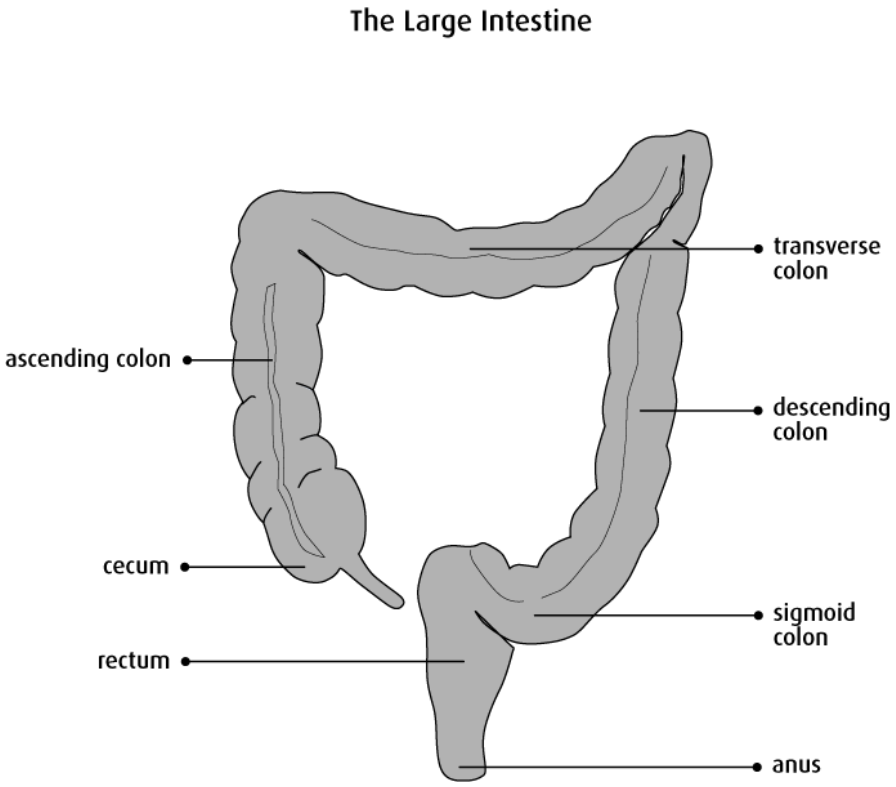


Figure 1-1. Anatomy of the large intestine.

Adapted from: www.cancer.ca/en/cancer-information/cancer-type/colorectal/colorectal-cancer/

1.2.2 Developments in Systemic Therapy for Colorectal Cancer (2000 to 2012)

Standard treatment for colorectal cancer is complex and highly dependent upon characteristics of the disease, such as genetic characteristics of the tumor cells, how advanced the tumor is at patient presentation and what types of treatments had been used to treat it previously. Like many other diseases, colorectal cancer develops resistance to treatments used on it over time through evolution. Tumour cells which are sensitive to a regimen of chemotherapy or targeted therapy die off, leaving cells with decreased sensitivity. Over time, if the cancer cells are not destroyed by the treatment, evolutionary selective pressures will prefer cells that can thrive despite cytotoxic treatment[4]. When a tumor has been observed to have grown despite a type or combination of chemotherapy, it is described as having “progressed”. When a treatment is deemed ineffective, medical oncologists will prescribe a new type of treatment if one is available. The differing types of drugs or regimens to be attempted are known as “lines” of therapy, and it should be noted that changes in dosage or administration time

without altering the types of drugs are not considered novel lines. At the beginning of the study period, few lines of therapy were available for colorectal cancer patients, and the use of 5-fluorouracil with leucovorin was considered to be standard first line therapy.

Between 2000 and 2012, the number of approved systemic therapy regimens for treating colorectal cancer in both the adjuvant and metastatic disease settings grew at a vastly increased rate compared to the decades prior. These developments had a profound impact on the complexity of treatment for colorectal cancer from diagnosis to palliative care, consequently resulting in a greater burden of care for both providers and patients in return for improved quality of life, extended progression free survival, and even improved overall survival. One source, for example, reports that 5-year relative survival in the United States has increased from 48.6% in 1975 to 66.4% in 2009[5].

To better understand how use of chemotherapy at BC Cancer has affected the complexity of treatment for colorectal cancer between 2000 and 2012, it is important to first have a firm understanding of how these drugs are administered, and of how novel medical innovations are reviewed and approved in Canada and in British Columbia. Drug approval in Canada is a two-tiered process, where the federal government's Health Canada generally first issues a notice of compliance after ascertaining clinical safety and efficacy, and then provincial agencies determine whether to approve based on cost-effectiveness[6]. In addition to discussing the timeline for the approval of oncologic drugs for treating colorectal cancer in Canada and BC, approval in the United States by the US FDA will also be discussed due to the comparability of the evidence used. The decision to discuss approvals by the US FDA but not the European Medical Association (EMA) is due to the geographic proximity of Canada and the US, and the relatively frequent establishment of joint US-Canadian clinical trials.

1.2.3 Capecitabine (Xeloda)

Capecitabine, marketed as Xeloda, is a prodrug of 5-fluorouracil (5FU), an agent which had been a mainstay of chemotherapy for colorectal cancer since 1962 when it was reported to be effective for treating breast, colorectal, stomach, cervix, ovary, and hepatoma cancers[7]. 5FU is usually administrated via intravenous infusion either as an intravenous bolus or via continuous infusion to a patient depending on the regimen[8]. Comparatively, capecitabine could be administered orally, which reduced the treatment burden for patients since it could be administered without the need to insert an IV-line.

Capecitabine was initially approved on April 30th 1998 by the US FDA for treatment of metastatic breast cancer[9], then for first-line treatment of metastatic colorectal carcinoma when treatment with fluoropyrimidine monotherapy is preferred on April 30th of 2001[10,11]; this approval was granted following completion of the randomized controlled trial SO14796, a large phase III study where 602 patients were randomized to treatment with capecitabine or 5FU/LV[12]. Oral capecitabine was found to achieve non-inferiority for OS and DFS compared with IV 5FU/LV and was associated with meaningful safety advantages and improved convenience. Further testing in the adjuvant colon cancer setting was performed in the capecitabine in Adjuvant Colon Cancer Therapy (X-ACT) trial which enrolled 1987 patients in 164 centers[13,14]. The study found non-inferior DFS, significantly fewer fluoropyrimidine-related grade 3 or 4 adverse events, fewer AE-related hospital admissions, savings in direct costs in drug administration and AE-related costs, and reduced patient travel time and costs. When used as adjuvant therapy for colon cancer, it was estimated that the total cost savings achieved by using capecitabine instead of 5FU/LV were £4,969 in the UK and $1,935 in the United States when both direct and indirect costs were considered. It should be noted that benefits were more limited in the US than the UK due to substantially higher cost for the drug acquisition of capecitabine in the US ($10,174 compared to £2,081). These findings led to the approval of capecitabine in the adjuvant setting for colon cancer on June 15th 2005 by the US FDA[15].

Compared to the US FDA, Health Canada authorized capecitabine several months earlier. Health Canada issued a NOC for capecitabine as an antineoplastic agent on August 31st of 1998[16], authorized first line treatment of patients with metastatic colorectal cancer on July 17th 2000[17], and approved use of capecitabine for adjuvant treatment of patients with colorectal cancer on December 7th of 2005[18]. BC Cancer incorporated capecitabine into its BC Cancer Agency Cancer Drug Manual in 2001[19].

In addition to being approved for monotherapy, capecitabine has also been approved for use with oxaliplatin in the XELOX regimen[20–22]. Multiple studies have also been performed to show that regimens substituting 5FU/LV with capecitabine are non-inferior, and retain superior cost-effectiveness around the world. For example, one study performed in an Italian hospital found that in the adjuvant setting XELOX costed €1,402.10 less than FOLFOX4 per cycle and €18,623.40 over the entire duration of treatment. Despite higher direct drug costs in the XELOX regimen, considerable savings were achieved in XELOX by decreases in expenditures associated with administration, catheter positioning, and therapy maintenance[23]. In Hong Kong, it was found that total treatment cost for FOLFOX4 costed 37% more than XELOX, with XELOX requiring decreased direct and indirect costs for both patients and providers[24].

Despite the higher drug costs associated with capecitabine, it would need to cost 4 times its value before the average per patient cost of XELOX would be equal to FOLFOX. XELOX was also found to be more cost-effective than FOLFOX in Japan[25], China[26], and the United States[27].

1.2.4 Oxaliplatin (Eloxatin), FOLFOX, and XELOX

Oxaliplatin (marketed as Eloxatin) is a type of chemotherapy agent known as a platinum-based alkylating agent, which works by non-specific cytotoxicity. It is generally used to treat colorectal cancer as part of a multidrug regimen including fluorouracil, leucovorin, and oxaliplatin (FOLFOX).

Oxaliplatin first received accelerated approval by the FDA on August 9th 2002 for use as part of the FOLFOX regimen to treat advanced colorectal cancer following disease recurrence or progression on bolus 5-FU/LV and irinotecan (FOLFIRI) [28,29]. Accelerated approval for previously treated metastatic colorectal cancer patients was granted following a multicenter, open-label, randomized, three-arm controlled superior study conducted in the US and Canada which enrolled 821 patients comparing patients on oxaliplatin + 5FU/LV (FOLFOX), 5FU/LV, and monotherapy oxaliplatin[30]. In this study, 73.3% of patients on FOLFOX achieved either a complete response, partial response, or disease stabilization compared with 48.5% among patients on 5FU/LV and 46.4% among patients on oxaliplatin. Additionally, patients on FOLFOX had a median time to progression of 5.3 months compared to 2.6 months among 5FU/LV patients (p=0.001).

FOLFOX was approved by the FDA on January 9th 2004 for the initial therapy of advanced colorectal cancer following another North American multicenter open-label randomized controlled study which found that FOLFOX was superior to FOLFIRI along multiple metrics: median overall survival of 19.4 months and 14.6 months respectively, HR 0.65 (0.53-0.80), p<0.0001; median time to progression of 8.7 months and 6.9 months respectively, HR 0.74 (0.61-0.89), p=0.0014; and complete or partial response rate of 45.3% and 32.5% respectively, p=0.0075[31,32].

On November 4th of 2004, the FDA approved FOLFOX for adjuvant treatment of stage III colon cancer following the MOSAIC study which assessed FOLFOX in the adjuvant setting among both stage II and stage III colon cancer patients[33,34]. This study enrolled 2246 patients at 146 centers in 20 countries, randomizing 1123 patients to FOLFOX and 1123 patients to 5FU/LV. Use of FOLFOX among stage III patients showed a higher rate of 3-year DFS (72.2% vs 65.3%, HR 0.76 [0.62-0.92]) and 5-year DFS

(66.4% vs. 58.5%, HR 0.76 [0.64-0.91]) compared with 5FU/LV alone. Similarly, 6-year OS was higher in stage III patients using FOLFOX than those using 5FU/LV (72.9% vs. 68.3%, HR 0.80 [0.66-0.98]). DFS and OS among stage II patients were higher than stage III patients but did not show significant differences between the two arms.

In Canada, confidential data for oxaliplatin was initially not submitted to Health Canada due to incomplete intellectual property protection, and submission may have resulted in immediate genericization of the drug[35]. The situation was eventually resolved, and in 2006 Sanofi-Aventis submitted data to Health Canada for review. The drug was finally authorized federally on June 15th 2007[36] and shortly thereafter authorized for use in the adjuvant setting for stage 3 colon cancer patients on December 18th 2007[37]. BC Cancer incorporated oxaliplatin into its Cancer Drug Manual in 2001, and patients could be provided access through the Special Access Program in the absence of a notice of compliance from Health Canada[35,38].

Oxaliplatin has also been used in combination with capecitabine (capecitabine) following its introduction as a non-inferior drug to 5FU with safety benefits and savings in direct and indirect costs for both healthcare providers and patients. The regimen combining Eloxatin and capecitabine is known as XELOX, and it is used as a non-inferior alternative for FOLFOX for both first-line and subsequent lines of treatment for metastatic colorectal cancer[20,22,39].

1.2.5 Bevacizumab (Avastin)

Bevacizumab (market name Avastin) is an IV administered recombinant humanized monoclonal antibody vascular endothelial growth factor (VEGF) inhibitor[40]. Bevacizumab functions by selectively binding to the VEGF protein which drives vascularization, thereby slowing tumor growth by inhibiting the ability of tumors to form blood vessels. Bevacizumab was approved by the FDA on February 26th 2004 for 1st line treatment for metastatic colorectal cancer in combination with 5FU based treatments following a randomized clinical trial of 813 patients[41]. In this study, patients were randomized to FOLFIRI with bevacizumab or FOLFIRI with placebo. The bevacizumab arm was superior to the placebo arm in a number of ways including: median duration of survival of 20.3 months compared to 15.6 months (HR 0.66, $p<0.001$), median duration of PFS was 10.6 months compared to 6.2 months (HR 0.54, $p<0.001$), rate of response of 44.8% compared to 34.8 ($p=0.004$), and the median duration of the response was

10.4 months compared to 7.1 months (HR for progression 0.62, p=0.001)[42]. Health Canada issued a notice of compliance for bevacizumab on September 9th 2005[43], and BC Cancer incorporated bevacizumab into its BC Cancer Agency Cancer Drug Manual in April 2006[44].

Due to its high cost, economic feasibility and cost-effectiveness are major considerations surrounding the use of bevacizumab. In the United States, 1 cycle (8 weeks) of bevacizumab is estimated to cost $9,324 and was estimated to have an incremental cost-effectiveness ratio of $571,240 per quality-adjusted life-years QALY during first-line therapy, and $364,083 per QALY in the second line setting[42,45]. Another cost-effectiveness analysis performed in England and Wales found adding bevacizumab in addition to 5FU/LV in first-line treatment of metastatic colorectal cancer would cost £88,436 per QALY gained[46]. Cost-effectiveness studies for bevacizumab tend to view it as not cost-effective, due to the high price for drug acquisition associated with its modest clinical benefits. A study of bevacizumab in the cervical cancer setting concluded that in order for it to be cost-effective, the price of bevacizumab would need to be 25% of its baseline price[47].

1.2.6 Anti-EGFR drugs cetuximab (Erbitux) and panitimumab (Vectibix)

Two anti-EGFR drugs to treat metastatic colorectal cancer were released between 2000 and 2012, both of which were monoclonal antibodies that target the EGFR proteins often overexpressed on the surface of cancer cells. The first of these drugs, cetuximab (Erbitux), received accelerated approval by the FDA on February 12th 2004 for the treatment of metastatic colorectal cancer in patients who are refractory to irinotecan-based chemotherapy[48]. Approval was granted based on early findings in a randomized clinical trial with 329 patients with irinotecan-refractory metastatic colorectal cancers[49]. The study did not test for a control group, but instead tested cetuximab plus irinotecan and cetuximab monotherapy. This study found that although cetuximab plus irinotecan had improved rates of response and improved time to progression, both arms had significant clinical activity in irinotecan-refractory colorectal cancer. The efficacy of cetuximab was further explored in a phase III randomized trial titled “cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer” (CRYSTAL), which enrolled 1,217 patients between August 2004 and October 2005. Patients were randomly enrolled to receive either cetuximab plus FOLFIRI or FOLFIRI alone. The study showed that cetuximab plus FOLFIRI modestly extended median PFS to 8.9 months compared to 8 months in the control arm (p=0.036). Response rate

also increased in the arm receiving cetuximab, at 46.9% compared to 38.7% in the control arm (p=0.005)[50].

Panitumumab was approved by the FDA on September 27th in 2006[51], following completion of a phase III trial evaluating monotherapy panitumumab against best supportive care in patients with metastatic colorectal cancer[52]. By October 2nd 2007, the FDA had granted accelerated approval for the expansion of cetuximab monotherapy to colorectal cancer after failure of both irinotecan and oxaliplatin-based regimens, and authorized cetuximab monotherapy for patients with metastatic colorectal cancer who were intolerant to irinotecan-based chemotherapy[53]. By July 17th 2009, the FDA narrowed the use of both cetuximab and panitimumab to only patients with wildtype *KRAS,* following recommendations by its Oncologic Drugs Advisory Committee (ODAC)[54]. This change was made following review of multiple clinical trials, although trailing a year behind a similar motion by the European Medicines Agency following findings of the lack of efficacy of anti-EGFR therapies in patients with the *KRAS* mutation[55]. Further analysis of the CRYSTAL trial was published in 2015 that corroborated that significant benefit in all efficacy endpoints were observable in patients with wildtype *RAS*, while patients with *RAS* mutations did not derive benefits from the addition of cetuximab to FOLFIRI[56].

Authorization for Erbitux in Canada was initially granted on September 9th 2005 by Health Canada for use in combination with irinotecan for metastatic colorectal cancer patients who have been chemorefractory on other irinotecan-based therapies[57]. Erbitux was eventually authorized for use with FOLFIRI in the first line setting for metastatic colorectal cancer[58]. BC Cancer developed a monograph for use of Erbitux on June 1st 2009, approximately the same time that the FDA narrowed the use of cetuximab to patients with *KRAS* wildtype colorectal cancer[59].

The other anti-EGFR drug, panitimumab (Vectibix), was first approved by the FDA on September 27th 2006 for treatment of EGFR-expressing metastatic colorectal cancer with disease progression on fluoropyrimidine, oxaliplatin, and irinotecan containing chemotherapy regimens[60]. This approval was granted based on preliminary results from clinical trial 20020408, which enrolled 463 participants with previously treated EGFR expressing metastatic colorectal cancer between January 2004 to June 2005[61]. Patients were randomized to either panitimumab plus best supportive care or best supportive care alone. This study found that patients who received panitimumab plus best supportive care had a median PFS of 8 (95% CI 7.9-8.4) weeks compared to 7.3 (95% CI 7.1-7.7) weeks among patients who received best supportive care alone. Furthermore, patients who received panitimumab had better objective response rates (p<0.0001). OS was not significantly different between the two arms, but the study

attributed this lack of difference to confounding associated with rapid crossovers from the control arm to the intervention arm. The phase III clinical trial entitled 'panitimumab randomized trial in combination with chemotherapy for metastatic colorectal cancer to determine efficacy' (PRIME) further demonstrated the clinical efficacy of panitimumab in the first-line setting for metastatic colorectal cancer. This study found that patients who were administered panitimumab plus FOLFOX had superior median PFS (p=0.03) and significantly improved OS among wildtype *KRAS* patients (p=0.03)[62]. Following these findings, the FDA approved panitimumab plus FOLFOX for the treatment of metastatic colorectal cancer on May 23rd, 2014[63]. The ASPECCT randomized clinical trial compared panitimumab monotherapy with cetuximab monotherapy, finding that OS among patients receiving panitimumab was non-inferior to those receiving cetuximab[64]. Although it was approved later than cetuximab, panitimumab was marketed at a lower price, with projected cost savings of $9,468 (16.5%) per patient treated with panitimumab instead of cetuximab[65].

Health Canada issued a notice of compliance to Amgen on April 3rd of 2008, authorizing its use for the treatment of metastatic colorectal cancer[66]. Panitimumab was included in BC Cancer Cancer Drug Manual on August 1st 2009, just two months after Erbitux was approved in British Columbia[67].

Although both panitimumab and cetuximab are widely used to treat chemo-refractory colorectal cancer, it is well recognized that the price associated with each are significantly higher than previous systemic therapy drugs. For comparison, the 2014 cost for 1 cycle (8 weeks) of the relatively expensive drug bevacizumab in the United States was estimated to be $9,324, but even that pales in comparison to the $20,856 per cycle cost for cetuximab, and total treatment costs across all cycles were estimated to be $39,000[68]; panitimumab was marketed at approximately 20% less than cetuximab[65].

1.2.7 Regorafenib (Stivarga) and aflibercept (Zaltrap)

Regorafenib (Stivarga) and aflibercept (Zaltrap) were among the most recent FDA-approved drugs to fall within the study period of interest between 2000 and 2012, and continued the trend for increasing costs for diminishing clinical benefits[69]. While both of these drugs were approved at BC Cancer well after the period of interest, they will still be discussed here due to the possibility that patients may still have accessed them through either clinical trials, compassionate access programs, or special access programs.

Aflibercept is an intravenously administered fusion protein compound which binds to the VEGF protein, thereby performing a similar role as bevacizumab. It was approved on July 25th 2012 by the FDA for use in combination with FOLFIRI in patients with metastatic colorectal cancer, following positive findings in the randomized placebo-controlled trial VELOUR. The VELOUR trial enrolled a total of 1,226 patients with metastatic colorectal cancer who were chemo-refractory to oxaliplatin based therapy. Patients were randomized to FOLFIRI plus aflibercept or FOLFIRI plus placebo, with the intervention arm showing improved median OS of 13.5 months to 12.1 months (HR 0.82, p=0.0032) and improved median PFS of 6.9 months to 4.8 months (HR 0.76, p=0.0007). While it's hypothetically possible for patients in British Columbia to access aflibercept prior to the end of 2012, this drug was not authorized by Health Canada until February 12th 2014[70], and has not yet been included in BC Cancer Cancer Drug Manual as of 2017.

Regorafenib is an orally administered small molecule multi-kinase inhibitor which target a number of proteins associated with cancer processes, including angiogenic, stromal, and oncogenic targets. It was approved by the FDA on September 20th 2012 for use in patients with metastatic colorectal cancer who have progressed on fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, as well as anti-VEGF therapy and anti-EGFR therapy, if the cancer has the wildtype form of *KRAS*. Approval was granted following the large multicenter randomized trial "CORRECT" which enrolled 760 patients with metastatic colorectal which progressed on all other FDA-approved therapies[71–74]. This study randomized patients at a 2 to 1 regorafenib to placebo ratio and found that patients receiving regorafenib benefited from improved median OS to 6.4 months compared to 5.0 months in the placebo arm (HR 0.77, 95% CI 0.64-0.94, p=0.0052). Median PFS was also improved from 1.9 months to 1.7 months in the placebo arm (HR 0.49, 95% CI 0.42-0.58, P<0.0001). Regorafenib provided on average a benefit of 0.04 QALYs (0.13 life-years) at a cost of $40,000 USD, comparable to an incremental cost-effectiveness ratio of $900,000 per QALY[75]. Regorafenib was issued a notice of compliance by Health Canada for their new drug submission on March 11th 2013[76], and included in BC Cancer Cancer Drug Manual on February 1st 2015[77].

1.2.8 Economic Burden of Illness in Oncologic Care (US and Canada)

While the primary objective of this study is not to assess monetary costs of oncologic care, the importance of monetary considerations for healthcare providers cannot be denied. In order to provide readers with contextual knowledge to consider alongside the findings of this study, a brief introduction of the economic burden of illness in oncologic care in the US and Canada is provided.

Today, the increasing cost of oncologic care is a well-studied area with studies ranging from studies of clinic-level expenditures to national or even international estimates of economic burden. These studies have demonstrated that in developed nations around the world, the cost of oncologic care is growing at a rate which outpaces GDP growth in many if not most countries, and at a disproportionately higher rate than expenditures in many other areas of healthcare[78,79]. This increased cost is the result of a combination of factors including: a surge in the prevalence of certain tumors due to an aging demographic and extended patient survival following cancer diagnosis[80–82]; increased expenses for systemic therapy, especially as it pertains to novel agents such as targeted drugs[83]; and the increased use of hospital resources, equipment, and other healthcare professional services associated with these factors[84].

To demonstrate this, an analysis of the increasing cost of oncologic care in the United States found that from the period of 1998-2000 to 2010-2012, the annual total US oncologic care expenditure increased 37.4% from $104.5 billion to $143.6 billion dollars adjusted to US 2014 Dollars[85]. During the 14 years analysis period of this study, the total prevalent cases grew at an annualized 1.2%, but was outpaced by the 2.9% annualized increase in expenditures after adjusting for inflation. A detailed breakdown found that over the analysis period, expenditures associated with: hospital increased from $57.8B to $74.1B (+28.2%), nursing home and home health increased from $7.0B to $9.5B (+35.7%), professional and clinical services increased from $34.7B to $50.8B (+46.4%), and retail prescription medications increased from $3.0B to $9.2B (+206.7%). In this study, professional and clinical services included the cost of prescription drugs that were administered and billed during the same patient encounter.

In a comparable timeframe, the cost of oncologic care in Canada has also increased from $2,462.4 million in 1998 to $3,828.2 million in 2008 (55.4% increase) in CA 2010 Dollars[86,87]. During this analysis period the total two-year prevalence cases increased on average 1.5% each year[88], but was outpaced by the 4.11% annualized increase in expenditures after adjusting for inflation[86,87]. Statistics Canada measured direct costs of oncologic care in four categories: hospitals, drugs, physician care, and additional direct costs. Over the analysis period, expenditures associated with: hospitals remained nearly constant from $2,344.9M to $2,329.4M (<1% change), physician care increased from $268.2M to $467.1M (+74.2%), and drugs increased from $268.2M to $467.1M (+74.2%). Economic burden of illness data for 2012 was not available from Statistics Canada, making it difficult to compare results directly with the US study.

In virtually all measurements of the economic burden of illness in oncologic care encountered during literature review, studies and government reports alike provide a birds-eye view macro approach to estimating the burden of oncologic care. This approach has the advantage of being relatively simple to perform when analyzing on a regional to national scale, especially when appointment-level or individual-level data is not readily available. Conversely, a macro approach also means that only aggregated metrics are assessed, without a deeper understanding of details on the individual-level. Additionally, the results of studies currently available in literature also tend to present the burden of illness in monetary terms; although these results are often adjusted for inflation, it is impossible to insulate monetary measures from factors in the larger economic environment. Factors ranging from different monetary values associated with healthcare resources and services across jurisdictions to currency exchange rates may affect the price associated with oncologic care. The consequence of this is that it can be difficult to compare trends in the burden of care across healthcare regions or to directly measure changes in services provided on the individual level.

1.2.9 Treatment Complexity of Oncologic Care

The increase in use of oncologic care has primarily been measured in the form of expenditures and health economics, so it is difficult to determine the actual change in cancer resource use from a health services perspective. In this study, some of the influences on the cost of systemic therapy are examined, the number of clinic or chemotherapy infusion visits and their duration. In contrast to monetary measures, direct measures of oncologic care such as the duration of chemotherapy infusion treatment (CIT) visits or the frequency of medical oncologist clinic visits (hereafter referred to as clinic visits) are readily comparable between countries and over time.

Use of hospital scheduling data or comparable electronic medical records in analyses enable the description of these direct measures at the individual-level and appointment-level without making assumptions about the “average” individual or appointment; a feat which is not possible when using a macro level approach. A detailed discussion of the degree of challenge in comparing cost-studies of colorectal cancer treatment can be found in a 2013 systematic review by Yabroff et al, which emphasized how heterogeneity in approaches, data sources, and other study characteristics severely limit the ability to compare studies across countries and settings[89]. In contrast to “top-down” approaches which use aggregated data to estimate per-individual costs, studies which directly use per-individual data can analyze more granular data without making as many sweeping assumptions.

Furthermore, in contrast to studies which measure cost of oncologic care in only monetary terms, studies which present the findings in physical metrics such as duration and number of visits can be readily compared across countries and settings.

During the review of existing literature in 2014, only one study was found which assessed treatment complexity as defined in this thesis. Sumpio et al (2016) used the same terminology to describe modern chemotherapy and supportive care visits, defining treatment complexity as three main metrics: the number of visits, the total duration of visits, and the average duration per visit[90]. The authors reviewed electronic medical records from 121 patients with stages III and IV cancer, originating from a single NCI-designated Comprehensive Cancer Center in the Northeastern United States. This small study found that colon/esophageal patients experienced the most hours overall in treatment (mean of 23.5 hours) and the lengthiest chemotherapy infusion visits of all diagnosis groups (61.2% of patients spending on average more than 3 hours per visit), a finding which correlated well with the common use of the multidrug FOLFOX regimen. Sumpio et al found no studies available to compare the time burden of oncologic care, which was consistent with the literature review conducted during this study. By using data at a per-individual level, Sumpio et al successfully described important metrics in resource use at a cancer center for chemotherapy infusion visits and associated supportive care visits without making assumptions about the "average" population. Although this study successfully accomplished its goals to describe treatment complexity as a snapshot in time, the sample was limited to just a single center and included relatively few patients.

This study aimed to perform an analysis on the treatment complexity of chemotherapy for the outpatient management of stage I-IV colorectal cancer at 5 large cancer centers offering predominantly medical oncology and radiation oncology care and treatment delivery. The measures of treatment complexity included in this study are intended to capture changing resource needs in medical oncology. Significant trends in treatment complexity will have relevance for design and planning of oncologic care delivery centers and manpower planning of oncologists, oncology nurses and pharmacy. It will also have implications for patients with regards to time spent commuting, and time spent at treatment centers receiving chemotherapy infusions.

