Predictors and Impact of Guideline Adherent Care in those with Rectal Cancer: An Evidence Based Review and Population Health Research Study

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Abstract

Rectal cancer is a common and complex disease, requiring multidisciplinary care. Clinical practice guidelines are available to provide health care providers evidence-based recommendations regarding which investigations and interventions should be offered to individuals with a new diagnosis of rectal cancer. The primary objectives of this thesis were to (i) perform an evidence based review (systematic review and meta-analysis) of the previous literature evaluating predictors of guideline adherent care; (ii) define a common Canadian definition of guideline adherent care for the purposes of this thesis, (iii) create a novel resource based on provincially maintained data to allow for a comprehensive assessment of practice patterns and outcome of those with rectal cancer, and (iv) use this novel resource to identify important predictors of guideline adherent rectal cancer care in Ontario.

First, a review of all available Canadian provincial clinical practice guidelines was completed to determine what would be considered the minimum requirements of "Guideline Adherent Care" in Canada. Seven provinces produced guidelines, and the agreements and disagreements between the available guidelines were reviewed. There were few areas of controversy and a common definition was created, which was used in subsequent chapters.

Next, an exhaustive systematic review of the previous literature evaluating predictors of guideline recommended rectal cancer care was undertaken. The association (both the direction and magnitude) between potential predictors and each aspect of guideline adherence was determined. More than 70 studies were included in the qualitative analyses, with 118 predictor-outcome pairs being assessed. More than 30 studies were included in the quantitative analyses, which included 27 meta-analyses. Commonly assessed predictors were identified, as were those

which were less commonly assessed. Non-modifiable risk factors such as age, sex/gender, comorbidity score and ethnicity were commonly included in previous publications, while non-modifiable risk factors such as type of hospital and physician volume were less so. Age, ethnicity and comorbidity score were frequently identified to be important predictors within the review, while care provider factors were infrequently evaluated.

The Ontario Rectal Cancer Cohort ("OntaReCC") was then created. The OntaReCC is a novel resource that provides comprehensive data on the demographics, practice patterns and outcomes of those with rectal cancer between 2010 – 2019. This is a unique resource, and one that can be update as additional data is made available. It includes more than 18,000 rectal cancer patients, and provides data on the investigations and treatments each individual received, as well as provides data on survival and other important outcomes.

Using the OntaReCC, analyses of the associations between potential predictor and adherence outcomes was undertaken. Overall guideline adherence (i.e. adherence to every aspect of recommended care) was poor. Less than 25% of those in the "curative intent group" met the minimum requirements of overall. Age was an important predictor of many aspects of guideline adherent care, with increasing age being negatively associated with adherence. Interestingly, co-morbidity score was found to be an inconsistent predictor of adherence with increasing comorbidity score being negatively associated with some components of adherence, while being positively associated with other components. Both cancer centre designation and surgeon volume were important modifiable predictors of adherence. Those treated at a regional cancer centre and those managed by a high volume surgeon were much more likely to be adherent to many of the aspects of guideline adherent care. Adherence to recommended staging investigations was highly correlated with receiving the appropriate treatments.

Guideline adherent care is an important measure of the quality of the delivery of cancer care within Ontario. This thesis identified opportunities for improving adherence, including directing care to high volume surgeons and regional cancer centres, which in turn have the potential to improve outcomes. Focusing resources on improving adherence to readily available, cost effective and proven investigations and interventions would be an effective strategy in improving outcomes in those with rectal cancer in Ontario.

I dedicate this work to my family who have supported me through 20 years of clinical and research training.

Acknowledgements

Professors Carl Henneghan and Clare Bankhead provided academic support of this doctoral thesis. Their expertise in the field of evidence based medicine have been invaluable in completing this work. I am grateful for their willingness to discuss this research, as well as my interests beyond this work. I also acknowledge their guidance in keeping this thesis on track, and ensuring the "my bookshelf" was not overcrowded. I also thank the Centre for Evidence Based Health Care, Kellogg College and the Department of Continuing Education in ensuring completion of this work despite significant challenges brought on by the global pandemic.

I would like to acknowledge the Department of Surgery at Queen's University, specifically Dr. John Rudan (former Department Head) and Dr. Ross Walker (current Department Head), in the steadfast support of my pursuit of completing this work. This included financial support and protected academic time, which is unique for a Canadian Surgeon. I would like to also acknowledge my colleagues at Kingston Health Sciences Centre, specifically Dr. Hugh MacDonald, Dr. Antonio Caycedo and Dr. Ameer Farooq, for allowing me the time and freedom to pursue this work. I wish to acknowledge Dr. Chris Booth of Queen's University, who has provided me with inspiration, mentorship and support in ways I wasn't aware were possible. I would also like to acknowledge Mr. Chad McClintock of Queen's University for his expertise and commitment in helping build the foundations of this work. I would like to acknowledge Mr. Weidong Kong of Cancer Care and Epidemiology at Queen's University, for his oversight and expertise to ensure that the work contained within this thesis is of high quality. I would also like to acknowledge Ms. Tina Dyer, whose expertise was invaluable.

I am profoundly grateful to my family who have supported me throughout my clinical and research training. Thank you to my parents (Susan and Vijay) for their unwavering confidence in my abilities, and my in-laws (Fred and Sue) for their belief in me and my aspirations. I am grateful to my children; Adelaide, Evelyn, Holden and William; for the joy you bring and the inspiration to work through adversity. Finally, I thank my partner Shauna, as none of this work would have been possible without her patience, understanding and guidance, as well as supporting me in many ways that are hard to fully capture here.

Personal Statement

I am a colorectal surgeon, whose clinical focus is treating those with rectal cancer. During my training and early career, I have witnessed significant differences in the quality of care provided to individuals with rectal cancer. The variation exists despite rectal cancer care being well described, readily accessible and relatively inexpensive. As a consequence of these experiences, I wished to understand what drove the differences in care, and identify potential opportunities for improvement. The work was partly inspired by my colleagues, Dr. Chris Booth and Dr. Bishal Gyawali. They created a call for the "Cancer Ground Shot", defined as: "ensuring access to interventions that are already proven to work before focusing on the development of new interventions". The common sense in their work challenged me to do so in mine.

The work presented in this thesis is a culmination of my previous research and clinical training. My research training included completing a Mc of Epidemiology at the London School of Hygiene and Tropical Medicine (2011-12) and Doctoral training through the Evidence Based Health Care Program at the University of Oxford, (2016-2025). My clinical training included general surgery at the University of Western Ontario (2009-2014) and fellowship training at Memorial Sloan Kettering Cancer Center/New York Presbyterian Hospital (2014-15).

The experiences I gained completing this thesis has been invaluable to me, and the practical and theoretical knowledge which resulted will undoubtedly aid me in my future pursuits. I hope that the work presented in this thesis (and future work generated from the Ontario Rectal Cancer Cohort) will positively impact the delivery of rectal cancer care within Canada and beyond.

Reflections on the Doctor of Philosophy Learning Journey

My pursuit of a Doctor of Philosophy in Evidence Based Health at the University of Oxford began with a panel interview in the Spring of 2016. I have recently reviewed the proposal I presented at that time, which has provided me with great insight into where I was as a researcher (and person) at the start of this work, and where I am now. Completing this DPhil has greatly enhanced my research skills and ability.

The systematic review challenged my ability to organize, interpret and present the findings from dozens of studies. The studies identified in the review broadly reflected those in the Cancer Research domain, in that they were from numerous settings, included a variety of types of patients, occurred over may different time periods and used many different definitions of exposures and outcomes. Completing this review enhance my ability to deal with the ambiguity of the literature, create a coherent narrative and summarize the results.

Creating a new population level database from data sources not intended for that purpose taught me a great deal on how to overcome numerous logistical challenges. I was required to work with a number of individuals from several institutions to ensure that I was able to access sensitive personal data governed by Provincial Legislation. I also needed to understand the gaps and deficiencies in the data and to ensure that the most current data was available and utilized. Creating the database also re-enforced the importance of having robust and justifiable definitions of the variables, while recognizing that "real-world" data isn't perfect. Overcoming these obstacle and deficiencies taught me a great deal about the processes required to complete population health research.

Describing and analysing the data required an understanding of which data were available, and which analyses were most appropriate. Unique to this DPhil were the limits placed on how the data could be accessed and by whom. These limitations forced me to work closely with data-analysts. I needed to ensure that the correct data was being used, and to ensure that the analysts were using the statistical models I had deemed most appropriate. Creating the data and results was an iterative and collaborative process which required building solid relationships through clear and open communication. I learnt a great deal about managing deficiencies in the data, interpreting initial results and identifying weaknesses in the analyses. My population health research methodology skills and knowledge were greatly enhanced through this work.

Finally, being able to summarize the work as well as the implications for practice and future research was an important skill set that was greatly enhanced during the completion of this thesis. Placing my findings in the context of clinical practice and current research solidified the impact of my work, and allowed me to identify the future directions for my independent research program.

Completing this DPhil was a tremendous experience for me. The skills and knowledge I gained will be invaluable as I pursue my independent research program. I will forever be grateful to my supervisors (Dr. Carl Heneghan and Dr. Clare Bankhead) and the University of Oxford for giving me the opportunity to pursue this research.

Statement of Contributions

This doctoral thesis is independent and original work of which I am the sole author. My academic supervisors, Professors Carl Heneghan and Clare Bankhead contributed intellectual guidance on the overall research methodology, interpretation of results and structure of this work. Other individuals making contributions to this work include:

Mr. Chad McClintock (CM) and Mr. Weidong Kong (WK) (Data Analysts, Cancer Care and Epidemiology, Queens University, Kingston, Canada), provided analytical support in the creation of the Ontario Rectal Cancer Cohort (chapter 5) and analyses presented in Chapter 6. Dr. Chris Booth (Professor of Oncology, Queen's University) and Dr. Tim Hanna (Professor of Oncology, Queen's University) both aided in defining and validating oncology related treatments (chemotherapy and radiation therapy) used in Chapters 5 and 6. Dr. Adam Fundytus (Oncology Clinical Fellow, Queen's University) provided expertise in determining and classifying relevant chemotherapy regimens and doses. Ms. Tina Dyer (Program Manager, Cancer Care and Epidemiology, Queens University, Kingston, Canada) submitted applications to Cancer Care Ontario on my behalf for permission to access the linked provincial databases used to create the Ontario Rectal Cancer Cohort. She ensured the maintenance of ethics for this study. Ms. Dyer also created the databases used for pathology data abstraction. Ms. Sarah Pickett (Data Abstractor, Cancer Care and Epidemiology, Queen's University, Kingston, Canada) abstracted histopathology data from pathology reports, the results of which were linked to administrative databases to create the Ontario Rectal Cancer Cohort (Chapter 5). Dr. Sydney Candy (General Surgeon, former Queen's University Medical Student) was the second reviewer and data abstractor for the systematic review chapters (Chapter 4). Dr. Zuhaib Mir (General Surgeon,

former Queen's University Surgical Trainee) was the second reviewer and data abstractor for the review of Canadian Clinical Practice Guidelines (Chapter 3).

Definitions and Terminology used in this Thesis

Adenocarcinoma – Cancer that forms in glandular tissue which exists in a number of organs, including in the lining of the gastrointestinal tract.

Adjuvant Therapy – Typically refers to chemotherapy, which is given after surgical resection. The intent of adjuvant therapy is to provide systemic treatment to reduce the risk of distant metastatic (or recurrent) disease.

Carcinogenesis – The formation of cancer cells from normal cells

Chemotherapy Regimen – The name of the combination of chemotherapy drugs used.

Clinical Practice Guideline (CPG) – Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. (2)

Colonoscopy – An endoscopic examination of the entire large intestine (including the colon and rectum) using a flexible camera. Colonoscopy allows for direct visualization of abnormalities, as well as allows for interventions such as biopsy or removal of tissue.

Complete Response – When there is no residual cancer after neoadjuvant treatments. This includes complete pathologic response, in which there is no residual cancer in the surgical specimen, and complete clinical response, in which there is no apparent tumor on endoscopy, physical exam and diagnostic imaging.

Computed Tomography (CT Scan or CAT Scan) – A diagnostic imaging test that uses a series of Xrays to generate images of the body.

Diagnostic Imaging – A variety of non-invasive methods used to view the inside of the human body

Distant Disease – Synonymous with Metastasis and is spread of cancer to a location remote from where it originated.

Flexible Sigmoidoscopy – An endoscopic examination of the distal colon (sigmoid colon) and rectum using a flexible camera. Flexible sigmoidoscopy allows direct visualization of abnormalities in this distal large intestine as well as allows for interventions such as biopsy or removal of tissue.

Gastrointestinal Tract – The passageway of the digestive system that leads from the mouth to the esophagus, stomach, small intestine, large intestine (colon and rectum) and finally the anus.

Local Excision – Excision of the wall of the rectum only. Typically done for early stage cancer or benign pathology.

Local Regional disease – The Tumor ("t") and nodal ("n") extent of disease based on the AJCC classification of rectal cancer. This disease is typically treated with local measures such as surgical resection and/or radiation

Long Course Chemoradiation – Combination of radiation therapy and chemotherapy. 25 – 30 doses of radiation are given daily and concurrently with chemotherapy.

Lymph Node – A gland which is part of the lymphatic system and are part of the immune system. Lymph nodes filter foreign particles, including cancer cells.

Magnetic Resonance Imaging (MRI) – A diagnostic imaging test that uses magnetic fields and radio waves to generate images of the body.

Medical Oncologist - A physician who specializes in the treatment of cancers using medical therapies such as chemotherapy and immunotherapy.

Metachronous Cancer – The development of a second (or more) primary cancer more than 6 months after the initial diagnosis and at remote location from the original cancer. (see synchronous below)

Metastasis – Spread of cancer to a location remote from where it originated

Micro metastasis – Radiologic occult metastasis, the target of systemic chemotherapy treatment.

Multidisciplinary Cancer Conference (MCC) – A meeting of clinicians involved in the care of those with rectal cancer. Relevant investigations or previous treatments may be reviewed with the intent to arrive at a consensus for the treatment of the individual with rectal cancer.

Multidisciplinary Care – Care provided by multiple types of specialists and/or health care practitioners

Multimodal Care – Includes combing multiple types of treatments, such as radiation and surgery or chemotherapy and radiation.

Neoadjuvant Therapy – Treatment given before surgical resection, with the goal to shrink (or downsize) the cancer to allow for complete resection. Also reduces the risk of local recurrence in the future.

Non-operative Management – A treatment approach where surgery is not performed on those who have had an apparent complete response to pre-operative treatment. (see organ preservation)

Over staging - Where "clinical stage" assigns a higher stage of disease than the true stage of disease.

Organ Preservation – A concept, where major surgical resection is deferred in those who either had a complete response to neoadjuvant treatments, or are eligible for local excision.

Palliative Care Physician – A physician who specializes in symptom management, especially in those approaching end of life

Pathologist – A physician who specializes in the interpretation of histopathology

Radiation Oncologist - A physician who specializes in the treatment of cancers using radiation therapy

Radiologist – A physician who specializes in the interpretation of diagnostic imaging.

Rectal Cancer – Adenocarcinoma arising from the rectum

Rectum – Along with the colon forms the large intestine. The rectum is the last portion of the digestive tract and is distinguished from the colon based on anatomical location, function and composition. (Figure 1.1)

Recurrence, Local – Development of cancer in a previously treated location

Recurrence, Distant– Development of cancer in a remote location from a previously treated cancer

Short Course Radiation – Typically 5 doses of radiation given daily prior to surgical resection

Stage, Clinical – Cancer stage based on pre-treatment investigations such as diagnostic imaging

Stage, Pathologic - Cancer stage based on histopathology findings following surgical resection of the cancer. Pathology stage has an additional category based on whether the cancer was treated with chemotherapy and/or radiation therapy prior to resection

Staging Investigations – The diagnostic imaging tests required to assign a clinical (or pre-treatment) cancer stage.

Surveillance – The tests or assessments typically performed after completion of cancer treatments.

Synchronous Cancer – Two or more primary cancers coexisting at the time of diagnosis or within 6 months of diagnosis. (See metachronous cancer above)

Total Mesorectal Excision – Type of surgical resection used to remove the rectal cancer, surrounding fat, lymph nodes and blood vessels. Considered the standard of care for those undergoing surgery for rectal cancer.

Total Neoadjuvant Therapy (TNT) – A new approach to treating locally advanced rectal cancer where all radiation and chemotherapy are given prior to surgical resection.

Transrectal Ultrasound (TRUS) – A diagnostic imaging test is can be used to assess local-regional stage of disease.

Ultrasound (U/S) – A diagnostic imaging test that uses sound waves to generate images of the body

Abbreviations Used in this Thesis

ALR – Cancer Activity Level Reporting Databases

CCO – Cancer Care Ontario

CCI – Canadian Classification of Interventions

CEA – Carcinoembryonic Antigen

CIHI – Canadian Institute of Health Information

CIHI – DAD – Canadian Institute of Health Information Discharge Abstract Database.

CPG – Clinical Practice Guideline

CRT – Long course chemo-radiation therapy

CT – Computed Tomography

ERUS – Endorectal Ultrasound

ICD – International Classification of Diseases

LHIN – Local Health Integration Networks

M Stage – Metastatic Disease Stage

MCC – Multidisciplinary Cancer Conference

MRI – Magnetic Resonance Imaging

N Stage – Nodal Stage

OCR – Ontario Cancer Registry

OH – Ontario Health

OHIP – Ontario Health Insurance Plan

OntaReCC – Ontario Rectal Cancer Cohort

RPDB – Registered Persons Database

SC – Short Course radiation

T Stage – Tumor Stage

TME – Total Mesorectal Excision

U/S – Ultrasound

Table of Contents

List of Tables

List of Figures

Chapter 1 Overview and Structure of the Thesis

1.1 Overview of the Thesis

Clinical practice guidelines for patients with rectal cancer represent a consensus opinion, based on the available evidence, describing how individuals with rectal cancer should be cared for. Thus, guideline adherent care represents the "Standard of Care" for those with rectal cancer and the definition of such can be used to assess how a cancer system delivers care.

This thesis assessed guideline adherent care for those with rectal cancer. The thesis begins with a background on rectal cancer, which provides context and common terminology used throughout the thesis (***Chapter 2)***. It then describes the available clinical practice guidelines in Canada and establishes a common definition of guideline adherent care (***Chapter 3)***. This definition was used throughout the thesis and represents the minimal adherent care for those with rectal cancer. A large systematic review and meta-analysis of barriers and/or facilitators associated with receipt of guideline adherent care was completed (***Chapter 4***). The results of this review were used to inform the creation of the Ontario Rectal Cancer Cohort ("OntaReCC") (***Chapter 5***).

The OntaReCC is a resource created specifically for this work. Prior to this thesis, there was no widely available, comprehensive data set of those with rectal cancer treated in Ontario, Canada. The OntaReCC was derived from a number of linked, population level, administrative databases. The data contained in these resources is routinely collected whenever a health service is delivered in the universal, publicly funded health care system that exists within Ontario, Canada. Almost all cancer care is provided within this publicly funded system, which resulted in

the OntaReCC having near complete capture of the requisite data needed to address this thesis' objectives and aims.

This newly created and unique database was then interrogated to: describe the care given; investigate the associations between potential barriers and facilitators of receipt of adherent care; and evaluate the impact of (non) adherent care on cancer outcomes (***Chapter 6***). The implications of this research is then discussed in terms of policy, practice and future research (***Chapter 7***).

1.2 Thesis Justification

The care of those with a new diagnosis of rectal cancer requires a number of timely pre-treatment investigations, multimodal treatment, and ongoing surveillance or follow up. Navigating the complexities of rectal cancer can be challenging, and thus clinical practice guidelines have been developed to provide a framework for clinicians treating those with rectal cancer. Much effort and resources have been devoted to the development and distribution of clinical practice guidelines for rectal cancer by Canadian Health Authorities.

Adherence to guideline recommended care is thus a marker of the quality of care being delivered, and is an indication of how the cancer care system is performing. Over the last several years, Cancer Care Ontario (the provincial health authority) has begun using specific aspects of guideline adherent care as performance indicators for hospitals and regional cancer programs. Despite the usefulness and impact of understanding guideline adherence, there has been no previous comprehensive assessment of guideline adherent care in those with rectal cancer in a Canadian setting. Furthermore, our current understanding of how the Ontario cancer system, and by extension the Canadian cancer system, functions is limited. Few publications from Canada

have provided an assessment of adherence to individual aspects of recommended rectal cancer guidance, let alone an assessment of overall adherence to care. This can be attributed to a lack of a comprehensive, accessible dataset of those diagnosed with rectal cancer. Identifying barriers to guideline adherent rectal cancer care allows for an opportunity to improve the performance of the cancer system. In addition, determining the impact of guideline adherent care on outcomes provides justification for why improving this system is important.

The work presented here fills these gaps. First, the Ontario Rectal Cancer Cohort (OntaReCC) was created to provide a comprehensive and contemporary resource describing those with rectal cancer and their care from pre-diagnosis to the end of follow up (or death. Second, the OntaReCC was utilized to determine guideline adherence in Ontario, determine predictors of guideline adherent care, and determine the impact of guideline adherent care on important outcomes.

Prior to embarking on the creation of the OntaReCC, it was important to determine which factors were previously assessed for their associations (positively or negatively) with aspects of guideline recommended care. In addition, it was important to determine which factors were under-assessed in the literature despite potentially playing an important role in predicting guideline adherent care. Prior to this thesis, there was no published systematic review describing predictors of the complete spectrum of guideline adherent rectal cancer care. Thus, an exhaustive systematic review was completed to address these gaps in knowledge.

Finally, it was important to define "guideline adherent" care in the Canadian setting. The overall objectives and aims of this thesis focused on predictors and impact of guideline adherent care, and a reliable definition was required. Prior to the work presented in this thesis, there had not been an attempt to consolidate the numerous provincial guidelines into a single Canadian

specific clinical practice guideline. By doing so, the objectives of this work could be met, and a new common definition could be available to those pursuing similar research work or by clinicians who reside in areas without a local clinical provincial guideline available to them.

1.3 Thesis Aims

The primary aim was to develop a contemporary and comprehensive cohort of individuals diagnosed with rectal cancer, and to use this resource to determine (i) the current practice patterns and outcomes; (ii) the receipt of guideline adherent care, and (iii) the associations between receiving guideline adherent care and outcomes. Secondary aims of this work were to establish a definition of "guideline adherent care" in Canada and to review the current evidence assessing predictors of receipt of guideline adherent care.

1.4 Research Methodology

This thesis uses two primary research methodologies. First, the principals of systematic reviews and meta-analyses methodology were used to assess the currently available clinical practice guidelines and to analyse previous publications assessing barriers and facilitators to guideline adherent rectal cancer care. Second, the principals of population health research methodology were then used to create, describe and analyse the Ontario Rectal Cancer Cohort. In doing so, the thesis aims and objectives could be accomplished.

1.5 Research Objectives

The specific research objectives of this thesis include:

1. **Create a common definition of "Guideline Adherent Care" in Canada**
    1.1. Identify all available Canadian provincial clinical practice guidelines in use during the study period
    1.2. Compare areas of agreement and disagreement between these clinical practice guidelines
    1.3. Create a common definition based on the minimal accepted recommendations for each phase of care (staging, treatment, surveillance)

2. **Identify and assess the impact of previously assessed barriers and facilitators ("predictors) of guideline adherent rectal cancer care**
    2.1. Perform systematic reviews of studies assessing the associations between "predictors" and receipt of guideline adherent staging, treatment and surveillance
    2.2. Identify predictors which were either frequently assessed and/or those associated with guideline adherent care
    2.3. Summarize the association between the identified predictors and guideline adherent care using both qualitative and quantitative methods.

3. **Create a comprehensive database of individuals with Rectal Cancer from Ontario, Canada ("OntaReCC")**
    3.1. Identify all individuals with Rectal Cancer in Ontario between 2010 – 2019
    3.2. Identify or define patient, disease and care provider characteristics from linked administrative data holdings

3.3. Abstract histopathology data from pathology reports

3.4. Identify or define investigations or interventions which are included within the "Guideline Adherent Care" common definition

4. **Identify barriers and facilitators of "Guideline Adherent Care" in those with Rectal Cancer from Ontario, Canada**

4.1. Determine the magnitude and direction of associations between potential predictors and individual aspects of guideline adherent care

4.2. Determine the magnitude and direction of associations between potential barriers and facilitators and overall guideline adherent care

5. **Determine the associations between guideline adherent care and outcomes**

5.1. Determine the association of guideline adherent staging and subsequent guideline adherent treatments

1.6 Structure of the Thesis

1.6.1 Chapter 2: Rectal Cancer Review

Chapter 2 aims to understand the complexity of rectal cancer as a disease requiring a multidisciplinary approach by providing the reader an overview of rectal cancer, including the incidence, pathophysiology, disease presentation, treatments and outcomes.

1.6.2 Chapter 3: Creation of a Canadian Definition of Guideline Adherent Care

The aim of Chapter 3 was to establish a definition of guideline adherent rectal cancer care in Canada. This was achieved by reviewing previously published Canadian provincial clinical practice guidelines (CPG). A search of provincial health authorities' resources as well as a search of the literature was performed, which identified seven provincial clinical practice guidelines. There was general agreement between the recommendations for staging (or pre-treatment) investigations, treatment by stage of disease, and surveillance (or follow up) after treatment completion. Areas of disagreement were reviewed. A common Canadian definition of "Guideline Adherent Care" was created based on common elements throughout each available clinical practice guideline.

1.6.3 Chapter 4: An Evidenced Based Review of Barriers and Facilitators to Guideline Adherent Care

The aim of Chapter 4 was to perform a systematic review and meta-analysis of publications assessing the association between a barrier or facilitator and any aspect of guideline adherent care. A total of 72 studies were included in the systematic review and 39 studies were included in the meta-analyses. A number of important and/or commonly assessed predictors were identified; and the direction and magnitude) of association between these predictors and guideline adherent care was determined.

1.6.4 Chapter 5: The Ontario Rectal Cancer Cohort, "OntaReCC"

The aim of Chapter 5 was to describe the methodology used to create the Ontario Rectal Cancer Cohort ("OntaReCC"), and provide a descriptive analysis of demographics, treatment patterns and outcomes in those with Rectal Cancer in Ontario during the study period. The methods used to identify eligible individuals was described. In addition, the data sources and definitions of important predictors, as well as each aspect of guideline adherent care, was provided. A detailed descriptive analysis was reported. The data from the Ontario Rectal Cancer Cohort was used for the subsequent chapter.

1.6.5 Chapter 6: Predictors and Impact of Guideline Adherent Rectal Cancer Care

The aim of Chapter 6 was to use data from the OntaReCC to identify barriers and facilitators of guideline adherent care, as well as to determine the impact of guideline adherent care on outcomes. The chapter begins with a descriptive analysis of guideline adherent care. The associations between potential predictors and adherent care was then determined. Younger age was found to be associated with all aspects of adherent care, while other patient characteristics (sex, comorbidity score, rurality, income quintile) were inconsistently associated with adherent care. Care provider factors (cancer centre level designation and surgeon volume) were consistently associated with receipt of adherent care.

This chapter also reports how the impact of adherence was determined. Adherence to staging investigations was positively associated with adherence to treatments. It was also associated with the "opportunity" for treatments, which was defined as having an assessment by relevant specialty (i.e. radiation oncologist or medical oncologist).

1.6.6 Chapter 7: Discussion, Recommendations and Future Research

Chapter 7 provides an overview of the thesis, highlights the important findings and discusses the implications of the work. The chapter also reviews the strengths and limitations of this work as a whole. Finally, future research as a direct and indirect result of this work is described.

1.7 Key Accomplishments

One of the outcomes of the work presented in this thesis, has been my inclusion in Cancer Care Ontario's Surgical Quality Improvement Program. This group advises Cancer Care Ontario – Ontario Health regarding the creation of quality metrics, and quality improvement initiatives. The group has recently met and has created the quality metrics used to assess regional and institutional performance. These metrics will be in use for the next 3 years. Following my involvement in the quality improvement group (as well as some of my other experiences), I was appointed as the Southeastern Ontario Surgical Oncology lead. Within this role, I am engaged in assessing and improving the quality of the delivery of surgical care for cancer, regardless of the disease site.

1.7.1 Grants and Funding

This work was funded through a number of research grants. This included the Canadian Institutes of Health Research Operating Grant ($100,000 CAD), The Department of Surgery, Queen's University Project Grant ($50,000 CAD), The Clinical Teachers Association of Queen's University Endowment Fund ($20,000 CAD), University Hospital Kingston Foundation's Interdisciplinary Cancer Research Grant ($38,900 CAD). Additional funding has been secured

for the future research proposed, including: The Southeastern Ontario Medical Organization (SEAMO) Established Researcher Fund ($180,000 CAD) and the American Society of Colon and Rectum Surgeons Project Grant ($20,000 USD).

1.7.2 Publications and Presentations

At the time of submission, a number of papers from this thesis have been either published in a peer reviewed journal (1-5) or presented at academic conference (6-19). A summary of published papers and submitted or in preparation manuscripts is described below:

1. "Management of rectal cancer in Canada: an evidence-based comparison of clinical practice guidelines" – A review article which identifies all available Canadian clinical practice guidelines and reviews similarities, differences and quality of the CPGs. (Published in the Canadian Journal of Surgery, 2020)
2. "The Variations in Care and Real-world Outcomes in Individuals With Rectal Cancer: Protocol for the Ontario Rectal Cancer Cohort" – A summary of some of the methods used to develop the Ontario Rectal Cancer Cohort (Published in JMIR Research Protocols, 2022)
3. "A systematic review to identify the barriers to care in rectal cancer patients, and the effects on staging investigations, treatment delivery and surveillance or follow up" – The protocol of the systematic review described in Chapter 4. (Published on PROSPERO, 2018)
4. "Local excision for T1 rectal cancer: A population-based study of practice patterns and oncological outcomes" – An assessment of outcomes for those undergoing local

excision (vs. radical resection) for T1 rectal cancer. (Published in Colorectal Diseases, 2025)

5. "An assessment of cancer centre level designation and guideline adherent care in those with rectal cancer: A population based retrospective cohort study" – This paper reports the impact of cancer centre level designation on guideline adherence. (Published in the Journal of Cancer Policy, 2024).
6. "Fragmentation of Multimodal Rectal Cancer Care: A Population-Level Retrospective Cohort Study" – This study assesses whether treatment at different institutions results in less timely care or poorer outcomes. (Accepted by Journal of Surgical Oncology, March 2025)
7. "Revisiting the rationale for radical resection in low-risk early rectal cancer: a population-level perspective" – This study compares T1 vs. T2 rectal cancer to determine whether local excision (vs. radical resection) could be considered (submitted to Colorectal Diseases, January 2025).
8. "Rectal Cancer in the very young (age < 40), a more aggressive disease?" – This study explores why those who are very young have worse survival than patients in older age groups, despite similar stage of presentation. (In preparation for JAMA Oncology)

1.8 Chapter 1 References

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Chapter 2 Rectal Cancer Review

2.1 Chapter Overview

This chapter provides the reader an overview of rectal cancer, including the incidence, pathophysiology, disease presentation, treatments, and outcomes. The chapter also describes the role of clinical practice guidelines, and the potential controversies surrounding guideline adherent care.

2.2 Chapter Aims and Objectives

The primary aim of this chapter is to explain why rectal cancer is a complex disease, requiring multidisciplinary care.

2.3 Rectal Cancer Incidence in Canada

Within Canada, approximately 200,000 new cancers are diagnosed annually. Colorectal cancer represents the 2nd most commonly diagnosed cancer in men (14.1% of all new cancers) and the 3rd most commonly diagnosed cancer in women (11.7%). Approximately 1 in 14 Canadians will develop colorectal cancer over their lifetime with 1 in 29 Canadians ultimately dying from colorectal cancer. The incidence of colorectal cancer has largely been unchanged over the last 2 decades (~80/100,000 in males and ~60/100,000 in females).(1) Rectal cancer represented 33.9% of all colorectal cancer diagnoses between 2011 – 2015. (2) Interestingly,

males make up a larger proportion of those with rectal cancer (62.6%) than those with colon cancer (52.5%). (2)

2.4 Rectal Cancer Histology and Anatomy

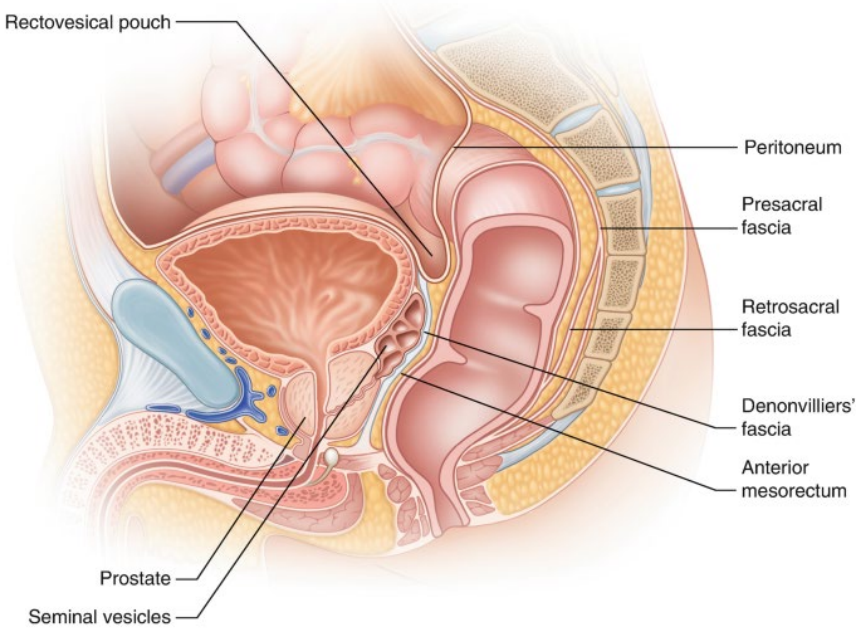
Although colon and rectal cancer are often described as one entity, the management and outcomes differ between the two. Unlike the colon, the majority of the rectum is *extraperitoneal*[1] and is not contained within the *visceral peritoneum*. Without this protective layer, cancer invasion into surrounding organs (such as the bladder, prostate, vagina, uterus and/or sacrum) can occur. (Figure 2-1) In addition, the potential of inadequate surgery is much higher which results in an increased risk of *local recurrence*. For these reasons, *multimodal* and *multidisciplinary care* is more commonly required in those with rectal cancer when compared to those with colon cancer. (3)

It bears mentioning that distinguishing rectal cancer from colon cancer can be challenging. The transition from the sigmoid colon to the rectum occurs at the "recto-sigmoid" junction. This transition occurs where the Tenia Coli, (the longitudinal muscle fibres of the colon) coalesce. Determining whether a cancer is a rectal cancer or colon cancer is based on endoscopic and diagnostic imaging. Two common definitions and classifications have been proposed including: (i) The relationship between the cancer and the anterior peritoneal reflection, often determine through diagnostic imaging; and (ii) The height of the cancer in relation to an anatomic landmark (anal verge, sphincter muscle complex), which can be determined endoscopically or through diagnostic imaging. (4, 5) Typically cancers are designated as rectal cancers if < 15 cm from the anal verge. (6) The anal verge is an externally located anatomic landmark, and those with a long

1 Terms in Italics are defined in the introductory sections

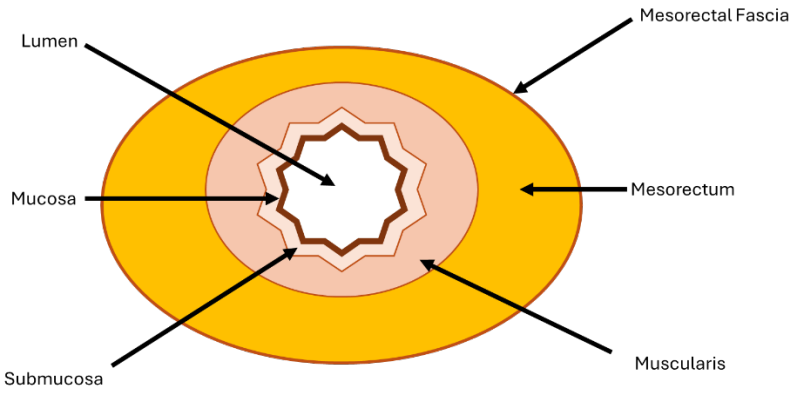
anal canal, typically males, may be prone to erroneously being diagnosed with “colon cancer” as opposed to rectal cancer.

Figure 2-1 The Rectum and adjacent structures (adapted from the ASCRS Textbook of Colon and Rectal Surgery) (7)



By convention, “Rectal Cancer” refers to adenocarcinoma of the rectum, as this histology is found in > 90% of all cancers originating in the rectum. (1) *Adenocarcinoma* is defined as arising from the glandular tissue which exists in the rectal mucosa and lines the inner layer of the rectum (Figure 2 - 2). There are several well described colorectal *carcinogenesis* pathways (8), which ultimately results in adenocarcinoma of the rectum. Other histology’s, such as neuroendocrine cancer, lymphoma, squamous cell carcinomas and melanomas, are rare and managed differently and have different expected prognoses. (9-11)

Figure 2-2 Layers of the Rectum and Mesorectum



2.5 Symptoms and Presentation

Those with rectal cancer may be symptomatic or asymptomatic, with the majority (up to 75%) presenting with symptoms that led to a diagnosis. (12) Symptoms commonly associated with rectal cancer include rectal bleeding, changes in the frequency or caliber of bowel movements and/or rectal pain. If symptoms occur, direct visualization and biopsy using either *colonoscopy* or *flexible sigmoidoscopy* can be done to confirm the diagnosis. In some instances, *diagnostic imaging* (such as computed topography or magnetic resonance imaging) will be performed first and will suggest the diagnosis. These tests require follow up with colonoscopy or flexible sigmoidoscopy for confirmation.(13) In those without symptoms, population level screening programs exists to identify those with pre-cancerous lesions and/or early stage of disease to allow for earlier intervention and improved outcomes. Although the initial screening test differs based on jurisdiction, confirmation with colonoscopy or flexible sigmoidoscopy is required. (14)

2.6 Staging Classification of Rectal Cancer

Although there are several classifications which describes the extent and spread of rectal cancer the most widely adopted (and the one used in Canada) is the *American Joint Committee on Cancer* (AJCC) staging system. This staging classification is often referred to as "TNM" as it classifies rectal cancer based on the depth of primary tumor invasion ("T" stage), the number of involved regional lymph nodes ("N" stage) and the presence or absence of distant disease (also known as metastatic disease) ("M" stage). (Table 2-1) This staging classification system includes an overall stage of disease. Stage of disease is often described as "early stage" (Stage I), "locally advanced" (Stage II or Stage III) or metastatic (Stage IV). (Table 2-2).