As of the writing of this thesis, this is the second study that has evaluated treatment complexity in oncology with this definition, and the first study to evaluate trends in treatment complexity. Due to the scarcity of previous research, treatment complexity has not been demonstrated to directly contribute to patient burden of care. Nor have any research on treatment complexity as defined in this study been

conducted as of this thesis to evaluate whether increased treatment complexity directly can be used by providers to detect adherence to protocol or workflow efficiencies.

Despite the lack of previous research, treatment complexity in oncologic care represents a closer description of the experiential realities as lived by patients and healthcare providers. Regardless of the value of a specific service delivered in a specific location, the meaning of one clinic visit or one chemotherapy visit can reasonably be assumed to be interpreted the same. Furthermore, the direct consequences on patients, such as an extra commute trip to receive treatment or time spent in clinic can also be inferred to be the same.

This easily interpretable metric of how much sheer volume of treatment services is being delivered is also helpful to healthcare providers. For providers, demand projections and throughput are ultimately described in terms of the numbers of expected services deliverable, even if their actual capacity to expand a facility to meet demand may be limited by available funding. Given the current scarcity of metrics like treatment complexity in literature, it is therefore proposed in this thesis that treatment complexity is important due to the following advantages that it holds over monetary metrics: it provides a closer description of actual services delivered, it can be interpreted consistently across jurisdictions where the value for specific services may differ greatly, and it can be utilized in demand projections of oncologic care needs.

2 METHODOLOGY

2.1 STUDY LOCATION & STUDY POPULATION CHARACTERISTICS

BC Cancer is the branch of the Provincial Health Services Authority which is responsible for developing treatment protocols and funding all publicly funded systemic cancer therapy delivered to BC residents, it is the sole provider of cancer radiation therapy in the province and an estimated 40% of all systemic cancer therapy delivered in the 6 comprehensive cancer centers. It consists of a network of regional and community treatment centres categorized from level 1 to level 4. Level 1 centres offer the minimum level of oncologic care services, and are limited to administering chemotherapy, while level 4 centres are teaching hospitals which offer comprehensive oncologic care. This study included data from all adult residents of British Columbia who were referred for colorectal cancer to any of the 6 level 4 regional centres in the province between January 1st 2000 and December 31st 2012. The six regional cancer centres open in British Columbia as of December 21st 2012 were the Abbotsford hospital and Cancer Centre, the Sindi Ahluwalia Hawkins Centre for the Southern Interior, the Centre for the North, the Fraser Valley Cancer Centre, the Vancouver Cancer Centre, and the Vancouver Island Centre. The Centre for the North in Prince George only opened early 2012 near the end of the study period, compared to the other five centres which were already open as of the beginning of the study.

2.2 SCOPE OF SERVICES INCLUDED

The full spectrum of oncologic care services provided in British Columbia is incredibly complex and involves numerous interacting components ranging from screening and diagnostic processes to treatments to end-of-life care. A single study to evaluate all moving parts is unfeasible due to challenges such as the lack of a common appointment scheduling system between all components, the differences in metrics which would be used to describe each service, and the sheer number of different components that would need to be included. This study focuses specifically on medical oncology treatments provided to colorectal cancer patients, and does not address any other component of the oncologic care services spectrum. Figure 2-1 below provides a non-exhaustive overview of the oncologic care services provided in British Columbia.

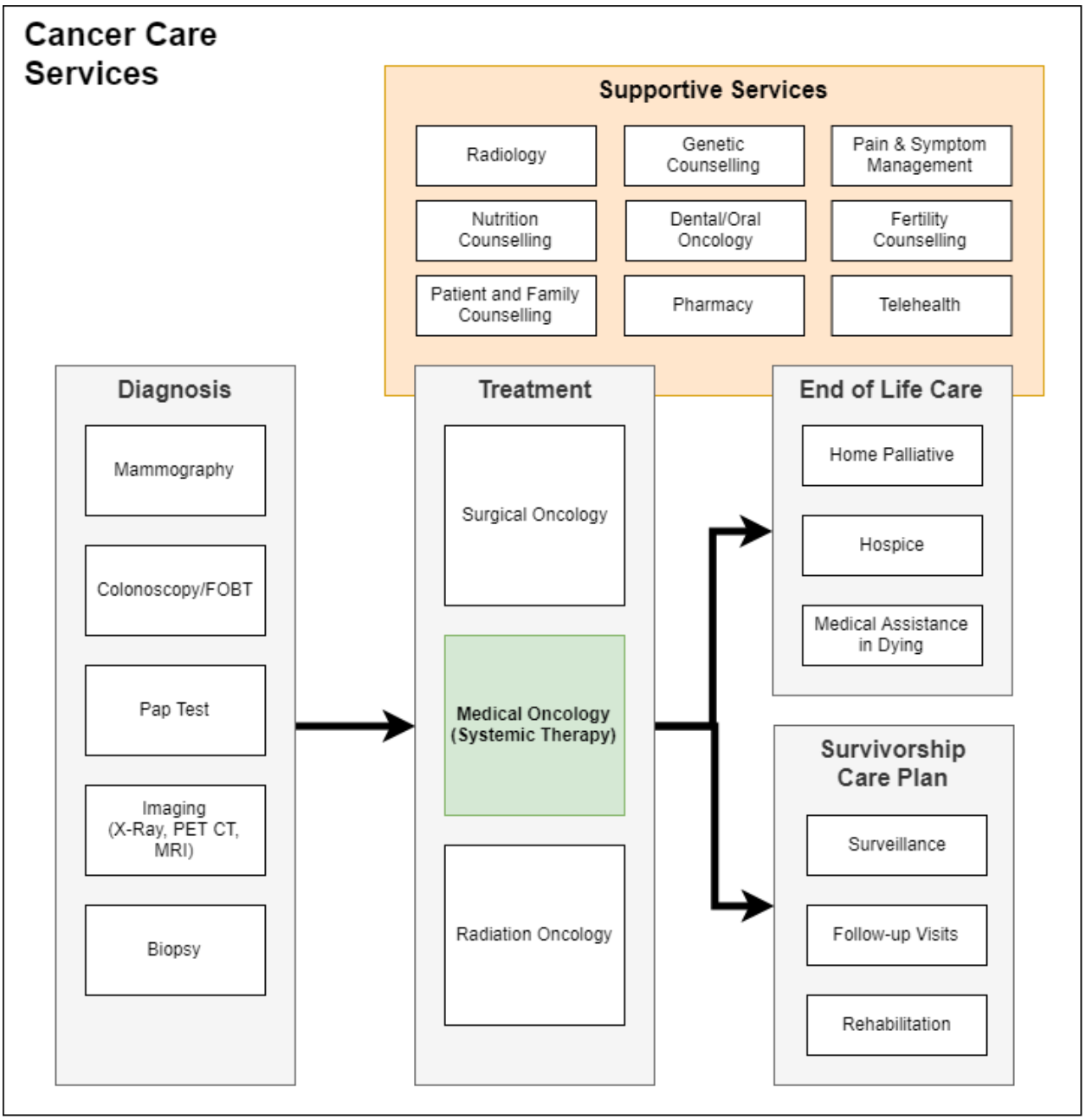


Figure 2-1. Spectrum of Oncologic care Services in British Columbia. *This diagram provides a non-exhaustive overview of the various oncologic care services provided in British Columbia. Note that this diagram includes only services directly relating to the patient's healthcare, and does not include the array of additional services that provide financial or logistical support to patients.*

2.3 Description of Data Sources

To conduct this study, data needed to be acquired and linked from a number of sources. Patient disease data at admission and appointment scheduling data were collected from BC Cancer's clinical database used in day-to-day clinical practice. Appointment scheduling data included clinical appointments to see medical oncologists, oncology nurses, and appointments for radiation treatment and systemic therapy delivery in Chemotherapy Infusion Treatment (CITs) visits. Dates and characteristics of cancer progression including recurrence and metastatic disease were collected from the Gastrointestinal Cancers Outcomes Unit (GICOU) at BC Cancer, which routinely enters this data while reviewing patient charts. Prescription data, including dosage, date dispensed, and characteristics of the agent dispensed were collected by BC Cancer Pharmacy. Finally, , the neighbourhood annual household income of the neighbourhood where patients resided was obtained from Population Data BC. Following research ethics approval and approval from all involved data stewards, the data was linked by each patient's uniquely identifying PHN (Provincial Health Number) by a data steward. Data from all sources were then assigned a study ID, and then all data were de-identified before being provided for analysis.

The data collected were multi-level in nature: level 1 data consisting of scheduling events that describes each clinic visit or CIT visit, or prescription data that describes the date and dosage of each agent dispensed to patients; level 2 data consists of patient disease characteristics, time of progression and type (recurrence or metastases), and patient characteristics such as socioeconomic status or urban-rural residency.

2.4 Defining the Metrics of Treatment Complexity

As with the definition for treatment complexity used by Sumpio et al, this study based metrics of treatment complexity on visit numbers and visit durations[90]. Visit numbers were: (1) the visit count, described as the total number of visits in a phase of care; and (2) the visit rate, described as the number of visits in a phase of care for each year that a patient was treated in that phase of care. Visit durations were: (1) the mean visit duration, specifically the average number of minutes for each visit in a phase of care; (2) the total visit duration, defined as the summated duration in minutes of all visits in a phase of care; and (3) the duration rate, defined as the total duration in minutes of all visits in a phase of care, standardized for each year that a patient was treated in that phase of care.

Furthermore, the objective of this study was not to perform a single measurement of treatment complexity at a specific point in time, but to measure trends in treatment complexity over time. For this purpose, changes in visit count over time are measured as a visit ratio, which is the expected number of visits for patients initiating a phase of care in a given year divided by the expected number of visits of patients who initiated that phase of care one year earlier. Changes in visit rate over time is measured as a visit rate ratio, defined as the visit rate for patients initiating phase of care in a given year divided by the visit rate of patients who initiated that phase of care one year earlier.

Trends in mean duration per visit and total duration of all visits in a phase of care are similarly measured as a geometric ratio describing annual multiplicative changes. Additionally, total duration of all visits was also measured as a rate ratio describing the trend in minutes of clinic per year in a phase of care. Measurements of the number of prescriptions and rate of prescriptions were similarly described as the prescription ratio and prescription rate ratio.

2.5 Defining Phases of Care

Treatment phases in this study was defined based on phases that are commonly defined by other health services research and health economics studies in oncology, with slight modification. In Oliveira et al 2017[91], for example, the following three phases of care were defined: (1) initial care, which includes any initial course of treatment and any adjuvant therapy, up to 6 months after diagnosis; (2) continuing care, which includes any treatment thereafter; and (3) terminal care, which captures any treatment in the last 12 months of life, including both palliative care services. The phase-based approach is used widely due to the different natures of treatment in each of these phases, and the usefulness of assessing treatments in these areas in a clinically relevant manner[91–95]. Compared to these previous studies, however, this study aimed to assess trends in oncologic care over a period of time when many novel therapeutics have been developed. To more fully capture the impact of these novel developments on multiple points through the natural history of colorectal cancer, a definition for phase-of-care was required which could differentiate treatments between metastatic and non-metastatic disease. For that purpose, this study introduced a 5-phase system with the following phases of care (Figure 2-2):

(Phase 1) initial treatment of non-metastatic (referred to as M0) disease, which captures any pre-or post-operative chemotherapy and radiation therapy of non-metastatic disease, during the first 6 months after diagnosis of non-metastatic (M0) disease;

(Phase 2) continued treatment or surveillance of M0 disease at BC Cancer clinics, taking place 6 months or longer after diagnosis of non-metastatic disease;

(Phase 3) initial treatment of metastatic (M1) disease, which captures any curative or palliative treatment during the first 6 months following diagnosis of metastatic disease or after metastatic relapse of the primary disease;

(Phase 4) continued treatment of M1 disease, which includes any curative or palliative treatment taking place 6 months or longer after diagnosis of metastatic disease; and

(Phase 5) terminal care, which includes any treatment which takes place during the last 6 months or less before a patient died.

Where there was any overlap, the phase with the larger number takes precedence. For example, if a patient was referred with non-metastatic (M0) disease and passed away 7 months later, then they would be considered to have spent 1 month in phase 1 of care and 6 months in phase 5 of care. As such, patients diagnosed with non-metastatic disease and subsequently relapsed would be represented in all 5 phases. Patients who presented with metastatic disease would only be represented in phases 3-5, while patient presenting with early stage who did not relapse would only be represented in phases 1-3.

Since the length that each patient may spend in a given phase of care can vary, two patients who initiated the same phase at the same time may progress to a later phase at different times, if at all. The treatment plan that a medical oncologist would consider for a patient who progressed to a later phase of care would be based on the options available at the time of phase initiation, rather than time of referral, hence analyses in this study focused on year of phase initiation rather than year of referral.

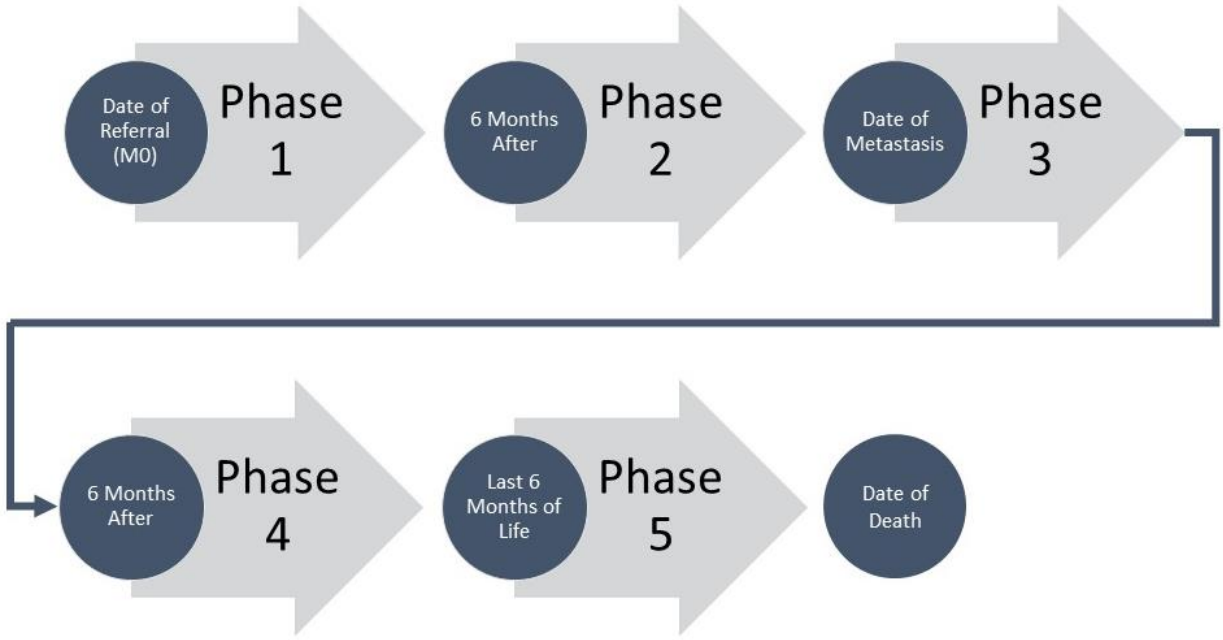


Figure 2-2. Visualization of the 5-phase definition for phase of care. *The 5-phase definition for phase of care allows for greater differentiation for treatment received for non-metastatic disease (M0) and treatment received for metastatic disease (M1), which the conventional 3-phase definition did not.*

2.6 Calculating Length of Care in Each Phase-of-Care

For each patient, the duration of time that they spent in each phase of care was calculated using the same three key dates used to define phases of care: the date of referral, date of metastatic disease, and the date of death. Using the definitions from Figure 2-2, the start date for each patient for each phase of care was calculated as the first date of the current phase of care until the first date of the next phase of care. In the case where the patient did not have a next phase of care, then for phases 1 to 4 the end of the phase was calculated as the most recent appointment. The most recent appointment was identified by searching BC Cancer's clinic appointment scheduling data, pharmacy prescriptions data, and radiation oncology treatment appointment data. For patients in phase 5 of care, the end of the phase was defined as the patient's date of death. Length of care for each phase was measured as the number of years spent in a given phase of care, with the smallest denomination being a single day. For example, a patient who spent 100 days in phase 2 of care would be considered to have a length of care of 0.27 years for that phase. Phases 1, 3, and 5 are capped at a maximum length of care of 0.50 by their definitions.

2.7 Missing Data and Multiple Imputation

Missing data was addressed differently depending on whether the missing field was in level 1 or in level 2. Level 1 data were complete with the exception of a considerable number of cases missing valid information on the duration in a phase. After follow-up with individuals knowledgeable with BC Cancer's Cancer Agency Information System (CAIS), it was determined that default duration values were generally pre-specified by type of appointment and by facility. In some instances, default values were either 0 or 1, which were not valid approximations for the length of the appointments they were specified with. In these cases, the data was treated as missing at complete random, and all analyses relating to the duration of clinic or chemotherapy treatment visits used multiple imputation by chained equations (MICE) to address the missing information. Multiple imputation is a method of predicting missing data akin to repeated draws from a Bayesian prediction model to generate multiple imputed data-sets[96]. Missing duration data were imputed via multiple imputation by chained equations, using the *mice* and *lme4* packages from R to perform two-level predictive mean matching based on appointment type and patient. Duration data was imputed with a single imputation cycle, as only a single level 1 data had missing value. Imputations were repeated using single iterations to generate 21 parallel imputed datasets, from which parallel analyses are performed. In the final step, all quantities from the analysis such as models' intercepts, effects, and errors are pooled following Rubin's rules[97,98]. The full process is visualized in Figure 2-3, which was adapted from Buuren et Groothuis-Oudshoorn[98].

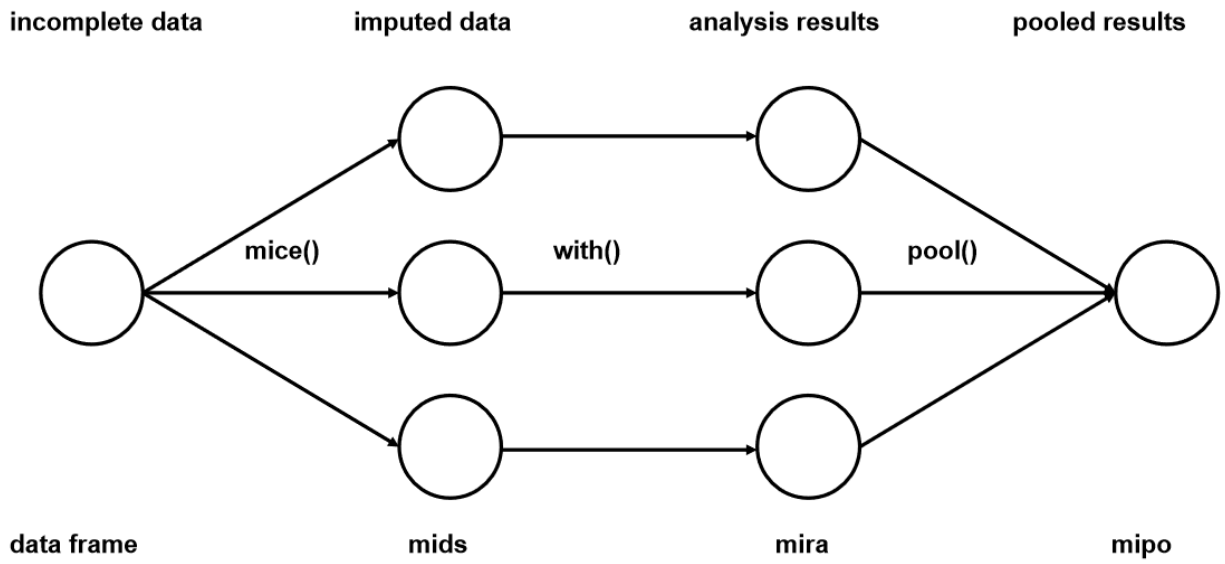


Figure 2-3. Main steps of multiple imputation[98]*. The original data frame with incomplete data is first imputed multiple times, which repeats the prediction process a specified number of times. Analyses are then performed for each imputed data set, and all quantities relating to the analyses are pooled at the end.*

Cases with missing level 2 data were excluded with the exception of patients missing tumor stage, where the tumor stage could be calculated from American Joint Committee on Cancer (AJCC) TNM scores for colon and rectal cancer[99]. T describes the invasiveness of the primary tumor, N describes whether the cancer had spread to lymph nodes (nodal metastases), and M describes whether the cancer had metastasized to distant organs. AJCC TNM scores were stored separately with each of T, N, and M scores being available both at the surgical and clinical levels in BC Cancer's CAIS database. Clinical TNM scores were used first whenever they were available, due to the greater relevance of disease status during first clinical assessment to treatment. However, if any of T, N, or M scores were missing, the missing scores were supplemented from the surgical TNM scores. After consultation with medical oncologists at BC Cancer, it was further established that it would be reasonable to assume that no distant metastases were present for cases where metastatic disease was unknown. This means that if both T and N status were known, then an overall tumor stage could be assigned to the patient even if it was not initially provided in the data. Table 2-1 presents how disease stage was assigned based on T, N, and M scores in this study.

Table 2-1. AJCC Colon and Rectal Cancer Anatomic Stage and Prognostic Groups. *The following scheme was used to assign an overall disease stage when it was not provided with the initial data. Note that while the full AJCC schemes finer categories such as stage 4A or 4B, this study used a more simplified scheme.*

Anatomic Stage/Prognostic Groups			
Stage	**T**	**N**	**M**
0	Tis	N0	M0, MX
1	T1,T2	N0	M0, MX
2	T3,T4	N0	M0, MX
3	Any	N1,N2	M0, MX
4	Any	Any	M1

All missing data imputation and related data analyses were completed using the 'mice' package in R created and maintained by Buuren et Groothuis-Oudshoorn (2011)[98].

2.8 Regression Analyses

Two types of outcomes were evaluated in this study: visit-type outcomes and duration-type outcomes.

Visit-type outcomes, which are counts, can be fit by generalized linear models such as the Poisson Regression model. Given the nature of oncologic treatment, however, overdispersion was a strong possibility as it was expected that there would be a large variation in the number of clinic and chemotherapy treatment visits that patients would make. Both the negative binomial regression model and the quasi-Poisson regression models were considered for modelling visit-type outcomes, as both are capable of addressing overdispersion. All analyses with visit-type outcomes were performed using both statistical techniques, and generally results were similar between the two methods. However, incorporation of model offsets to adjust for length of treatment produced very different results. Comparisons between negative binomial regression models and quasi-Poisson regression models were made using the likelihood ratio test for non-nested hypotheses designed as described Vuong[100]. Quasi-Poisson regression were found to better fit the data in most scenarios, and were selected as the model used to describe visit-type outcomes of complexity in this study. Overviews and comparisons of these two statistical methodologies are provided in the following references[101–103]. Visit-type outcomes in this study included: the total number of clinic visits in each phase, and the total number of chemotherapy treatment visits in each phase. Outcomes were modelled once as visit count (no offset), and once as visit intensity (offset by the log of the length of treatment in years).

Duration-type outcomes are continuous, and simple linear regression models were first considered. However, due to the magnitude of the increase in some measures, some models produced negative predicted values in some years of the study. For this reason, duration-type outcomes were modelled on the log scale as the optimal models to estimate duration-type data. All tabulated and visualized results for duration-type outcomes were first modelled on the log-scale, and then exponentiated before tabulation.

As discussed in section 2.75, duration-type models needed to be repeated for each of 21 multiply imputed datasets, before all quantiles from the models are pooled at the end per Rubin's Rules[96,97]. Rubin's Rules for combining a quantile $\bar{\theta}_m$ from models generated in *m* sets of imputed data is, for the estimator, simply to calculate an average as in the following equation:

$$\bar{\theta}_m = \frac{1}{m}\sum_{i=1}^{m} \hat{\theta}_i$$

The total variance T_m associated with $\bar{\theta}_m$, on the other hand, can be calculated by combining within-imputation variance and between-imputation variance using the following equation:

$$T_m = \bar{U}_m + \left(1 + \frac{1}{m}\right) B_m \text{ where;}$$

$$\bar{U}_m = \frac{1}{m}\sum_{i=1}^{m} U_i$$

U_i represents the variance of quantile $\bar{\theta}_i$ in a single set of imputed data belonging to m sets of parallel imputed data. $\bar{U}_m$ represents the averaged value of U_i across all sets of imputed data, and is referred to as the within-imputation variability. B_m describes between-imputation variability, and can be described as the variance of the imputed data which are generated by the inherent randomness associated with data imputation. Detailed calculations for these equations can be found in the following references[96,97].

Duration-type outcomes in this study included: the mean duration of each clinic visit in each phase of care, the mean duration of each chemotherapy treatment visit in each phase of care, the total duration of all clinic visits in each phase of care, and the total duration of all chemotherapy treatment visits in each phase of care. Analyses of total duration in either clinic visits or chemotherapy treatment were modelled once as total duration, and once as total duration of treatment standardized by the length of treatment in a phase of care.

Despite similarities between colon and rectal cancers, and their frequent grouping as colorectal cancer, there are distinct differences in how the two are treated. For example, preoperative radiotherapy is known to be effective for improving survival and reducing recurrence for rectal cancer patients, however its effects are less evident among colon cancer patients[104]. Incorporation of radiotherapy into preoperative and adjuvant treatments affect whether, when, and how much chemotherapy were administered for the patient, and hence it was valid to suggest that patients should be modelled separately depending on whether they had colon or rectal cancer. To determine whether patients should be modelled as a single cohort of colorectal cancer patients or two separate cohorts of colon and rectal cancer patients, interaction term tests were performed for each outcome and each phase of care. Where the effect of interaction terms in the model was statistically significant, trends in treatment complexity were modelled as two separate cohorts of colon and rectal cancer patients. For models where interaction terms were not significant, trends in treatment complexity were modelled for a single cohort of colorectal cancer patients.

Modelling of the duration-type data may occur on one of two levels depending on the metric being modelled: the "scheduling level" or the "patient level". Mean duration of each visit was modelled on the "scheduling level", which meant that a single patient may have many visits in a single phase of care. Since repeated visits by the same patient could reasonably be expected to be more similar than visits by other patients, it was essential to control for possible data clustering and within-cluster dependence of observations. To account for possible data-clustering, all mean duration models are modelled using General Estimating Equations with gamma distribution and a log link, with type-of-visit included as a control. Total duration and rate of total duration metrics used data on the "patient level", meaning that a single patient would only be one observation in a single phase of care. A simple linear regression with Gamma distribution and log-link was used to model data at the "patient level".

Some patients were referred to BC Cancer only for second opinions, or for other reasons were either not eligible for or refused to participate in additional treatment. It was decided that these patients were different from patients who received treatment at BC Cancer, so patients who were in a given phase of care for less than 7 days were excluded from analyses relating to that phase of care.

3 RESULT

3.1 DEMOGRAPHIC AND DISEASE CHARACTERISTICS OF THE STUDY POPULATION

Table 3-1 describes the demographic characteristics and stage at referral of the study population. A total of 8,548 colon cancer patients and 6,609 rectal cancer patients were eligible for inclusion in the final data set. Age, sex, and household income did not change significantly with year of referral. Community size and stage at referral were significantly associated with year of referral. The odds for belonging in a community with population between 100,000 to 499,999 decreased (OR = 0.965, p<0.001) while odds for belonging in a community with a population of 500,000 or more increased (OR = 1.010, p=0.266).

Table 3-1. Demographic and disease at diagnosis characteristics of the study population. *The number and distribution of both colon and rectal cancer patient groups across a number of demographic and disease at diagnosis characteristics are described.*

		Colon		Rectal		Colorectal	
		Patients	**%**	**Patients**	**%**	**Patients**	**%**
Age	**18 to 50**	847	9.9%	702	10.6%	1549	10.2%
	51 to 60	1578	18.5%	1444	21.8%	3022	19.9%
	61 to 75	3828	44.8%	2961	44.8%	6789	44.8%
	76 or older	2295	26.8%	1502	22.7%	3797	25.1%
	Total	8548	100.0%	6609	100.0%	15157	100.0%
Sex	**Female**	4076	47.7%	2420	36.6%	6496	42.9%
	Male	4472	52.3%	4189	63.4%	8661	57.1%
	Total	8548	100.0%	6609	100.0%	15157	100.0%
Quintile Annual Household Income	**Lowest**	1645	19.8%	1279	19.8%	2924	19.8%
	Low	1641	19.7%	1283	19.9%	2924	19.8%
	Medium	1625	19.6%	1277	19.8%	2902	19.7%
	High	1696	20.4%	1327	20.6%	3023	20.5%
	Highest	1703	20.5%	1283	19.9%	2986	20.2%
	Total	8310	100.0%	6449	100.0%	14759	100.0%
Community Size (Population)	**<10,000**	1108	13.2%	1022	15.7%	2130	14.3%
	10,000 to 99,999	2090	24.8%	1500	23.0%	3590	24.0%
	100,000 to 499,999	1810	21.5%	1081	16.6%	2891	19.3%
	500,000+	3408	40.5%	2923	44.8%	6331	42.4%
	Total	8416	100.0%	6526	100.0%	14942	100.0%
Stage at Referral	**I**	522	6.1%	1015	15.4%	1537	10.1%
	II	2009	23.5%	1645	24.9%	3654	24.1%
	III	3017	35.3%	2384	36.1%	5401	35.6%
	IV	3000	35.1%	1565	23.7%	4565	30.1%
	Total	8548	100.0%	6609	100.0%	15157	100.0%

This trend may be driven by the growth of communities in the Lower Mainland over the 500,000 population mark, or by a higher rate of growth in the larger communities than relatively smaller ones. Stage at referral also changed, with the primary change being that patients were more likely to be referred to BC Cancer with stage 3 disease (34.1% in 2000 and 36.8% in 2012, OR = 1.015, $p<0.001$) and less likely to be referred with stage 1 disease (9.8% in 2000 and 7.3% in 2012, OR = 0.966, $p<0.001$). These changes were significant, but may represent increased referral of patients diagnosed with stage 1 disease to either observation or to continued care at community oncology network centres which are not part of BC Cancer.

Among colon and rectal cancer patients, almost half of all patients were in the age range between 60 to 75 years old, household income approached uniform distribution, and more than 60% of patients lived in communities with populations over 100,000 in both groups. Gender distribution included more males in both colon and rectal cancer patient populations, but whereas there were only 4.6% more males than females among colon cancer patients, among rectal cancer patients there were 26.8% more males than females. This observation was expected, as the male to female ratio for colorectal cancer is known to increase progressively from the cecum to the rectum[105]. While not shown in this table, it is also known that prevalence of colon and rectal cancer differs across racial and ethnic groups, although the exact genetic or environmental mechanisms for this are unknown. Note that due to incomplete data, reported community size and quintile annual household income totals do not include all colon and rectal cancer patients used to generate regression models in this study. As none of the regression models adjust for these demographic characteristics, this discrepancy does not adversely affect regression models in any way.

Table 3-2 highlights the number of patients who initiated each phase of care by tumour subgroup, as well as the proportion of patients in each tumour subgroup who initiated each phase of care. As stated in section 2.5, any one patient could have initiated multiple phases of care, however they may very well not have entered all phases of care as well. A total of 10,297 patients initiated phase one of care at referral, 3,197 initiated phase three of care at referral, and 1,627 initiated phase five of care at referral. It was noted that most patients did initiate phase 1 of care among both colon and rectal tumour subgroups, and that distributions in proportion of patients referred to each phase of care were similar between the two tumour subgroups. While mostly similar, it seemed that a higher proportion of rectal cancer patients initiated phases 1 and 2 of care, compared to colon cancer patients. In contrast, fewer rectal cancer patients initiated phases 3 to 5 of care. This trend is likely due to the relative convenience

of delivering chemotherapy at smaller BC Cancer sites or affiliated local clinics, so colon patients in phases 1 and 2 of care could receive chemotherapy at smaller sites rather than teaching hospitals. In contrast, rectal cancer patients in phases 1 and 2 of care are frequently referred for radiotherapy, which tend to be located at larger centers of care.

Table 3-2. Number of Patients who Initiated Each Phase of Care. *The number and proportion of patients referred between the years 2000 and 2012 who started each phase of care at any point during their course of treatment. Proportions are calculated in each tumour subgroup (colon, rectal, or colorectal) as the number of patients who initiated a phase of care divided by the total number of patients in that tumour group who initiated any phase of care.*

Phase of Care	Colon		Rectal		Colorectal	
	Patients	%	Patients	%	Patients	%
Phase 1	5413	63.3%	4884	73.9%	10297	67.9%
Phase 2	3637	42.5%	3572	54.0%	7209	47.6%
Phase 3	2882	33.7%	1999	30.2%	4881	32.2%
Phase 4	2068	24.2%	1465	22.2%	3533	23.3%
Phase 5	4133	48.4%	2919	44.2%	7052	46.5%
Any	8548	100.0%	6609	100.0%	15157	100.0%

In the study population, the number of patients initiating treatment in every phase increased with later year of initiation, and among both colon and rectal cancer patients (Figure 3-1 and Figure 3-2). In 2001 in particular, the number of patients who initiated phase 2 (adjuvant therapy after the first six months from follow-up), increased by or more than two-fold among colorectal cancer patients compared to in 2000. It should be noted, however, that part of the dramatic increase from 2000 to 2001 is associated with the study design. The earliest referral date that patients were included in was January 1st 2000, and the earliest date that patients could start continuing phase of care (phase 2 and 4) was July 1st 2000. This means that the number of patients in the continuing phases in 2000 represent those accrued in only half a year compared to the full year in other years. Since the study modeled complexity of treatment per individual, the changes in complexity are not affected by the increasing number of cases initiating phases of care over time.

Figure 3-1. Number of patients by Year of Treatment Phase Initiation among Colon Cancer Patients

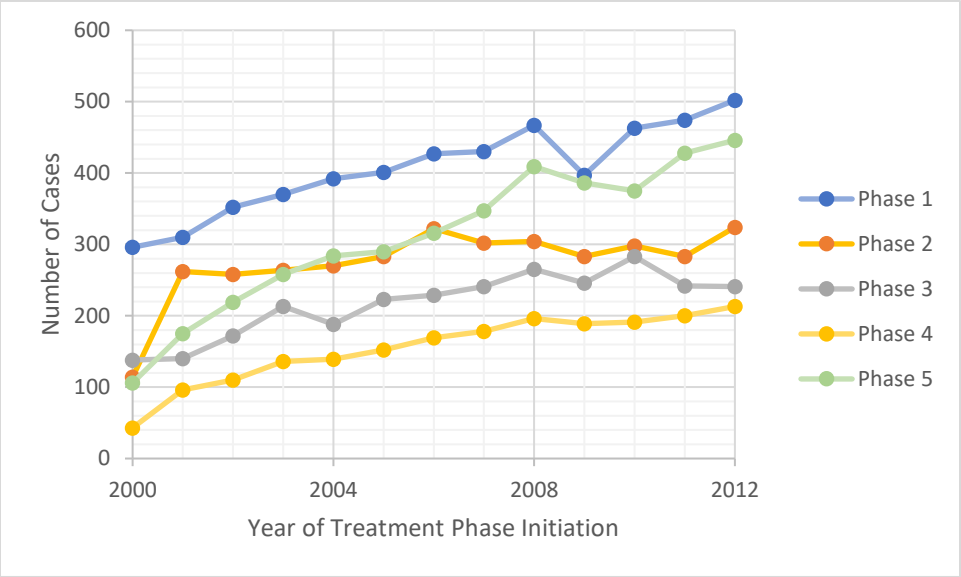
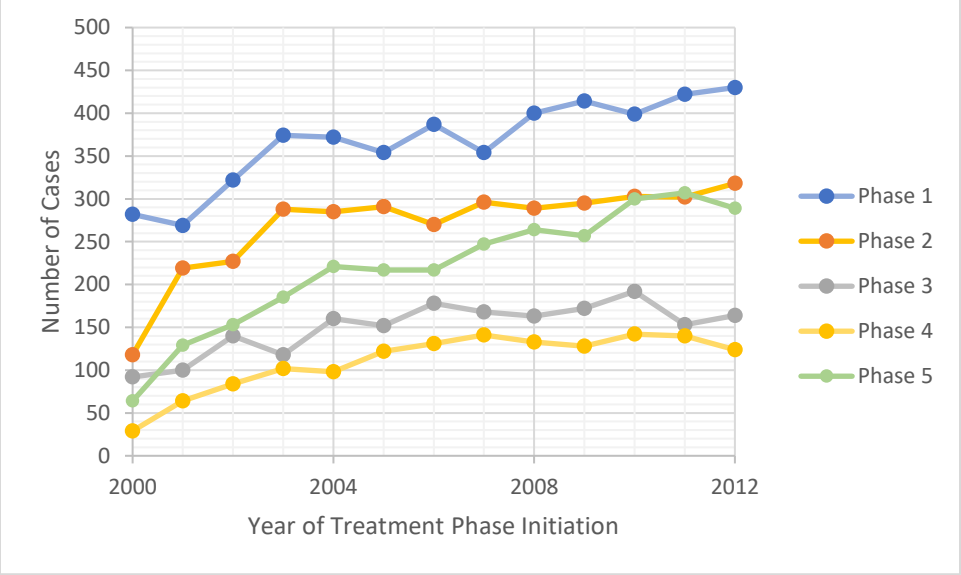


Figure 3-2. Number of patients by Year of Treatment Phase Initiation among Rectal Cancer Patients



3.2 FREQUENCY AND INTENSITY OF CLINIC AND CIT VISITS

The number of clinic visits significantly increased with later year of initiation in all phases of care. The number of clinic visits per year, when adjusted for length in phase of care, had significantly and increasing trends with the exception of visits during the last six months of life (phase five of care), which showed no significant trends (Table 3-3). The greatest increase in the total number of clinic visits was observed in phases 2 and 4, both of which represent continued phases of care following referral for non-metastatic non-recurrent disease and metastatic or recurrent disease respectively (Table 3-4). In phase 2, the increase was 3.375 (+127.8%) among colon cancer patients and 6.076 (+293.8%) among rectal cancer patients over the study period. In phase 4, the increase was 7.974 clinic visits per year (+67.7%) among colorectal cancer patients over the study period.

Evaluation of the number of clinic visits per year found that once results were adjusted for length of phase duration, the greatest increases over the study period were observed in phase 1 of care, with a net increase of 5.891 visits per year (+49.4%) among colon cancer patients and 11.740 visits per year (+94.5%) among rectal cancer patients (Table 3-4). Notably, in all six models of clinic visits where significant differences between tumour subgroups was observed, a greater increase was observed among rectal cancer patients than colon cancer patients in all cases. Comparing the models against aggregated means for each year, trends appear to have been fairly consistent from year to year with only minor fluctuations, except for during phase 5 of care (Figure 3-3 and Figure 3-5). Two separate trends were present in this metric, as the number of clinic visits per year among patients in phase 5 of care decreased considerably between 2004 and 2006, but rapidly increased again from 2006 to 2012.

Trends observed in CIT visits were significant in all phases of care, with all models of CIT visits and CIT visits per year in phase one of care having trends for fewer visits with later year of initiating a phase of care, and trends for significantly more visits in all other phases of care (Table 3-5). Colon patients who initiated phase one of care in 2012 would experience 3.579 (-38.7%) fewer CIT visits or 5.920 (-27.1%) fewer CIT visits per year compared to those who initiated phase one of care in 2000 (Table 3-6). Rectal cancer patients could expect 1.490 (-23.4%) fewer visits or 2.541 (-17.6%) fewer visits per year. In all other phases of care, patients in 2012 would expect more visits, with the greatest increase being in

phase four of care at 24.762 (+315.4%) more visits or 12.240 (+298.0%) more visits per year among colorectal cancer patients. Reviewing the observed mean CIT visits and CIT visits by year of phase initiation revealed that the increases were only gradual in phase 2 of care, with trends in phases 1, 3, 4, and 5 being influenced by a downward pressure in the early half of the study period which was then overpowered in the latter half of the study period (Figure 3-4 and Figure 3-6).

Table 3-3. Clinic visit ratio and visit rate ratio stratified by visit type, tumor site, and phase of care. *Trends in the frequency and intensity of clinic visits are presented with 95% confidence intervals. Ratios describe the average multiplicative change in the number of visits (visit ratio) or the rate of visits per year (visit rate ratio) with each later year of phase initiation. Where significant differences between colon and rectal cancer patients were present, colon and rectal patients were evaluated separately. Where differences were not significant, models were combined into a single colorectal cohort.*

Metric	Phase	Coefficient	Colon (95% CI)	Rectal (95% CI)	Colorectal (95% CI)
Number of Clinic Visits	1	Intercept	5.043 (4.741 - 5.361)	5.457 (5.206 - 5.717)	-
		Ratio	1.019 (1.011 - 1.027)	1.051 (1.045 - 1.057)	-
	2	Intercept	2.642 (2.248 - 3.090)	2.068 (1.793 - 2.375)	-
		Ratio	1.071 (1.050 - 1.092)	1.121 (1.103 - 1.139)	-
	3	Intercept	-	-	4.936 (4.664 - 5.221)
		Ratio	-	-	1.032 (1.025 - 1.040)
	4	Intercept	-	-	11.787 (10.629 - 13.046)
		Ratio	-	-	1.044 (1.031 - 1.057)
	5	Intercept	-	-	3.486 (3.245 - 3.742)
		Ratio	-	-	1.015 (1.006 - 1.024)
Number of Clinic Visits per Year	1	Intercept	11.934 (10.955 - 12.979)	12.424 (11.751 - 13.127)	-
		Rate Ratio	1.034 (1.022 - 1.045)	1.057 (1.050 - 1.064)	-
	2	Intercept	-	-	0.487 (0.440 - 0.537)
		Rate Ratio	-	-	1.192 (1.178 - 1.206)
	3	Intercept	-	-	11.734 (11.092 - 12.405)
		Rate Ratio	-	-	1.028 (1.021 - 1.035)
	4	Intercept	-	-	6.354 (5.789 - 6.962)
		Rate Ratio	-	-	1.036 (1.025 - 1.048)
	5	Intercept	-	-	8.477 (7.859 - 9.133)
		Rate Ratio	-	-	1.007 (0.998 - 1.016)

Table 3-4. Absolute differences in clinic visits and visits per year stratified by visit type, tumor site, and phase of care. *The expected number of visits or visits per year for each phase of care at the beginning of the study period in 2000 and the end of the study period in 2012 is presented. Absolute difference is calculated as the expected value in 2012 subtracted from the expected value in 2000. Difference (%) is calculated as the absolute difference divided by the expected value at the beginning of the study period.*

		Colon				Rectal				Colorectal			
Metric	Phase	2000	2012	Absolute Difference	Difference (%)	2000	2012	Absolute Difference	Difference (%)	2000	2012	Absolute Difference	Difference (%)
Number of Clinic Visits	1	5.043	6.321	1.278	25.3%	5.457	9.913	4.456	81.6%	-	-	-	-
	2	2.642	6.017	3.375	127.8%	2.068	8.144	6.076	293.8%	-	-	-	-
	3	-	-	-	-	-	-	-	-	4.936	7.203	2.267	45.9%
	4	-	-	-	-	-	-	-	-	11.787	19.761	7.974	67.7%
	5	-	-	-	-	-	-	-	-	3.486	4.168	0.682	19.6%
Number of Clinic Visits per Year	1	11.934	17.825	5.891	49.4%	12.424	24.164	11.740	94.5%	-	-	-	-
	2	-	-	-	-	-	-	-	-	0.487	4.007	3.520	722.8%
	3	-	-	-	-	-	-	-	-	11.734	16.344	4.610	39.3%
	4	-	-	-	-	-	-	-	-	6.354	9.713	3.359	52.9%
	5	-	-	-	-	-	-	-	-	8.477	9.217	0.740	8.7%

Table 3-5. CIT visit ratio and visit rate ratio stratified by visit type, tumor site, and phase of care. *Trends in the frequency and intensity of CIT visits are presented with 95% confidence intervals. Ratios describe the average multiplicative change in the number of visits (visit ratio) or the rate of visits per year (visit rate ratio) with each later year of phase initiation. Where significant differences between colon and rectal cancer patients were present, colon and rectal patients were evaluated separately. Where differences were not significant, models were combined into a single colorectal cohort.*

Metric	Phase	Coefficient	Colon (95% CI)	Rectal (95% CI)	Colorectal (95% CI)
Number of CIT Visits	1	Intercept	9.241 (8.527 - 10.001)	6.361 (5.838 - 6.919)	-
		Ratio	0.960 (0.949 - 0.971)	0.978 (0.967 - 0.990)	-
	2	Intercept	-	-	1.303 (1.062 - 1.586)
		Ratio	-	-	1.111 (1.085 - 1.137)
	3	Intercept	-	-	3.112 (2.803 - 3.449)
		Ratio	-	-	1.073 (1.059 - 1.086)
	4	Intercept	-	-	7.851 (6.632 - 9.247)
		Ratio	-	-	1.126 (1.105 - 1.148)
	5	Intercept	1.990 (1.685 - 2.338)	1.108 (0.874 - 1.390)	-
		Ratio	1.031 (1.011 - 1.052)	1.083 (1.055 - 1.113)	-
Number of CIT Visits per Year	1	Intercept	21.843 (20.426 - 23.335)	14.438 (13.371 - 15.570)	-
		Rate Ratio	0.974 (0.965 - 0.983)	0.984 (0.974 - 0.995)	-
	2	Intercept	-	-	0.271 (0.215 - 0.339)
		Rate Ratio	-	-	1.207 (1.176 - 1.241)
	3	Intercept	-	-	7.388 (6.697 - 8.136)
		Rate Ratio	-	-	1.068 (1.056 - 1.081)
	4	Intercept	-	-	4.107 (3.549 - 4.736)
		Rate Ratio	-	-	1.122 (1.104 - 1.140)
	5	Intercept	4.885 (4.164 - 5.704)	2.621 (2.077 - 3.275)	-
		Rate Ratio	1.024 (1.005 - 1.044)	1.074 (1.046 - 1.103)	-

Table 3-6. Absolute differences in CIT visit ratio and visit rate ratio stratified by visit type, tumor site, and phase of care. *The expected number of visits or visits per year for each phase of care at the beginning of the study period in 2000 and the end of the study period in 2012 is presented. Absolute difference is calculated as the expected value in 2012 subtracted from the expected value in 2000. Difference (%) is calculated as the absolute difference divided by the expected value at the beginning of the study period.*

		Colon				Rectal				Colorectal			
Metric	Phase	2000	2012	Absolute Difference	Difference (%)	2000	2012	Absolute Difference	Difference (%)	2000	2012	Absolute Difference	Difference (%)
Number of CIT Visits	1	9.241	5.662	-3.579	-38.7%	6.361	4.871	-1.490	-23.4%	-	-	-	-
	2	-	-	-	-	-	-	-	-	1.303	4.608	3.305	253.6%
	3	-	-	-	-	-	-	-	-	3.112	7.248	4.136	132.9%
	4	-	-	-	-	-	-	-	-	7.851	32.613	24.762	315.4%
	5	1.990	2.870	0.880	44.2%	1.108	2.885	1.777	160.3%	-	-	-	-
Number of CIT Visits per Year	1	21.843	15.923	-5.920	-27.1%	14.438	11.897	-2.541	-17.6%	-	-	-	-
	2	-	-	-	-	-	-	-	-	0.271	2.591	2.320	856.1%
	3	-	-	-	-	-	-	-	-	7.388	16.270	8.882	120.2%
	4	-	-	-	-	-	-	-	-	4.107	16.347	12.240	298.0%
	5	4.885	6.493	1.608	32.9%	2.621	6.173	3.552	135.5%	-	-	-	-

Figure 3-3. Observed and expected number of clinic visits. *The expected and observed number of clinic visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean number of clinic visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients. Tabulated values for phases one to five can be found in appendix tables Table **A1** to Table **A5** respectively.*

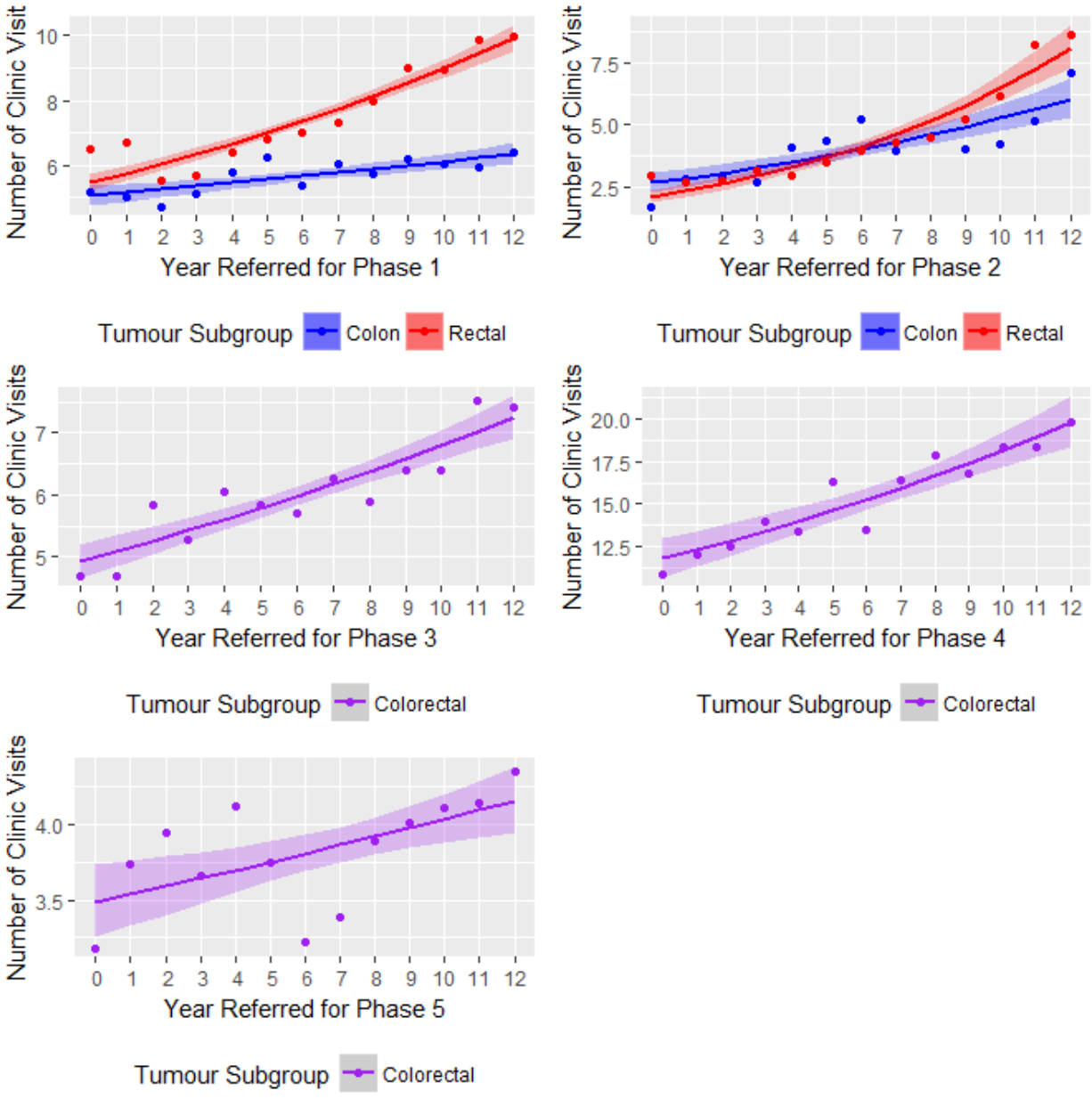


Figure 3-4. Observed and expected number of CIT visits. *The expected and observed number of CIT visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean number of CIT visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients. Tabulated values for phases one to five can be found in appendix tables Table* ***A6*** *to Table* ***A10*** *respectively.*

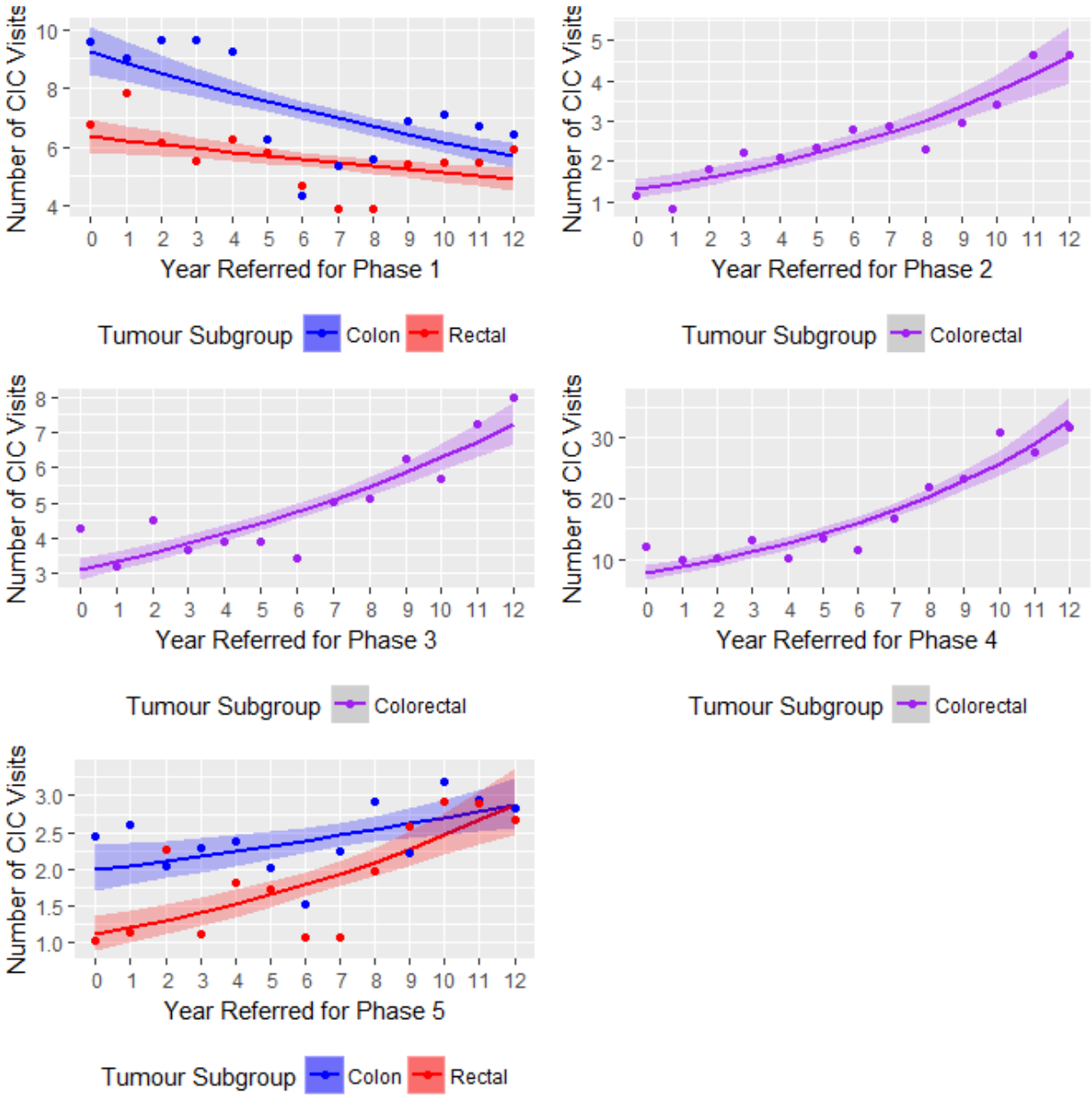


Figure 3-5. Observed and expected number of clinic visits per year. *The expected and observed number of clinic visits per year for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean number of clinic visits per year in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients. Tabulated values for phases one to five can be found in appendix tables* ***Table A1*** *to* ***Table A5*** *respectively.*