Table 2-1 The American Joint Commission on Cancer (AJCC) Rectal Cancer Staging Classification System (8th edition) (15)

Stage	Level of Involvement
Tumor	
T1	Limited to mucosa and submucosa
T2	Extension into but not through muscularis propria
T3	Invasion of perirectal fat
T4a	Invasion of the peritoneal reflection
T4b	Invasion of adjacent organs such as the prostate, vagina or bladder
Nodes	
N0	No involved lymph nodes
N1	Fewer than four regional nodes involved
N2	More than four regional nodes involved
Metastasis	
M0	No metastasis
M1	Distant metastasis

Table 2-2 American Joint Commission on Cancer (AJCC) overall staging and prognosis. (1, 15)

Overall Stage of Disease			5 Year Overall Survival
Early Stage	Stage I	T1 - T2, N0, M0	88%
Locally Advanced	Stage II	T3 - T4, N0, M0	50 - 81%
Locally Advanced	Stage III	T (any), N1 -2, M0	58 - 83%
	Stage IV	T (any), N (any), M1	13%

During the "staging" or diagnostic phase, tests are completed to allow for a pre-treatment, or "clinical stage", to be assigned. Clinical stage is used to guide treatment decisions, including the intent of treatment (curative vs. non-curative) and the need for multimodality treatment. "Pathologic stage" is distinct from the clinical stage as it is determined based on the histopathology of the surgical specimen. The accuracy of the clinical stage is determined by the characteristics of the staging investigations, and may not accurately reflect the true stage of disease. Pathologic stage is considered the gold standard for staging of disease in those who have not received pre-surgical treatments. Pre-operative treatments often impair the accuracy of pathologic staging as "downstaging" (or treatment response) can occur.

2.7 Multidisciplinary Management of Rectal Cancer

As described in section 2.4, rectal cancer is often managed by multidisciplinary teams. Members of these teams include surgeons, radiation oncologists, medical oncologists, palliative care physicians, specialized nurses, radiologists and pathologists. The management of rectal cancer includes three primary phases. The first is the staging investigation phase, during which the requisite pre-treatment diagnostic investigations are completed. The second is the treatment phase, during which treatment is delivered. The final is the surveillance (or follow-up) phase, during which routine investigations occur in an attempt to identify potentially treatable recurrent cancer.

2.7.1 Diagnostic Investigations

To obtain a clinical stage, several pre-treatment investigations are typically completed. These investigations assess the tumor and nodal stage (referred to as "local-regional" disease),

assess for the presence of metastatic disease ("distant" disease) or look for "synchronous" colon cancers. (Table 2 – 3)

Table 2-3 Commonly used investigations following a diagnosis of rectal cancer

Assessment of Synchronous Colon Cancers
Colonoscopy
CT Colonography
Assessment of Local-Regional Disease
MRI Pelvis
Transrectal Ultrasound (TRUS)
Assessment of Metastatic Disease
Chest Xray, CT Chest
Abdominal Ultrasound, CT Abdomen, MRI Abdomen

CT Computed Topography, MRI Magnetic Resonance Imaging,

The primary modalities used to assess local regional stage are Transrectal Ultrasound (TRUS) and Magnetic Resonance Imaging of the Pelvis (MRI). Concordance between clinical staging and pathologic staging (in those who have not had pre-operative treatments) has been reported to be between 73 – 80% for "T" Stage and 60 – 89% for "N" Stage. (16) Importantly, 10 – 26% of patients with rectal cancer will be "overstaged" (i.e. assigned a higher clinical stage than the true stage) which can result in overtreatment. (17) Similarly, 10 – 20% of those undergoing surgical resection only will be "understaged" and will have a higher pathologic stage than clinical stage which can result in additional treatments being needed. (18)

Metastatic disease assessment includes investigations to assess for the presence of thoracic metastases, liver metastases and other abdominal metastases, as these are the most common sites of metastatic rectal cancer.(19) If the initial assessment suggests metastatic disease, a confirmatory biopsy may be necessary for confirmation.

Colonoscopy is used to ensure that another colon cancer isn't present at the time of rectal cancer diagnosis. These cancers are referred to as "synchronous cancers" and can occur in up to

8% of individuals. (20) The presence of a synchronous colon cancer may alter the type or extent of surgical resection. In addition, multiple synchronous colorectal cancers may suggest a pre-disposing hereditary syndrome such as Lynch Syndrome.

2.7.2 Treatment of Rectal Cancer

The initial treatment of rectal cancer is determined based on the assigned clinical stage identified through diagnostic investigations. Prior to treatment commencing, patient details are often reviewed at a Multidisciplinary Cancer Conference (MCC). MCC provides an opportunity for clinicians to review all relevant investigations with their peers with the intent to seek consensus on the most appropriate treatments for the individual with rectal cancer. The treatment of rectal cancer can include surgery, radiation therapy or chemotherapy.

2.7.2.1 Surgical Treatments

In general, most individuals seeking curative intent treatment will undergo surgery in the form of either local excision or surgical resection. Local excision is a limited surgery, which removes the cancer and adjacent rectal wall from the underlying structures (Figure 2 – 4). It is typically reserved for those with low risk disease. In those who undergo a local excision and are found to have high risk disease, radical resection can be offered. Radical resection, also known as "Total Mesorectal Excision" (TME), is a technique which removes the entire rectum, adjacent fat, lymph nodes and blood vessels. TME is considered the "standard of care" when radical surgical resection is required (Figure 2 – 5).

Figure 2-3: Local excision of an early stage rectal cancer (21)

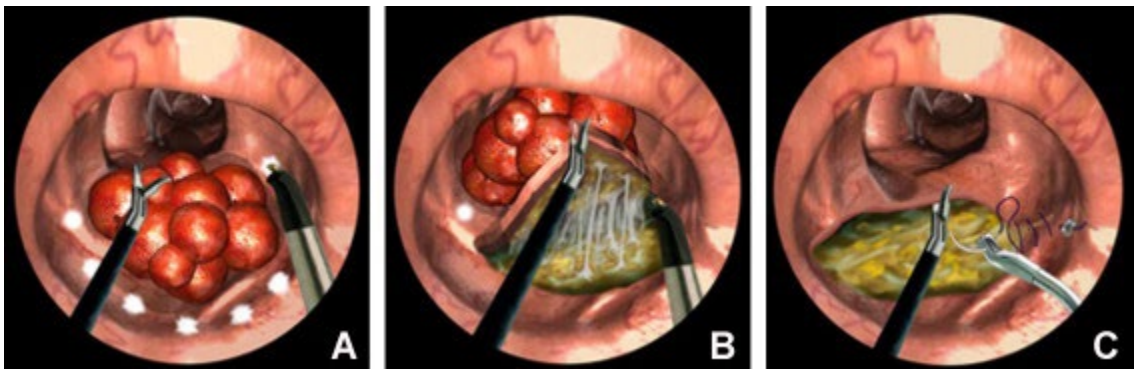
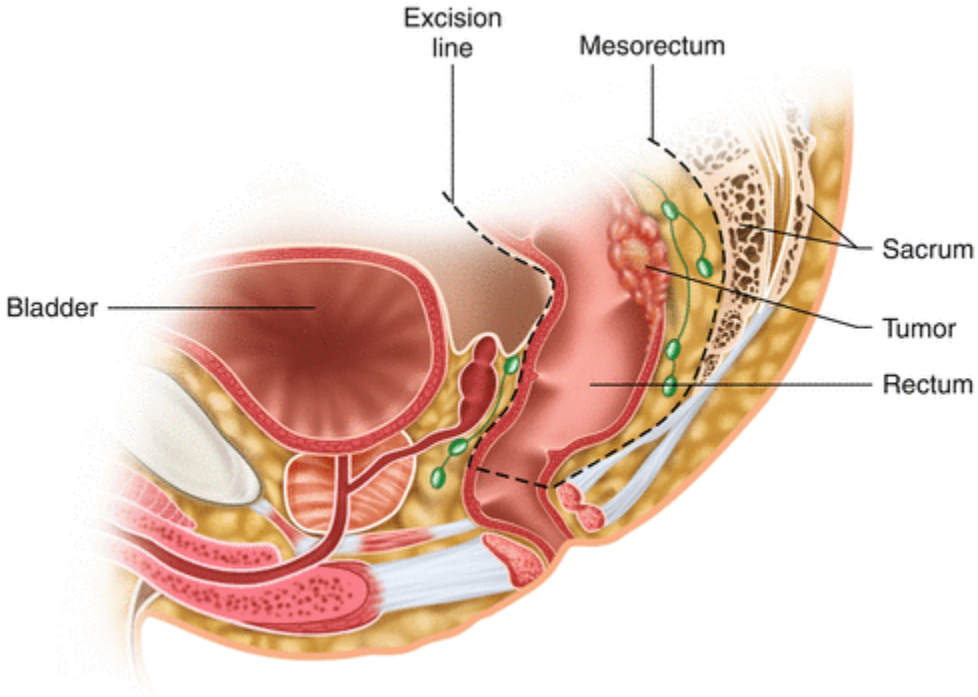


Figure 2-4: Total Mesorectal Excision (TME) for Rectal Cancer (22)



2.7.2.2 Neoadjuvant Treatments

Neoadjuvant therapy typically refers to treatments given prior to surgical resection. The purpose of neoadjuvant therapy is to reduce local recurrence, as well as to downstage the cancer to allow for complete resection. (23, 24) It is typically offered to those who have locally advanced disease based on pre-treatment investigations. It may be given to those with presumed early stage disease, who are "upstaged" after radical resection. Radiation therapy is the primary

neoadjuvant therapy modality. Radiation therapy is typically delivered using external beam radiation, where radiation is focused on the cancer from a machine outside the body. The duration of treatment is short, usually less than 15 minutes, and occurs over a number of sequential days. In those with rectal cancer, the two most common approaches are "Short Course" Radiation (SCRT) and "Long Course Chemoradiation" (CRT). Short course radiation includes a total of 5 fractions, given once per day over five days, with a dose of 5 Gray. Long course chemoradiation includes a total of 25 – 30 fractions, given once per day, over 5 – 6 weeks, with a dose of 1.8 Gray. 5-Fluorouracil based chemotherapy is given concurrently as a radiation sensitizing agent during long course chemoradiation. Radiation sensitizing chemotherapy is distinct from systemic chemotherapy described below, in that its effects only appear local-regionally. (25)

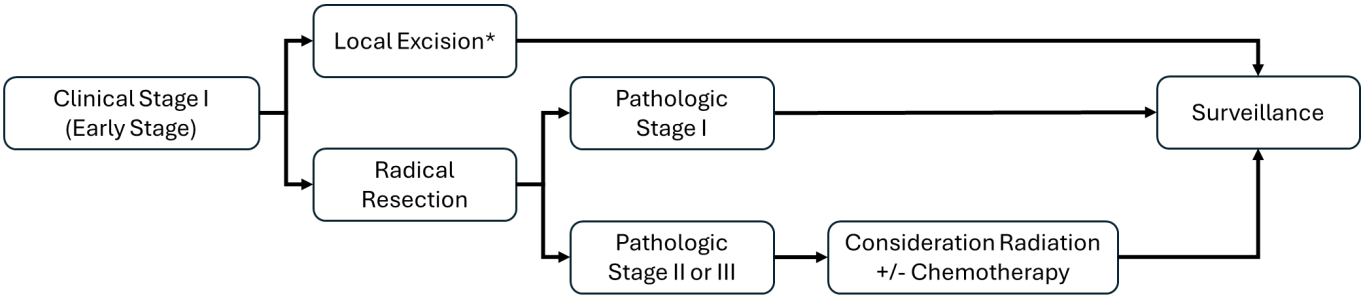
2.7.2.3 Adjuvant Treatments

In the treatment of rectal cancer, systemic chemotherapy is referred to as "adjuvant" therapy. The purpose of which is to treat distant "micro metastases" which may be present at the time of diagnosis, but not identifiable on diagnostic imaging. Adjuvant therapy can reduce the risk of developing metastatic disease and improve survival, and is typically offered to those with locally advanced disease. There are several options for adjuvant chemotherapy, all of which are Fluoropyrimidine based. The most commonly used combination is 5-Fluorouracil, Leucovorin and Oxaliplatin ("FOLFOX"). 5-Fluorouracil is intravenous, and may be replaced by its oral version, Capecitabine ("CAPEOX"). It is typically given over 3 – 6 months and started within 3 months of surgery. (26, 27) "Palliative" Chemotherapy refers to chemotherapy provided to those with metastatic disease. A number of options exists, many of which are Fluoropyrimidine

based. The purpose of palliative chemotherapy is to slow the progression of disease, improve survival and/or to alleviate the symptoms of cancer.(28)

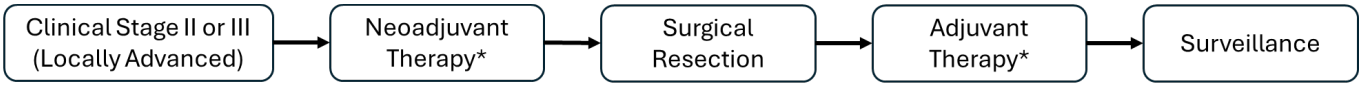
A summary of the treatment options for both early stage and locally advanced disease appear in Figures 2 – 5 and 2 – 6.

Figure 2-5 Treatment Pathway, Early Stage Disease



* Local Excision for T1 cancers without high risk features.
If high risk features, proceed to radical resection

Figure 2-6 Treatment Pathway, Locally Advanced Disease



* Neoadjuvant or Adjuvant Therapy may be omitted in those with favourable disease characteristics

2.7.2.4 Total Neoadjuvant Therapy, Watch and Wait and Organ Preservation in Rectal Cancer

Total Neoadjuvant Therapy, "Watch and Wait" and "Organ Preservation" are increasingly utilized approaches for treating rectal cancer and are worth mentioning. In those who receive neoadjuvant therapy, there is a possibility of having a complete response to treatment, in which no residual cancer can be detected in the surgical specimen. This outcome can occur in 20 – 30% of patients. For these reasons there has been increasing interest in "organ

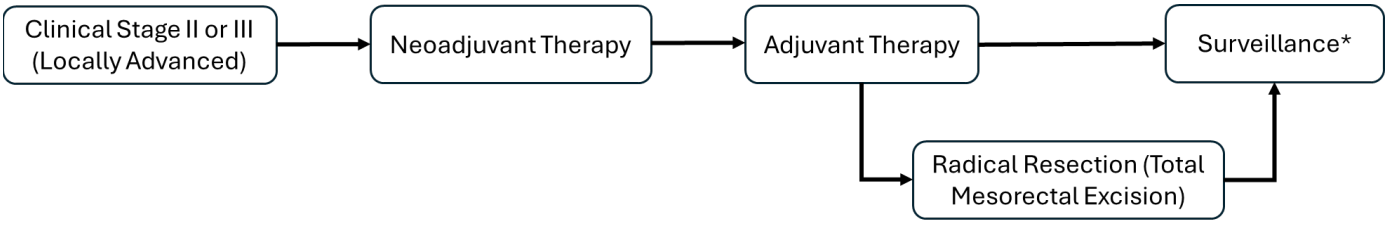
preservation" or "non-operative management", where a radical resection can be avoided in those with a complete clinical response. (29) This option requires close observation to allow for identification of regrowth of the cancer in the rectal wall, or the development of lymph node metastases in the mesorectum, both of which would lead to radical resection. (30) This treatment approach is referred to as "Watch and Wait".

In order to increase the number of patients eligible for "Watch and Wait", Total Neoadjuvant Therapy (TNT) may be given. Total neoadjuvant therapy delivers both neoadjuvant therapy (short course radiation or long course chemoradiation therapy) and systemic chemotherapy prior to surgical resection. TNT has gained popularity over the last several years as it can increase the chance of a "complete clinical response". (31)

"Organ Preservation" generally refers to avoiding radical rectal resection for rectal cancer. This concept includes the above described "Watch and Wait" approach, as well as using local excision in well selected patients. Local excision alone has been offered for early T1 cancers, and there has been recent interest in offering local excision in combination with chemotherapy for more advanced disease. (32)

Both total neoadjuvant therapy, watch and wait, and non-operative management are exciting, but controversial approaches to treating those with rectal cancer. The role of these approaches has yet to be fully defined. (33, 34) The use of TNT and watch and wait first appeared in American Clinical Practice Guidelines in 2018, but, as of this writing, have not been recommended in any Canadian Guidelines. Figure 2 – 7 demonstrates the treatment pathway for TNT and non-operative management.

Figure 2-7 Total Neoadjuvant Therapy and Non-operative Management Pathway



* Non-operative management for those with a complete clinical response

2.7.3 Surveillance following Treatment

Surveillance (or follow-up) following treatment is typically offered to those who underwent curative intent treatment. The purpose is to identify asymptomatic recurrent or metastatic disease, which may be amenable to treatment. Surveillance investigations include an assessment of lung, liver and abdominal metastases using diagnostic imaging, typically performed annually for up to 5 years. Local recurrence or new colorectal cancer is assessed using flexible sigmoidoscopy and/or colonoscopy, typically performed 6 – 12 months after surgery and then every 3 - 5 years. Finally, the tumor marker, Carcinoembryonic Antigen (CEA), can be used, typically drawn every 6 months for up to 5 years. This blood test may be elevated in those with occult metastatic disease and can be helpful in determining whether additional investigations are warranted. (Table 2 - 4).

Table 2-4 Surveillance Investigations

Assessment of Metastatic Disease
Computed Tomography (CT) Chest
Computed Tomography (CT) Abdomen/Pelvis
Abdominal Ultrasound
Abdominal Magnetic Resonance Imaging
Positron Emission Tomography
Assessment of Luminal Recurrence or new Colorectal Cancer
Colonoscopy
Flexible Sigmoidoscopy
Tumor Marker
Carcinoembryonic Antigen (CEA)

2.8 Clinical Practice Guidelines and Rectal Cancer

The care of those with a new diagnosis of rectal cancer requires timely pre-treatment investigations, multimodal treatment, and ongoing surveillance or follow up. Navigating the complexities of rectal cancer can be challenging, and thus clinical practice guidelines have been developed to provide a framework for clinicians treating those with rectal cancer. These guidelines have been produced by specialty societies, advocacy groups and governmental institutions. The number of available guidelines demonstrate the intense interest in ensuring individuals with rectal cancer receive appropriate care. Limitations of clinical practice guideline have been described and may limit their use in routine practice. (35)

2.9 How this chapter fits into the thesis as a whole

This chapter provides the reader of the thesis background on the diagnosis and management of rectal cancer. The concepts and terminology introduced in this chapter will be used throughout the thesis.