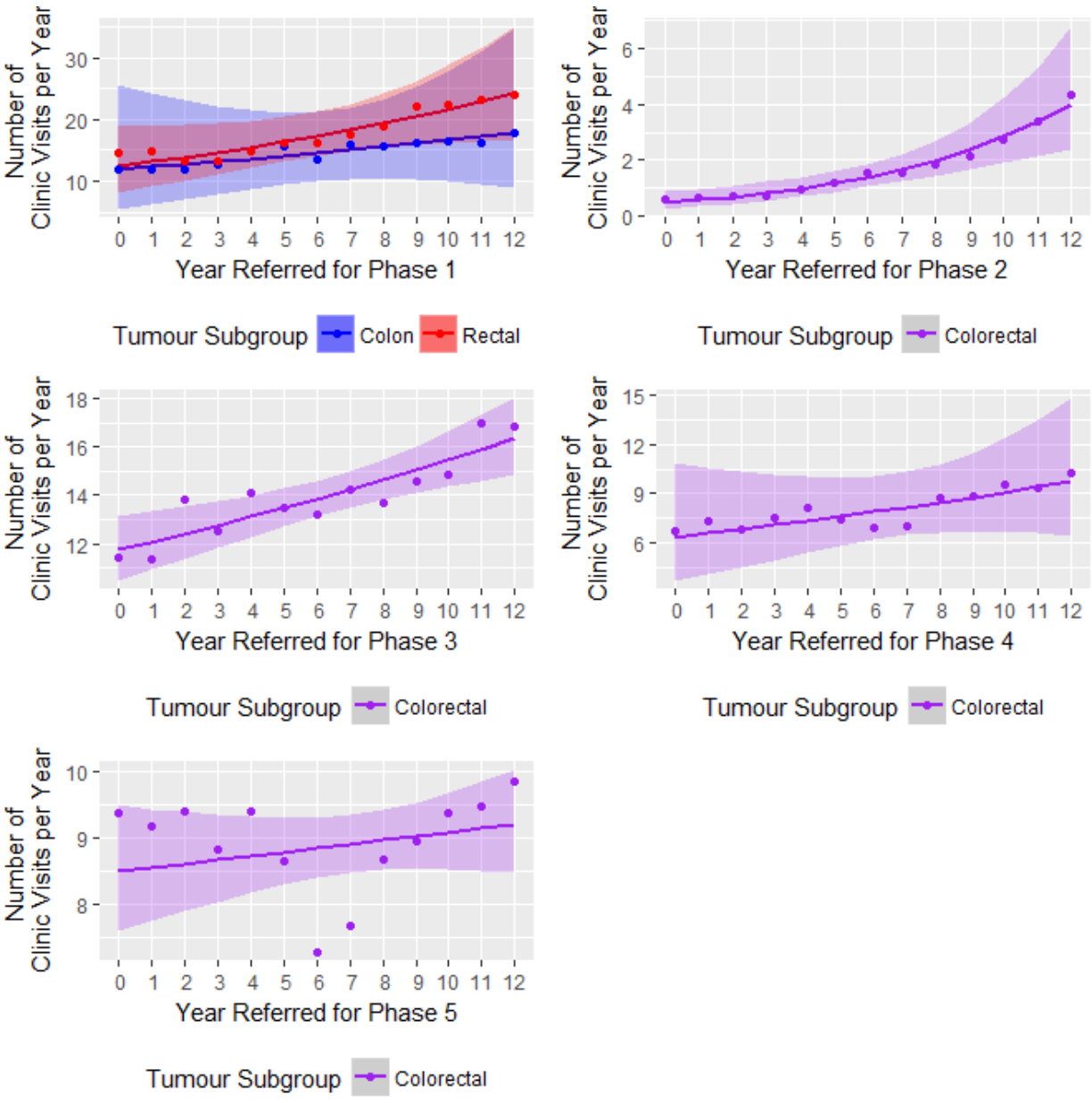
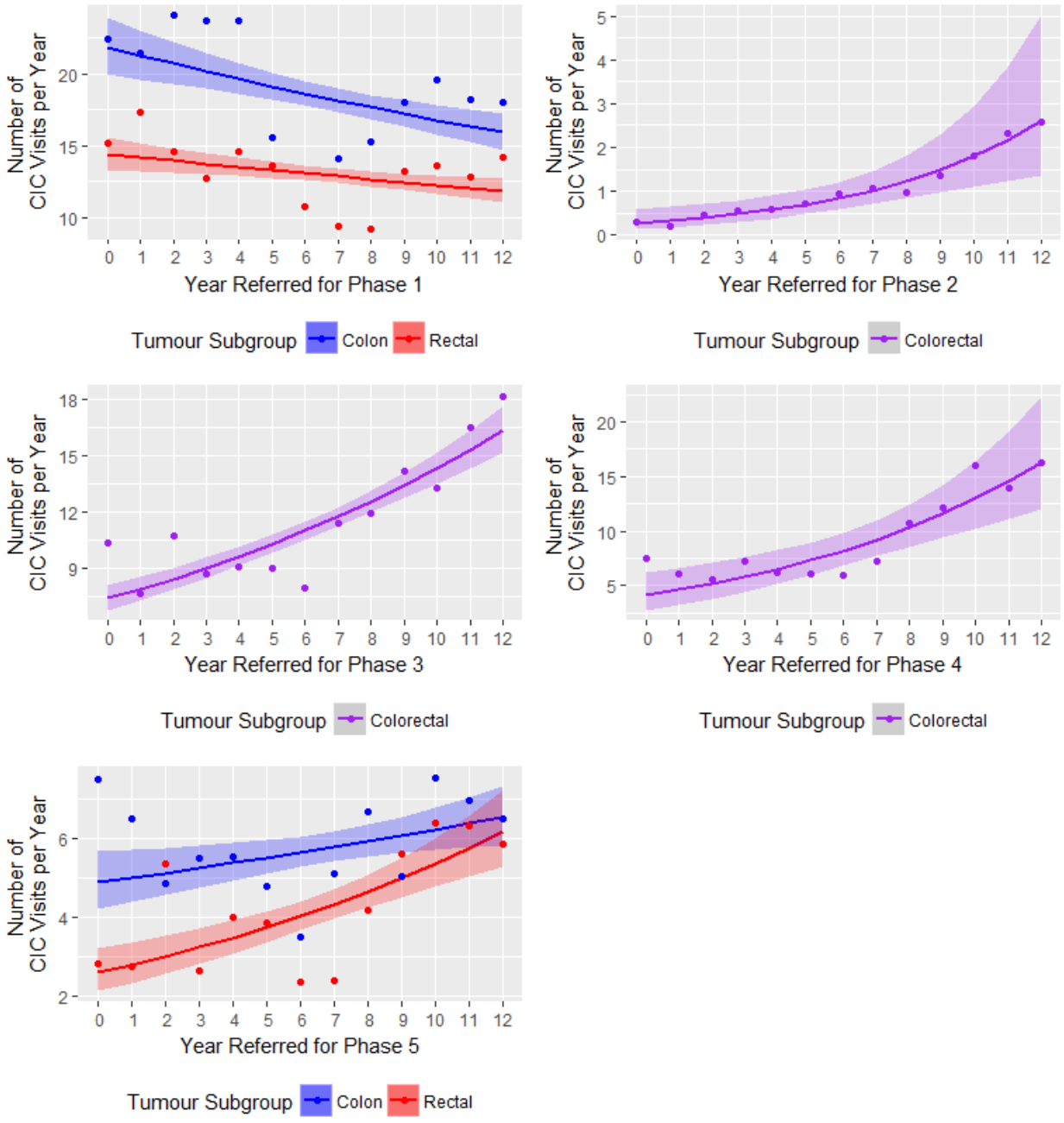


Figure 3-6. Observed and expected number of CIT visits per year. *The expected and observed number of CIT visits per year for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean number of CIT visits per year in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients. Tabulated values for phases one to five can be found in appendix tables* ***Table A6*** *to* ***Table A10*** *respectively.*



3.3 NUMBER OF CHEMOTHERAPY PRESCRIPTIONS AND RATE OF CHEMOTHERAPY PRESCRIPTIONS

Despite significant differences in trends between colon and rectal cancer patients in some models of chemotherapy visits, effect modification by tumour subgroup was not significant in any of the models of chemotherapy prescription. Of the 10 models describing trends in chemotherapy prescriptions among colorectal cancer patients, 6 had significant and increasing trends for the ratio and rate ratio of chemotherapy prescriptions with later year of phase initiation. The prescription ratio and rate ratio did not change among colorectal cancer patients in phase 1 of care and phase 5 of care, which represent the first 6 months following referral with initial non-metastatic colorectal cancer and the last 6 months of life respectively. The steepest trend was in phase 2 of care, where the prescription ratio was 1.079 with each later year of phase initiation and the prescription rate ratio was 1.173. Trends in the rate and rate ratios of chemotherapy prescriptions are visualized in Figure 3-7 and Figure 3-8 respectively.

In absolute differences, the greatest increase in number of prescribed chemotherapy agents was observed in phase 4 of care, where colorectal cancer patients initiating phase 4 of care in 2012 could expect 31.553 (+108.2%) more prescriptions than those initiating phase 4 in 2000 (Table 3-8). If results were adjusted for length in phase of care, then the number of prescriptions per year remains highest during phase 4 of care at 14.410 more prescriptions per year (+92.3%) but with a comparably high increase of 13.585 (+51.1%) additional prescriptions per year in phase 3 of care. Both phase 3 and 4 of care describe treatment for metastatic or recurrent colorectal cancer. Visual inspection of trends found two separate trends in the observed prescriptions in phase 1 of care the number of prescriptions, with a decreasing trend between 2000 and 2007, and a rapid increase between 2008 to 2012 (Figure 3-8). In phase 3 of care, number of chemotherapy prescriptions remained steady from 2000 to 2004, but was considerably higher in 2005 to 2012. Number of prescriptions increased drastically and steadily between 2002 and 2012 for phase 4 of care.

Table 3-7. Chemotherapy prescription ratio and prescription rate ratio stratified by visit type, tumor site, and phase of care. *Trends in the frequency and intensity of chemotherapy prescriptions are presented with 95% confidence intervals. Ratios describe the average multiplicative change in the number of prescriptions (prescription ratio) or the rate of prescriptions per year (prescription rate ratio) with each later year of phase initiation. Where significant differences between colon and rectal cancer patients were present, colon and rectal patients were evaluated separately. Where differences were not significant, models were combined into a single colorectal cohort. While colon and rectal models for prescription ratios and prescription rate ratios were tested for each phase of care, all were combined due to the absence of significant differences in all comparisons.*

Metric	Phase	Coefficient	Colorectal (95% CI)
Number of Chemotherapy Prescriptions	1	Intercept	12.823 (12.103 - 13.577)
		Ratio	0.994 (0.986 - 1.002)
	2	Intercept	3.623 (3.047 - 4.283)
		Ratio	1.079 (1.057 - 1.102)
	3	Intercept	11.185 (10.230 - 12.209)
		Ratio	1.040 (1.028 - 1.051)
	4	Intercept	29.172 (26.075 - 32.562)
		Ratio	1.063 (1.049 - 1.078)
	5	Intercept	6.102 (5.225 - 7.093)
		Ratio	1.017 (0.998 - 1.036)
Number of Chemotherapy Prescriptions per Year	1	Intercept	29.732 (28.289 - 31.232)
		Rate Ratio	1.004 (0.997 - 1.011)
	2	Intercept	0.755 (0.626 - 0.904)
		Rate Ratio	1.173 (1.147 - 1.200)
	3	Intercept	26.581 (24.419 - 28.893)
		Rate Ratio	1.035 (1.024 - 1.046)
	4	Intercept	15.613 (13.924 - 17.467)
		Rate Ratio	1.056 (1.042 - 1.071)
	5	Intercept	14.831 (12.693 - 17.252)
		Rate Ratio	1.009 (0.990 - 1.028)

Table 3-8. Absolute differences in chemotherapy prescriptions stratified by visit type, tumor site, and phase of care. *The expected number of prescriptions or prescriptions per year for each phase of care at the beginning of the study period in 2000 and the end of the study period in 2012 is presented. Absolute difference is calculated as the expected value in 2012 subtracted from the expected value in 2000. Difference (%) is calculated as the absolute difference divided by the expected value at the beginning of the study period.*

		Colorectal			
Metric	Phase	2000	2012	Absolute Difference (Prescriptions)	Difference (%)
Number of Prescriptions	1	12.823	11.930	-0.893	-7.0%
	2	3.623	9.022	5.399	149.0%
	3	11.185	17.908	6.723	60.1%
	4	29.172	60.725	31.553	108.2%
	5	6.102	7.470	1.368	22.4%
Number of Prescriptions per Year	1	29.732	31.191	1.459	4.9%
	2	0.755	5.123	4.368	578.5%
	3	26.581	40.166	13.585	51.1%
	4	15.613	30.023	14.410	92.3%
	5	14.831	16.514	1.683	11.4%

Figure 3-7. Observed and expected number of chemotherapy prescriptions. *The expected and observed number of chemotherapy prescriptions for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean number of chemotherapy prescriptions in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*

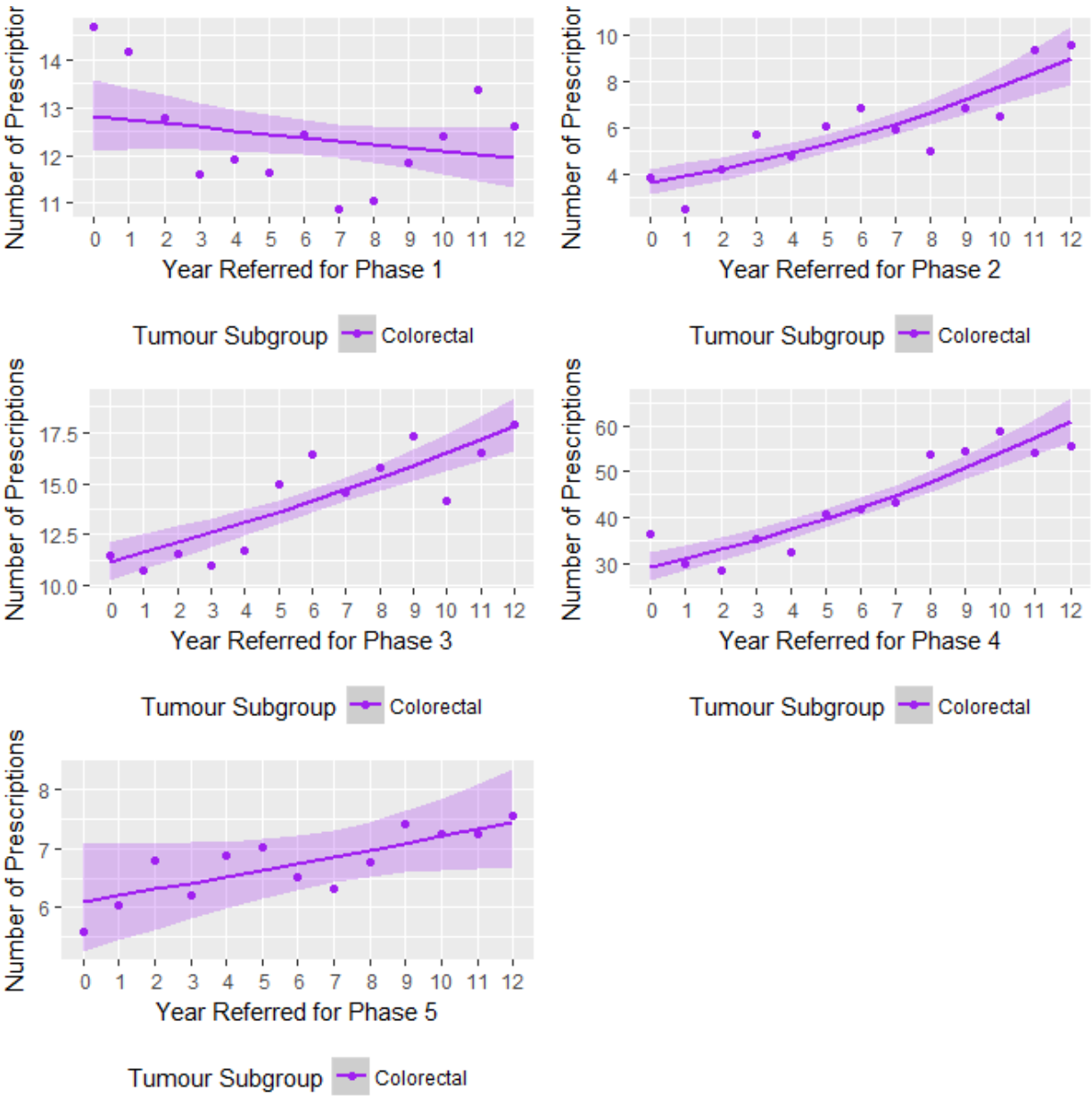
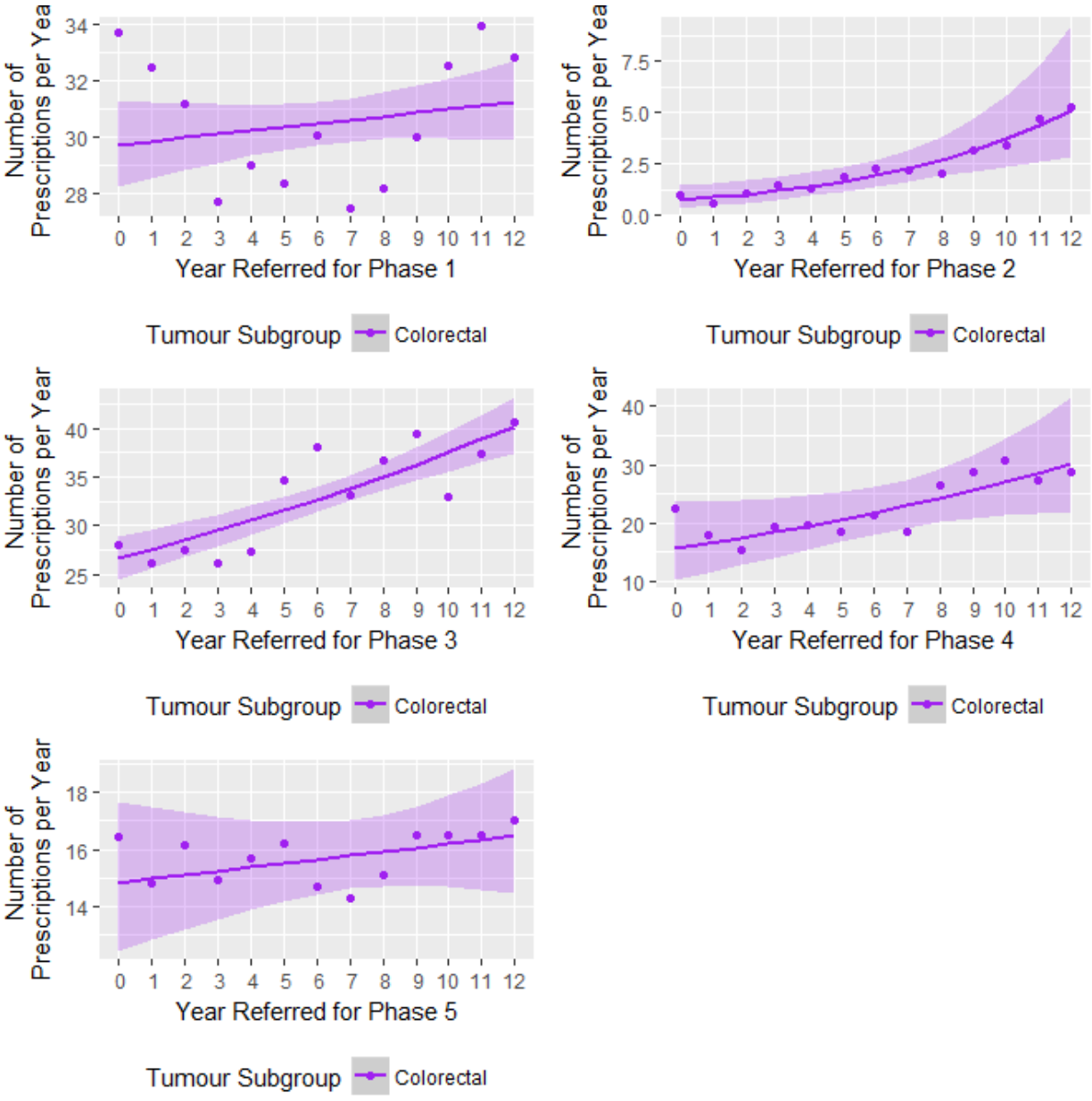


Figure 3-8. Observed and expected number of chemotherapy prescriptions per year. *The expected and observed number of chemotherapy prescriptions for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean number of chemotherapy prescriptions in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*



3.4 DURATION PER VISIT, TOTAL DURATION IN-PHASE, AND TOTAL DURATION PER YEAR IN-PHASE OF CLINIC AND CIT VISITS

The duration of clinic visits and CIT visits were described in 44 total statistical models, of which 41 found increasing duration with later year of phase initiation and the remaining 3 found no significant trends. Duration was described in three metrics: duration per visit, total duration for all visits in a given phase of care, and total duration per year in a given phase of care. All models were described in minutes, and modeled using generalized linear models with log-linked gamma distribution, and results are reported as an intercept (metric in the year 2000) and the ratio at which the metric changed with later year of phase initiation.

Clinic visits increased only modestly on a per-visit basis, however due to increases in the total number of clinic visits the total duration of all visits increased more substantially (Table 3-9). The mean duration of clinic visits at the beginning of the study period ranged between 21.65 minutes in phase 2 of care among rectal cancer patients to 32.69 minutes in phase 1 of care, and increased at a ratio of between 1.01 and 1.04 with each later year of phase initiation. The total duration of clinic visits at the beginning of the study period ranged from 74.48 minutes in phase 2 among rectal cancer patients to 309.48 minutes in phase 4 of care, and increased at a ratio of 1.04 to 1.12 year over year. Adjusted for the length in a phase of care, total duration of visits per year at the beginning of the study period ranged from 61.71 minutes per year to 408.69 minutes per year, and trends ranged from no significant change to a ratio of 1.15 year over year.

Trends in increasing CIT visits were generally quite substantial, with a ratio of 1.10 or higher increase in 17 out of 22 models (Table 3-10). The mean duration of CIT visits at the beginning of the study period ranged between 18.60 minutes per visit in phase 2 of care among rectal cancer patient to 52.91 minutes among colon cancer patients in phase 2 of care, with increases ranging between a ratio of 1.05 to 1.16 with each later year of phase initiation. The total duration of CIT visits at the beginning of the study period ranged from 145.86 minutes in phase 5 of care to 441.80 minutes in phase 1 of care among colon cancer patients, with trends ranging from 1.00 to a ratio of 1.21 with each later year of phase initiation. Total duration of CIT visits per year at

the beginning of the study period was lowest in phase 2 of care, at 127.33 minutes and 203.06 minutes among colon and rectal cancer patients respectively. Total duration of CIT visits per year at the beginning of the study period was highest among phase 1 patients, at 913.95 minutes per year and 832.01 minutes per year among colon and rectal cancer patients respectively. Trends with later year of phase initiation ranged from 1.00 among rectal cancer patients in phase 1 of care to 1.24 among colon cancer patients in phase 2 of care.

When interpreted as absolute and proportional increases between the beginning of the study period in the year 2000 and the end of the study period in 2012, the total change in duration of care for the average patient in each phase of care becomes more apparent. For example, the expected total duration of clinic visits during phase 4 of care among colorectal cancer patients increased 295 minutes, nearly doubled from their expected total duration of clinic visits in the year 2000 (Table 3-11). The total duration of CIT visits during phase 4 of care among colorectal cancer patients increased even more drastically from 505 minutes in the year 2000 to 5826.19 minutes in the year 2012, representing an absolute increase of 5321 minutes or 1052.9% increase over 13 years (Table 3-12).

Table 3-9. Change in mean visit duration, total visit duration of all visits, and total visit duration per year of all clinic visits in a phase of care. *Change in visit duration is described as change in minutes with each later year of phase initiation for a phase of care. A total of six metrics of duration are included in this table, with five phases of care. The significance of effect modification by tumour subgroup was evaluated, and where no significant effect was detected colon and rectal cancer cohorts were pooled and modelled together.*

Metric	Phase	Coefficient	Colon (95% CI)	Rectal (95% CI)	Colorectal (95% CI)
Mean Duration per Visit	1	Intercept	30.50 (29.83,31.18)	32.69 (32.18,33.21)	-
		Ratio	1.03 (1.03,1.03)	1.01 (1.01,1.01)	-
	2	Intercept	23.85 (22.23,25.57)	21.65 (20.27,23.12)	-
		Ratio	1.01 (1.00,1.01)	1.02 (1.01,1.03)	-
	3	Intercept	27.61 (26.84,28.41)	29.20 (28.30,30.13)	-
		Ratio	1.04 (1.03,1.04)	1.03 (1.02,1.03)	-
	4	Intercept	-	-	22.16 (21.66,22.67)
		Ratio	-	-	1.02 (1.01,1.02)
	5	Intercept	26.54 (25.74,27.37)	27.62 (26.59,28.69)	-
		Ratio	1.02 (1.01,1.02)	1.01 (1.01,1.02)	-
Total Duration of Visits	1	Intercept	-	-	150.85 (146.21,155.63)
		Ratio	-	-	1.07 (1.07,1.08)
	2	Intercept	102.45 (87.69,119.70)	74.48 (64.62,85.85)	-
		Ratio	1.07 (1.05,1.09)	1.12 (1.10,1.14)	-
	3	Intercept	-	-	143.66 (136.88,150.77)
		Ratio	-	-	1.07 (1.06,1.07)
	4	Intercept	-	-	309.48 (281.11,340.72)
		Ratio	-	-	1.05 (1.04,1.07)
	5	Intercept	120.51 (112.20,129.44)	108.81 (99.33,119.19)	-
		Ratio	1.04 (1.03,1.05)	1.05 (1.04,1.07)	-
Total Duration of Visits per Year	1	Intercept	-	-	373.52 (359.03,388.60)
		Ratio	-	-	1.07 (1.07,1.08)
	2	Intercept	-	-	61.71 (52.75,72.20)
		Ratio	-	-	1.15 (1.13,1.17)
	3	Intercept	-	-	404.15 (375.46,435.03)
		Ratio	-	-	1.06 (1.05,1.07)
	4	Intercept	344.30 (296.00,400.49)	228.73 (187.90,278.43)	-
		Ratio	1.00 (0.98,1.02)	1.04 (1.02,1.07)	-
	5	Intercept	-	-	408.69 (377.45,442.53)
		Ratio	-	-	1.03 (1.02,1.04)

Table 3-10. Change in mean visit duration, total visit duration of all visits, and total visit duration per year of all CIT visits in a phase of care. *Change in visit duration is described as change in minutes with each later year of phase initiation for a phase of care. A total of six metrics of duration are included in this table, with five phases of care. The significance of effect modification by tumour subgroup was evaluated, and where no significant effect was detected colon and rectal cancer cohorts were pooled and modelled together.*

Metric	Phase	Coefficient	Colon (95% CI)	Rectal (95% CI)	Colorectal (95% CI)
Mean Duration per Visit	1	Intercept	20.69 (19.98,21.43)	27.26 (26.24,28.32)	-
		Ratio	1.15 (1.14,1.16)	1.05 (1.04,1.06)	-
	2	Intercept	52.91 (35.03,79.92)	18.60 (16.82,20.56)	-
		Ratio	1.06 (1.02,1.10)	1.16 (1.15,1.18)	-
	3	Intercept	27.88 (26.41,29.44)	30.62 (28.63,32.75)	-
		Ratio	1.13 (1.12,1.14)	1.10 (1.08,1.11)	-
	4	Intercept	32.62 (29.98,35.49)	43.51 (34.25,55.27)	-
		Ratio	1.13 (1.12,1.14)	1.10 (1.08,1.13)	-
	5	Intercept	-	-	25.87 (24.48,27.34)
		Ratio	-	-	1.13 (1.12,1.14)
Total Duration of Visits	1	Intercept	441.80 (395.92,493.00)	403.27 (356.16,456.61)	-
		Ratio	1.10 (1.08,1.11)	1.00 (0.99,1.02)	-
	2	Intercept	-	-	182.66 (128.65,259.35)
		Ratio	-	-	1.17 (1.13,1.22)
	3	Intercept	-	-	225.66 (202.11,251.95)
		Ratio	-	-	1.14 (1.12,1.15)
	4	Intercept	-	-	505.34 (412.08,619.70)
		Ratio	-	-	1.21 (1.18,1.24)
	5	Intercept	-	-	145.86 (125.89,169.00)
		Ratio	-	-	1.15 (1.13,1.18)
Total Duration of Visits per Year	1	Intercept	913.95 (820.35,1018.22)	832.01 (736.20,940.29)	-
		Ratio	1.09 (1.08,1.11)	1.00 (0.99,1.02)	-
	2	Intercept	127.33 (79.90,202.90)	203.06 (136.93,301.13)	-
		Ratio	1.24 (1.17,1.31)	1.19 (1.14,1.25)	-
	3	Intercept	-	-	518.61 (465.22,578.13)
		Ratio	-	-	1.13 (1.11,1.14)
	4	Intercept	-	-	472.54 (372.14,600.03)
		Ratio	-	-	1.17 (1.14,1.21)
	5	Intercept	-	-	354.00 (306.51,408.84)
		Ratio	-	-	1.14 (1.12,1.16)

Table 3-11. Comparison of change in mean visit duration, total visit duration of all visits, and total visit duration per year of clinic visits in a phase of care. *Absolute difference and percentage difference in model-predicted duration of clinic visits in each phase of care in the year 2000 and in the year 2012. Where trends were significantly different by tumour subgroup, colon and rectal cancer patients were evaluated separately.*

		Colon				Rectal				Colorectal			
Metric	**Phase**	**2000**	**2012**	**Absolute Difference (Minutes)**	**Difference (%)**	**2000**	**2012**	**Absolute Difference (Minutes)**	**Difference (%)**	**2000**	**2012**	**Absolute Difference (Minutes)**	**Difference (%)**
Mean Duration of Visits	1	30.50	44.20	13.70	44.9%	32.69	38.44	5.75	17.6%	-	-	-	-
	2	23.85	26.20	2.35	9.9%	21.65	27.31	5.66	26.1%	-	-	-	-
	3	27.61	45.77	18.16	65.8%	29.20	41.88	12.68	43.4%	-	-	-	-
	4	-	-	-	-	-	-	-	-	22.16	27.11	4.95	22.3%
	5	26.54	33.09	6.55	24.7%	27.62	31.80	4.18	15.1%				
Total Duration of Visits	1	-	-	-	-	-	-	-	-	150.85	367.76	216.91	143.8%
	2	102.45	244.16	141.70	138.3%	74.48	322.97	248.48	333.6%	-	-	-	-
	3	-	-	-	-	-	-	-	-	143.66	335.08	191.42	133.2%
	4	-	-	-	-	-	-	-	-	309.48	604.57	295.09	95.3%
	5	120.51	195.60	75.09	62.3%	108.81	214.41	105.59	97.0%	-	-	-	-
Total Duration of Visits per Year	1	-	-	-	-	-	-	-	-	373.52	951.58	578.06	154.8%
	2	-	-	-	-	-	-	-	-	61.71	379.37	317.66	514.8%
	3	-	-	-	-	-	-	-	-	404.15	824.36	420.21	104.0%
	4	344.30	359.40	15.09	4.4%	228.73	400.59	171.86	75.1%	-	-	-	-
	5	-	-	-	-	-	-	-	-	408.69	628.75	220.06	53.8%

Table 3-12. Comparison of change in mean visit duration, total visit duration of all visits, and total visit duration per year of CIT visits in a phase of care. *Absolute difference and percentage difference in model-predicted duration of CIT visits in each phase of care in the year 2000 and in the year 2012. Where trends were significantly different by tumour subgroup, colon and rectal cancer patients were evaluated separately.*

		Colon				Rectal				Colorectal			
Metric	**Phase**	**2000**	**2012**	**Absolute Difference (Minutes)**	**Difference (%)**	**2000**	**2012**	**Absolute Difference (Minutes)**	**Difference (%)**	**2000**	**2012**	**Absolute Difference (Minutes)**	**Difference (%)**
Mean Duration of Visits	1	20.69	128.87	108.18	522.8%	27.26	51.31	24.05	88.2%	-	-	-	-
	2	52.91	114.47	61.56	116.4%	18.60	131.73	113.13	608.3%	-	-	-	-
	3	27.88	133.71	105.83	379.5%	30.62	100.90	70.28	229.5%	-	-	-	-
	4	32.62	162.95	130.33	399.5%	43.51	153.66	110.15	253.2%	-	-	-	-
	5	-	-	-	-	-	-	-	-	25.87	127.09	101.22	391.2%
Total Duration of Visits	1	441.80	1443.90	1002.10	226.8%	403.27	424.65	21.38	5.3%	-	-	-	-
	2	-	-	-	-	-	-	-	-	182.66	1458.62	1275.96	698.5%
	3	-	-	-	-	-	-	-	-	225.66	1189.09	963.44	426.9%
	4	-	-	-	-	-	-	-	-	505.34	5826.19	5320.86	1052.9%
	5	-	-	-	-	-	-	-	-	145.86	944.50	798.64	547.5%
Total Duration of Visits per Year	1	913.95	2917.68	2003.73	219.2%	832.01	877.02	45.01	5.4%	-	-	-	-
	2	127.33	2000.71	1873.38	1471.3%	203.06	1974.28	1771.22	872.3%	-	-	-	-
	3	-	-	-	-	-	-	-	-	518.61	2435.55	1916.94	369.6%
	4	-	-	-	-	-	-	-	-	472.54	3707.21	3234.67	684.5%
	5	-	-	-	-	-	-	-	-	354.00	1898.10	1544.10	436.2%

Figure 3-9. Observed and expected mean duration of clinic visits (minutes). *The expected and observed mean duration of clinic visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean duration of clinic visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*

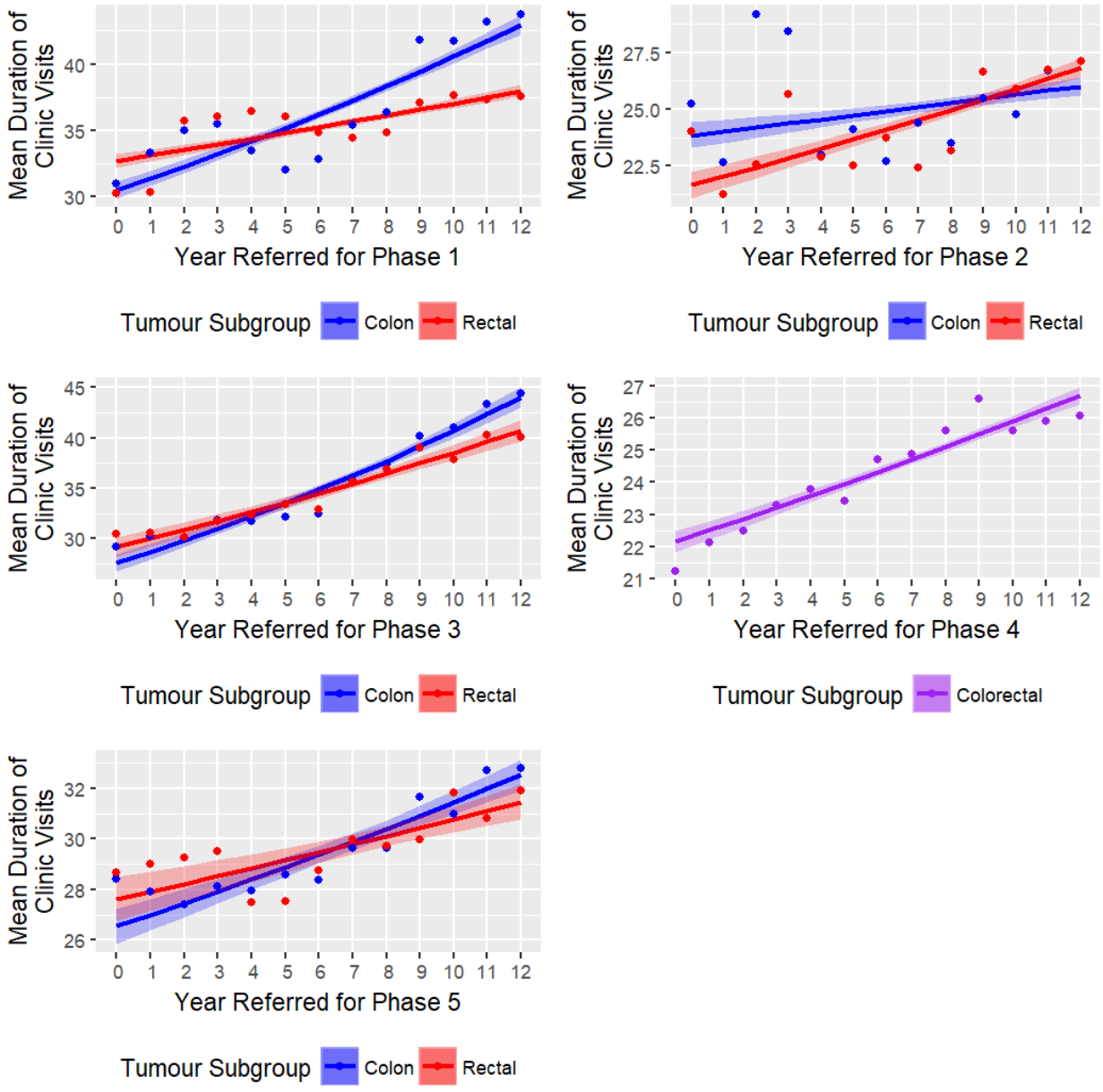


Figure 3-10. Observed and expected mean duration of CIT (minutes). *The expected and observed mean duration of CIT visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected mean duration of CIT visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*

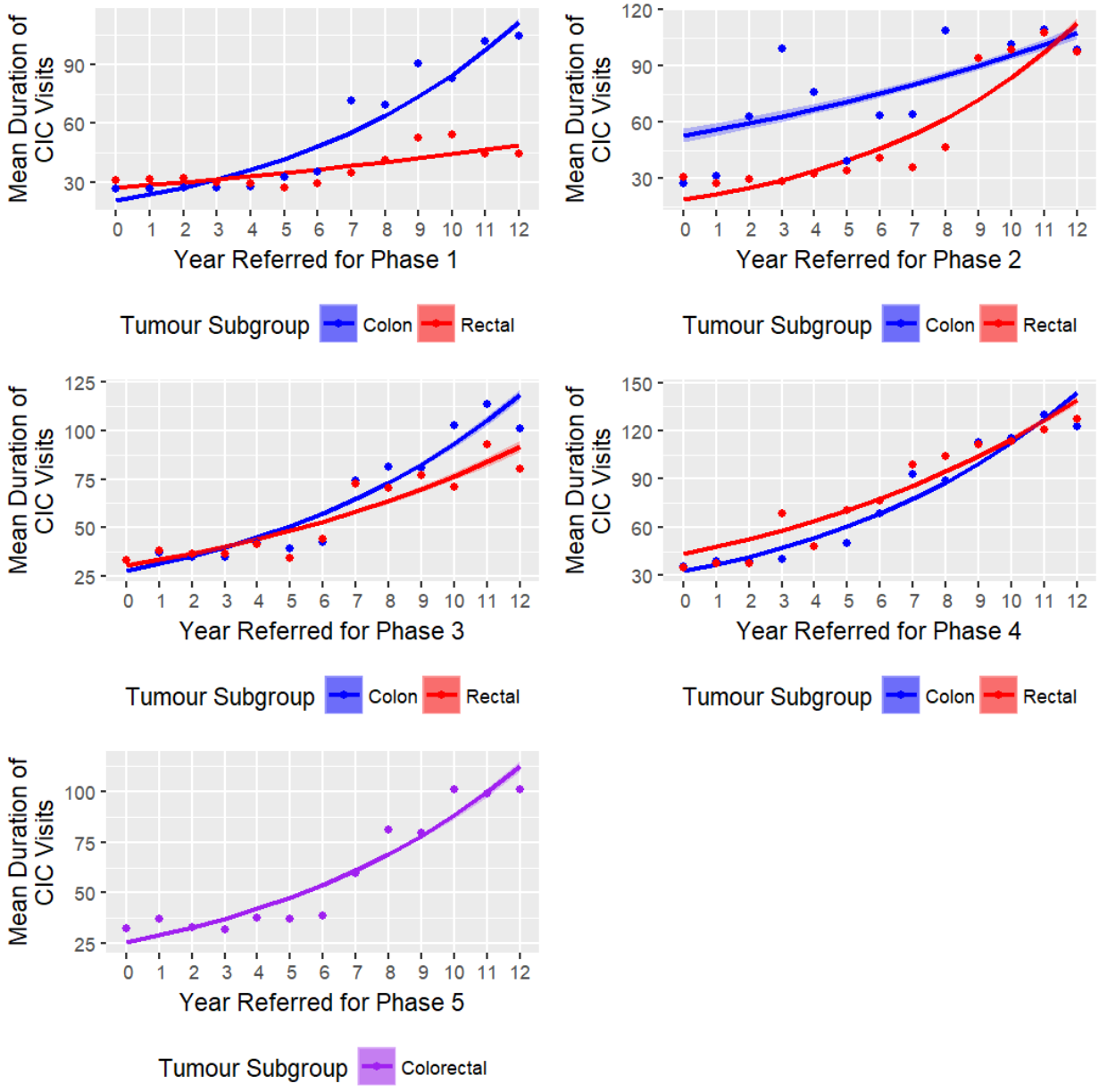


Figure 3-11. Observed and expected total duration of clinic visits (minutes). *The expected and observed total duration of clinic visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected total duration of clinic visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*

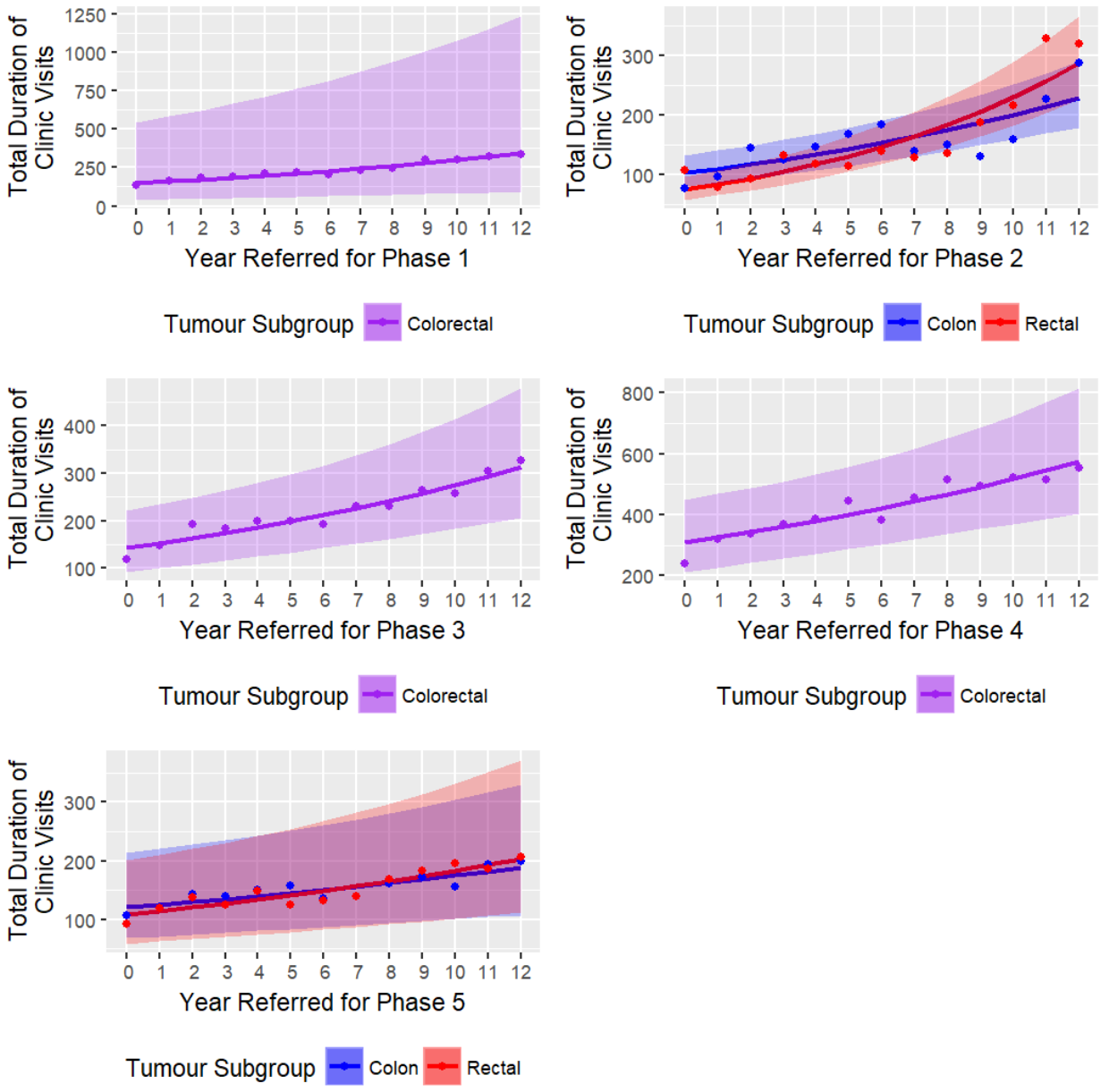


Figure 3-12. Observed and expected total duration of CIT visits (minutes). *The expected and observed total duration of CIT visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected total duration of CIT visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*

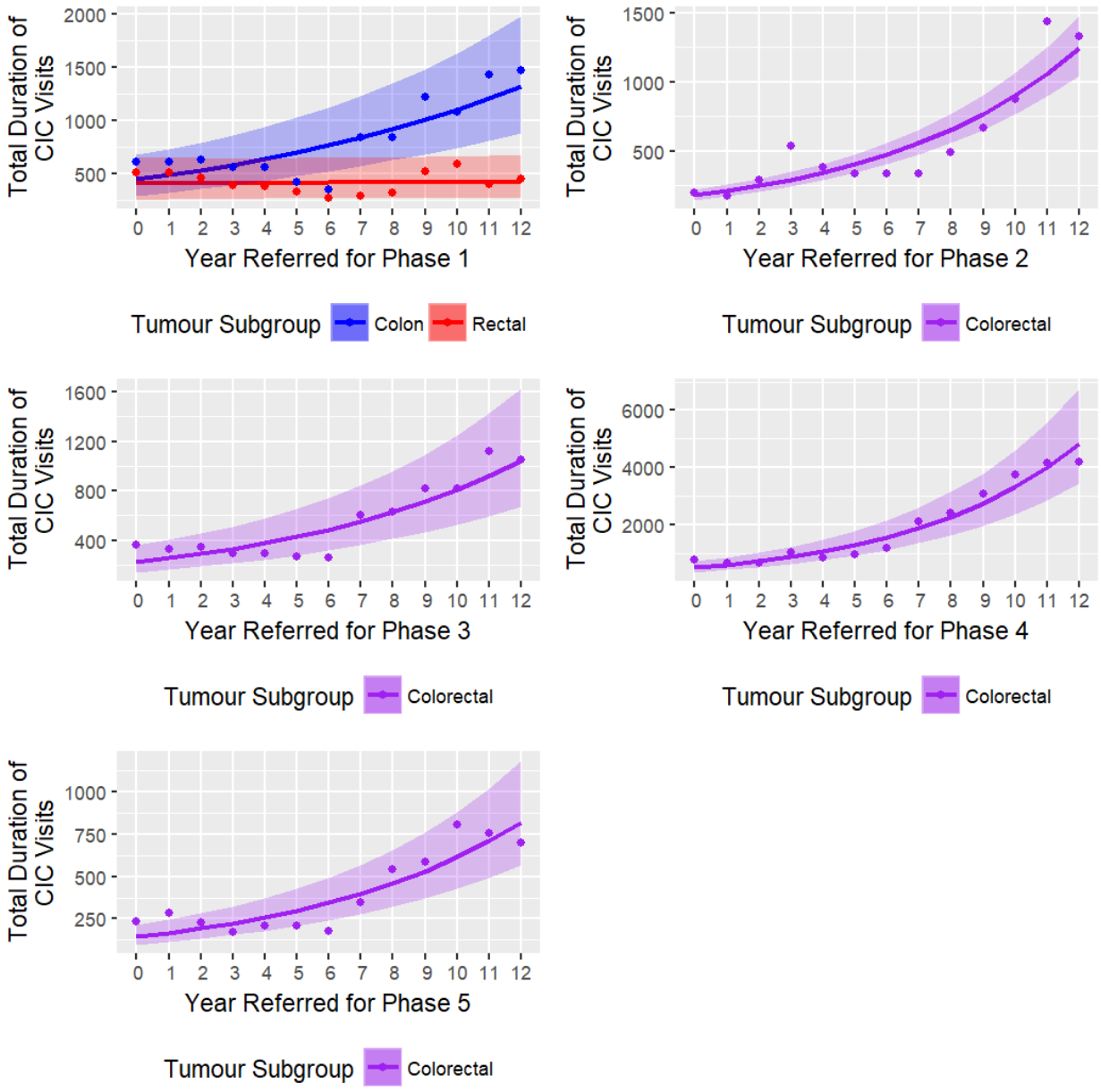


Figure 3-13. Observed and expected total duration of clinic visits per year (minutes/year). *The expected and observed total duration per year of clinic visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected total duration per year of clinic visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*

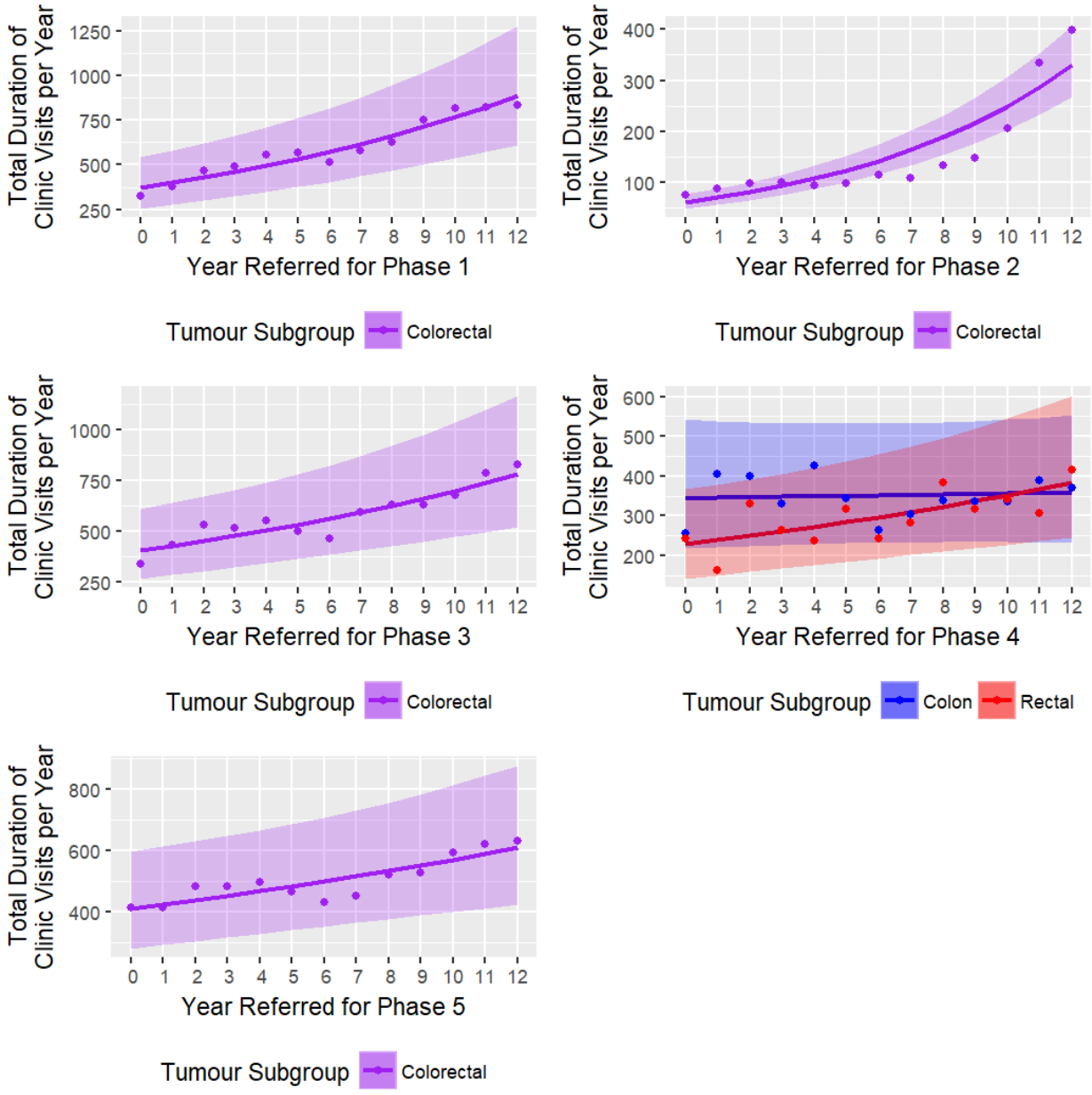
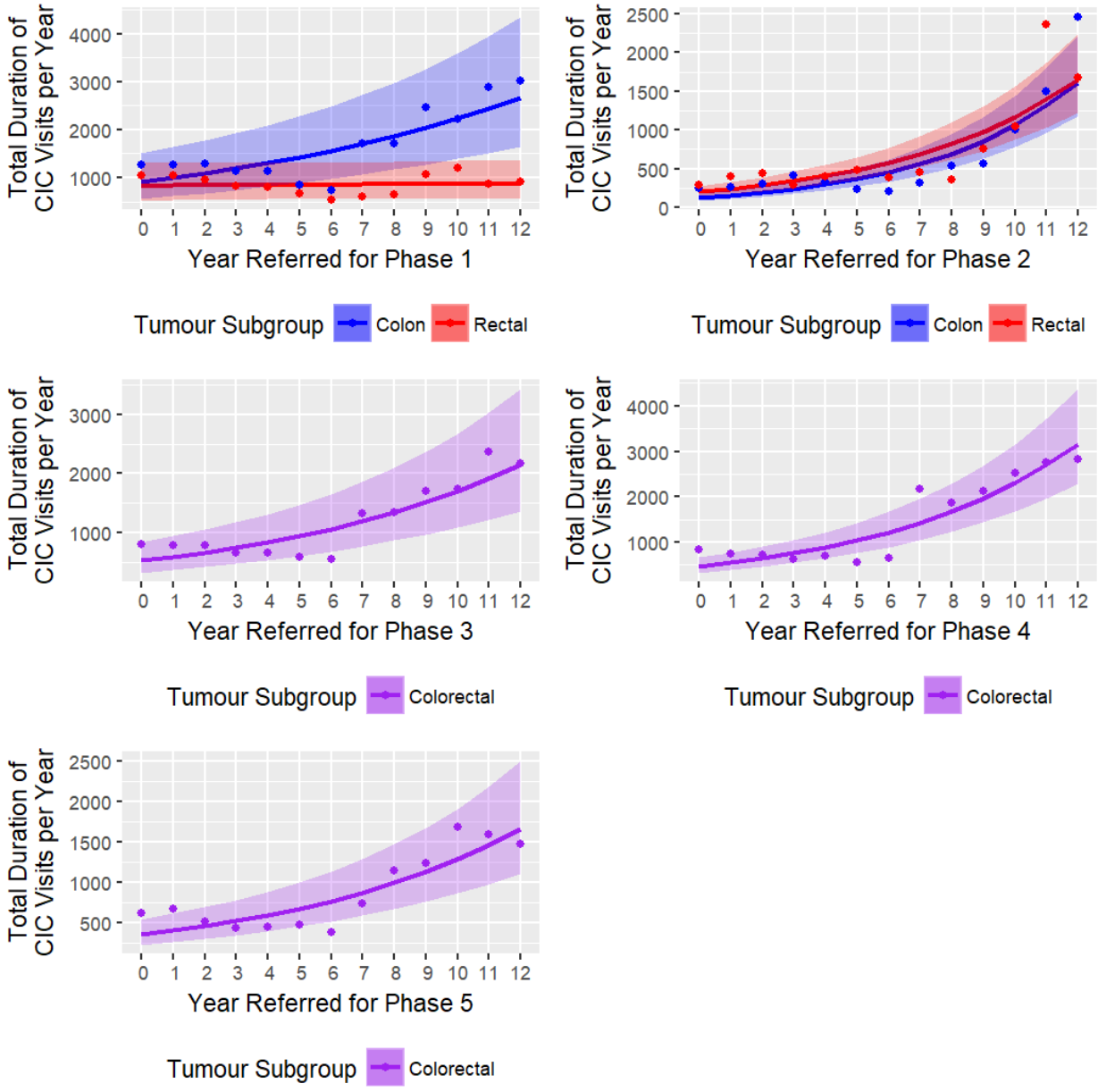


Figure 3-14. Observed and expected total duration of CIT visits per year (minutes/year). *The expected and observed total duration per year of CIT visits for each phase of care is presented from 2000 (year 0) to 2012 (year 12). The expected total duration per year of CIT visits in a phase of care for each year of phase initiation is depicted as a line, and 95% confidence intervals for estimates are represented as colored regions above and below the line. The observed mean is depicted as solid points. Based on the results of interaction analyses, results are presented either stratified for colon and rectal cancer patients or as a single cohort of colorectal cancer patients.*



4 DISCUSSION

4.1 OVERVIEW OF MACRO TRENDS IN TREATMENT COMPLEXITY OVER TIME

The overwhelming pattern in models of treatment complexity in this study was of an increasing trend. Of the 81 total models, 69 showed significant and increasing trends in complexity, 8 did not find significant trends, and only 4 which showed significant and decreasing trends. Of the 8 models not finding significant trends, 7 were in phases 1 and 5. By 2000, the beginning of the study period, patients with non-metastatic non-recurrent metastatic colorectal cancer were already being considered for a standard 6-month course of adjuvant chemotherapy. Due to the availability of early line chemotherapy during this phase of care even at the beginning of the study, it was unsurprising that in some models there were no significant trends during phase one of care. Phase five of care describes treatment received during the final six months of life, so a number of factors including the patients' health during this period and possible exhaustion of available chemotherapy options may have limited possible increases in treatment complexity as pertaining to medical oncology. The four models which found decreasing trends in treatment complexity described the number of CIT visits and visits per year during phase 1 of care among both colon and rectal cancer patients. This trend was the result of the increasing popularity of monotherapy orally administered capecitabine, which replaced monotherapy 5-fluorouracil and thereby reduces the need for patients to attend CIT visits.