2.10 Chapter 2 Summary

- Rectal cancer is a commonly diagnosed malignancy in Canadians.
- Rectal cancer may be asymptomatic or symptomatic, and requires direct visualization for confirmation of diagnosis
- Once a diagnosis is established, a number of pre-treatment investigations ("Staging Investigations") are required to determine the clinical disease stage, and guide future treatment
- Treatment requires multidisciplinary care, including surgery, radiation therapy and chemotherapy
- Following treatment, a number of investigations are required to assess for cancer recurrence
- A number of clinical practice guidelines are available to help clinicians provide high quality and consistent care

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Chapter 3 Defining the Minimum Requirements of Guideline Adherent Rectal Cancer Care in Canada

3.1 Chapter Overview

A review of Canadian clinical practice guidelines (CPGs) was conducted. A search of provincial health authorities as well as a search of the literature was performed to identify pertinent CPGs. This search yielded seven provincial clinical practice guidelines. Although the quality of the guidelines varied substantially, there was general agreement between the recommendations for staging (or pre-treatment) investigations, treatment by stage of disease, and surveillance (or follow up) after treatment completion. Areas of disagreement were discussed. A definition of the "Minimum Requirements of Guideline Adherent Care" in Canada was proposed based on common elements throughout each available clinical practice guideline. Features of this chapter have been published in the Canadian Journal of Surgery. (1)

3.2 Chapter Aims and Objectives

The overall objective of this chapter was to identify all available provincial clinical practice guidelines for the treatment of rectal cancer to establish a definition of "minimum requirements of guideline adherent care" in Canada. The specific aims were to:

- Determine which staging investigations, treatments and surveillance investigations were commonly recommended by each provincial clinical practice guideline
- Determine which recommendations were controversial, or inconsistent between provincial clinical practice guidelines

- Propose a general definition of the minimum requirements of guideline adherent care in Canada, which will be used in the subsequent chapters

3.3 Background

There are 10 provinces and 3 territories in Canada. The 10 provinces include British Columbia (population 5.1 million), Alberta (population 4.4 million), Saskatchewan (population 1.2 million), Manitoba (population 1.4 million), Ontario (population 14.7 million), Quebec (population 8.6 million), New Brunswick (population 780,000), Nova Scotia (population 980,000), Prince Edward Island (population 160,000), Newfoundland and Labrador (population 520,000). The 3 territories include the Yukon (population 40,000), Northwest (population 45,000) and Nunavut (population 39,000) (Figure 3 – 1). (2)

Figure 3-1 Canadian Political Divisions(3)

Canada has a publicly funded health care system which provides "*universal coverage for medically necessary health care services provided on the basis of need, rather than the ability to pay.*" (4) Within this system, each province or territory is required to "*administer and deliver most of Canada's health care services, with all provincial and territorial health insurance plans expected to meet national principles set out under the Canada Health Act. Each provincial and territorial health insurance plan covers medically necessary hospital and doctors' services that are provided on a pre-paid basis, without direct charges at the point of service. The provincial and territorial governments fund these services with assistance from federal cash and tax transfers*."(4)

Although guidelines are an important resource for health care providers, funding for treatments are not directly affected by adherence. Thus, these documents provide guidance to clinicians only. As almost all cancer related therapies are funded through the above described systems, approvals are still required for these therapies. Approval from Health Canada is a required, as well as approval from the "pan Canadian Oncology Drug Review" is required for cancer drugs. This program evaluates the relative clinical benefits based on clinical indication. There is no equivalent system for funding of radiation therapy or surgical interventions, which are determined by the treating clinician. Many provinces have established cancer authorities to distribute cancer services and monitor the quality of this system. These authorities may also publish clinical practice guidelines to aide clinicians and other health care providers in delivering consistent, evidence based care. It should be noted that there is no pan-Canadian health authority. Thus provincial authorities represent the highest level of governmental oversight.

Guideline recommended care represents a consensus opinion, based on evidence based reviews, of what constitutes the "standard of care" for most patients. Much effort and resources have been devoted to the development and distribution of clinical practice guidelines for rectal cancer. In addition to government authorities, guidelines are also produced by specialty societies and advocacy groups. Some examples of specialty societies or advocacy groups publishing guidelines are numerous and include: The American Society of Colon and Rectum Surgeons (ASCRS), The Association of Coloproctology of Great Britain and Ireland (ACPGBI), The National Comprehensive Cancer Network (NCCN), The National Institute of Health (NIH), The American Cancer Society (ACS), The National Cancer Institute (NCI), The American Society of Clinical Oncology (ASCO), and The European Society of Medical Oncology (ESMO).

3.4 Chapter Methods

The methods for this review are described below. Although this chapter uses systematic elements, it does not meet the definition of a "systematic review". As described in the chapter aims, the purpose of this chapter was to identify Canadian based clinical practice guidelines readily available to clinicians. Thus, the methods below describe the identification of well known clinical practice guidelines applicable to Canadian clinicians, but does not include an exhaustive search for any and all guidelines. Unless explicitly stated, all work in this chapter was completed by the primary author of this thesis (Sunil Patel).

3.4.1 Clinical Practice Guideline Eligibility and Identification

Clinical Practice Guidelines were eligible for inclusion, if they were produced by a Canadian provincial health authority or similar. If the authority produced more than one version of the guideline, any version active during the period of interest (2010 – 2019) was included. This time period was selected in anticipation of the work conducted in Chapter 5 and 6 of this thesis. Within these chapters, individuals diagnosed between 2010 – 2019 were included. Thus, this chapter includes guidelines available during this entire period to ensure that the "minimum requirements of guideline adherent care" definition would be applicable to the earlier period of study. Using the minimum requirements allows for an inclusive definition, and one that would be applicable across all Canadian Jurisdictions. It also represents a Canadian consensus of the minimum requirements of care for those with rectal cancer.

A search for clinical practice guidelines published by each provincial cancer authority was initially conducted between July and August, 2018, and then updated in August 2022. This included searching the relevant provincial or territory's authority's website, as well as journal

publications using the following search terms: [(Rectal Cancer) AND ((Clinical Practice Guideline) OR (Recommended Care))] AND [(Province) OR (Canada) OR (Territory)]. If an applicable guideline could not be identified, the cancer authority was contacted directly to determine whether one existed.

The following provincial and territory authorities were searched for clinical practice guidelines: The British Columbia Cancer Agency, Alberta Health Services, Saskatchewan Cancer Agency, Cancer Care Manitoba, Cancer Care Ontario, Institut national d'excellence en santé et en services sociaux and Groupe d'étude en oncologie du Québec, Cancer Care Nova Scotia, Newfoundland and Labrador Health and Community Services, New Brunswick Health, Health Prince Edward Island, The Yukon Department of Health and Social Service, the Northwest Territories Health and Social Services Authority, and the Department of Health - Government of Nunavut.

In addition to the provincial health authorities, clinical practice guideline produced by major Canadian based Cancer Societies and Organizations were considered. These included: The Canadian Cancer Society; Canadian Partnership against Cancer; The Canadian Task Force on Preventative Health Care; Cancer Advocacy Coalition of Canada; Canadian Cancer Action Network.

3.4.2 Data Elements and Collection

Once a guideline was selected for inclusion, each was reviewed by two individuals (Sunil Patel and Zuhaib Mir), with any discrepancies resolved. The following data elements were extracted and inputted into an excel table created for that purpose:

- Year of publication

- Pre-treatment or Staging Recommendations: Local Regional Staging Recommendations; Metastatic (Abdomen and Chest) Staging Recommendations; Colonoscopy Recommendations; Tumor Marker Recommendations
- Treatment Recommendations (by stage of disease): Surgical Treatment; Neoadjuvant Therapy; Adjuvant Therapy
- Surveillance (or follow up after treatment) Recommendations: Assessment for Local Regional Recurrence; Assessment for Metastatic Disease; Colonic Assessment; Tumor Marker; Clinical Assessments

The recommendations from each guideline were included in an excel table and organized by phase of treatment (staging, treatment or surveillance), by province and by guideline version (if applicable).

3.4.3 Synthesis Methods

Once the recommendations were abstracted from the relevant guidelines, comparisons between recommendations were made. Agreements and disagreements between provincial recommendations were determined. In addition, substantive changes between different versions of a province's guideline were identified to account for potential changes in practice during the study period. A general definition of "guideline adherent care" was then created using an inclusive approach. This approach included all potential options, assuming no substantial disagreement existed (i.e. 2 conflicting treatment options). If substantial disagreement did exist, there was a plan to prioritize Cancer Care Ontario Recommendations, as the most applicable local clinical practice guideline. (Note: this was not necessary).

3.4.4 Clinical Practice Guideline Quality Assessment

An assessment of the quality of the included guidelines was not included in this chapter. The aim of the chapter was to determine which guidelines were accessible to clinicians and could be potentially used for management of those with rectal cancer. Following the completion of the work described in this chapter, a separate publication was completed which assessed guideline quality (Dr. Zuhaib Mir was primary Author, I was the senior author). This publication utilized some of the work described in this chapter. This publication appears in Appendix Chapter 3.(1)

3.5 Chapter Results

From the 10 provinces and 3 territories, 7 provincial health authorities had clinical practice guidelines available for review (Table 3 – 1). (5-15) (Note these references are to the most current version of the guideline) Three provinces (Prince Edward Island, New Brunswick, Newfoundland and Labrador) and the three territories did not produce a relevant clinical practice guideline. Multiple versions of guidelines were identified from British Columbia (2012 and 2021), Alberta (2013, 2014, 2017), Saskatchewan (2011, 2013, 2019), Manitoba (2014, 2015) and Ontario (2013, 2014, 2016, 2018, 2020). Data from each version was abstracted, and differences between versions of the same guideline were included in the summary of disagreements described below.

Table 3-1 Summary of Assessed Provincial Clinical Practice Guidelines

Province	Guideline Available	Year
British Columbia	Yes	2012/2021
Alberta	Yes	2013/2014/2017
Saskatchewan	Yes	2011/2013/2019
Manitoba	Yes	2014/2015
Ontario	Yes	2013/2014/2016/2018/2020
Quebec	Yes	2016
Nova Scotia	Yes	2016
Newfoundland & Labrador	No	–
New Brunswick	No	–
Prince Edward Island	No	–
Nunavut	No	–
Northwest Territories	No	–
Yukon	No	–

None of the other major Canadian Cancer Organizations or Societies produced relevant clinical practice guidelines during the inclusion period.

3.5.1 Recommended Staging Investigations

All clinical practice guidelines recommended carcinoembryonic antigen (CEA) testing, which is a tumor marker used in colorectal cancer. Each guideline also recommended an attempt at complete colonoscopy to rule out synchronous (or pre-existing) colon cancers. There were no disagreements between subsequent versions of guidelines in this regard. All clinical practice guidelines also recommended an assessment of local regional staging. The two modalities recommended included Transrectal Ultrasound (TRUS) and/or magnetic resonance imaging (MRI). Four guidelines preferred MRI, 1 preferred TRUS, and 2 did not recommend one modality over another. Two guidelines made recommendations for MRI or TRUS based on specific clinical circumstances. These recommendations did not differ substantially between subsequent versions of the authority's guideline.

An assessment for the presence of metastatic disease was recommended by each clinical practice guideline. This included an assessment of lung metastasis through chest imaging and liver/abdominal metastasis through abdominal imaging. The guidelines were consistent in preferring computed tomography (CT) of the abdomen. Most guidelines also preferred CT Chest (6 guidelines) while one recommended either CT Chest of Chest Xray (CXR). (Table 3 – 2) Each guideline allowed for alternatives to CT for abdominal staging if contraindications existed. Alternatives could include ultrasound or magnetic resonance imaging.

Table 3-2: Pre-Treatment Staging Investigations – Diagnostic Imaging

Province	Local Regional Staging (MRI or TRUS)	Abdominal Staging	Chest Staging
British Columbia	No preference	CT Abdomen/Pelvis preferred	CT Chest
Alberta	MRI preferred (especially if SC planned)	CT Abdomen/Pelvis preferred	CT Chest
Saskatchewan	No preference	CT Abdomen/Pelvis preferred	CT Chest
Manitoba	TRUS preferred (especially for small or low tumours) MRI for all stenotic tumours	CT Abdomen/Pelvis preferred	CXR or CT Chest
Ontario	MRI preferred TRUS for low tumours	CT Abdomen/Pelvis preferred	CT Chest
Quebec	MRI preferred	CT Abdomen/Pelvis preferred	CT Chest
Nova Scotia	MRI preferred	CT Abdomen/Pelvis preferred	CT Chest

MRI Magnetic Resonance Imaging; TRUS Transrectal Ultrasound; CT Computed Tomography; CXR Chest Xray

3.5.2 Stage Specific Treatment

In all identified clinical practice guidelines, treatment recommendations were based on stage of disease. In each guideline, stage of disease was described as Stage I (early stage) and Stage II/III (locally advanced disease). Thus treatment recommendations for Stage II and for

Stage III disease did not differ substantially. In two provincial guidelines (British Columbia and Alberta), additional adjuvant chemotherapy options were available for "high risk" disease. These details are reported below.

3.5.2.1 Preoperative Treatment

In general, radiation therapy was not recommended for stage I (early stage) disease. Two provinces provided specific clinical scenarios in which radiation therapy could be considered in early stage disease (Table 3 – 3). For those with locally advanced disease (Stage II and Stage III), all provinces recommended preoperative radiation therapy. Three provinces recommended long course chemoradiation therapy, which includes chemotherapy given concurrently with 25 – 30 doses of radiation. Three provinces used clinical criteria to determine whether long course chemoradiation or short course radiation (where 5 doses of radiation is given without chemotherapy) should be used. One province did not state a preference. There were no substantial changes between subsequent versions of guidelines. (Table 3 – 3)

Table 3-3: Preoperative Treatment, by stage of disease

Province	Early Stage (Stage I)	Locally Advanced (Stage II & III)
British Columbia	Not Recommended	SCRT for non-fixed, upper 2/3 location CRT for fixed or predicted +CRM
Alberta	Not Recommended	SCRT for "amenable to resection" CRT preferred for stage II/III, and if "not amenable to resection"
Saskatchewan	CRT for select T_2N_0 and low tumours	CRT standard
Manitoba	Not Recommended	SCRT preferred CRT for down-staging, sphincter preservation
Ontario	Not Recommended	CRT Preferred
Quebec	For sphincter preservation	No specific preference but states that majority of clinicians use CRT
Nova Scotia	Not Recommended	CRT preferred

SCRT Short Course Radiation; CRT Long course Chemoradiation; CRM Circumferential Margin

3.5.2.2 Surgical Resection

For early stage rectal cancer, all provinces recommended surgical intervention. Five described clinical scenarios in which local excision would be appropriate. Two specifically describe the importance of total mesorectal excision technique. For locally advanced rectal cancer, all provinces recommended for radical resection (i.e. Total Mesorectal Excision). In addition, all provinces provided recommendations on when surgery should occur in relation to completion of short course radiation, while 6 of 7 provinces made specific recommendations for when surgery should occur following completion of long course chemoradiation. There were no substantial difference between versions of guidelines. (Table 3 – 4)

Table 3-4: Surgical Recommendations, by stage

Province	Early Stage (Stage I)	Locally Advanced (Stage II & III)
British Columbia	Local Excision (a) or Radical Resection	Surgery within 10 days of SCRT completion surgery within 6-10 weeks of CRT completion
Alberta	Local Excision (a) or Radical Resection	Surgery within 1 week of SCRT completion Surgery within 6-8 weeks of CRT completion
Saskatchewan	Local Excision (a) or Radical Resection	Surgery within 7-10 days of SCRT completion Surgery within 6-8 weeks of CRT completion
Manitoba	Highlights importance of TME technique	"Immediate" surgery following SCRT completion Surgery within 6-8 weeks of CRT completion
Ontario	Highlights importance of TME technique	Surgery within 10 days of SCRT completion Surgery within 4-6 weeks of CRT completion
Quebec	Local Excision (a) or Radical resection	"Immediate" surgery following SCRT completion Does not specify time to surgery for CRT
Nova Scotia	Local Excision (a) or Radical Resection	Surgery within 10 days of SCRT completion Surgery within 6-10 weeks of CRT completion

(a) Local Excision can be considered in select clinical situations
TME Total Mesorectal Excision; TAE Transanal Excision; SC Short Course Radiation; CRT Long course Chemoradiation

3.5.2.3 Adjuvant Chemotherapy

All provinces recommend against postoperative adjuvant chemotherapy in early stage disease (Stage I), while recommending for postoperative adjuvant chemotherapy for locally

advanced disease (Stage II/III). One guideline (Alberta), described situations in which Stage II disease would not require adjuvant chemotherapy, which included not receiving preoperative neoadjuvant therapy and not having any high risk features. One guideline (British Columbia) recommends the addition of Oxaliplatin for those with Stage III disease, and recommends for Capecitabine for those with Stage II disease. All other clinical practice guidelines did not discriminate between Stage II and Stage III disease when considering adjuvant chemotherapy. Specific recommendations on type and duration varied across the provincial guidelines, but all recommended for Fluoropyrimidine-based therapy (i.e. 5- Fluorouracil or Capecitabine) with or without oxaliplatin. There was no substantial difference between versions of guidelines for eligibility of adjuvant chemotherapy. Versions differed in terms of specific chemotherapy regimens and duration. (Table 3 – 5)

Table 3-5: Adjuvant Chemotherapy Recommendations

Province	Early Stage (Stage I)	Locally Advanced (Stage II & III)
British Columbia	Not Recommended	Capecitabine x 6 months post-SCRT Capecitabine x 4 months post-CRT For stage III disease, FOLFOX may be considered, especially if N+
Alberta	Not Recommended	6 months of adjuvant therapy are recommended for (CAPOX, FOLFOX, or Capecitabine): (1) Those who receive neoadjuvant CRT. (2) In those with stage II disease who did not receive neoadjuvant CRT and have "high-risk features"
Saskatchewan	Not Recommended	Capecitabine, 5-FU, FOLFOX, or CAPOX x 6 months
Manitoba	Not Recommended	Fluoropyrimidine-based therapy offered post-operatively
Ontario	Not Recommended	Fluoropyrimidine-based therapy post-operatively; Oxaliplatin-based therapy or Capecitabine for high risk of systemic recurrence
Quebec	Not Recommended	5FU or FOLFOX for 8-12 cycles
Nova Scotia	Not Recommended	5FU or Capecitabine; FOLFOX if high risk of recurrence

SCRT Short Course; CRT Long Course; N+ node positive; CAPOX Capecitabine and Oxaliplatin; 5FU 5- Fluorouracil; FOLFOX 5FU, Leucovorin and Oxaliplatin;

3.5.3 Surveillance following completion of treatment

All provinces recommended for routine History and Physical, Carcinoembryonic Antigen (CEA), Abdominal and Chest Imaging and Colonoscopy following completions of treatment. Four of the provinces also recommended for rigid or flexible proctosigmoidoscopy. The specific interval between assessments and duration of assessments varied between provinces. In general, History and Physical was to occur every 3 – 6 months for the first 2 – 3 years and then every 6 – 12 months until 5 years after treatment. CEA was generally recommended to occur at the time of

history and physical exam. Abdominal and Chest imaging was to occur annually for at least 3 years in all provincial guidelines. CT was recommended and preferred for abdominal and pelvic imaging in all guidelines, while chest imaging could include either CT or Xray. Each guideline allowed for alternatives to CT if contraindications existed, including Ultrasound or Magnetic Resonance Imaging. Colonoscopy was generally recommended at 1 year after surgery, with subsequent colonoscopy in 3 – 5 years. There was no substantial variation in these recommendations based on version of guideline, although later versions tended to favour CT chest over CXR. (Table 3 – 6)

Table 3-6: Post Treatment Surveillance or Follow Up Recommendations

Province	History/Physical	CEA	Abdominal and Chest Imaging	Colonoscopy	Flexible Sigmoidoscopy
British Columbia	q 3-6 mo x 3 y then q 6 mo x 2 y	At each visit	Annually x 3 y	At 1 & 4 y post-op Every 5 y thereafter	
Alberta	Not specified	q 3 mo x 3 y	Annually x 2 y (+/– 3rd year)	At 1 & 4 y post-op Every 5 y thereafter	
Saskatchewan	q 3-6 mo x 3 y then q 6-12 mo x 2 y Annually thereafter	q 3-6 mo x 3 y then q 6-12 mo x 2 y	Annually x 3 y	At 1 y post-op If no polyps, every 3-5y thereafter	q 6 mo for 5 y*
Manitoba	q 3 mo x 3 y then q 6 mo x 2 y	q 3 mo x 3 y	Annually x 3 y	At 1 & 3 y post-op Every 5 y thereafter	q 6 mo for 3 y post-op*
Ontario	q 6 mo x 5 y	At each visit	Annually x 3 y	At 1 y post-op Every 5 y thereafter	6 mo for 2-5 y post-op*
Quebec	q 3-6 mo x 3 y then Annually	At each visit	Annually x 3 y	At 1 y post-op If no polyps, every 3-5 y thereafter	
Nova Scotia	q 3 mo x 3 y then q 6 mo x 2 y	At each visit	Annually x 3 y	At 1 y post-op No specific surveillance recommendation thereafter	at 6, 18, 24, and 36 months post-op

*Mo Months; q every; y year; *If no pelvic radiation*

3.5.4 Management of Metastatic Disease

All 7 provinces recommended individualized treatment for those with Stage IV (i.e. metastatic disease), as described in Table 3 – 7. Six provinces made specific recommendations for radiation and/or surgery based on the intent of treatment and patient symptoms. All 7 recommended select use of chemotherapy, with multiple regimens proposed. Finally, 3

recommended routine assessment by palliative care teams, 1 recommended select use of palliative care and 3 did not specifically recommend for or against palliative care assessment.

Table 3-7: Recommendations for Stage IV disease

Province	Radiation Therapy	Surgery	Chemotherapy	Palliative Care Assessment
British Columbia	Selective Use in those with potential for cure or with symptoms	Selective Use in those with potential for cure or with symptoms	Multiple Regimens proposed	Based on Clinical Status
Alberta	Selective Use in those with potential for cure or with symptoms	Selective Use in those with potential for cure or with symptoms	Should be considered, if tolerable	
Saskatchewan	Selective Use in those with potential for cure or with symptoms	Selective Use in those with potential for cure or with symptoms	Multiple Regimens proposed	
Manitoba			Decision to treat based on assessment and patient preference	Recommended
Ontario	Selective Use in those with potential for cure or with symptoms	Selective Use in those with potential for cure or with symptoms	Multiple Regimens proposed	Recommended
Quebec	Selective Use in those with potential for cure or with symptoms	Selective Use in those with potential for cure or with symptoms	Multiple Regimens proposed	
Nova Scotia	Selective Use in those with potential for cure or with symptoms	Selective Use in those with potential for cure or with symptoms	Multiple Regimens proposed	Recommended

3.5.5 Summary of Agreements and Disagreements between Guidelines

Table 3 - 8 summarizes the general agreements and disagreements between the available provincial clinical practice guidelines. There was broad agreement in all domains. For instance, all provinces recommended for similar staging investigations, the routine need for preoperative therapy in locally advanced disease (but not routine use in early stage disease), the need for adjuvant chemotherapy in locally advanced disease, and the need for multimodal surveillance

after treatment completion. The areas of disagreement arose based on specific clinical scenarios (i.e. the role of local excision in early stage cancer), or treatment options available (i.e. the use of short course radiation vs. long course chemoradiation therapy). Table 3 – 9 summarizes the specific areas of disagreement between the clinical practice guidelines.

Table 3-8: Summary of Agreements between provincial clinical practice guidelines

	Early Stage Disease (State I)	Locally Advanced Disease (Stage II & III)
Staging Investigations		
Colonoscopy	7 of 7 recommend	
Carcinoembryonic Antigen	7 of 7 recommend	
Local Regional Staging	7 of 7 recommend	
Assessment of Chest Metastasis	7 of 7 recommend	
Assessment of Abdominal Metastasis	7 of 7 recommend	
Neoadjuvant Radiation Therapy		
Routine Use	2 Recommend in specific scenarios; 5 Recommend against	7 of 7 Recommend
Surgical Therapy		
Local Excision	5 Recommend in specific scenarios; 2 do not recommend for or against	7 of 7 Recommend against
Total Mesorectal Excision	7 of 7 Recommend	7 of 7 Recommend
Adjuvant Chemotherapy		
Routine Use	7 of 7 Recommend against	7 of 7 Recommend
Surveillance		
History and Physical	7 of 7 recommend	
Carcinoembryonic Antigen	7 of 7 recommend	
Abdominal and Chest Imaging	7 of 7 recommend	
Colonoscopy	7 of 7 recommend	
Stage IV (Metastatic Disease)		
Radiation Therapy	7 of 7 recommend selective use	
Surgery	7 of 7 recommend selective use	
Chemotherapy	7 of 7 recommend selective use	
Palliative Care	4 of 7 recommend routine or selective use, 3 did not recommend for or against	

Table 3-9: Summary of areas of disagreements between clinical practice guidelines

	Early Stage Disease (Stage I)	Locally Advanced Disease (Stage II & III)
Staging Investigations		
Local Regional Staging	Recommended MRI (4 CPG); TRUS (1 CPG); no preference (2 CPG)	
Assessment of Chest Metastasis	Recommend CT Chest (6 CPG); no preference (1 CPG)	
Neoadjuvant Radiation Therapy		
Routine Use	2 Recommended for in specific scenarios; 5 recommend against	CRT Preferred (3 CPG), SCRT Preferred (1 CPG); CRT vs. SCRT Based on Pretreatment Criteria (2 CPG); No preference (1 CPG)
Surgical Therapy		
Local Excision	4 Recommend in specific scenarios; 3 do not recommend for or against Local Excision	
Adjuvant Chemotherapy		
Type of Regimen		Multiple
Duration of Regimen		Multiple
Surveillance		
History and Physical	First 3 years: q3 mo (2 CPG) vs. q 3 - 6 mo (3 CPG) vs. q6 mo (1 CPG) vs. not specified (1 CPG) Year 3 - 5: q6 mo (4 CPG) vs. q6-12 mo (1 CPG) vs. q12mo (1 CPG) vs. not specified (1 CPG)	
Carcinoembryonic Antigen	At each visit (4 CPG) vs. q3mo x 3 y (2 CPG) vs. q3-6 mo x3y then q6 - 12 mo x 2 y (1 CPG)	
Abdominal and Chest Imaging	Annually x 2y (1CPG) vs. Annually x 3 y (6 CPG)	
Colonoscopy	All recommend at 1 year followed by subsequent at: 3 y (3 CPG) vs. 3 - 5 y (2 CPG) vs. 5 y (1 CPG) vs. no recommendation (1 CPG)	

MRI Magnetic Resonance Imaging; CPG Clinical Practice Guideline; TRUS Endorectal Ultrasound; CT Computed Tomography; CRT Long-course Chemoradiation Therapy; SCRT Short Course Radiation Therapy; mo month; q every; y year

3.6 A Definition of the Minimum Requirements of Guideline Adherent Care in Canada

A definition of the minimum requirements of guideline adherent care in Canada is presented in table 3 – 10. This definition represents the minimum required investigations or interventions based on the 7 provincial clinical practice guidelines. The definition includes the

need for the following staging investigations: Colonoscopy, CEA, Assessment of Chest and Abdominal Metastasis, Assessment of Local-regional stage of disease. The following is required for early stage (Stage I) disease: Appropriate Surgical Treatment. The following is required for locally advanced disease (Stage II/III): Preoperative Neoadjuvant Therapy, Appropriate Surgery Treatment and Adjuvant Chemotherapy with 5FU based chemotherapy. The following is required for surveillance or follow up: Routine History, Physical and CEA; Colonoscopy at 1 year and then every 3 – 5 years; Annual assessment of Chest and Abdominal Metastasis for at least 2 years. Stage IV disease was not explicitly included in this definition as all CPGs recommended for individualized care based on intent of treatment, symptoms and patient preference.

Table 3-10: Minimum requirements of Guideline Recommended Care in Canada

<table>
<tr><th></th><th>Early Stage (Stage I)</th><th>Locally Advanced (Stage II & III)</th></tr>
<tr><td rowspan="5">Staging Investigations</td><td colspan="2">Colonoscopy</td></tr>
<tr><td colspan="2">Carcinoembryonic Antigen</td></tr>
<tr><td colspan="2">CT Chest or Chest Xray</td></tr>
<tr><td colspan="2">CT Abdomen/Pelvis</td></tr>
<tr><td colspan="2">MRI Pelvis or Transrectal Ultrasound</td></tr>
<tr><td rowspan="3">Treatment</td><td rowspan="3">Radical Resection or Local Excision</td><td>SCRT or CRT</td></tr>
<tr><td>Radical Resection</td></tr>
<tr><td>Systemic Chemotherapy (Fluoropyrimidine-based therapy)</td></tr>
<tr><td rowspan="4">Surveillance/ Follow-up</td><td colspan="2">History and Physical Exam at least q6months x 3 years</td></tr>
<tr><td colspan="2">Carcinoembryonic Antigen with each History and Physical Visit</td></tr>
<tr><td colspan="2">Colonoscopy at 1 year following surgery then every 3 - 5 years</td></tr>
<tr><td colspan="2">Chest (CT or CXR) and Abdominal (CT) imaging every year x at least 2 years</td></tr>
</table>

SCRT Short Course Radiation Therapy; CRT Long Course Chemoradiation; CT Computed Tomography; MRI Magnetic Resonance Imaging; CRT Chemoradiation Therapy; CXR Chest Xray

It should be noted that diagnostic imaging modalities included 2 options for both Chest Imaging (CT or Chest Xray) and Pelvic Imaging (MRI or transrectal ultrasound). In these instances, each diagnostic modality was recommended in at least one guideline over the study period. The purpose of this chapter was not to determine which modality should be used, but to

report what options existed. As the above definition is meant to represent the "minimum requirements" of guideline recommended care, both options were included.

3.7 Discussion

This chapter identified 7 provincial health authorities which published rectal cancer clinical practice guidelines between 2010 – 2020. These were used to determine a definition of guideline adherent care in Canada. There was good agreement between the different clinical practice guidelines. When differences did occur, they tended to be driven where two options were available (i.e. MRI vs. Transrectal Ultrasound; Short Course Radiation vs. Long Course Chemoradiation). These differences were included in the common definition as viable options. The definition proposed is thus an inclusive one and would be applicable to each jurisdiction.

3.7.1 Strengths and Limitations

The strengths of this chapter includes the comprehensive review of all available clinical practice guidelines, including updated versions, which were in place during the study period. This approach ensured that important management options were not overlooked, and that all health authorities producing guidelines within Canada were represented. The definition of guideline adherent care in Canada is inclusive in that it represents the minimum requirements of recommended care. Thus the definition is consistent with each available clinical practice guideline.

There are some limitations to this work which should be discussed. The purpose of this chapter was to create a definition of guideline adherent care, which could be used in the subsequent chapters and would be an indicator of the quality of care being delivered. The

presumption was that the available provincial clinical practice guidelines are accepted by health care providers and represent the "gold standard" of care. There are a number of clinical practice guidelines readily available from other non-Canadian organizations. These guidelines may be in popular use by Canadian health care providers, but were not included in this review. There may be important differences between the excluded clinical practice guidelines and those that were included. Comparing the definition proposed with the well known National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines does demonstrates some differences. For instance the ESMO guideline recommends considering radiation as the sole treatment for early stage cancers in specific clinical circumstances, while the NCCN guidelines recommends for the use of Positron Emission Tomography (PET) in those with metastatic disease in specific clinical circumstances. (16, 17) Although these differences are applicable to only a small number of patients, they would be considered "non-adherent" care in the Canadian context.

In addition to alternative guidelines being available, providers may offer treatments that are new, supported by high level evidence but do not yet appear in clinical practice guidelines. For instance several high quality studies have demonstrated the safety of excluding radiation in low risk stage II disease, while others have demonstrated the effectiveness of local excision and chemotherapy in some high risk stage I and low risk stage II cancers. (18, 19) Both of these approaches would be considered "non-adherent" based on the created definition, but still represents "high quality" care. These treatments options will likely be included in subsequent versions of the provincial clinical practice guidelines as they become more widely accepted.

Finally, the proposed definition of guideline adherent care provides a general guidance for rectal cancer care. The specific details of each aspect of care was not included. For instance,

the recommendation for 5-FU based chemotherapy in those with locally advanced disease appears in the proposed guideline. The proposed guideline does not specifically recommend for a specific chemotherapy route, regimen or duration. A general definition was preferred, as this definition was meant to be inclusive, and useful in the population health research described in the subsequent chapters, thus an overly detailed definition was not justified.

3.7.2 Implications for Practice

At the provincial or health authority level, this chapter has demonstrated that there is duplication of work being conducted across Canada. The guidelines do not differ substantially, and it is unclear why separate guidelines need to be developed by multiple Health Authorities. Canadian Provincial Health Authorities should consider consolidating their resources and regularly produce a Canadian wide guideline.

At the patient level, this chapter has identified some viable alternatives between the identified clinical practice guidelines (such as short course radiation vs. long course chemoradiation or MRI vs. Transrectal Ultrasound). Although local opinion and resource limitations may result in a preference of one alternative over another, care providers should recognize that different treatments are available (and recommended) which can allow for better individualized care by these providers.

3.7.3 Implications for Research

There are several implications for future research as a result of the findings presented in this chapter. Comparisons between different jurisdictions' clinical practice guidelines should be

understood when determining what is guideline adherent care. As multiple guidelines are readily available, researchers should be aware that there may be alternative care pathways consistent with "guideline adherence" that a patient may be receiving. Using an inclusive definition will ensure the appropriate interpretation of studies assessing the quality of care being delivered. The common definition created in this chapter, and the methodology described, could be used by researchers interested in guideline adherent rectal cancer care.

Future research could utilize regional difference in guideline recommended care as a natural experiment to compare real world outcomes when different treatment options are available. For instance, Saskatchewan, Ontario and Nova Scotia recommend for long course chemoradiation therapy for those with locally advanced disease, while Manitoba, Alberta and British Columbia recommend short course radiation in those with favourable disease. Researchers could use this difference to compare the real world difference between short and long course neoadjuvant therapy in those with favourable disease. Similarly, intensity of surveillance between provinces varied considerably. The resource utilization and effectiveness of high intensity vs. low intensity surveillance could be compared. This is notably one area with very little high-quality evidence available.

3.8 How this chapter fits into the thesis as a whole

This chapter provides a common Canadian definition of guideline adherent care. This definition was used in subsequent chapters as both an exposure and outcome.

3.9 Chapter 3 Summary

- Available Canadian Provincial Clinical Practice Guidelines were identified and reviewed
- A definition of the minimum requirement of guideline adherent care in Canada was created based on the available Canadian Clinical Practice Guidelines.

3.10 Chapter 3 References

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Chapter 4 An Evidenced Based Review of the Predictors of Guideline Adherent Care

4.1 Chapter Overview

This chapter describes an exhaustive systematic review and meta-analysis assessing the predictors of guideline adherent rectal cancer care. The results of this chapter are organized based on the phase of treatment, including: receipt of guideline adherent staging investigations; receipt of guideline adherent treatment; receipt of guideline adherent surveillance. Portions of this work have been presented previously. (1-4) A summary of the associations between predictors and adherence outcomes are presented based on both the narrative synthesis as well as the quantitative analysis.

4.2 Chapter Aims and Objectives

The overall objective of this chapter was to systematically review the previously published literature assessing the association between potential barriers and facilitators (i.e. potential predictors) and the receipt of guideline adherent rectal cancer care. The specific aims of this chapter were to:

- Identify which predictors have commonly been ***assessed*** for their association with specific aspects of guideline adherent care
- Identify which predictors have been found to be ***associated*** with multiple aspects of guideline adherent care

- Identify which predictors have been rarely assessed, but should be considered for their association with guideline adherent care
- Determine which factors should be included in the Ontario Rectal Cancer Cohort

4.3 Background

The management of patients with rectal cancer is complex and requires a number of diagnostic and treatment modalities, as described in ***Chapter 2***. To help clinical teams navigate the complexities of rectal cancer care, clinical practice guidelines (CPG) have been created. These CPGs are widely available and often represents the "best evidence" for management of this population. (5-8) Patients with a new diagnosis of rectal cancer first require staging investigations, which allow for a clinical stage to be assigned. Once a clinical stage is established, appropriate treatments are recommended and could include surgery, radiation and/or chemotherapy. Finally, surveillance after treatment is often recommended to identify potentially treatable local-regional and/or distant recurrences.

Prior to the work presented in this chapter, there has been no systematic assessment of which factors were acting as barriers or facilitators to guideline adherent care. Furthermore, there has been no quantitative assessment of the available literature describing the magnitude and direction of associations between these factors and the specific components of guideline adherent care. Identifying which non-modifiable factors are associated (positively or negatively) with guideline adherent care would allow clinicians and policy makers to identify those who are at elevated risk of non-adherent care. Recognizing which modifiable risk factors are associated with guideline adherent care would guide policy makers in selecting quality improvement initiatives to increase adherence to recommended care. Identifying both non-modifiable and

modifiable risk factors would allow researchers interested in guideline adherent care the ability to include all relevant factors in their studies. Researchers can also compare the results of their studies with those of previously published works.

4.4 Chapter Methods

The chapter methods are described below. The systematic review was registered in PROSPERO. (2) Unless explicitly stated, all work in this chapter was completed by the primary author of this thesis (Sunil Patel).

4.4.1 Study Eligibility

Studies were eligible for inclusion if they reported the association between a potential barrier or facilitator (i.e. exposure) and the receipt of any aspect of guideline adherent rectal cancer care (i.e. outcome). Eligible exposures included patient related and care provider related (described in detail in section 4.4.5), while eligible adherence outcomes included staging investigations, treatments and/or surveillance investigations (described in detail in section 4.4.6).

Studies were included if published between 2000 and 2020. Restriction on year of publication was used as clinical practice guidelines for rectal cancer care were first published in the mid 1990's (National Comprehensive Cancer Network, NCCN), and this period represents the modern era of rectal cancer treatment which includes multimodal treatments and modern diagnostic imaging. Observational studies, including cohort studies or case-control studies, were eligible for inclusion.