The macro trend findings of this study are that, with some exceptions, patients being treated in 2012 on average experienced more treatment complexity in the form of increasing number, frequency, and duration of clinic and CIT visits.

4.2 INCREASING NUMBER, FREQUENCY, AND DURATION OF CIT VISITS

The observation of increasing number, frequency, and duration of CIT visits in this study is consistent with the hypothesis that the development of novel agents has led to a net greater number, frequency and duration of CIT visits per patient. Two main pressures on CIT visits can

be observed throughout the study period: the increased use of oral chemotherapy in single agent regimen which decreased treatment complexity relating to CIT by replacing IV-administered chemotherapy requiring CIT visits, and the gradual increase in the number of available chemotherapy agents which added additional lines of therapy and resulted in larger multi-agent regimens. The contributions of specific novel chemotherapy agents which were introduced during the study period to one of these two main pressures are discussed below.

4.2.1 Oral Chemotherapy

The introduction of capecitabine in the setting of colorectal oncologic care had been found in many studies and real world observations to be associated with a decrease in treatment complexity and cost[23,106–110]. This study found comparable results, with decreased treatment complexity of colorectal cancer patients in many of the metrics evaluated correlating with the introduction of capecitabine monotherapy and capecitabine-containing regimens. The mechanism by which capecitabine accomplishes this is well described in literature. Capecitabine reduces the need for patients to install chemotherapy injection ports which need to be regularly inspected, it reduces patient need for CIT visits, and it reduces the duration of clinic or CIT visits that patients do need to make by reducing the number of agents that need to be administered intravenously.

At the BC Cancer Agency, capecitabine may be prescribed as monotherapy capecitabine, in combination with oxaliplatin (CAPOX), or in combination with irinotecan (CAPIRI). When it is prescribed as a monotherapy agent, capecitabine directly replaces a prescription of 5-fluorouracil and leucovorin, results in no CIT visits, and hence does not alter the chemotherapy visit duration of patients receiving it. When prescribed in combination with other chemotherapy agents during the study period, those other agents are always intravenously administered. For that reason, capecitabine administered as part of a multi-drug regimen will still result in a chemotherapy visit and an equal number of prescriptions. The frequency of visits is different, however, as 5-fluorouracil based regimens require visits every 14 days, compared to every 21 days for capecitabine-containing multidrug regimens. Compared to 5-fluorouracil multi-drug regimens such as FOLFOX and FOLFIRI, capecitabine-containing multi-drug regimens may result in shorter duration CIT visits due to no longer needing to infuse 5-fluorouracil and leucovorin.

Note that although leucovorin can be infused simultaneously with other agents such as oxaliplatin, and fluorouracil is usually gradually infused over 46 hours each cycle using an infuser in the outpatient setting, the logistics and maintenance involved in 5-fluorouracil containing regimens may still cause chemotherapy visit durations to be longer than visits in capecitabine-containing regimens.

The expected effects of capecitabine on treatment complexity were clearly observed in phase 1 beginning with patients referred in 2002, following shortly after capecitabine was incorporated into the BC Cancer Agency Drug Manual. A decrease in the number, frequency, total duration, and total duration per year of CIT visits among colon and rectal cancer patients referred between 2002 and 2006. A closer inspection reveals several patterns corresponding with the introduction of different capecitabine-containing regimens. For example, patients referred from 2005 to 2006 among colon cancer patients and 2005 to 2008 among rectal cancer patients experienced drastically decreasing number and frequency of CIT visits, which corresponded with the introduction of monotherapy capecitabine as a standard treatment protocol at the BC Cancer Agency. This trend persisted for longer among rectal cancer patients, perhaps due to rectal cancer patients needing to receive radiotherapy in addition to chemotherapy. It is possible that the increased burden of care from receiving radiotherapy provided additional motivation for rectal cancer patients to take the lower complexity chemotherapy option. During this same period, mean duration of CIT visits increased substantially, possibly associated with the smaller proportion of CIT visits were associated with the relatively short duration monotherapy 5FU. Total duration and total duration per year of CIT visits decreased as well for patients referred in 2005 to 2006. In contrast, these metrics increased for patients referred in 2006 or later due to the increased use of oxaliplatin-based regimens in phase 1 of therapy. After this period, the effect of capecitabine on reducing treatment complexity was gradually overshadowed by the effect of other agents. Many of the same effects by capecitabine on treatment complexity can be observed in other phases of care, to a lesser extent especially since it is the only agent during this study period which was widely reported in literature to decrease treatment complexity. However, compared to in treatment phase 1, trends in treatment complexity of later phases of care tend to be driven more by the introduction of other novel chemotherapy agents. This is because the chemotherapy regimens in later lines of therapy tend to have more agents, which limits the complexity-reducing benefit of replacing intravenously administered 5-fluorouracil with capecitabine.

4.2.2 Oxaliplatin and Irinotecan

There was a general trend of increasing treatment complexity throughout the study period, which correlated with the increased use of oxaliplatin and irinotecan among colorectal cancer patients at the BC Cancer Agency. Oxaliplatin was prescribed in British Columbia in all years of the study, however it was initially prescribed infrequently and virtually exclusively in continued care more than 6 months after initial referral for metastatic disease (phase 4) until 2002. From 2002 onwards, there was greater use of oxaliplatin to treat colorectal cancer patients in phases 2 to 5 at the BC Cancer Agency, and oxaliplatin use among patients in phase 1 also increased shortly thereafter in 2003. These trends correspond with the approval of oxaliplatin in the United States (January 2004) and the completion of clinical trials demonstrating the efficacy of oxaliplatin. As discussed in the introduction, oxaliplatin was not formally approved in Canada until 2007 due to an intellectual property filing error. Despite this, oxaliplatin was used by patients at the BC Cancer Agency, which contributed to increased treatment complexity. This observation suggests that when health benefits can be clearly demonstrated, inclusion of new treatment regimens and protocols by healthcare providers at BC Cancer and likely other Canadian cancer centres can outpace the formal approval process.

The introduction of oxaliplatin was a driving factor behind increasing the total duration of CIT visits in years after 2003. Oxaliplatin based multidrug regimens include FOLFOX and CAPOX, both regimens which expanded upon existing regimens rather than replacing them. When prescribed in combination with 5-fluorouracil and leucovorin (FOLFOX), oxaliplatin increased the duration of each chemotherapy visit, but does not increase the number of CIT visits. When prescribed in combination with capecitabine (CAPOX), oxaliplatin increased the number of CIT visits, as patients receiving capecitabine monotherapy do not need to make CIT visits. This has the interesting effect of increasing the average number of CIT visits and decreasing the duration of each visit. Since the only agent that needs to be intravenously delivered in the CAPOX regimen is oxaliplatin, it is a simpler chemotherapy visit compared with patients who need to receive FOLFOX. The inclusion of irinotecan and irinotecan-containing multidrug regimens contribute to the general trend of increasing treatment complexity in a similar manner as oxaliplatin. Irinotecan-containing regimens such as FOLFIRI and CAPIRI are considered as

comparable alternatives to their oxaliplatin counterparts and are generally considered interchangeable in order of treatment. Patients who progress on oxaliplatin-based multidrug regimens are frequently considered for irinotecan-based multidrug regimens, and vice versa. One multidrug regimen in which irinotecan is used but which oxaliplatin is not is the FOLFIRI regimen.

4.2.3 Anti-EGFR Targeted therapy

Panitimumab and cetuximab are both anti-EGFR targeted therapy which are administered intravenously and are both most frequently used to treat advanced colorectal cancer which have developed resistance to both the FOLFOX and FOLFIRI regimens. Their use contributed to the increasing number of CIT visits and chemotherapy duration in phase 4, as they tend to be prescribed in the third line or later setting for patients diagnosed with metastatic disease. These drugs represent novel therapies used in addition to existing lines of therapy, but do not replace any existing regimens. Due to these factors, both panitimumab and cetuximab increased both the number of CIT visits and the total duration of CIT visits. Cetuximab is generally administered in combination with irinotecan, with the first cycle taking three and a half hours followed by each additional cycle taking two and a half hours. Comparatively, panitumumab is usually administered as a monotherapy agent at BC Cancer, with the first cycle taking just one hour and the following cycles taking just half an hour if tolerated by the patient. In this study, cetuximab was first observed to be used among colorectal cancer patients in 2004, corresponding to the phase III CRYSTAL trial which assessed the efficacy of cetuximab combined with irinotecan for treatment-naïve metastatic colorectal cancer[50]. Both cetuximab and panitumumab were used in greater frequencies following their incorporation into standardized protocols at BC Cancer in 2009. This corresponded with findings in 2009 that these two anti-EGFR drugs should be used only among patients with wildtype *KRAS*, a restriction which clarified which patients may benefit from them[54].

4.2.4 Bevacizumab

Bevacizumab is generally indicated for first line therapy in the palliative setting for metastatic or recurrent disease, in combination with either the FOLFOX or FOLFIRI regimens. Second line therapy is generally only considered for patients who have undergone metastectomies, which precluded them from receiving pre-operative bevacizumab. For these reasons, the introduction of bevacizumab only affected patients receiving care in phases 3, 4, and 5. This was consistent with what was observed, as bevacizumab was first dispensed in phase 4 of care, with the majority of cycles dispensed in phases 3, 4, and 5 over the study period. Interestingly, bevacizumab was also used in greater amounts in phase 2 of care from 2003 onwards. Bevacizumab is usually dispensed over 10 to 15 minutes during the same chemotherapy visit as when other agents such as fluorouracil, leucovorin, irinotecan, and oxaliplatin. Consequently, increased use of bevacizumab contributes to increase duration of chemotherapy visit, but not increased number of CIT visits.

4.3 Increasing Number and Frequency of Chemotherapy Prescriptions Dispensed

Developments in chemotherapy for colon and rectal cancer between 2000 and 2012 has, for the most part, resulted in additional lines of therapy being added rather than replacement of conventionally used agents. Patients who initiated a phase of care in later years, therefore, could reasonably be expected to receive more cycles of chemotherapy dispensed than those who initiated treatment earlier. Oxaliplatin and bevacizumab were used to supplement existing agents, which resulted in more drugs dispensed in existing cycles. Use of panitimumab and cetuximab were implemented either as standalone monotherapy, or concurrently with irinotecan. Use of raltitrexed tended to be as monotherapy. The use of these additional lines of therapy may result in increased overall number of chemotherapy prescriptions dispensed, but the frequency may decrease due to the simpler regimens or increase if the patients may otherwise have remained on observation instead. The introduction of capecitabine was the only instance during the study period where an agent was introduced to replace an existing line of therapy. In this study, both leucovorin and 5-fluorouracil are both counted as chemotherapy agents dispensed, although they are generally dispensed together. As a consequence of this

decision in the methodology, the use of capecitabine in lieu of 5-fluorouracil with leucovorin has the effect of decreasing the number and frequency of chemotherapy dispensed.

While it's difficult to ascertain the exact contribution that each of the above chemotherapy agents contributed to the macro trend in the number and frequency of chemotherapy prescriptions dispensed on a year to year basis, it is possible to associate specific phases of care with these agents. For example, capecitabine would usually be administered during a patient's initial line of therapy, which would occur during phase 1 of care for patients referred with non-metastatic disease. As observed in Table 3-7, among both colon and rectal cancer patients, the number and frequency of prescriptions dispensed did not increase over the study period in Phase 1 despite the increased number of treatment options available for patients who progressed during their first 6 months of therapy.

The number and frequency of prescriptions dispensed increased among these patients who were referred with metastatic disease and thus would receive their first line of care during phase 3 of care. One possible reason for this increase care, as well as increases in phases 2 and 4 of care, may be the decision to use of more potent regimens that include oxaliplatin (CAPOX) or irinotecan (CAPIR) even among patients who elect to use capecitabine instead of 5-fluorouracil and leucovorin. These regimens are less frequently used among patients with low risk tumors in phase 1 of care due to toxicity of these treatments. Interestingly, the number and frequency of prescriptions dispensed did not increase in phase 5 of care. This may reflect limitations in how much chemotherapy treatments patients may be able to receive as their health deteriorates with disease progression. It may also reflect a decision among some patients to receive less chemotherapy, which is then followed by disease progression.

4.4 Increasing Number, Frequency, and Duration of Clinic Visits

With the exception of clinic visits per year during phase 5 of care, both the number and frequency of clinic visits increased over the study period in all phases of care. At the same time, in all phases of care and among both colon and rectal cancer patients, a significant increasing trend was observed in: the mean duration of each visit, the total duration of all visits, and the total duration of all visits adjusted for length in a phase of care. The only exception here was for

total duration of visits per year among colon cancer patients in phase 4 of care. While no existing literature was found that studied the mechanisms driving the trend for increasing duration of clinic visits, there are a number of potential contributing factors.

In phase 1 of care, increasing number and frequency of clinic visits with later year of treatment phase initiation may represent an increasing proportion of patients who choose to receive adjuvant therapy rather than opt for observation only. The introduction of capecitabine may be associated with this pattern, as a slight upward trend could be observed in 2003 which correlate with the increased use of capecitabine at BC Cancer. The increased convenience of being able to take an oral prescription, rather than sitting down for hours for a chemotherapy infusion on a regular basis, may have convinced some patients to receive adjuvant chemotherapy rather than opting to remain on observation only post-surgery. The increased clinic visits would be associated with the follow-up visits that these patients would still make.

In phase 3 of care, the increase in number and frequency of clinic visits with later year of treatment phase initiation is modest, as even at the start of the study period patients are generally started on six months of treatment. However, some patients do progress during their first six months of treatment, which may result in discharge from BC Cancer due to exhaustion of available therapeutic options. A multitude of additional lines of therapy were introduced for treatment of metastatic colon cancer, with FOLFOX and FOLFIRI becoming prevalent for first and second-line therapies, the addition of bevacizumab to either of these regimens as a possible intermediate line, third-line anti-EGFR therapies such as panitimumab and cetuximab, and even more options such as raltitrexed became available near the end of the study period. For the patients who progressed during their first six months of treatment, these additional lines of therapy allow for a continuation treatment, which is associated with more clinic visits during phase 3.

The availability of additional lines of treatment has an even larger effect on phases 2 and 4 of care, which represent any treatment provided after the first six months of a patient being referred to BC Cancer with non-metastatic or metastatic cancer respectively. If only a single line of therapy is available, then patients would generally be treated over a maximum of 6 months per protocol, and only a few cycles of treatment would fall in phase 2 or 4. However, with the availability of additional lines, phase 1 patients who progress on a line of therapy may receive an additional line which would then last six months, with even more cycles passing into phase 2.

Patients with metastatic disease in phase 4 of care would continue receiving treatment until all available lines of chemotherapy were exhausted, until they no longer wished to continue treatment, or until their bodies cannot handle the toxicity of the treatment. In all examples above, patients would receive more clinic visits in phases 1 to 4.

Frequency and rate of clinic visits in phase 5 only increased among rectal cancer patients, with no significant trends being observed among colon cancer patients. One possible reason for this might be that rectal cancer patients receiving end-of-life care are more likely to discuss radiotherapy for the purposes of symptom control. In contrast, colon cancer is generally not sensitive to radiotherapy, and thus colon patients are more likely to be transferred from BC Cancer when all chemotherapy options are exhausted, so that they can focus on supportive care.

4.5 Significance of This Study: Healthcare Providers

The total and per capita economic burden of oncologic care around the world is rising, due to a multitude of factors including: aging populations resulting in more incidences of cancer, improved survivorship leading to increased duration of care, drastically increased costs of novel chemotherapy agents compared to conventional treatments, and increased hospital costs[111,112]. While this study does not directly evaluate increased cost, it does measure increased treatment complexity on a per patient basis, which can provide fundamental insights on increasing complexity in medical oncology.

In Europe, the total price-differential adjusted cost of health expenditure on cancer increased from €35.8 billion in 1995 to €83.2 billion in 2014 (+132%)[113]. Per capita, the increase amounted to €74 in 1995 to €164 in 2014 (+122%), in 2014 prices. The same study noted that total cancer drug sales in the EU increased from €9.2 billion in 2005 to €19.1 billion in 2014 (+108%), or on a per-capita basis €18 in 2005 to €38 in 2014 (+111%). In the United States, 5-year costs of care from January 1st 1999 through December 31st 2004 and among patients aged 65 and older were approximately $24.3 billion (in 2010 USD), with $3.6 billion attributable to colorectal cancer[95]. The authors also found that national direct and indirect costs among cancer patients of all ages in 2010 was $124.6 billion (in 2010 USD), with $14.14 billion attributable to colorectal cancer[82]. Another American study found that direct spending on cancer in the United States increased

+31.5% from $76.1 billion in 2000 to $100.1 billion in 2009, in 2010 USD[114]. Studies looking at per capita costs of colorectal cancer in the United States had found similarly drastic increases. One study found that among colorectal cancer patients, total direct costs had increased from $38,724 in 1999 to $56,839 in 2006 (+46.8%) in 2008 US dollars[115].

A review of relevant literature found two main sources of information on the economic burden of oncologic care in Canada during the study period. The first, are a series of reports by the Public Health Agency of Canada entitled the "Economic Burden of Illness in Canada (EBIC)", including reports in 1998 and 2005-2008[86,87]. In 1998, total direct costs associated with cancer (malignant neoplasms) were estimated to be $3.13 billion in 2010 constant dollars CAD: $2.34 billion was associated with hospital related expenses, $267.0 million with drugs, and $423.2 million with physician related expenses. Table 4-1 presents increases from 2005 to 2008, which outlines the disproportionate growth of drug-related expenses as a driver of increased direct costs for oncologic care in Canada. Although drug-related expenses increased the most in 2008 relative to 2005 levels, the bulk of the increase in absolute dollar terms was in hospital-related expenses. Colorectal cancer specific expenditures were not provided in the 1998 EBIC report.

Table 4-1. Comparison of the Direct Cost of Colorectal Cancer in 2005 and 2008 using Economic Burden of Illness in Canada Data[116]*. All expenses are in $1,000,000's. Expenditures across all years are described in 2010 constant Canadian Dollars. Percentages for each subgroup among hospital, drug, and physician are calculated as a proportion of the total direct health expenditures for that population.*

		2005		2006		2007		2008	
		$	%	$	%	$	%	$	%
Canada	Hospital	$316.4	75.5%	$330.0	75.8%	$377.0	74.5%	$383.9	71.4%
	Drug	$13.7	3.3%	$9.5	2.2%	$16.8	3.3%	$28.4	5.3%
	Physician	$88.9	21.2%	$96.0	22.0%	$112.5	22.2%	$125.4	23.3%
	Total Direct	$419.0	100.0%	$435.5	100.0%	$506.2	100.0%	$537.7	100.0%
British Columbia	Hospital	$31.4	68.9%	$34.3	68.2%	$42.8	67.7%	$41.3	66.3%
	Drug	$0.3	0.6%	$1.0	2.0%	$2.8	4.4%	$2.2	3.6%
	Physician	$13.8	30.4%	$15.0	29.9%	$17.6	27.9%	$18.8	30.1%
	Total Direct	$45.5	100.0%	$50.3	100.0%	$63.2	100.0%	$62.3	100.0%

While the metrics of treatment complexity investigated in this study do not directly demonstrate increases in dollar terms, they could reasonably be corroborated with the findings in previous economic studies which have been performed. On a per patient basis, patients are receiving more complex (number, frequency, and duration) chemotherapy treatment visits with later year of initiating a phase of care. This would translate into a need for more chemotherapy chairs and related supporting staff over longer periods of time, and in turn result in increased need for hospital resources. Similarly, the growing complexity of clinic visits translates into physicians spending more time with each patient over the course of their treatment, which increases workload and physician-related costs. Finally, the increased complexity of the chemotherapy prescriptions dispensed contributes to the substantial increase in drug-related costs observed in the study.

In almost all instances, the increased use of a novel chemotherapeutic agent appears to correlate with increased complexity of treatment. The introduction of capecitabine, however, is a notable exception which is correlated with a trend in decreased complexity of treatment in colorectal cancer. As an orally administered alternative to IV 5-fluorouracil and leucovorin, it reduces the burden on the healthcare system both by decreasing the complexity of CIT visits in terms of staff and space, but also allows for the possibility of decreased clinic visits. Attempts to investigate novel delivery systems for other agents used to treat colorectal cancer are already underway, including an orally delivered formulation of oxaliplatin encased in pH sensitive microparticles already having shown the ability to decrease tumour burden and decrease mortality in-vivo in a mouse model[117].

4.6 Significance of This Study: Patient Perspective

The findings of this study reveal important trends affecting patients receiving treatment for colon or rectal cancer at BC Cancer. In virtually all phases of care, and among both colon and rectal cancer patients, the average duration of each visit and the number and frequency of clinic and CIT visits were greater for patients who were referred to the BC Cancer Agency in later years. With the notable exception of capecitabine, each additional drug introduced during the study period contributed to the increased treatment complexity experienced by colorectal

cancer patients. Capecitabine had the unique characteristics of being administered orally and as a replacement for an existing intravenously administered drug. As a result, capecitabine reduced chemotherapy treatment visit waiting time, duration of time spent in CIT visits, time associated with commuting to chemotherapy clinics, and may have also contributed to a reduced number of clinic visits due to the relatively longer duration between CIT visits for capecitabine-containing multidrug regimens.

Comparatively, administration of oxaliplatin, irinotecan, and bevacizumab could extend patient chemotherapy treatment time by as much as two hours per visit and may reintroduce the need for patients who were on capecitabine to make additional CIT visits. The three other major drugs introduced during the study period, panitimumab, cetuximab, and raltitrexed, provided additional clinical benefit as later lines of therapy, but consequently increased the number, frequency, and duration of chemotherapy and clinic visits for patients.

4.7 STRENGTHS

Due to the centralized nature of oncologic care in British Columbia, this multi-center study has the advantage of including virtually all colorectal cancer patients referred to a teaching hospital level cancer center in British Columbia over the 13-year study period. Over the course of the study-period, the ratio of BC residents who were referred to BC Cancer to BC residents diagnosed with colorectal cancer has increased from 48.5% to 56.7%. The only study which was found in literature to assess the complexity of oncologic care included 121 subjects among a multitude of cancers over a 3-month period[90]. Comparatively, this study included 14,759 patients among colorectal cancer patients, from multiple centers and referred over a 13-year period. By focusing on a specific type of cancer, this study could associate observed changes over time with known changes in policy or trends in treatment. By including a much longer study period, it was possible to observe temporal trends rather than a small window in time. By including multiple similar centers throughout the province of British Columbia, this study not only widened the study sampling frame but also reduced possible effects limited to any single center.

The much larger sample included in this study further increased sensitivity to the effects of later referral on complexity, and to stratify analyses by phase of care. This was an approach that

could not be utilized in smaller studies. The inclusion of a 5-phase definition for phase of care also allowed this study to assess trends in complexity with greater differentiation between metastatic and non-metastatic diseases, compared to most other studies reviewed, which used a 3-phase definition that do not differentiate between the two.

Another advantage that this study has is that all cancer centers included are highly similar in several important ways. First, except for clinical trials, all BC Cancer Agency centers follow the same treatment guidelines at any point in time. Access to novel chemotherapy agents, changes in their indications, and approval of novel combinations of chemotherapy, are all authorized concurrently at all BC Cancer centers throughout the study period. Furthermore, Canadian citizens and permanent residents do not pay out of pocket for access to oncologic care provided by BC Cancer, which allows more equal access to care across the different geographic and socioeconomic regions serviced by BC Cancer centers. All of BC Cancer regional centers included in this study also use a common electronic medical record, which allow for models to be built on a greater number of comparable treatment characteristics. Since the analysis was based on administrative scheduling data, descriptions of clinic and CIT visits and durations were based on real schedules, rather than estimations from surveys or other sources.

4.8 LIMITATIONS

This study aimed to model the observed trends in the complexity of treatment for colorectal cancer patients referred to BC Cancer. Following this objective, the unadjusted effect of later patient referral on the complexity of treatment was evaluated. This study did not adjust for the age, gender, urban residency, socioeconomic status, or other demographic and disease characteristics. Another limitation of this study is that for patients receiving phase 3 or phase 4 of care, this study does not differentiate between patients whose tumors were previously treated in the adjuvant setting but have progressed, or patients who were referred with treatment-naïve metastatic disease. It is possible that trends in the complexity of treatment may be different between patients in these two groups, as their disease could theoretically respond very differently to treatment.

Due to the focus of this study on the averaged trends over time, rather than on the specific events or occurrences which drive changes in treatment complexity, the statistical models

presented in this study often do not follow the observed trends in treatment complexity. While it would be possible to create models which more closely approximate trends in treatment complexity by including additional terms to adjust for the introduction of new agents or practices, this approach is mutually exclusive with the primary objective of the study: to evaluate the averaged trends of treatment complexity during the study period.

Our study is based on administrative scheduling data and may not always reflect a patient's actual experience. Errors could also occur from data entry practices, such as the default values of 0 or 1 for the duration of visits for which no values were entered. In this instance, default values were unrealistic and hence considered to be "missing" entries which could only be included in analyses following multiple imputation. Although rigorous data curation was performed to identify and exclude impossible or implausible values in the data, the sheer volume of the data being reviewed means that there may still be uncorrected data entry errors.

One of the major limitations of this study is that models of trends in treatment complexity describe average trends over the 13-year study period. Study models do not adjust for the introduction of additional pressures or forces in the study which drive these trends and interpretation relies upon the interpreters' contextual knowledge of when novel chemotherapeutic agents, when they are introduced, approved for novel indications, or authorized for use in new combination regimens. The relative contributions of each of these changes in treatment policy are not evaluated in this study, so it is impossible to determine the magnitude or significance of individual changes, only that in most instances a significant aggregate effect could be observed.

While future studies may aim to determine whether some aspects of treatment complexity on oncologic care is beneficial or detrimental to patient care, these issues are not addressed within the scope of this study. The primary objective of this study was to identify whether there were significant trends in increasing treatment complexity, and to note that where treatment complexity increased there would be new challenges that providers and patients would need to face. This does not mean that increasing treatment complexity is averse to patients, as the additional treatments associated may provide a net positive balance of clinical outcomes and quality of life outcomes for patients, despite the increased burden of care for them. Likewise, increased time spent in clinic or for treatment may or may not be beneficial, as that depends on the net balance of an incredibly wide array of factors. Instead of discussing the value of

treatment for patients or whether changes in treatments complexity are worthwhile, this study only aims to provide an objective assessment of trends in treatment complexity during the study period, and to discuss some challenges which may arise as a result of these trends.

In addition to the limitations listed above, the oncologic care delivery model in British Columbia represents only one of many diverse strategies used to deliver services to patients. Due to possible differences in trends of treatment complexity between different models of oncologic care delivery, caution should be taken when interpreting findings from one delivery model in the context of another model of care. Keeping in mind possible differences attributable to delivery model, the underlying drivers of treatment complexity such as the approval of specific drugs may still have comparable effects.

4.9 Suggested Future Research

Future research can expand on this study in many directions, including a deeper exploration of the possible demographic or disease characteristics which may be related to the increase in treatment complexity with later patient referral. The introduction of the anti-EGFR class of targeted therapy, for example, would only affect patients who have a wildtype *KRAS* gene. This is an important factor, as cancers with a mutated *KRAS* gene do not respond to anti-EGFR therapy[118–120]. Other factors of interest may include whether geographic proximity of patients to a chemotherapy clinic may influence patient decision in their choice of chemotherapy regimens, which has an effect on treatment complexity. Future investigators may also evaluate whether household income modifies the effect of later referral on treatment complexity which was observed in this study. Yet another approach would be to investigate the role of age and patient health status on the treatment complexity of patients referred to BC Cancer. Researchers using a mixed-methods approach may also wish to consider the quantitative findings of this study and interview patients with varying levels of treatment complexity, to assess the real-world significance of treatment complexity on patients' quality of life.