4.4.2 Information sources and search strategy

Using an iterative process, with feedback from the primary supervisors, relevant search terms were identified and a search strategy created. The EMBASE and MEDLINE databases were queried using this strategy. The original search date was October 2018, with an updated search in July 2020. The search strategy was repeated based on the phase of care (Staging, Treatment, and Surveillance) in both databases using the applicable search terms. The common search terms used for each phase of care, as well as the specific search terms for each phase of care appear in Appendix Chapter 4 – 1. References from the included publications were reviewed to identify any additional relevant studies.

4.4.3 Selection and Data Collection Process

After the search was completed, all potential references were uploaded to EndNote (Clarivate, Philadelphia, USA). Assessment of study eligibility was completed independently and in duplicate by myself and Sydney Candy, a Queen's University Undergraduate Medical Student. Title and Abstract screen was conducted to identify potentially eligible studies. The two reviewers discussed and resolved discrepancies, and full texts were then retrieved. Duplicate and independent full text review was completed (by SP and SC), and discrepancies identified and resolved. This process was completed for both the original search (October 2018) and updated search (July 2020).

Once publications were identified for inclusion, data from each publication was extracted using a data extraction sheet created for this purpose. Data elements (described below) were inputted in this extraction sheet in duplicate (SP and SC) and discrepancies resolved.

4.4.4 Data Elements

The following data items were extracted:

- **Study Characteristics:** Author and Year of Publication, study design, study setting, clinical practice guideline used
- **Patient Characteristics:** Number of included patients, inclusion and exclusion criteria, year of diagnosis or treatment
- **Exposures:** The type of exposure (i.e. barrier/facilitator) assessed, how the exposure was defined and/or categorized
- **Outcomes:** The outcomes (i.e. specific aspect(s) of guideline adherent care) assessed, how the outcome was defined and/or categorized
- **Analysis:** The type of analysis completed (univariable, multivariable), the direction and magnitude of association between the exposure and outcomes.

4.4.5 Predictors of Guideline Adherent Care (i.e. exposures)

The primary exposures (i.e. the predictors) were broadly categorized as patient related or care provider related. These exposures are referred to as "potential predictors" throughout this chapter. *A priori* identified potential predictors are described below.

- **Patient Related:** Age, Gender and/or Sex, Ethnicity, Religion, Co-morbidities, Social Economic Status, Language, Geographic Location (rural vs. urban, distance from hospital or cancer centre), Type of Insurance, Symptoms, Acuity of Presentation (elective, emergency).
- **Care Provider Related:** Physician specialty arranging staging or surveillance investigations (Primary Care Physician, Surgeon, Oncologists, Gastroenterologist), Physician Volume, Type of physician practice (private practice, community practice,

academic practice, practice within a multidisciplinary cancer centre). Type of Hospital (community, academic, rural, urban, private, public), Presence of Multidisciplinary Care (Surgery, Radiation Oncology, Medical Oncology), Hospital Volume, Funding Model (publicly funded vs. private funding).

As this was an inclusive approach, any additional relevant potential predictors were eligible for inclusion.

A number of the above variables could be defined and/or categorized in several ways. For instance, co-morbidity could be described based on a specific co-morbidity (i.e. Diabetes or Heart Disease) or summarized through a number of different scoring systems. For the purposes of this systematic review and meta-analysis, all variables were captured based on how the study authors reported them. There was no attempt to re-classify or re-categorize variables. Studies were not excluded based on how the variables were reported. Within each results section, the definition and categorization was reported.

4.4.6 Adherence Outcomes

Eligible adherence outcomes included any aspect of guideline adherent rectal cancer care. Studies must have defined which clinical practice guideline was used. *A priori* defined outcomes are described below, and based on previous work. (9) In addition to the specific components of each phase of guideline adherent care, overall adherence to guideline recommendations was included as an outcome, if available.

- **Staging Investigations:** Local Regional staging (Magnetic Resonance Imaging and/or Transrectal Ultrasound), Assessment for distant metastasis (Computed tomography, Xray, Ultrasound, Positron Emission Tomography, magnetic resonance imaging),

assessment for synchronous colorectal cancer (colonoscopy, contrast enema, CT Colonography) and Tumor Markers (CEA).

- **Treatment:** Appropriate surgical technique (local excision or resection), appropriate use of neoadjuvant therapy (chemoradiation or radiation alone), appropriate use of adjuvant chemotherapy.
- **Surveillance/Follow Up Investigations:** Appropriate use of diagnostic imaging and/or colonoscopy, appropriate use of serum cancer markers, appropriate use of clinical assessments, appropriate frequency of investigations.

4.4.7 Risk of Bias Assessment

Study quality was assessed using the Newcastle-Ottawa Scale for assessing the quality of non-randomized studies in meta-analyses. (10) The Newcastle-Ottawa Scale assesses potential sources of bias including:

- **Selection Bias:** Representativeness of the exposed and control, ascertainment of exposure, the outcome being absent at the start of the study.
- **Comparability of the Exposed and Control:** Whether the exposed/control were matched in the design, or whether confounders were adjusted for in the analysis.
- **Outcome Assessment:** How the outcome was ascertained, adequacy of follow-up (i.e. loss to follow up) and adequacy of length of follow up.

Each include publication was reviewed in duplicated (SP and SC) with each category being assessed and scored.

4.4.8 Narrative Synthesis of Results

A summary of the relationship between each potential predictor - adherence outcome pair was completed. The relationship between the pairs were categorized as "Associated or Potentially Associated", "Not Associated", "Unclear Association" or "Not Assessed" based on the study results from included publications. (Table 4 – 1) All studies reporting an analysis of the association between the relevant predictor - adherence outcome pair were identified and included in the narrative synthesis of results. The study's multivariable analysis was then used to determine whether there was a statistically significant association (i.e. $P< 0.05$) between the predictor and adherence outcome. In those studies where a multivariable analysis was not available, the univariable results were used. For each predictor-adherence outcome pair, the number of studies with an available analysis was captured, as was the type of analysis reported (univariable vs. multivariable), whether the results were statistically significant or not, and the direction of association (positive or negative), if applicable.

Table 4-1: Definitions of Summary of Associations

Associated	All included studies reported a statistically significant association ($P < 0.05$) between the barrier/facilitator and the assessed outcome
Potentially Associated	At least one study reported a statistically significant ($P < 0.05$) association between the barrier/facilitator and the assessed outcome, with the remaining studies reporting no association ($P > 0.05$)
Not Associated	All included studies reported a non significant association ($P > 0.05$) between the barrier/facilitators and the assessed outcome
Unclear Association	At least one study reporting a positive and statistically significant association ($P < 0.05$) between the barrier/facilitator and the assessed outcome, and at least one study reporting a negative statistically significant association ($P< 0.05$) between the barrier/facilitator and the assessed outcome
Not Assessed	An association between the potential barrier/facilitator and the outcome was not assessed in any included study

4.4.9 Quantitative Analysis

A quantitative analysis (meta-analysis) was performed when at least 2 studies reported a multivariable analysis using a common categorization of the potential predictor (or exposure). To be included in this analysis, the odds ratio and 95% confidence interval (or standard error) must have been reported. Studies which reported univariable analysis only or did not report a 95% confidence interval or standard error were excluded from meta-analysis. The meta-analyses in this chapter were completed using previously published methods. (11) A random effects model was selected due to the expected heterogeneity between studies, driven by potentially different study settings, potentially different study populations, and potentially broad study periods. The pooled results were reported, as was the I^2 statistic, which is a measure of heterogeneity.

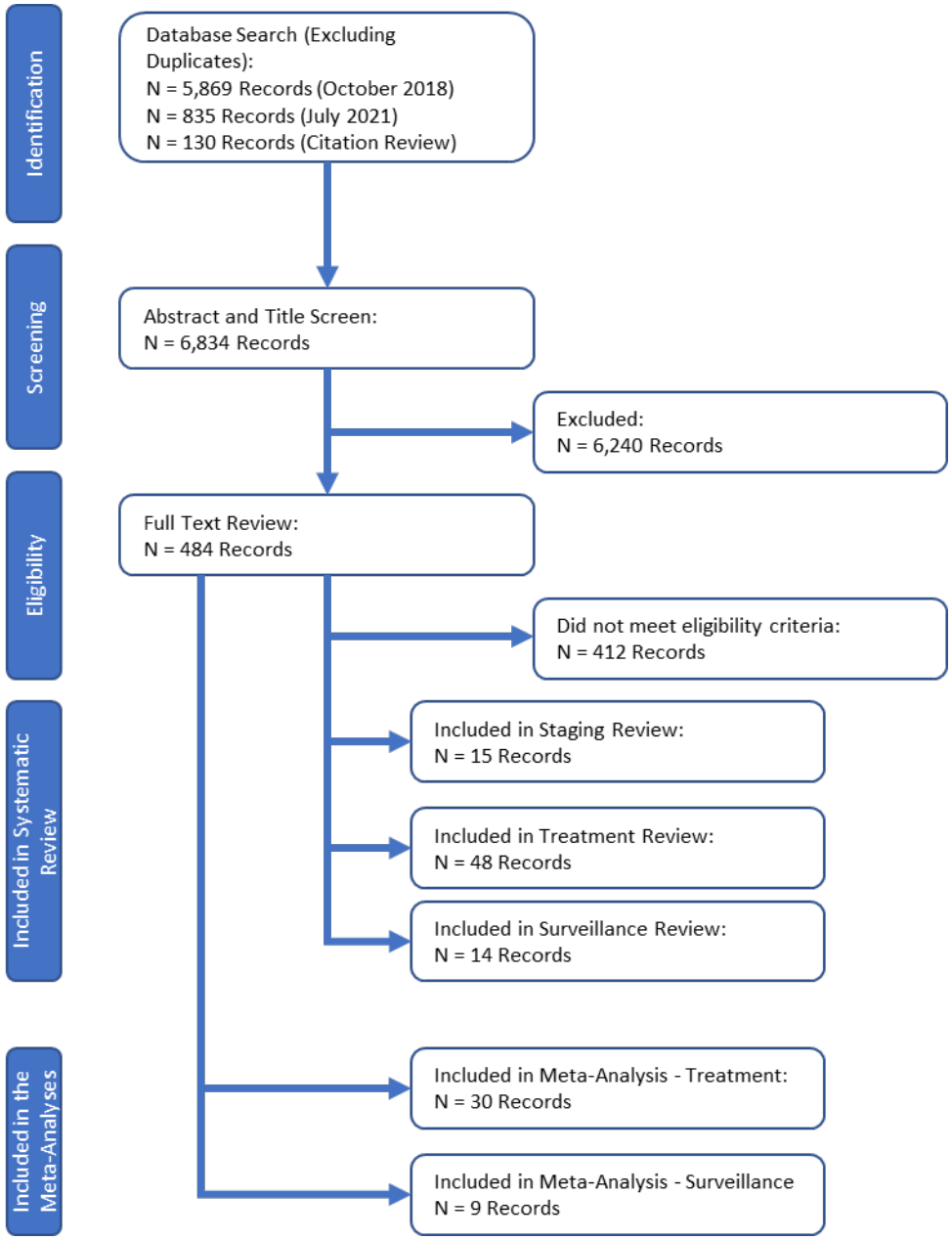
Heterogeneity was categorized as considerable ($I^2 > 75\%$), substantial ($I^2 = 50 – 75\%$) or low-moderate ($I^2 < 50\%$) based on previously published interpretations of heterogeneity. (12) The analyses where considerable heterogeneity ($I^2 > 75\%$) was identified were explored in greater detail. For the analyses a comparison of study populations, settings, exposures, outcomes and analytic methods was undertaken to better understand the causes of the heterogeneity. Studies with obvious outlying results were identified and the meta-analyses were re-run excluding these studies, to explore the impact of those studies on heterogeneity.

All analyses were completed using STATA 18.0 (StataCorp LLC, College Station, Texas, USA), using the “metan” command, which provided the results of the meta-analyses as well as produced the Forest plots.

4.5 Chapter Results

A total of 6,834 records were identified through the searches and citation review. Ultimately, 15 studies were included in the staging review (13-27), 48 studies in the treatment review (16, 20, 25, 28-72) and 14 studies in the surveillance review (73-87) (Figure 4-1). Of note, 5 studies (13, 16, 20, 22, 24, 25) were included in both the staging and treatment reviews. A total of 30 studies were included in at least one meta-analysis assessing treatment adherence and 9 studies in at least one meta-analysis assessing surveillance adherence (no staging adherence meta-analyses were possible).

Figure 4-1: Flowsheet of Included Studies



** 5 Studies included in both the staging and treatment review*

4.5.1 Characteristics of Included Studies

Tables 4 – 2, 4 – 3, and 4 – 4 summarize the studies included by phase of treatment (staging, treatment, surveillance). Specific study details can be found in Appendix Chapter 4 – 2 and includes: publication year; number of included patients; study population inclusion criteria;

study setting; diagnosis or treatment dates; predictors assessed; adherence outcome assessed; clinical practice guideline referenced. There was a large range in the number of patients between the included studies (N = 60 to N = 68,182). For each assessed outcome (staging, treatment, surveillance), the largest number of studies came from North America. Studies from Europe were available for the staging and treatment reviews, but not for the surveillance review. Notably, there are no studies from South America or Africa, and only one study from Asia.

There were a number of common patient related factors assessed across the reviews. These included: Age, Sex/Gender, Ethnicity, Geographic Location, Education, Socioeconomic Status and Health Insurance Type. Interestingly, care provider related factors were not frequently assessed in the surveillance review, but were in the staging and treatment review.

The reviews included articles assessing each aspect of guideline adherent care. This included (1) Staging Investigations: local-regional staging, metastatic staging, colonoscopy staging, CEA staging; (2) Treatment: radiation, chemotherapy and surgery; and (3) Surveillance Investigations: colonoscopy surveillance, metastatic surveillance, CEA surveillance and clinic surveillance. In addition, at least one article assessed "Overall Adherence" to guideline recommended care in each review. "Overall Adherence" refers to the study assessing whether an individual was adherent to each aspect of care. For instance, overall staging adherence required that an individual received local regional staging, metastatic disease assessment, colonoscopy and tumor marker. "Metastatic Disease" assessment was identified in both the staging and surveillance reviews. This term refers to diagnostic investigations (such as Computed Tomography, Magnetic Resonance Imaging, Ultrasound, Xray) used to determine whether distant metastatic disease was present.

The referenced clinical practice guideline varied substantially across studies and across reviews. For those articles included in the staging review, National or Provincial guidelines were used most. In the treatment review, the most used guidelines were from societies or organizations (National Comprehensive Cancer Network, National Institute of Health, American Cancer Society, National Cancer Institute, American Society of Colon and Rectum Surgeons). In the surveillance review, studies commonly used more than one guideline.

Table 4-2: Summary of Included Studies, staging review

	Staging Review (N = 15 Studies)
Year of Publication	2004 - 2020
Number of Patients	288 - 3899
Settings (N Studies)	North America (6), Europe (6) Australia (2), China (1)
Diagnosis or Treatment Years	1995 - 2017
Patient Related Predictors (N Studies)	Age (3), Gender/Sex (2), Ethnicity (2), Geographic Location (3), Education (1), Socioeconomic Status (1), Health Insurance Type (1)
Care Provider Related Predictors (N Studies)	Physician/Hospital Volume (3), Pathway/MDT (3), Hospital Type (4), Physician Specialty (1)
Outcomes Assessed (N Studies)	Local-regional Staging (10), Metastatic Staging (12), Colonoscopy (6), CEA (7), Overall (1)
Clinical Practice Guidelines Used (N Studies)	National/Provincial (7), NCCN (3), ACPGBI (1), ASCRS (1), Specific Guideline unstated (3)

CEA Carcinoembryonic Antigen; MDT Multidisciplinary Team; NCCN National Comprehensive Cancer Network; ACPGBI Association of Coloproctology of Great Britain and Ireland; ASCRS American Society of Colon and Rectum Surgery; NIH National Institute of Health; ACS American Cancer Society; NCI National Cancer Institute; ASCO American Society of Clinical Oncology

Table 4-3: Summary of Included Studies, Treatment Review

Treatment Review (N = 48 Studies)	
Year of Publication	2001 - 2021
Number of Patients	73 - 68,182
Settings (N Studies)	North America (34), Europe (9), Australia (4), China (1)
Diagnosis or Treatment Years (N Studies)	1976 - 2015
Patient Related Predictors (N Studies)	Age (45), Gender/Sex (36), Ethnicity (31), Co-Morbidities (28), Socioeconomic Status (19), Geography (13), Insurance Type (13), Marital Status (8), Education (5), Immigration Status (1)
Care Provider Related Predictors (N Studies)	Surgeon/Hospital Volume (16), Hospital Type (15), Pathway/MDT (8), Physician Type (1)
Outcomes Assessed (N Studies)	Radiation (33), Chemotherapy (13), Surgery (3), Overall (8)
Clinical Practice Guidelines Used (N Studies)	NCCN (11), NIH (11), National/Provincial (7), Multiple (6), ACS (2), NCI (2), ASCRS (1), Specific Guideline Unstated/Unclear (5)

MDT Multidisciplinary Team; NCCN National Comprehensive Cancer Network; ACPGBI Association of Coloproctology of Great Britain and Ireland; ASCRS American Society of Colon and Rectum Surgery; NIH National Institute of Health; ACS American Cancer Society; NCI National Cancer Institute; ASCO American Society of Clinical Oncology

Table 4-4: Summary of Includes Studies, Surveillance Review

Surveillance Review (N = 14 Studies)	
Year of Publication	2004 - 2018
Number of Patients	60 - 38,000
Settings (N Studies)	North America (12), Australia (2)
Diagnosis or Treatment Years (N Studies)	1993 - 2017
Patient Related Predictors (N Studies)	Age (13), Sex/Gender (12), Ethnicity (8), Co-Morbidities (7), Socioeconomic Status/Income (7), Geography (7), Insurance Type (2), Marital Status (3), Education (2), Employment (1), Other (1) (a)
Care Provider Related Predictors (N Studies)	Physician Specialty (4),
Outcomes Assessed (N Studies)	Colonoscopy (14), Metastatic (7), CEA (5), Clinic Visit (5), Overall (5)
Clinical Practice Guidelines Used (N Studies)	National/Provincial (2), NCCN (2), Multiple (8), ASCO (2)

(a) RCT comparing patient education intervention vs. not

CEA Carcinoembryonic Antigen; MDT Multidisciplinary Team; NCCN National Comprehensive Cancer Network; ACPGBI Association of Coloproctology of Great Britain and Ireland; ASCRS American Society of Colon and Rectum Surgery; NIH National Institute of Health; ACS American Cancer Society; NCI National Cancer Institute; ASCO American Society of Clinical Oncology

4.5.2 Study Quality

Study quality is summarized in Figures 4-2, 4-3, 4-4. The primary concern identified was the comparability of the exposed and control groups (i.e. those with and without the potential barrier or facilitator). Adjusted analysis (to account for known confounders) occurred in 5 of 15 staging review studies, 30 of 48 treatment review studies and 8 of 14 surveillance studies. The remaining studies reported an unadjusted analysis only, which raises concern of comparability between the exposed and control groups. The representativeness of the exposed/control groups was an additional quality concern. In some cases, the control groups were historic (Staging Review n = 2; Treatment Review n = 3) and in others one of the groups was not representative of the study population (i.e. from the Veteran's Affairs Hospital only, African American Patients Only, Single Institutions or Small Regions, Limited to specific age groups; Treatment Review n = 8, Surveillance Review n = 2). A small number of studies (Treatment Review n = 3; Surveillance Review n = 4) had inadequate follow up (i.e. follow up was not long enough for the phase of care to be completed) or inadequacy of follow up (i.e. > 10 % loss to follow up).

Figure 4-2: Study Quality, Surveillance Review

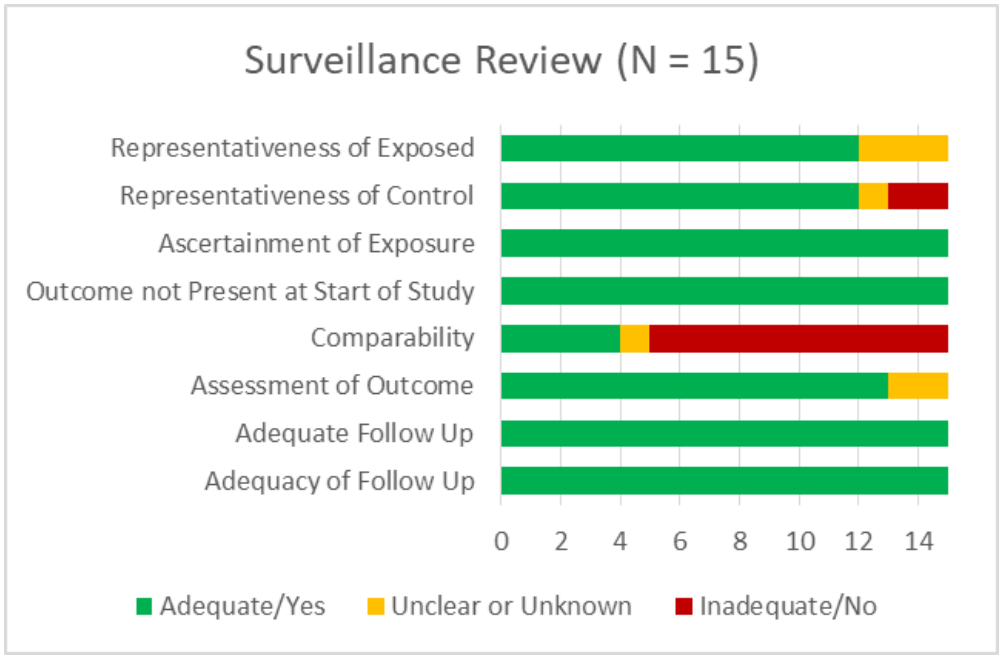


Figure 4-3: Study Quality, Treatment Review

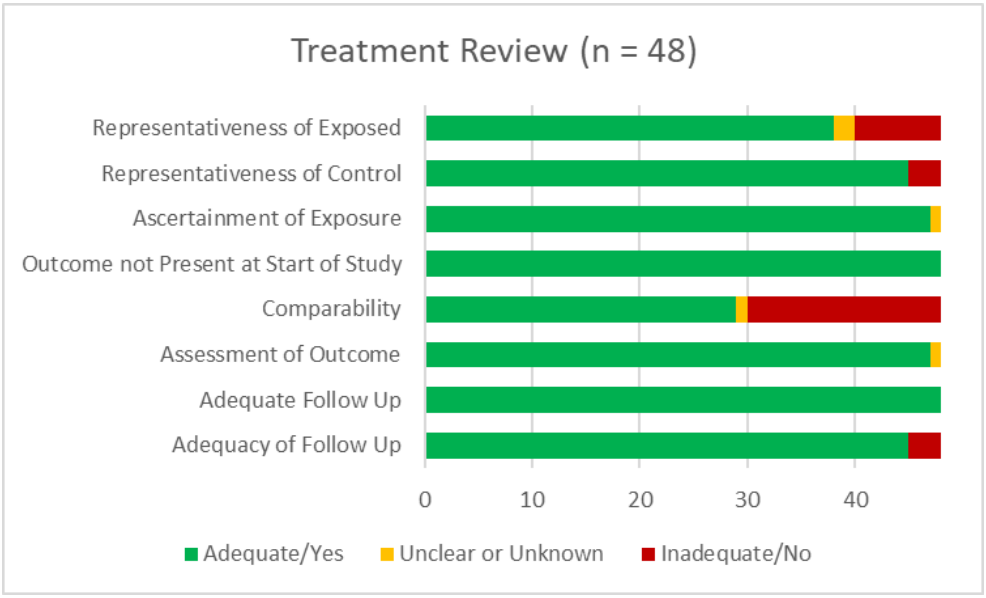
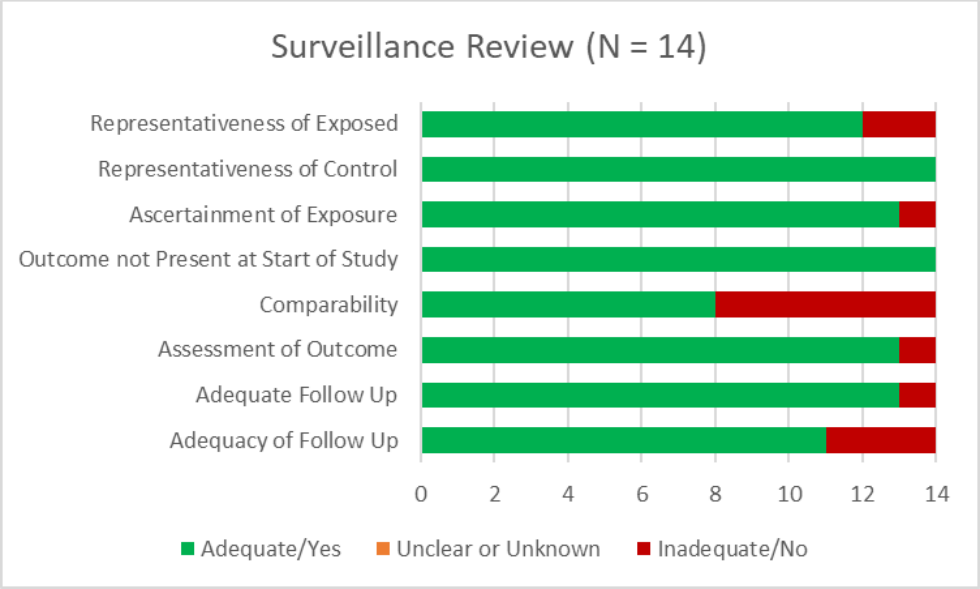


Figure 4-4: Study Quality, Surveillance Review



4.5.3 The association between potential predictors and guideline adherent care

Below, the association between potential predictors and guideline adherent care are described, with a section devoted to each potential predictor. Both the Narrative Synthesis and Quantitative Analysis (if available) are provided.

4.5.3.1 Age as a Potential Predictor of Guideline Adherent Care

Age, as a potential predictor, was assessed in at least one study for each identified aspect of guideline adherent care. The detailed study results are presented in Appendix Chapter 4 – 3.

A summary of the number of studies identified, and the type and direction of association appears in Table 4 – 5, based on the narrative synthesis. The following were found to be associated or potentially associated with age: Overall Staging (1 Study), Metastatic Staging (2 Studies), Overall Treatment (6 Studies), Adherent Radiation (24 Studies), Adherent Chemotherapy (7 Studies), Overall Surveillance (6 Studies), Metastatic Surveillance (6 Studies),

Colonoscopy Surveillance (11 Studies), CEA Surveillance (5 Studies). In each of these, ***increasing age*** was associated with ***decreasing adherence*** to guideline adherence. Age was not associated with local regional staging (1 study), colonoscopy staging (1 study), CEA staging (1 study) or appropriate surgery (1 study). Finally, one outcome, clinic surveillance, was found to have an "unclear association" with age. This finding was based on 3 included studies (73, 75, 84), two of which performed an adjusted analysis.(73, 84) In one study, 730 individuals of any age were assessed. Those <50 and 50 – 64 were more than twice as likely to attend clinical surveillance compared with those >75. (84) In the other two studies, only those over age 65 were included and found a small increase in the odds (73) or proportion (75) of attending clinical surveillance with increasing age.

Table 4-5: Narrative synthesis of the associations between age and each aspect of guideline adherent care, by number of included studies, type of association and direction of association

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	1	Univariable Only	Adherence associated with younger age
Local Regional Staging	1	Univariable Only	No Association
Metastatic Disease Assessment	2	Univariable Only	Adherence associated with younger age in all included studies
Colonoscopy	1	Univariable Only	No Association
Carcinoembryonic Antigen (CEA)	1	Univariable Only	No Association
Treatments			
Overall Treatment	6	Multivariable analysis	Adherence associated with younger age in all included studies
Radiation Therapy	24	19 of 26 analyses were multivariable	Adherence associated with younger age in 21 of 24 studies (22 of 26 analyses) (a)
Chemotherapy	8	9 of 10 analyses were multivariable	Adherence associated with younger age in 7 of 8 studies (8 of 10 analyses) (a)
Surgery	1	Multivariable analysis	No Association
Surveillance			
Overall Surveillance	6	4 of 6 analyses were multivariable	Adherence associated with younger age in 3 of 6 studies
Colonoscopy	11	7 of 11 analyses were multivariable	Adherence associated with younger age in 8 of 11 studies
Metastatic Disease Assessment	6	Multivariable analysis	Adherence associated with younger age in 4 of 6 studies
Clinic Assessment	3	2 of 3 analyses were multivariable	Unclear Association, Adherence associated with increased age in 2 studies, associated with decreased age in 1 study
Carcinoembryonic Antigen (CEA)	5	3 of 5 analyses were multivariable	Adherence associated with younger age in 4 of 5 studies.

(a) "Overall" includes a combination of guideline adherent care; Staging (Colonoscopy, Metastatic Assessment, Local-regional assessment, CEA); Treatment (Radiation, Surgery, Chemotherapy); Surveillance (Colonoscopy, Metastatic Disease Assessment, Clinic Assessment, CEA)

(b) Two studies stratified analysis by (1) Age less than or greater than 65 (2) Stage II vs. Stage III Disease

There was substantial variability in how age was used in the provided analysis. Age was included as a continuous variable (per year increase), as a categorical variable (age group) and as a binary variable (above and below a specific threshold). Those studies that reported it as a categorical variable had little consistency in the baseline (or referent group) used for analysis, the

age range of the groups (5 year vs. 10 year) or which groups were included. For this reason, only studies that reported a multivariable analysis with age as a continuous variable were included in a meta-analysis. This criterion was satisfied for two outcomes, receipt of guideline adherent radiation and receipt of guideline adherent chemotherapy.

Meta-analysis of the association between age (per year increase) and receipt of guideline adherent radiation found a negative association between age and adherence (OR 0.981, 95%CI 0.965 – 0.996, P < 0.001, I^2 97%, per year increase) based on inclusion of 6 studies (Figure 8 – 1, Appendix Chapter 4 – 4). There was considerable heterogeneity in this analysis (i.e. $I^2 > 75\%$). The studies included in this meta-analysis had similar settings and similar time periods. Two studies (52, 68) drew patients from a small region and thus had a smaller sample size than the remaining studies which were all population level studies. There was one obvious outlier (37) which reported a positive association between increasing age and adherent radiation. Excluding this study reduced the heterogeneity modestly (OR 0.97, 95%CI 0.96 – 0.97, $I^2 = 70\%$). (Figure 8 – 2, Appendix Chapter 4 – 4)

The receipt of guideline adherent chemotherapy decreased with increasing age (per year) (OR 0.94, 95%CI 0.91 – 0.97, P < 0.001, I^2 98%, per year increase) based on 4 studies. (Figure 8 – 3, Appendix Chapter 4 – 4) The magnitude of effect was larger for the association with chemotherapy compared with radiation. There was considerable heterogeneity in this analysis as well, although each study reported the same direction of effect (i.e. decreased adherence with increasing age). The studies included were similar in setting (the United States and Canada) and study period. One study (57) appeared to drive most of the heterogeneity based on an outlying effect estimate. Excluding this study reduced the heterogeneity (OR 0.93, 95%CI 0.92 – 0.95, I^2

= 52%) (Figure 8 – 4, Appendix Chapter 4 – 4). Summary of the meta-analyses appears in Table 4 – 6.

Table 4-6 Summary of the meta-analyses assesses age (per 1 year increase) and guideline adherent care

Adherence Outcome	Number of Studies	Odds Ratio, Per Year Increase	[95% Conf.	Interval]	Significant Testing	I^2
Radiation	6	0.981	0.965	0.996	P <0.001	97%
Chemotherapy	4	0.938	0.907	0.971	P < 0.001	98%

The results of the narrative synthesis and quantitative analyses were consistent for the two adherence outcomes (adherent radiation and adherent chemotherapy). For both types of analysis, there was a negative association between increasing age and receipt of adherent treatments.

4.5.3.2 Sex or Gender as a potential predictor of guideline adherent care

Sex (the biologic or expressed attributes) and gender (the socially constructed role) were included based on how they were reported in the original published study. For the purposes of this review, these two variables were grouped together. The detailed study results can be found in Appendix Chapter 4 – 3. Of the assessed aspects of guideline adherent care, Staging Colonoscopy, Staging CEA and Surveillance Metastatic Assessment were not assessed in any included study. The narrative synthesis is presented in Table 4 – 7 and includes the number of studies, types of analyses and type of association identified.

Table 4-7 Narrative synthesis of the associations between Sex/Gender and Guideline Adherent Care by number of studies, type of analyses and type of association

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	1	Univariable	No Association
Local Regional Staging	1	Multivariable Analysis	Males more likely to be adherent
Metastatic Disease Assessment	1	Univariable	No Association
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	5	3 of 5 analyses were multivariable	Males more likely to be adherent in 2 of 5 studies (remaining reported no association)
Radiation Therapy	20	16 of 20 analyses were multivariable	Males more likely to be adherent in 6 of 20 studies (remaining reported no association)
Chemotherapy	8	8 of 9 analyses were multivariable (a)	Unclear, Males more likely to be adherent in 3 analyses, Females more likely to be adherent in 2 analyses
Surgery	1	Multivariable Analysis	No Association
Surveillance			
Overall Surveillance	5	4 of 5 analyses were multivariable	Unclear, Males more likely to be adherent in 1 study, Females more likely to be adherent in 2 studies
Colonoscopy	10	5 of 10 were multivariable	Females more likely to be adherent in 1 study (remaining reported no association)
Metastatic Disease Assessment	None		
Clinic Assessment	4	1 of 4 analyses were multivariable	Females more likely to be adherent in 2 studies (remaining reported no association)
Carcinoembryonic Antigen (CEA)	5	3 of 5 analyses were multivariable	Females more likely to be adherent in 2 studies (remaining reported no association)

(a) One study stratified results by Stage II and Stage III disease

As shown in this table, Sex/gender was found to be associated or potentially associated with the following adherence outcomes: Local Regional Staging (1 Study), Overall Treatment (5 Studies), Appropriate Radiation (20 Studies), Colonoscopy Surveillance (10 Studies), CEA Surveillance (5 Studies), and clinic surveillance (4 Studies). The direction of effect differed based on the outcome. Being male was associated with increased adherence to local regional

staging, appropriate radiation, and overall treatment adherence, while being female was associated with increased adherence to colonoscopy surveillance, CEA surveillance and clinic surveillance. No association was found between sex/gender and overall staging (1 study), metastatic disease staging (1 study) and surgery (1 study).

There was an unclear association between sex/gender and adherence to chemotherapy, and adherence to overall surveillance. Eight studies assessed adherence to chemotherapy, with 2 finding females more likely to be adherent (33, 46) based on multivariable analysis of a large cohort of patients (N = 2,231 and N = 14,742). Three studies (56, 57, 61) found males more likely to be adherent based on multivariable analysis of both small (N = 494) (61) and large cohorts (N = 5,388 and N = 30,994). Interestingly, four of the five above studies (33, 46, 56, 57) are from the United States, with overlapping time periods (1994 – 2015) and similar guidelines used (NCCN and NIH). It should be noted that an additional two studies did not find an association between sex/gender and adherence to chemotherapy. (29, 50)

Overall surveillance adherence was found to more likely in females in two large cohort studies which used multivariable analysis (73, 75), and was found to be more likely in males in one other large cohort study using a multivariable analysis. (85) Each of these studies included individuals from the United States, were population based studies, and used similar clinical practice guidelines. Note, two additional small studies found no association between sex/gender and overall surveillance adherence. (77, 86)

Quantitative analysis (meta-analysis) was possible for the following associations with sex/gender: Overall (or combined) treatment adherence, adherent radiation, adherent chemotherapy, overall (or combined) surveillance adherence, colonoscopy surveillance adherence and CEA surveillance adherence. (Table 4 – 8)

Table 4-8: Summary of the Meta-analyses of the associations between sex/gender (male as referent) and adherence outcomes

Adherence Outcome	Number of Studies	Odds Ratio	[95% Conf.	Interval]	Significance Testing	I^2
Combined Treatment	3	0.898	0.681	1.183	P = 0.44	58%
Radiation	15	0.90	0.84	0.97	P < 0.001	74%
Chemotherapy	8	0.957	0.826	1.108	P = 0.55	80%
Combined Surveillance	4	1.116	0.927	1.343	P = 0.24	91%
Surveillance Colonoscopy	5	1.074	0.925	1.247	P = 0.35	51%
Surveillance CEA	3	1.157	1.092	1.226	P < 0.001	0%

Most comparisons showed no relationship with sex, with the exception of receipt of radiation and receipt of surveillance CEA. The Forest plots can be found in Appendix Chapter 4 – 4 (Figures 8 – 5 to 8 – 12). Females sex/gender was associated with a reduced odds of receiving radiation (OR 0.90, 95%CI 0.84 – 0.97, P < 0.001, I^2 74%), whereas it was associated with an increased odds of receiving surveillance CEA (OR 1.157, 95%CI CI 1.092 – 1.226, P < 0.001, I^2 0%). Heterogeneity was substantial (I^2 50% - 75%) or considerable (I^2 > 75%) in all but one of the meta-analyses. This was expected considering the wide range of publication years (2002 – 2021), difference in study settings (North America, Europe, Australia) and study types (single centre, population level).

Only one meta-analysis had low heterogeneity (Surveillance CEA). This analysis relied almost exclusively on one study (weighted 97%) which explains the low heterogeneity in this analysis.

Two of the meta-analyses demonstrated considerable heterogeneity and were explored further. The heterogeneity in the analysis of sex and adherent chemotherapy is challenging to explain. All included studies were multicentred studies, included similar numbers of patients and included patients over similar time periods. The study by Del Vecchio (33) is an outlier in that its effect estimate is much higher than any other study, while the study by Rayson (61) found a much lower effect estimate than any other study (Figure 8 – 7, Appendix Chapter 4 - 2).

Excluding these two studies modestly reduced heterogeneity (OR 0.94, 95%CI 0.81 – 1.1, I^2 = 78%) (Figure 8 – 8, Appendix Chapter 4 – 4).

The heterogeneity identified in the analysis of sex and overall surveillance was also difficult to explain based on study characteristics. All included studies had similar study periods, drew patients from similar settings (the United States), included those >65 years only, and had the same definition of "overall surveillance". One study (88) reported a different direction of effect. Excluding this study from the meta-analysis does reduce the heterogeneity considerably (OR 1.26, 95%CI 1.17 – 1.34, I^2 = 33%). (Figure 8 – 10, Appendix Chapter 4 – 4) The reasons for this study being an outlier isn't clear based on study population, outcome definition or type of analysis.