Despite the considerable volume of data analyzed in this study, it still covers only a subset of metrics in medical oncology, which is itself only one aspect of a more comprehensive treatment plan that most patients referred to BC Cancer are considered for. Radiation oncology is widely used for rectal cancer patients, often concurrently with chemotherapy, so future researchers

may attempt to assess how treatment complexity metrics including both radiation oncology and medical oncology have evolved over time[121–126]. Other aspects of oncologic care that future researchers may wish to investigate are: surgical oncology, including increased use of hepatic, pulmonary, and other metastectomies[127–130]; supportive care, including end-of-life palliative care, home support services, and other supportive care services provided throughout the treatment process[131–136]; and the use of additional services such as travel assistance, temporary lodging for medical appointments, or additional financial or social assistance for cancer patients[137–139].

Yet another approach for future research would be to convert the metrics of treatment complexity used in this study into monetary metrics used in health economics. Most current health economic studies estimate the direct cost of oncologic care calculated from aggregated data. A thorough search of relevant literature yielded no other multicenter study of the direct cost of oncologic care which used administrative scheduling records to count the number and duration of visits or services provided. If researchers could assign a cost per time, a cost per visit, or perhaps a cost dependent on both factors, then it would be possible to calculate direct costs at the centers included. Such an analysis would have the benefit of being grounded in real observable events, and the effect of increasing treatment complexity on the distribution of costs could be more thoroughly explored. Furthermore, if evaluated over a longer study period, trends in costs could be evaluated in the context of policy changes, the addition of novel treatments, or paradigm shifts in treatment guidelines.

One health economic study that was reviewed evaluated all-cause healthcare costs over two lines of therapy among patients with metastatic colorectal cancer who used cetuximab-containing regimens and bevacizumab-containing regimens[140]. The study concluded that patients who used cetuximab-containing regimens in their first line of therapy had higher all-cause healthcare costs compared to those who used bevacizumab-containing regimens, suggesting that the order of therapy received had a significant effect on costs of treatment. Based on the findings of this study, it would be reasonable to suggest that differing orders of various therapies may also affect treatment complexity. Future studies may wish to explore these trends using a phase-of-care approach.

Finally, the methodology used in this study could be expanded to evaluate trends in the treatment complexity for other cancers. One clear candidate for such studies is breast cancer,

for which medical and scientific advances in the 21st century have revolutionized how the disease is treated[141]. The development of DNA sequencing technology has allowed the genotyping and identification of breast cancer subgroups, each of which respond differently to treatments[142]. This pivotal discovery is only one among many others that have contributed to improved survival among breast cancer patients, including the introduction of an entire new class of treatment known as aromatase inhibitors, the addition of myriad new drugs such as gemcitabine, tamoxifen, and lapatinib, and the development of targeted therapies such as trastuzumab.

5 CONCLUSIONS

In this study, the treatment complexity of medical oncology services and treatments for colorectal cancer increased for most metrics in most of the phases of care that was evaluated. Patients referred to BC Cancer for colorectal cancer in any phase of care in 2012 can expect to receive more medical oncology related treatment and spend more time in treatment than patients who were referred in 2000. Patients referred in 2012 in most phases of care will on average spend more time in clinic visits, and more time in CIT visits, even after adjusting for the overall duration of their treatment. In a similar manner, medical oncologists and other healthcare providers can expect to see a patient referred in 2012 more times, more frequently, and for a longer duration than those referred earlier. The increasing trends in complexity of oncologic care observed for each colorectal cancer patient is expected to interact synergistically with the expected increase in incidence of colorectal cancer associated with an aging and growing population, resulting in an increased burden of care for healthcare providers. Current demand projections for oncologic care resources factor in changes in cancer incidence due to demographic changes, but the findings of this study underscore the need to further consider trends in resource use per patient in projections.

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APPENDIX

Appendix tables Table A1 to Table A25 provide tabulated numbers corresponding to figures Figure 3-3 to Figure 3-14 respectively.

Table A1. Predicted number of clinic visits and rate of clinic visits among colorectal cancer patients in phase one of care. *The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-3. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled separately due to significant effect modification by tumour subgroup on the association of later referral with metrics of complexity.*

	Visits (95% CI)			Visits per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	5.04 (4.74-5.36)	5.46 (5.21- 5.72)	-	11.93 (10.96-12.99)	12.42 (11.75-13.13)	-
2001	5.14 (4.87-5.43)	5.74 (5.50- 5.98)	-	12.34 (11.44-13.30)	13.13 (12.50-13.79)	-
2002	5.24 (4.99-5.50)	6.03 (5.81- 6.25)	-	12.75 (11.93-13.62)	13.88 (13.29-14.49)	-
2003	5.34 (5.12-5.57)	6.34 (6.14- 6.54)	-	13.18 (12.44-13.96)	14.67 (14.12-15.23)	-
2004	5.44 (5.25-5.65)	6.66 (6.48- 6.85)	-	13.62 (12.95-14.33)	15.50 (15.00-16.02)	-
2005	5.55 (5.37-5.73)	7.00 (6.83- 7.17)	-	14.08 (13.47-14.72)	16.38 (15.91-16.86)	-
2006	5.66 (5.49-5.83)	7.36 (7.20- 7.52)	-	14.56 (13.97-15.16)	17.31 (16.87-17.77)	-
2007	5.76 (5.60-5.94)	7.73 (7.57- 7.90)	-	15.04 (14.45-15.66)	18.30 (17.84-18.76)	-
2008	5.88 (5.70-6.06)	8.13 (7.95- 8.31)	-	15.55 (14.91-16.22)	19.34 (18.84-19.84)	-
2009	5.99 (5.79-6.20)	8.54 (8.34- 8.75)	-	16.07 (15.34-16.85)	20.44 (19.87-21.02)	-
2010	6.10 (5.87-6.35)	8.98 (8.74- 9.23)	-	16.62 (15.75-17.53)	21.60 (20.91-22.30)	-
2011	6.22 (5.95-6.51)	9.44 (9.15- 9.74)	-	17.17 (16.15-18.26)	22.83 (22.00-23.69)	-
2012	6.34 (6.03-6.67)	9.92 (9.57-10.28)	-	17.75 (16.55-19.04)	24.12 (23.13-25.17)	-

Table A2. Predicted number of clinic visits and rate of clinic visits among colorectal cancer patients in phase two of care. *The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-3. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled separately for number of visits due to significant effect modification by tumour subgroup on the association of later referral with number of clinic visits.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	2.64 (2.25-3.10)	2.07 (1.80-2.38)	-	-	-	0.49 (0.44-0.54)
2001	2.83 (2.46-3.26)	2.32 (2.04-2.63)	-	-	-	0.58 (0.53-0.63)
2002	3.03 (2.68-3.43)	2.60 (2.32-2.90)	-	-	-	0.69 (0.64-0.75)
2003	3.25 (2.91-3.62)	2.91 (2.64-3.21)	-	-	-	0.82 (0.77-0.88)
2004	3.48 (3.17-3.82)	3.26 (3.00-3.55)	-	-	-	0.98 (0.93-1.04)
2005	3.73 (3.43-4.04)	3.65 (3.40-3.93)	-	-	-	1.17 (1.11-1.23)
2006	3.99 (3.71-4.29)	4.10 (3.85-4.36)	-	-	-	1.39 (1.33-1.46)
2007	4.27 (3.99-4.58)	4.59 (4.34-4.86)	-	-	-	1.66 (1.60-1.73)
2008	4.58 (4.27-4.91)	5.14 (4.87-5.43)	-	-	-	1.98 (1.90-2.06)
2009	4.90 (4.55-5.29)	5.76 (5.44-6.10)	-	-	-	2.36 (2.26-2.47)
2010	5.25 (4.82-5.72)	6.46 (6.06-6.89)	-	-	-	2.81 (2.68-2.96)
2011	5.63 (5.10-6.21)	7.24 (6.72-7.80)	-	-	-	3.35 (3.17-3.55)
2012	6.03 (5.38-6.76)	8.11 (7.44-8.84)	-	-	-	4.00 (3.74-4.27)

Table A3. Predicted number of clinic visits and rate of clinic visits among colorectal cancer patients in phase three of care. *The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-3. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			**Visit per Year (95% CI)**		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	4.94 (4.67-5.22)	-	-	11.73 (11.10-12.41)
2001	-	-	5.10 (4.85-5.36)	-	-	12.06 (11.48-12.68)
2002	-	-	5.26 (5.04-5.50)	-	-	12.40 (11.87-12.95)
2003	-	-	5.43 (5.23-5.64)	-	-	12.74 (12.27-13.24)
2004	-	-	5.61 (5.43-5.80)	-	-	13.10 (12.68-13.54)
2005	-	-	5.79 (5.63-5.96)	-	-	13.47 (13.08-13.86)
2006	-	-	5.98 (5.82-6.14)	-	-	13.84 (13.49-14.20)
2007	-	-	6.17 (6.02-6.33)	-	-	14.23 (13.88-14.59)
2008	-	-	6.37 (6.21-6.54)	-	-	14.62 (14.25-15.01)
2009	-	-	6.58 (6.39-6.77)	-	-	15.03 (14.61-15.47)
2010	-	-	6.79 (6.57-7.02)	-	-	15.45 (14.95-15.97)
2011	-	-	7.02 (6.75-7.29)	-	-	15.88 (15.29-16.50)
2012	-	-	7.24 (6.93-7.57)	-	-	16.33 (15.63-17.05)

Table A4. Predicted number of clinic visits and rate of clinic visits among colorectal cancer patients in phase four of care. *The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-3. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	11.79 (10.64-13.06)	-	-	6.35 (5.79- 6.97)
2001	-	-	12.31 (11.24-13.48)	-	-	6.59 (6.07- 7.15)
2002	-	-	12.85 (11.86-13.93)	-	-	6.83 (6.35- 7.34)
2003	-	-	13.42 (12.52-14.39)	-	-	7.07 (6.64- 7.53)
2004	-	-	14.02 (13.20-14.89)	-	-	7.33 (6.95- 7.74)
2005	-	-	14.64 (13.89-15.41)	-	-	7.60 (7.26- 7.96)
2006	-	-	15.28 (14.60-15.99)	-	-	7.88 (7.57- 8.20)
2007	-	-	15.96 (15.30-16.64)	-	-	8.16 (7.87- 8.47)
2008	-	-	16.66 (15.98-17.38)	-	-	8.46 (8.15- 8.78)
2009	-	-	17.40 (16.63-18.21)	-	-	8.77 (8.42- 9.13)
2010	-	-	18.17 (17.25-19.14)	-	-	9.09 (8.68- 9.52)
2011	-	-	18.97 (17.87-20.15)	-	-	9.42 (8.93- 9.94)
2012	-	-	19.81 (18.48-21.25)	-	-	9.76 (9.17-10.39)

Table A5. Predicted number of clinic visits and rate of clinic visits among colorectal cancer patients in phase five of care. *The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-3. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	3.49 (3.25-3.74)	-	-	8.48 (7.86-9.14)
2001	-	-	3.54 (3.32-3.77)	-	-	8.53 (7.98-9.12)
2002	-	-	3.59 (3.40-3.80)	-	-	8.59 (8.10-9.11)
2003	-	-	3.64 (3.47-3.83)	-	-	8.65 (8.22-9.11)
2004	-	-	3.70 (3.55-3.86)	-	-	8.71 (8.34-9.10)
2005	-	-	3.75 (3.62-3.89)	-	-	8.77 (8.44-9.11)
2006	-	-	3.81 (3.69-3.93)	-	-	8.83 (8.54-9.13)
2007	-	-	3.86 (3.75-3.98)	-	-	8.89 (8.61-9.18)
2008	-	-	3.92 (3.80-4.04)	-	-	8.95 (8.67-9.24)
2009	-	-	3.98 (3.85-4.12)	-	-	9.01 (8.70-9.34)
2010	-	-	4.04 (3.89-4.20)	-	-	9.07 (8.72-9.45)
2011	-	-	4.10 (3.92-4.29)	-	-	9.14 (8.72-9.57)
2012	-	-	4.16 (3.95-4.38)	-	-	9.20 (8.72-9.71)

Table A6. Predicted number of chemotherapy visits and rate of chemotherapy visits among colorectal cancer patients in phase one of care.
The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-5. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled separately due to significant effect modification by tumour subgroup.

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	9.24 (8.53-10.01)	6.36 (5.84-6.92)	-	21.84 (20.44-23.35)	14.44 (13.38-15.58)	-
2001	8.87 (8.27- 9.52)	6.22 (5.77-6.71)	-	21.27 (20.06-22.56)	14.21 (13.28-15.19)	-
2002	8.52 (8.01- 9.06)	6.09 (5.70-6.50)	-	20.72 (19.68-21.81)	13.98 (13.18-14.83)	-
2003	8.18 (7.76- 8.64)	5.95 (5.62-6.30)	-	20.18 (19.30-21.11)	13.76 (13.07-14.48)	-
2004	7.86 (7.49- 8.24)	5.82 (5.54-6.12)	-	19.66 (18.89-20.45)	13.54 (12.94-14.16)	-
2005	7.55 (7.23- 7.88)	5.70 (5.44-5.96)	-	19.15 (18.47-19.85)	13.32 (12.78-13.88)	-
2006	7.25 (6.95- 7.56)	5.57 (5.33-5.82)	-	18.65 (18.01-19.31)	13.11 (12.60-13.63)	-
2007	6.96 (6.66- 7.27)	5.45 (5.21-5.70)	-	18.16 (17.52-18.83)	12.90 (12.39-13.42)	-
2008	6.68 (6.37- 7.01)	5.33 (5.08-5.60)	-	17.69 (17.00-18.41)	12.69 (12.14-13.26)	-
2009	6.42 (6.08- 6.77)	5.21 (4.93-5.51)	-	17.23 (16.47-18.03)	12.49 (11.88-13.12)	-
2010	6.16 (5.79- 6.56)	5.10 (4.79-5.43)	-	16.78 (15.94-17.67)	12.29 (11.61-13.00)	-
2011	5.92 (5.51- 6.35)	4.99 (4.64-5.36)	-	16.35 (15.41-17.34)	12.09 (11.33-12.90)	-
2012	5.68 (5.25- 6.16)	4.88 (4.50-5.30)	-	15.92 (14.89-17.02)	11.90 (11.05-12.80)	-

Table A7. Predicted number of chemotherapy visits and rate of chemotherapy visits among colorectal cancer patients in phase two of care.
The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-5. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	1.30 (1.07-1.59)	-	-	0.27 (0.22-0.34)
2001	-	-	1.45 (1.21-1.73)	-	-	0.33 (0.27-0.40)
2002	-	-	1.61 (1.37-1.88)	-	-	0.40 (0.33-0.47)
2003	-	-	1.78 (1.55-2.05)	-	-	0.48 (0.41-0.56)
2004	-	-	1.98 (1.76-2.23)	-	-	0.58 (0.50-0.66)
2005	-	-	2.20 (1.99-2.44)	-	-	0.70 (0.62-0.78)
2006	-	-	2.45 (2.24-2.68)	-	-	0.84 (0.76-0.93)
2007	-	-	2.72 (2.50-2.95)	-	-	1.01 (0.92-1.11)
2008	-	-	3.02 (2.79-3.27)	-	-	1.23 (1.12-1.34)
2009	-	-	3.35 (3.08-3.65)	-	-	1.48 (1.34-1.63)
2010	-	-	3.72 (3.38-4.09)	-	-	1.79 (1.60-1.99)
2011	-	-	4.13 (3.70-4.61)	-	-	2.16 (1.90-2.44)
2012	-	-	4.59 (4.04-5.21)	-	-	2.60 (2.25-3.01)

Table A8. Predicted number of chemotherapy visits and rate of chemotherapy visits among colorectal cancer patients in phase three of care. *The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-5. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	3.11 (2.81-3.45)	-	-	7.39 (6.70- 8.14)
2001	-	-	3.34 (3.04-3.66)	-	-	7.89 (7.24- 8.61)
2002	-	-	3.58 (3.30-3.89)	-	-	8.43 (7.81- 9.10)
2003	-	-	3.84 (3.58-4.12)	-	-	9.01 (8.43- 9.63)
2004	-	-	4.12 (3.88-4.38)	-	-	9.62 (9.08-10.19)
2005	-	-	4.42 (4.19-4.66)	-	-	10.28 (9.78-10.80)
2006	-	-	4.74 (4.53-4.97)	-	-	10.98 (10.51-11.47)
2007	-	-	5.09 (4.87-5.31)	-	-	11.73 (11.26-12.21)
2008	-	-	5.46 (5.23-5.70)	-	-	12.53 (12.02-13.05)
2009	-	-	5.86 (5.59-6.14)	-	-	13.38 (12.80-13.99)
2010	-	-	6.28 (5.95-6.63)	-	-	14.29 (13.59-15.03)
2011	-	-	6.74 (6.33-7.17)	-	-	15.27 (14.40-16.18)
2012	-	-	7.23 (6.73-7.77)	-	-	16.31 (15.25-17.44)

Table A9. Predicted number of chemotherapy visits and rate of chemotherapy visits among colorectal cancer patients in phase four of care.
The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-5. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	7.85 (6.65- 9.27)	-	-	4.11 (3.56- 4.74)
2001	-	-	8.84 (7.62-10.26)	-	-	4.61 (4.05- 5.24)
2002	-	-	9.95 (8.73-11.35)	-	-	5.17 (4.61- 5.79)
2003	-	-	11.21 (9.99-12.58)	-	-	5.80 (5.25- 6.41)
2004	-	-	12.62 (11.43-13.94)	-	-	6.51 (5.97- 7.09)
2005	-	-	14.21 (13.06-15.47)	-	-	7.30 (6.78- 7.85)
2006	-	-	16.00 (14.89-17.21)	-	-	8.19 (7.70- 8.71)
2007	-	-	18.02 (16.92-19.19)	-	-	9.19 (8.71- 9.70)
2008	-	-	20.29 (19.14-21.52)	-	-	10.31 (9.81-10.83)
2009	-	-	22.85 (21.52-24.26)	-	-	11.56 (10.99-12.17)
2010	-	-	25.73 (24.07-27.50)	-	-	12.97 (12.26-13.73)
2011	-	-	28.97 (26.81-31.31)	-	-	14.55 (13.62-15.56)
2012	-	-	32.62 (29.79-35.73)	-	-	16.33 (15.10-17.66)

Table A10. Predicted number of chemotherapy visits and rate of chemotherapy visits among colorectal cancer patients in phase five of care. *The number of visits and the number of visits per year were derived from the quasi-Poisson models presented in Table 3-5. The number of visits and visits per year represent the average that patients referred in a given year may be expected to experience. Number of visits and visits per year correspond with models of visit ratio and visit rate ratio respectively. Colon and rectal cohorts were modelled separately due to significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	1.99 (1.69-2.34)	1.11 (0.88-1.40)	-	4.89 (4.17-5.72)	2.62 (2.09-3.29)	-
2001	2.05 (1.77-2.37)	1.20 (0.98-1.48)	-	5.00 (4.35-5.76)	2.82 (2.30-3.45)	-
2002	2.12 (1.86-2.41)	1.30 (1.08-1.56)	-	5.13 (4.53-5.80)	3.02 (2.53-3.62)	-
2003	2.18 (1.95-2.44)	1.41 (1.20-1.65)	-	5.25 (4.72-5.85)	3.25 (2.78-3.80)	-
2004	2.25 (2.04-2.48)	1.52 (1.33-1.75)	-	5.38 (4.91-5.90)	3.49 (3.05-3.99)	-
2005	2.32 (2.13-2.52)	1.65 (1.47-1.86)	-	5.51 (5.09-5.97)	3.75 (3.34-4.21)	-
2006	2.39 (2.22-2.57)	1.79 (1.61-1.98)	-	5.65 (5.27-6.06)	4.03 (3.64-4.45)	-
2007	2.46 (2.30-2.64)	1.94 (1.77-2.12)	-	5.79 (5.42-6.17)	4.32 (3.96-4.72)	-
2008	2.54 (2.37-2.72)	2.10 (1.92-2.29)	-	5.93 (5.56-6.32)	4.64 (4.27-5.05)	-
2009	2.62 (2.43-2.82)	2.27 (2.07-2.49)	-	6.07 (5.66-6.51)	4.99 (4.56-5.45)	-
2010	2.70 (2.48-2.94)	2.46 (2.22-2.72)	-	6.22 (5.75-6.74)	5.36 (4.85-5.92)	-
2011	2.79 (2.53-3.07)	2.66 (2.36-3.00)	-	6.37 (5.81-6.99)	5.76 (5.13-6.46)	-
2012	2.87 (2.57-3.21)	2.88 (2.51-3.31)	-	6.53 (5.87-7.27)	6.18 (5.40-7.08)	-

Table A11. Predicted number of chemotherapy prescriptions and rate of chemotherapy prescriptions among colorectal cancer patients in phase one of care. *The number of prescriptions and the number of prescriptions per year were derived from the quasi-Poisson models presented in Table 3-7. The number of prescriptions and prescriptions per year represent the average that patients referred in a given year may be expected to experience. Number of prescriptions and prescriptions per year correspond with models of prescription ratio and prescription rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	12.82 (12.11-13.58)	-	-	29.73 (28.30-31.24)
2001	-	-	12.75 (12.12-13.41)	-	-	29.86 (28.58-31.19)
2002	-	-	12.67 (12.12-13.25)	-	-	29.98 (28.85-31.16)
2003	-	-	12.60 (12.12-13.10)	-	-	30.11 (29.11-31.13)
2004	-	-	12.52 (12.10-12.96)	-	-	30.23 (29.36-31.14)
2005	-	-	12.45 (12.07-12.83)	-	-	30.36 (29.57-31.17)
2006	-	-	12.37 (12.02-12.73)	-	-	30.49 (29.74-31.25)
2007	-	-	12.30 (11.95-12.66)	-	-	30.61 (29.86-31.39)
2008	-	-	12.23 (11.85-12.61)	-	-	30.74 (29.93-31.58)
2009	-	-	12.16 (11.74-12.59)	-	-	30.87 (29.95-31.81)
2010	-	-	12.08 (11.61-12.58)	-	-	31.00 (29.95-32.08)
2011	-	-	12.01 (11.47-12.58)	-	-	31.13 (29.92-32.38)
2012	-	-	11.94 (11.34-12.58)	-	-	31.26 (29.89-32.69)

Table A12. Predicted number of chemotherapy prescriptions and rate of chemotherapy prescriptions among colorectal cancer patients in phase two of care. *The number of prescriptions and the number of prescriptions per year were derived from the quasi-Poisson models presented in Table 3-7. The number of prescriptions and prescriptions per year represent the average that patients referred in a given year may be expected to experience. Number of prescriptions and prescriptions per year correspond with models of prescription ratio and prescription rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	3.62 (3.06- 4.30)	-	-	0.75 (0.63-0.91)
2001	-	-	3.91 (3.36- 4.55)	-	-	0.89 (0.75-1.04)
2002	-	-	4.22 (3.69- 4.82)	-	-	1.04 (0.90-1.20)
2003	-	-	4.55 (4.05- 5.12)	-	-	1.22 (1.07-1.38)
2004	-	-	4.91 (4.44- 5.44)	-	-	1.43 (1.28-1.59)
2005	-	-	5.30 (4.86- 5.79)	-	-	1.68 (1.53-1.84)
2006	-	-	5.72 (5.30- 6.18)	-	-	1.97 (1.81-2.14)
2007	-	-	6.18 (5.75- 6.64)	-	-	2.31 (2.14-2.49)
2008	-	-	6.67 (6.20- 7.16)	-	-	2.71 (2.51-2.93)
2009	-	-	7.19 (6.65- 7.78)	-	-	3.18 (2.92-3.45)
2010	-	-	7.76 (7.10- 8.48)	-	-	3.73 (3.39-4.10)
2011	-	-	8.38 (7.56- 9.28)	-	-	4.37 (3.91-4.88)
2012	-	-	9.04 (8.03-10.18)	-	-	5.13 (4.51-5.82)

Table A13. Predicted number of chemotherapy prescriptions and rate of chemotherapy prescriptions among colorectal cancer patients in phase three of care. *The number of prescriptions and the number of prescriptions per year were derived from the quasi-Poisson models presented in Table 3-7. The number of prescriptions and prescriptions per year represent the average that patients referred in a given year may be expected to experience. Number of prescriptions and prescriptions per year correspond with models of prescription ratio and prescription rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	11.19 (10.24-12.22)	-	-	26.58 (24.44-28.91)
2001	-	-	11.63 (10.75-12.58)	-	-	27.51 (25.53-29.65)
2002	-	-	12.09 (11.28-12.95)	-	-	28.48 (26.67-30.41)
2003	-	-	12.57 (11.84-13.35)	-	-	29.48 (27.84-31.21)
2004	-	-	13.07 (12.40-13.77)	-	-	30.51 (29.04-32.06)
2005	-	-	13.58 (12.98-14.22)	-	-	31.58 (30.25-32.98)
2006	-	-	14.12 (13.56-14.71)	-	-	32.69 (31.45-33.98)
2007	-	-	14.68 (14.12-15.27)	-	-	33.84 (32.61-35.11)
2008	-	-	15.26 (14.66-15.89)	-	-	35.02 (33.71-36.39)
2009	-	-	15.87 (15.18-16.59)	-	-	36.25 (34.75-37.82)
2010	-	-	16.50 (15.68-17.36)	-	-	37.52 (35.76-39.38)
2011	-	-	17.15 (16.18-18.19)	-	-	38.84 (36.74-41.07)
2012	-	-	17.83 (16.67-19.08)	-	-	40.20 (37.71-42.86)

Table A14. Predicted number of chemotherapy prescriptions and rate of chemotherapy prescriptions among colorectal cancer patients in phase four of care. *The number of prescriptions and the number of prescriptions per year were derived from the quasi-Poisson models presented in Table 3-7. The number of prescriptions and prescriptions per year represent the average that patients referred in a given year may be expected to experience. Number of prescriptions and prescriptions per year correspond with models of prescription ratio and prescription rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	29.17 (26.11-32.60)	-	-	15.61 (13.94-17.49)
2001	-	-	31.02 (28.10-34.25)	-	-	16.49 (14.91-18.25)
2002	-	-	32.99 (30.23-36.00)	-	-	17.43 (15.94-19.05)
2003	-	-	35.08 (32.51-37.85)	-	-	18.41 (17.04-19.89)
2004	-	-	37.30 (34.94-39.83)	-	-	19.45 (18.20-20.79)
2005	-	-	39.67 (37.50-41.97)	-	-	20.55 (19.41-21.75)
2006	-	-	42.19 (40.17-44.30)	-	-	21.71 (20.67-22.80)
2007	-	-	44.86 (42.91-46.90)	-	-	22.94 (21.94-23.98)
2008	-	-	47.70 (45.67-49.83)	-	-	24.23 (23.20-25.31)
2009	-	-	50.73 (48.41-53.16)	-	-	25.60 (24.43-26.83)
2010	-	-	53.95 (51.16-56.89)	-	-	27.05 (25.64-28.53)
2011	-	-	57.37 (53.93-61.02)	-	-	28.57 (26.84-30.41)
2012	-	-	61.00 (56.78-65.54)	-	-	30.19 (28.07-32.47)

Table A15. Predicted number of chemotherapy prescriptions and rate of chemotherapy prescriptions among colorectal cancer patients in phase five of care. *The number of prescriptions and the number of prescriptions per year were derived from the quasi-Poisson models presented in Table 3-7. The number of prescriptions and prescriptions per year represent the average that patients referred in a given year may be expected to experience. Number of prescriptions and prescriptions per year correspond with models of prescription ratio and prescription rate ratio respectively. Colon and rectal cohorts were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Visit (95% CI)			Visit per Year (95% CI)		
Year	**Colon**	**Rectal**	**Colorectal**	**Colon**	**Rectal**	**Colorectal**
2000	-	-	6.10 (5.24-7.11)	-	-	14.83 (12.72-17.29)
2001	-	-	6.20 (5.42-7.11)	-	-	14.96 (13.06-17.15)
2002	-	-	6.31 (5.60-7.11)	-	-	15.10 (13.39-17.02)
2003	-	-	6.42 (5.78-7.12)	-	-	15.23 (13.72-16.90)
2004	-	-	6.52 (5.96-7.14)	-	-	15.36 (14.04-16.81)
2005	-	-	6.63 (6.13-7.17)	-	-	15.50 (14.34-16.76)
2006	-	-	6.74 (6.29-7.23)	-	-	15.64 (14.60-16.75)
2007	-	-	6.86 (6.43-7.32)	-	-	15.78 (14.79-16.83)
2008	-	-	6.97 (6.53-7.45)	-	-	15.92 (14.91-16.99)
2009	-	-	7.09 (6.60-7.62)	-	-	16.06 (14.95-17.25)
2010	-	-	7.21 (6.64-7.83)	-	-	16.20 (14.93-17.58)
2011	-	-	7.33 (6.67-8.06)	-	-	16.34 (14.87-17.97)
2012	-	-	7.45 (6.68-8.32)	-	-	16.49 (14.78-18.40)

Table A16. Predicted mean duration, total duration, and total duration per year of clinic visits among colorectal cancer patients in phase one.
Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification by tumour subgroup was significant, colon and rectal cancer patients were modelled separately.

	Mean Duration per Visit (95% CI)		Total Duration of Visits (95% CI)	Total Duration of Visits per Year (95% CI)
Year	Colon	Rectal	Colorectal	Colorectal
2000	30.50 (29.89 - 31.12)	32.69 (32.20 - 33.20)	150.85 (41.63 - 546.56)	373.52 (256.57 - 543.77)
2001	31.38 (30.82 - 31.95)	33.10 (32.65 - 33.56)	161.55 (44.68 - 584.08)	401.38 (277.62 - 580.31)
2002	32.29 (31.78 - 32.80)	33.52 (33.12 - 33.93)	173.01 (47.94 - 624.41)	431.32 (300.07 - 619.96)
2003	33.22 (32.77 - 33.68)	33.94 (33.58 - 34.30)	185.29 (51.41 - 667.76)	463.49 (323.98 - 663.07)
2004	34.19 (33.78 - 34.60)	34.37 (34.05 - 34.68)	198.44 (55.12 - 714.39)	498.06 (349.37 - 710.01)
2005	35.17 (34.80 - 35.55)	34.80 (34.51 - 35.08)	212.52 (59.07 - 764.55)	535.20 (376.31 - 761.19)
2006	36.19 (35.84 - 36.55)	35.23 (34.97 - 35.49)	227.60 (63.29 - 818.53)	575.12 (404.82 - 817.06)
2007	37.24 (36.89 - 37.60)	35.67 (35.42 - 35.93)	243.75 (67.77 - 876.64)	618.02 (434.95 - 878.13)
2008	38.32 (37.94 - 38.71)	36.12 (35.86 - 36.39)	261.04 (72.55 - 939.23)	664.11 (466.75 - 944.92)
2009	39.43 (38.99 - 39.87)	36.57 (36.29 - 36.87)	279.56 (77.64 - 1006.65)	713.64 (500.26 - 1018.05)
2010	40.57 (40.05 - 41.09)	37.03 (36.70 - 37.37)	299.40 (83.05 - 1079.31)	766.87 (535.53 - 1098.14)
2011	41.74 (41.14 - 42.36)	37.50 (37.11 - 37.89)	320.64 (88.81 - 1157.63)	824.07 (572.63 - 1185.92)
2012	42.95 (42.24 - 43.68)	37.97 (37.52 - 38.42)	343.40 (94.94 - 1242.09)	885.53 (611.61 - 1282.14)

Table A17. Predicted mean duration, total duration, and total duration per year of clinic visits among colorectal cancer patients in phase two.
Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification of tumour subgroup was significant, colon and rectal cancer patients were modelled separately.

	Mean Duration per Visit (95% CI)		Total Duration of Visits (95% CI)		Total Duration of Visits per Year (95% CI)
Year	Colon	Rectal	Colon	Rectal	Colorectal
2000	23.85 (23.29 - 24.41)	21.65 (21.08 - 22.23)	102.45 (79.21 - 132.53)	74.48 (57.57 - 96.36)	61.71 (49.55 - 76.86)
2001	24.02 (23.52 - 24.53)	22.04 (21.52 - 22.57)	109.53 (85.44 - 140.42)	83.38 (65.02 - 106.92)	70.96 (57.24 - 87.98)
2002	24.19 (23.75 - 24.65)	22.44 (21.97 - 22.92)	117.10 (92.05 - 148.96)	93.34 (73.35 - 118.78)	81.60 (66.07 - 100.78)
2003	24.37 (23.97 - 24.77)	22.84 (22.42 - 23.27)	125.19 (99.06 - 158.21)	104.49 (82.65 - 132.11)	93.84 (76.22 - 115.52)
2004	24.55 (24.20 - 24.89)	23.25 (22.88 - 23.63)	133.84 (106.46 - 168.26)	116.98 (93.00 - 147.14)	107.90 (87.87 - 132.50)
2005	24.72 (24.42 - 25.03)	23.67 (23.34 - 24.01)	143.08 (114.24 - 179.20)	130.95 (104.49 - 164.10)	124.08 (101.23 - 152.09)
2006	24.90 (24.64 - 25.17)	24.10 (23.81 - 24.39)	152.97 (122.41 - 191.15)	146.59 (117.23 - 183.30)	142.69 (116.53 - 174.70)
2007	25.08 (24.84 - 25.33)	24.53 (24.27 - 24.80)	163.53 (130.95 - 204.22)	164.10 (131.33 - 205.06)	164.08 (134.05 - 200.83)
2008	25.27 (25.02 - 25.51)	24.97 (24.72 - 25.23)	174.83 (139.88 - 218.52)	183.71 (146.88 - 229.76)	188.68 (154.08 - 231.04)
2009	25.45 (25.19 - 25.71)	25.42 (25.16 - 25.69)	186.91 (149.17 - 234.19)	205.65 (164.03 - 257.83)	216.96 (176.97 - 265.99)
2010	25.63 (25.34 - 25.93)	25.88 (25.58 - 26.18)	199.82 (158.85 - 251.36)	230.22 (182.91 - 289.77)	249.49 (203.12 - 306.46)
2011	25.82 (25.48 - 26.17)	26.35 (26.00 - 26.70)	213.62 (168.91 - 270.18)	257.72 (203.67 - 326.11)	286.90 (232.96 - 353.33)
2012	26.01 (25.61 - 26.41)	26.82 (26.42 - 27.24)	228.38 (179.37 - 290.79)	288.50 (226.49 - 367.51)	329.91 (266.99 - 407.65)

Table A18. Predicted mean duration, total duration, and total duration per year of clinic visits among colorectal cancer patients in phase three. *Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification by tumour subgroup was significant, colon and rectal cancer patients were modelled separately.*

	Mean Duration per Visit (95% CI)		Total Duration of Visits (95% CI)	Total Duration of Visits per Year (95% CI)
Year	Colon	Rectal	Colorectal	Colorectal
2000	27.61 (26.81 - 28.44)	29.20 (28.27 - 30.16)	143.66 (92.83 - 222.33)	404.15 (267.09 - 611.53)
2001	28.71 (27.97 - 29.47)	30.02 (29.18 - 30.89)	153.33 (100.08 - 234.92)	426.93 (284.53 - 640.59)
2002	29.85 (29.17 - 30.54)	30.87 (30.10 - 31.65)	163.65 (107.74 - 248.58)	450.99 (302.73 - 671.86)
2003	31.03 (30.42 - 31.65)	31.73 (31.05 - 32.43)	174.67 (115.80 - 263.46)	476.41 (321.67 - 705.59)
2004	32.26 (31.71 - 32.82)	32.63 (32.02 - 33.25)	186.43 (124.26 - 279.68)	503.26 (341.32 - 742.05)
2005	33.54 (33.04 - 34.05)	33.55 (33.00 - 34.10)	198.98 (133.12 - 297.42)	531.63 (361.65 - 781.50)
2006	34.87 (34.39 - 35.35)	34.49 (33.98 - 35.01)	212.37 (142.35 - 316.84)	561.59 (382.63 - 824.25)
2007	36.25 (35.77 - 36.73)	35.46 (34.95 - 35.98)	226.67 (151.95 - 338.14)	593.25 (404.24 - 870.63)
2008	37.69 (37.17 - 38.22)	36.46 (35.91 - 37.02)	241.93 (161.90 - 361.51)	626.68 (426.42 - 920.99)
2009	39.18 (38.58 - 39.79)	37.48 (36.85 - 38.12)	258.21 (172.20 - 387.18)	662.01 (449.17 - 975.69)
2010	40.74 (40.02 - 41.47)	38.54 (37.79 - 39.29)	275.59 (182.85 - 415.39)	699.32 (472.45 - 1035.12)
2011	42.35 (41.49 - 43.23)	39.62 (38.74 - 40.52)	294.15 (193.82 - 446.40)	738.74 (496.25 - 1099.70)
2012	44.03 (43.00 - 45.08)	40.74 (39.70 - 41.80)	313.95 (205.14 - 480.48)	780.37 (520.56 - 1169.86)

Table A19. Predicted mean duration, total duration, and total duration per year of clinic visits among colorectal cancer patients in phase four.
Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification by tumour subgroup was significant, colon and rectal cancer patients were modelled separately.

	Mean Duration of Visits (95% CI)	Total Duration of Visits (95% CI)	Total Duration of Visits per Year (95% CI)	
Year	Colorectal	Colorectal	Colon	Rectal
2000	22.16 (21.84 - 22.49)	309.48 (212.75 - 450.20)	344.30 (218.68 - 542.10)	228.73 (142.67 - 366.71)
2001	22.51 (22.22 - 22.80)	325.84 (226.64 - 468.45)	345.44 (221.67 - 538.31)	238.81 (150.60 - 378.66)
2002	22.86 (22.60 - 23.12)	343.06 (241.09 - 488.17)	346.58 (224.40 - 535.28)	249.32 (158.75 - 391.59)
2003	23.22 (22.99 - 23.45)	361.20 (256.03 - 509.55)	347.73 (226.83 - 533.06)	260.31 (167.06 - 405.60)
2004	23.58 (23.38 - 23.78)	380.29 (271.43 - 532.80)	348.88 (228.93 - 531.67)	271.77 (175.52 - 420.81)
2005	23.95 (23.78 - 24.13)	400.39 (287.22 - 558.15)	350.03 (230.68 - 531.13)	283.75 (184.09 - 437.35)
2006	24.32 (24.17 - 24.48)	421.55 (303.33 - 585.85)	351.19 (232.06 - 531.48)	296.24 (192.72 - 455.37)
2007	24.70 (24.56 - 24.85)	443.84 (319.71 - 616.16)	352.35 (233.04 - 532.73)	309.29 (201.40 - 474.99)
2008	25.09 (24.94 - 25.24)	467.30 (336.29 - 649.34)	353.51 (233.64 - 534.90)	322.92 (210.07 - 496.38)
2009	25.48 (25.32 - 25.65)	492.00 (353.02 - 685.69)	354.68 (233.83 - 537.99)	337.14 (218.72 - 519.68)
2010	25.88 (25.69 - 26.08)	518.01 (369.86 - 725.48)	355.85 (233.64 - 542.00)	351.99 (227.32 - 545.05)
2011	26.29 (26.06 - 26.52)	545.39 (386.79 - 769.02)	357.03 (233.07 - 546.92)	367.50 (235.84 - 572.66)
2012	26.70 (26.43 - 26.97)	574.22 (403.77 - 816.61)	358.21 (232.14 - 552.74)	383.69 (244.27 - 602.67)

Table A20. Predicted mean duration, total duration, and total duration per year of clinic visits among colorectal cancer patients in phase five.
Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification by tumour subgroup was significant, colon and rectal cancer patients were modelled separately.

	Mean Duration of Visits (95% CI)		Total Duration of Visits (95% CI)		Total Duration of Visits per Year (95% CI)
Year	Colon	Rectal	Colon	Rectal	Colorectal
2000	26.54 (25.86 - 27.24)	27.62 (26.76 - 28.50)	120.51 (67.86 - 214.03)	108.81 (58.75 - 201.54)	408.69 (279.84 - 596.88)
2001	27.00 (26.38 - 27.63)	27.92 (27.15 - 28.71)	125.09 (70.99 - 220.41)	114.64 (62.40 - 210.60)	422.46 (291.59 - 612.07)
2002	27.46 (26.90 - 28.02)	28.22 (27.53 - 28.93)	129.83 (74.18 - 227.24)	120.78 (66.21 - 220.32)	436.70 (303.50 - 628.34)
2003	27.93 (27.44 - 28.43)	28.53 (27.92 - 29.15)	134.76 (77.42 - 234.56)	127.25 (70.16 - 230.79)	451.41 (315.53 - 645.81)
2004	28.41 (27.97 - 28.85)	28.84 (28.31 - 29.39)	139.88 (80.71 - 242.42)	134.06 (74.25 - 242.06)	466.62 (327.62 - 664.59)
2005	28.89 (28.51 - 29.28)	29.16 (28.69 - 29.64)	145.19 (84.04 - 250.84)	141.24 (78.47 - 254.22)	482.34 (339.74 - 684.78)
2006	29.39 (29.04 - 29.74)	29.47 (29.05 - 29.90)	150.70 (87.38 - 259.89)	148.81 (82.83 - 267.34)	498.59 (351.85 - 706.52)
2007	29.89 (29.56 - 30.23)	29.80 (29.40 - 30.20)	156.42 (90.75 - 269.60)	156.78 (87.31 - 281.52)	515.39 (363.90 - 729.93)
2008	30.40 (30.05 - 30.75)	30.12 (29.71 - 30.53)	162.36 (94.13 - 280.04)	165.17 (91.90 - 296.86)	532.75 (375.86 - 755.13)
2009	30.92 (30.53 - 31.31)	30.45 (30.00 - 30.90)	168.52 (97.51 - 291.25)	174.02 (96.61 - 313.46)	550.70 (387.70 - 782.24)
2010	31.45 (31.00 - 31.90)	30.78 (30.27 - 31.30)	174.92 (100.88 - 303.29)	183.34 (101.42 - 331.43)	569.26 (399.38 - 811.39)
2011	31.99 (31.46 - 32.52)	31.12 (30.52 - 31.72)	181.55 (104.24 - 316.22)	193.16 (106.34 - 350.88)	588.43 (410.89 - 842.70)
2012	32.53 (31.92 - 33.16)	31.46 (30.76 - 32.16)	188.45 (107.58 - 330.10)	203.51 (111.34 - 371.95)	608.26 (422.21 - 876.29)

Table A21. Predicted mean duration, total duration, and total duration per year of chemotherapy visits among colorectal cancer patients in phase one. *Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Colon and rectal cancer patients were modelled separately due to significant effect modification by tumour subgroup.*

	Mean Duration of Visits (95% CI)		Total Duration of Visits (95% CI)		Total Duration of Visits per Year (95% CI)	
Year	Colon	Rectal	Colon	Rectal	Colon	Rectal
2000	20.69 (20.32 - 21.07)	27.26 (26.63 - 27.90)	441.80 (290.33 - 672.28)	403.27 (251.57 - 646.44)	913.95 (554.09 - 1507.51)	832.01 (522.35 - 1325.24)
2001	23.82 (23.44 - 24.20)	28.62 (28.03 - 29.21)	483.94 (321.22 - 729.08)	404.87 (254.50 - 644.09)	999.31 (611.63 - 1632.73)	835.39 (529.10 - 1318.98)
2002	27.42 (27.03 - 27.80)	30.04 (29.50 - 30.60)	530.09 (354.87 - 791.83)	406.49 (257.17 - 642.49)	1092.64 (674.18 - 1770.85)	838.78 (535.24 - 1314.46)
2003	31.56 (31.17 - 31.95)	31.54 (31.04 - 32.05)	580.65 (391.44 - 861.31)	408.11 (259.57 - 641.65)	1194.69 (742.02 - 1923.53)	842.19 (540.72 - 1311.73)
2004	36.33 (35.93 - 36.72)	33.12 (32.65 - 33.59)	636.03 (431.08 - 938.41)	409.73 (261.66 - 641.60)	1306.27 (815.41 - 2092.62)	845.61 (545.48 - 1310.87)
2005	41.81 (41.40 - 42.23)	34.77 (34.32 - 35.22)	696.69 (473.92 - 1024.16)	411.36 (263.43 - 642.36)	1428.28 (894.63 - 2280.23)	849.04 (549.48 - 1311.92)
2006	48.13 (47.66 - 48.60)	36.50 (36.05 - 36.95)	763.13 (520.12 - 1119.69)	413.00 (264.88 - 643.95)	1561.67 (979.95 - 2488.74)	852.49 (552.67 - 1314.95)
2007	55.40 (54.85 - 55.96)	38.32 (37.84 - 38.81)	835.92 (569.81 - 1226.30)	414.64 (265.99 - 646.38)	1707.53 (1071.61 - 2720.82)	855.95 (555.05 - 1319.97)
2008	63.77 (63.08 - 64.47)	40.23 (39.68 - 40.79)	915.64 (623.13 - 1345.46)	416.30 (266.75 - 649.67)	1867.01 (1169.91 - 2979.48)	859.43 (556.59 - 1327.03)
2009	73.41 (72.50 - 74.32)	42.24 (41.59 - 42.89)	1002.97 (680.26 - 1478.77)	417.95 (267.18 - 653.81)	2041.38 (1275.13 - 3268.10)	862.92 (557.30 - 1336.13)
2010	84.50 (83.32 - 85.69)	44.34 (43.57 - 45.12)	1098.63 (741.35 - 1628.08)	419.62 (267.26 - 658.83)	2232.04 (1387.58 - 3590.45)	866.42 (557.18 - 1347.29)
2011	97.26 (95.72 - 98.83)	46.55 (45.63 - 47.49)	1203.41 (806.61 - 1795.40)	421.29 (267.01 - 664.70)	2440.51 (1507.58 - 3950.77)	869.94 (556.27 - 1360.48)
2012	111.95 (109.95 - 114.00)	48.87 (47.79 - 49.98)	1318.18 (876.24 - 1983.02)	422.97 (266.45 - 671.43)	2668.45 (1635.50 - 4353.78)	873.47 (554.59 - 1375.70)

Table A22. Predicted mean duration, total duration, and total duration per year of chemotherapy visits among colorectal cancer patients in phase two. *Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification by tumour subgroup were significant, colon and rectal cancer patients were modelled separately.*

	Mean Duration of Visits (95% CI)		Total Duration of Visits (95% CI)	Total Duration of Visits per Year (95% CI)	
Year	Colon	Rectal	Colorectal	Colon	Rectal
2000	52.91 (49.58 - 56.46)	18.60 (17.86 - 19.36)	182.66 (149.99 - 222.44)	127.33 (89.89 - 180.36)	203.06 (147.64 - 279.28)
2001	56.15 (52.96 - 59.53)	21.62 (20.85 - 22.41)	214.31 (177.48 - 258.79)	157.38 (112.13 - 220.88)	241.89 (177.18 - 330.22)
2002	59.58 (56.55 - 62.77)	25.13 (24.34 - 25.95)	251.45 (209.84 - 301.33)	194.52 (139.74 - 270.78)	288.13 (212.44 - 390.80)
2003	63.22 (60.38 - 66.20)	29.22 (28.41 - 30.05)	295.03 (247.84 - 351.21)	240.43 (173.94 - 332.32)	343.22 (254.46 - 462.95)
2004	67.09 (64.45 - 69.84)	33.97 (33.15 - 34.80)	346.16 (292.40 - 409.79)	297.17 (216.26 - 408.35)	408.85 (304.48 - 548.99)
2005	71.19 (68.77 - 73.71)	39.49 (38.67 - 40.32)	406.14 (344.57 - 478.73)	367.30 (268.53 - 502.40)	487.02 (363.93 - 651.73)
2006	75.55 (73.32 - 77.84)	45.90 (45.08 - 46.74)	476.53 (405.50 - 559.99)	453.99 (333.00 - 618.94)	580.13 (434.52 - 774.55)
2007	80.17 (78.10 - 82.29)	53.37 (52.51 - 54.23)	559.11 (476.55 - 655.96)	561.13 (412.38 - 763.54)	691.05 (518.19 - 921.58)
2008	85.07 (83.07 - 87.12)	62.04 (61.10 - 62.99)	656.00 (559.26 - 769.47)	693.56 (509.97 - 943.24)	823.18 (617.26 - 1097.79)
2009	90.28 (88.18 - 92.42)	72.12 (71.00 - 73.26)	769.68 (655.38 - 903.92)	857.24 (629.78 - 1166.87)	980.57 (734.42 - 1309.20)
2010	95.80 (93.42 - 98.23)	83.84 (82.40 - 85.32)	903.06 (766.95 - 1063.34)	1059.56 (776.65 - 1445.50)	1168.05 (872.82 - 1563.12)
2011	101.66 (98.80 - 104.59)	97.47 (95.54 - 99.44)	1059.56 (896.31 - 1252.55)	1309.61 (956.49 - 1793.11)	1391.37 (1036.15 - 1868.38)
2012	107.87 (104.38 - 111.49)	113.31 (110.70 - 115.98)	1243.18 (1046.19 - 1477.25)	1618.69 (1176.43 - 2227.21)	1657.40 (1228.70 - 2235.67)

Table A23. Predicted mean duration, total duration, and total duration per year of chemotherapy visits among colorectal cancer patients in phase three. *Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification by tumour subgroup was significant, colon and rectal cancer patients were modelled separately.*

	Mean Duration of Visits (95% CI)		Total Duration of Visits (95% CI)	Total Duration of Visits per Year (95% CI)
Year	Colon	Rectal	Colorectal	Colorectal
2000	27.88 (26.90 - 28.90)	30.62 (29.22 - 32.09)	225.66 (142.39 - 357.61)	518.61 (319.92 - 840.72)
2001	31.46 (30.47 - 32.48)	33.56 (32.19 - 34.99)	256.43 (163.34 - 402.56)	584.14 (364.15 - 937.02)
2002	35.49 (34.50 - 36.50)	36.79 (35.46 - 38.16)	291.40 (187.14 - 453.75)	657.95 (413.91 - 1045.86)
2003	40.04 (39.06 - 41.03)	40.32 (39.04 - 41.64)	331.14 (214.10 - 512.16)	741.08 (469.74 - 1169.14)
2004	45.17 (44.21 - 46.14)	44.19 (42.97 - 45.45)	376.30 (244.59 - 578.93)	834.71 (532.25 - 1309.07)
2005	50.96 (50.02 - 51.91)	48.44 (47.27 - 49.64)	427.61 (279.00 - 655.39)	940.18 (602.05 - 1468.20)
2006	57.49 (56.54 - 58.45)	53.09 (51.95 - 54.27)	485.93 (317.76 - 743.08)	1058.97 (679.84 - 1649.52)
2007	64.85 (63.86 - 65.87)	58.19 (57.01 - 59.40)	552.19 (361.35 - 843.83)	1192.77 (766.34 - 1856.50)
2008	73.17 (72.04 - 74.32)	63.78 (62.47 - 65.13)	627.50 (410.27 - 959.75)	1343.48 (862.31 - 2093.13)
2009	82.54 (81.16 - 83.95)	69.91 (68.35 - 71.51)	713.07 (465.08 - 1093.31)	1513.23 (968.60 - 2364.07)
2010	93.12 (91.36 - 94.92)	76.63 (74.69 - 78.62)	810.31 (526.40 - 1247.36)	1704.42 (1086.13 - 2674.69)
2011	105.06 (102.78 - 107.39)	83.99 (81.56 - 86.50)	920.82 (594.91 - 1425.26)	1919.78 (1215.88 - 3031.18)
2012	118.52 (115.57 - 121.55)	92.06 (89.00 - 95.22)	1046.39 (671.38 - 1630.87)	2162.34 (1358.94 - 3440.70)

Table A24. Predicted mean duration, total duration, and total duration per year of chemotherapy visits among colorectal cancer patients in phase four. *Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Where effect modification by tumour subgroup was significant, colon and rectal cancer patients were modelled separately.*

	Mean Duration of Visits (95% CI)		Total Duration of Visits (95% CI)	Total Duration of Visits per Year (95% CI)
Year	Colon	Rectal	Colorectal	Colorectal
2000	32.62 (31.78 - 33.49)	43.51 (42.11 - 44.94)	505.34 (352.62 - 724.19)	472.54 (335.20 - 666.15)
2001	36.92 (36.06 - 37.79)	47.94 (46.57 - 49.35)	609.90 (429.56 - 865.95)	553.68 (396.00 - 774.13)
2002	41.78 (40.92 - 42.66)	52.83 (51.49 - 54.20)	736.10 (522.67 - 1036.68)	648.74 (467.33 - 900.57)
2003	47.28 (46.43 - 48.15)	58.21 (56.92 - 59.53)	888.41 (635.15 - 1242.64)	760.13 (550.89 - 1048.85)
2004	53.51 (52.68 - 54.36)	64.15 (62.92 - 65.40)	1072.23 (770.81 - 1491.53)	890.64 (648.61 - 1222.99)
2005	60.56 (59.75 - 61.38)	70.68 (69.53 - 71.86)	1294.10 (934.11 - 1792.81)	1043.57 (762.71 - 1427.84)
2006	68.54 (67.76 - 69.33)	77.89 (76.79 - 79.00)	1561.87 (1130.36 - 2158.10)	1222.74 (895.73 - 1669.15)
2007	77.56 (76.79 - 78.34)	85.83 (84.76 - 86.91)	1885.04 (1365.78 - 2601.73)	1432.69 (1050.56 - 1953.81)
2008	87.78 (86.97 - 88.60)	94.58 (93.46 - 95.70)	2275.09 (1647.72 - 3141.32)	1678.68 (1230.51 - 2290.08)
2009	99.34 (98.40 - 100.29)	104.22 (102.94 - 105.51)	2745.84 (1984.87 - 3798.57)	1966.91 (1439.37 - 2687.79)
2010	112.42 (111.24 - 113.62)	114.84 (113.26 - 116.44)	3314.00 (2387.44 - 4600.16)	2304.62 (1681.48 - 3158.70)
2011	127.23 (125.68 - 128.80)	126.55 (124.52 - 128.60)	3999.73 (2867.54 - 5578.94)	2700.32 (1961.82 - 3716.83)
2012	143.99 (141.94 - 146.07)	139.45 (136.84 - 142.10)	4827.34 (3439.42 - 6775.32)	3163.96 (2286.11 - 4378.92)

Table A25. Predicted mean duration, total duration, and total duration per year of chemotherapy visits among colorectal cancer patients in phase five. *Duration of visits in minutes was predicted from multiply imputed regression analyses models presented in Table 3-9. Mean duration describes the average duration of a single visit. Total duration represents the total number of minutes in all visits in the phase of care. Total duration per year is the rate representing the number of minutes for each year spent in a phase of care. Colon and rectal cancer patients were modelled jointly due to the absence of significant effect modification by tumour subgroup.*

	Mean Duration of Visits (95% CI)	Total Duration of Visits (95% CI)	Total Duration of Visits per Year (95% CI)
Year	Colorectal	Colorectal	Colorectal
2000	25.87 (24.94 - 26.84)	145.86 (98.59 - 215.78)	354.00 (230.19 - 544.39)
2001	29.24 (28.30 - 30.22)	168.40 (114.86 - 246.90)	402.81 (264.53 - 613.38)
2002	33.05 (32.11 - 34.02)	194.42 (133.65 - 282.82)	458.35 (303.60 - 691.99)
2003	37.36 (36.42 - 38.32)	224.46 (155.32 - 324.38)	521.56 (347.97 - 781.74)
2004	42.22 (41.30 - 43.16)	259.15 (180.28 - 372.53)	593.48 (398.26 - 884.40)
2005	47.72 (46.82 - 48.64)	299.20 (208.95 - 428.42)	675.32 (455.13 - 1002.03)
2006	53.94 (53.04 - 54.85)	345.43 (241.85 - 493.38)	768.44 (519.31 - 1137.08)
2007	60.96 (60.04 - 61.90)	398.81 (279.52 - 569.01)	874.40 (591.61 - 1292.36)
2008	68.90 (67.87 - 69.95)	460.44 (322.59 - 657.20)	994.97 (672.91 - 1471.18)
2009	77.88 (76.64 - 79.14)	531.59 (371.76 - 760.15)	1132.17 (764.16 - 1677.42)
2010	88.02 (86.44 - 89.63)	613.74 (427.81 - 880.48)	1288.29 (866.43 - 1915.56)
2011	99.49 (97.44 - 101.58)	708.58 (491.63 - 1021.28)	1465.94 (980.89 - 2190.84)
2012	112.45 (109.77 - 115.18)	818.08 (564.21 - 1186.19)	1668.08 (1108.85 - 2509.35)