The meta-analyses found similar results to the narrative syntheses in the assessment of adherence to radiation (females less likely) and adherence to surveillance CEA (females more likely). Interestingly, the narrative synthesis also found females less likely to be adherent to overall treatment and more likely to be adherence to surveillance colonoscopy. In both cases, the meta-analysis did not identify a statistically significant association, but the direction of effect was the same.

4.5.3.3 Ethnicity as a potential predictor of guideline adherent care

All identified studies were from the United States. Ethnicity was categorized in several ways. Including as a binary variable (white vs. non-white, n = 2 studies; black vs. white, n = 3 studies) or as a categorical variable with at least 3 categories (white vs. black vs. other, n = 8 study; Asian Pacific Islander vs. Black vs. other, n = 2 studies; Black vs. Hispanic vs. White, n = 7 studies; Black vs. White vs. Hispanic vs. Asian, n = 2 studies; White vs. Black vs. Asian vs.

Other, n = 1 study; White vs. Black vs. Asian vs. Other, n = 1 study; White vs. Black vs. Hispanic vs. Other, n = 8 studies). Detailed study results are presented in Appendix Chapter 4 – 3.A summary of the reported association between ethnicity and adherence outcomes from the narrative synthesis can be found Table 4 - 9.

Black ethnicity was reported to be associated with worse adherence to Chemotherapy (7 studies), Surgery (2 Studies), Overall Surveillance (4 Studies), Colonoscopy Surveillance (7 Studies), Clinic Assessment (2 Studies) and CEA Surveillance (4 Studies). There was no reported association between ethnicity and Overall Staging (1 Study), Metastatic Staging (1 Study), and Overall treatment (2 Studies). The only unclear association was with appropriate radiation (18 Studies). Of all the studies assessing this association, only one found "Black" individuals more likely than "white" individuals to receive appropriate radiation (37). This was a large cohort study (N = 4961) of individuals from the United States treated between 1988 – 2006. This study also found that "Asian" and "Hispanics" were less likely to receive appropriate radiation than "Black" or "White" individuals. Contradicting these findings were five studies (35, 40, 58, 66, 71) which found "Black" individuals to be less likely to receive appropriate radiation. Each of these were large population based studies (N = 2,716 to N = 68,182), also from the United States and over the same treatment period.

Table 4-9 The Narrative synthesis of the associations between ethnicity and outcomes, reported by number of studies, type of analysis and type of association

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	1	Univariable	No Association
Local Regional Staging	None		
Metastatic Disease Assessment	1	Univariable	No Association
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	2	Univariable	No Association in 2 of 2 studies
Radiation Therapy	18 (a)	14 of 19 analyses were multivariable	Unclear Association, White ethnicity more adherent in 4 studies (compare with Black +/- Asian +/- Hispanic), Black and Asian more adherent in 1 study (compared with White), Hispanic and Asian more adherent in 1 study (compared with White and Black) (remaining 13 studies reported no association)
Chemotherapy	7 (a)	9 o 9 analyses were multivariable	Black ethnicity associated with less adherence in 3 analyses (remaining reported no association)
Surgery	2 (a)	3 analyses were multivariable)	Black ethnicity associated with less adherence in all 3 analyses
Surveillance			
Overall Surveillance	4	4 of 4 analyses were multivariable	Black ethnicity associated with less adherence in 2 analyses (remaining reported no association)
Colonoscopy	7	5 analyses were multivariable	Black ethnicity associated with less adherence in 4 analyses (remaining reported no association)
Metastatic Disease Assessment	None		
Clinic Assessment	2	1 analysis was multivariable	Black ethnicity associated with less adherence in 2 analyses
Carcinoembryonic Antigen (CEA)	4	2 analyses were multivariable	Black ethnicity associated with less adherence in 2 analyses

(a) Studies reported stratified analysis by (1) Age > vs < 65; (2) Stage II vs. Stage III disease
(b) Study reported two types of adherent surgery

Quantitative analysis (meta-analysis) was possible to assess the association between ethnicity and the following outcomes: Adherent Radiation, Adherent Chemotherapy, Overall Surveillance Adherence, Colonoscopy Surveillance Adherence, and CEA Surveillance Adherence. (Appendix Chapter 4 – 4, Figures 8 – 13 to 8 – 21) In each case, comparison between black ethnicity and white ethnicity (referent variable) was possible. Hispanic ethnicity vs. white ethnicity (referent variable) comparison was possible in most outcomes, except CEA surveillance. Meta-analysis of other ethnicity groups could not be completed due to lack of pertinent data. A summary of the results of each meta-analysis can be found in Table 4 – 10.

Table 4-10 Summary of Meta-analyses of ethnicity and the association with outcomes

Outcome	Number of Studies	Odds Ratio	[95% Conf.	Interval]	Significant Testing	I^2
Black vs. White (referent)						
Adherent Radiation	12 (13 analyses) (a)	0.84	0.78	0.91	< 0.001	49%
Adherent Chemotherapy	6 (8 analyses) (a)	0.8	0.7	0.92	0.002	42%
Overall Surveillance	3	0.65	0.5	0.84	0.03	70%
Colonoscopy Surveillance	4	0.75	0.69	0.82	< 0.001	0%
CEA Surveillance	2	0.76	0.67	0.86	< 0.001	0%
Hispanic vs. White (referent)						
Adherent Radiation	7 (8 analyses) (a)	0.94	0.86	1.04	0.25	39%
Adherent Chemotherapy	4 (6 analyses) (a)	1.04	0.93	1.16	0.49	0%
Overall Surveillance	3	1.02	0.84	1.23	0.85	53%
Colonoscopy Surveillance	2	1.01	0.91	1.11	0.91	0%

(a) Several studies reported multiple analyses (i.e. age < vs >= 65; Stage II vs. Stage III), each of which were included in the meta-analysis.

All meta-analyses identified black ethnicity to be negatively associated guideline adherence compared to white ethnicity, whereas Hispanic ethnicity was not associated with adherence (when compared to white ethnicity). An important potential source of heterogeneity within the meta-analyses was the variability in ethnicity grouping. Although white ethnicity was the reference group for each of the multivariable analyses, many studies included other ethnicity groups: “other”, n = 2 studies; Hispanic, n = 2 studies; Hispanic vs. Other vs. Asian Pacific

Islander, n = 1 study; Hispanic vs. Other, n = 3 studies. Although the comparison include in the meta-analysis was Black vs. White, having such variability in the other included groups, implies a potentially very different study population. In addition, the results included in the meta-analyses were drawn from multivariable models which included these other categories. This difference in statistical models may also contribute to the heterogeneity.

Comparing the narrative synthesis and the meta-analyses found general agreement. All meta-analyses identified a negative association between black ethnicity (compared to white ethnicity) and adherence, which was similar to most of the narrative synthesis. The exception being the that the narrative synthesis identified an unclear association between black ethnicity and adherent radiation while the meta-analysis demonstrated a negative association between black ethnicity and adherent radiation.

4.5.3.4 Socioeconomic Status as a potential predictor of guideline adherent care

Socioeconomic Status was reported in several ways, including in tertiles ("low" vs. "medium" vs. "high"), quartiles (Q1 – Q4), quintiles (Q1 – Q5), binary ("low" vs. "high") or median income (with interquartile ranges). One study used a measure of "disadvantage" (26), while the rest used household income as the unit of measure. The detailed study results can be found in Appendix Chapter 4 – 3.

The narrative synthesis of the association between socioeconomic status and nine adherence outcomes was possible (Table 4 – 11). This included adherence to metastatic staging, staging colonoscopy, overall treatment, radiation, chemotherapy, overall surveillance, colonoscopy surveillance, CEA surveillance and clinic surveillance. No studies assessed adherence to overall staging, local regional staging, CEA staging, surgery, or surveillance for

metastatic disease. Of the available adherence outcomes, 5 were found to have an association or potential association with socioeconomic status, including Overall Treatment (2 studies), Radiation (12 studies, 13 analyses), Chemotherapy (3 studies, 6 analyses), surveillance colonoscopy (5 studies) and surveillance CEA (2 studies). In all cases, higher socioeconomic status was associated with increasing adherence to guideline recommended care. In 4 of the assessed outcomes, no association was reported with socioeconomic status. These included metastatic staging (1 study), staging colonoscopy (1 study), overall surveillance (1 study), clinic surveillance (1 study). Detailed study results can be found in Appendix Chapter 4 – 3.

Table 4-11: Summary of the narrative synthesis of the associations between socioeconomic status and outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	None		
Metastatic Disease Assessment	1	Multivariable	No Association with socioeconomic status
Colonoscopy	1	Multivariable	No Association with socioeconomic status
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	2	1 of 2 were multivariable	Increased Socioeconomic Status associated with increased adherence
Radiation Therapy	12 (13 analyses)	9 of 13 were multivariable	3 of 13 analyses reported an association between increased socioeconomic status and increased adherence (9 of 13 reported no association)
Chemotherapy	3 (6 analyses)	6 of 6 were multivariable	2 of 6 analyses reported an association between increased socioeconomic status and increased adherence (4 of 6 reported no association)
Surgery	None		
Surveillance			
Overall Surveillance	1	Multivariable	No Association with socioeconomic status
Colonoscopy	5	4 of 5 multivariable	5 of 5 studies reported Increased Socioeconomic Status associated with increased adherence
Metastatic Disease Assessment	None		
Clinic Assessment	1	Multivariable	No Association with socioeconomic status
Carcinoembryonic Antigen (CEA)	2	1 of 2 were multivariable	1 Study (univariable analysis) reported increased socioeconomic status associated with increased adherence (1 study reported no association)

Meta-analysis was possible to determine the association between socioeconomic status and adherent radiation, and between socioeconomic status and adherent surveillance colonoscopy (Table 4 – 12). Studies assessing adherent radiation reported socioeconomic status

in tertiles (4 analyses), quartiles (4) and quintiles (1). For the meta-analysis, the lowest vs. the highest reported category were compared.

Table 4-12 Summary of the association between Socio Economic Status (lowest reported vs. highest reported group as the reference) and outcomes

Outcome	Number of Studies	Odds Ratio	[95% Conf.	Interval]	Significant Testing	I^2
Adherent Radiation	8 (9 analyses)	0.874	0.751	1.02	0.082	85%
Colonoscopy Surveillance	3	0.682	0.465	1	0.05	87%

The pooled analysis demonstrated a trend towards an association between lower socioeconomic status and lower adherence to radiation (OR 0.874, 95%CI 0.751 – 1.02, I^2 85%, P = 0.082) (Figure 8 – 22, Appendix Chapter 4 – 4). This analysis demonstrated considerable heterogeneity. There is one clear outlier (35) which reports a positive association between lower SES and adherence to radiation. All other included studies either report lower adherence in those with lower SES, or no association. The outlying study by Haas et al. is a population based study from the United States. Interestingly, the Haas study uses a similar source as three other population based studies (37, 66, 72) yet reported a different direction of effect. Repeating the meta-analysis but excluding this outlying study reduced the heterogeneity. (OR 0.78, 95%CI 0.69 – 0.89, I^2 = 55%) (Figure 8 – 23, Appendix Chapter 4 – 4)

Meta-analysis found an association between receipt of guideline adherent colonoscopy and socioeconomic status, with those in the low group less likely to be adherent (OR 0.682, 95%CI 0.465 – 1.00, I^2 87%, P = 0.05). (Figure 8 – 24, Appendix Chapter 4 - 4). The analysis of socio-economic status and receipt of adherent surveillance colonoscopy had considerable heterogeneity, primarily driven by one study. (82) Each included study did report the same direction of effect (lower SES was associated with less adherence). All studies included similar patient populations and were multicentred. Of the three studies two used tertiles (High vs. mid

vs. low) and one used a dichotomous categorization (high vs. low). The outlying study, Sisler et al (82), drew patients from Canada and a more contemporaneous period, whereas the other two were from the United States and from an older period (73, 78). Removing the outlying study reduced heterogeneity of the results (OR 0.88, 95%CI 0.75 – 1.03, I^2 = 54%). (Figure 8 – 25, Appendix Chapter 4 – 4)

The narrative synthesis and the quantitative analyses were similar. Although the meta-analysis for the association between SES and adherent radiation did not reach statistical significance, there was a trend towards an association in the same direction as the narrative synthesis with reduced adherence in those with lower SES. The narrative synthesis and quantitative assessments did provide the same conclusion between SES and colonoscopy surveillance, in that there was a negative association between lower SES and adherence.

4.5.3.5 Geographic Location as a potential predictor of guideline adherence care

Geographic location was assessed in two ways. The first was by specific geographic region, such as county, city, or larger region, the second was by type of residence categorized as rural vs. urban or similar. The detailed study results for both can be found in Appendix Chapter 4 – 3.

Geographic Region

Narrative synthesis was possible to determine the association between geographic region and a total of 9 adherence outcomes (Table 4 – 13). Most of the available adherence outcomes were associated with a specific geographic region, including adherence to metastatic staging (1 Study), colonoscopy staging (2 Studies), CEA staging (1 Study), overall treatment (1 Study), overall surveillance (1 Study), surveillance colonoscopy (4 Studies), surveillance clinic (1 Study) and surveillance CEA (1 Study). Only local regional staging (1 Study) was not associated with

geographic region. These adherence outcomes were evaluated in few studies (between 1 and 4 studies per outcome), and generally only included a univariable analysis, thus limiting the strength of the analysis. In addition, the results of these studies are likely less generalizable due to the very specific areas being assessed.

Table 4-13 Summary of the narrative synthesis of the association between geographic region and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	1	Univariable	No Association
Metastatic Disease Assessment	1	Univariable	Associated with geographic region
Colonoscopy	2	Univariable	Associated with geographic region
Carcinoembryonic Antigen (CEA)	1	Univariable	Associated with geographic region
Treatments			
Overall Treatment	1	Univariable	Associated with geographic region
Radiation Therapy	None		
Chemotherapy	None		
Surgery	None		
Surveillance			
Overall Surveillance	1	Univariable	Associated with geographic region
Colonoscopy	4	2 of 4 multivariable	2 of 4 reported an association
Metastatic Disease Assessment	None		
Clinic Assessment	1	Univariable	Associated with geographic region
Carcinoembryonic Antigen (CEA)	2	1 of 2 multivariable	2 of 2 reported an association

Rurality

The association between rurality and nine adherence outcomes were identified. Unlike specific geographic region, rurality (or remoteness) was not associated with adherence outcomes for most of the adherence outcomes using narrative synthesis (Table 4 – 14). Of the 8 adherence outcomes identified, only 2 were found to be potentially associated with rurality, including adherent radiation and adherent chemotherapy. For radiation adherence, two studies (39, 57) found those in a metropolitan setting (vs. rural or urban) were negatively associated with

adherent radiation. In contrast, for chemotherapy adherence, a less rural setting was positively associated with adherence, based on the results of a single study only. (61)

Table 4-14 Summary of the narrative syntehsis of the associations between rurality (or remoteness) and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	None		
Metastatic Disease Assessment	1	Multivariable	No Association
Colonoscopy	1	Multivariable	No Association
Carcinoembryonic Antigen (CEA)	1	Multivariable	No Association
Treatments			
Overall Treatment	2	1 of 2 Multivariable	No association
Radiation Therapy	6	3 of 6 Multivariable	Metro/Urban less likely to receive adherent radiation in 2 studies (1 multivariable); 4 studies found no association.
Chemotherapy	5 studies (6 analyses)	4 of 6 Multivariable Analyses	Urban more likely to receive adherent chemotherapy (1 of 6 analyses)
Surgery	None		
Surveillance			
Overall Surveillance	1	Univariable	No Association
Colonoscopy	1	Multivariable	No Association
Metastatic Disease Assessment	None		
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	None		

Meta-analyses could not be completed to assess the associations between rurality/remoteness and adherence outcomes, nor could it be completed for the associations between geographic region and adherence outcomes. For rurality, only radiation and chemotherapy adherence had more than 1 multivariable analysis completed, and in each case the exposures were categorized inconsistently (i.e. rural vs. urban, inner urban vs outer urban vs. rural vs. remote, rural vs. urban vs. metropolitan). For geographic region, each study assessed

very specific geographic locations (i.e. regions in France or within the Canadian Province of Manitoba) and thus could not be combined.

4.5.3.6 Education as a potential predictor of guideline adherent care

The detailed study results of publications assessing education as a predictor are available in Appendix Chapter 4 - 3. The associations between education and 8 adherence outcomes were included in a narrative synthesis (Table 4 – 15). There were 5 adherence outcomes positively associated with higher levels of education. These outcomes included local regional staging (1 study), metastatic disease staging (1 study), adherent radiation (5 studies, 1 reporting an association), colonoscopy surveillance (3 studies, 2 reporting an association) and CEA surveillance (1 study). There were no association between education and colonoscopy staging (1 study) or overall surveillance (1 study). In both instances, only a single study reporting an univariable analysis was identified.

Table 4-15 Summary of the narrative synthesis of the association between education and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	1	Univariable	Adherence associated with mid/highly educated
Metastatic Disease Assessment	1	Univariable	Adherence associated with mid/highly educated
Colonoscopy	1	Univariable	No Association
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	None		
Radiation Therapy	5	3 of 5 multivariable analysis	1 of 5 studies showed adherence with higher education
Chemotherapy	None		
Surgery	None		
Surveillance			
Overall Surveillance	1	Univariable	No association
Colonoscopy	3	2 of 3 multivariable	1 of 3 showed adherence with higher education (only on univariable analysis)
Metastatic Disease Assessment	None		
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	1	Univariable	Adherence associated with higher education

There were enough eligible studies to perform a meta-analysis for the association between education and receipt of adherent radiation. The highest reported education level (referent) was compared to the lowest. Three studies were included and the pooled results did not find an association between education level and radiation adherence (OR 0.99, 95%CI 0.79 – 1.23, I^2 91.1%). (Figure 8 – 26, Appendix Chapter 4 - 4) There was considerable heterogeneity in this analysis. Three studies were included, and all had large sample sizes. Two were from the United States (66, 72), while one was from the Netherlands (63). The two American studies reported different directions of effect, and drew patients from different periods (2004 – 2012 vs.

2010 – 2015). The study from Sineshaw et al. reported lower adherence with decreased education, while the other two reported no association. Excluding the outlying study (Sineshaw et al.) resulted in reducing the heterogeneity to 0% (OR 1.09, 95%CI 0.99 – 1.21, $I^2 = 0\%$). (Figure 8 – 27, Appendix Chapter 4 – 4).

Comparing the narrative synthesis results with the meta-analysis showed a similar finding, in that education was likely not associated with adherence to radiation. The narrative synthesis identified only one paper (of 5) reporting an association between education and adherent radiation. The meta-analysis ultimately found no association.

4.5.3.7 Multidisciplinary Care as a potential predictor of guideline adherent care

The association between multidisciplinary care and adherence outcomes, based on the narrative synthesis, is summarized in Table 4-16, with detailed study results found in Appendix Chapter 4 – 3. Multidisciplinary Care refers to the use of a multidisciplinary clinic (1 study), multidisciplinary tumor group discussion (4 studies) or introduction of a multidisciplinary care pathway (1 study). A total of 4 adherence outcomes were positively associated with multidisciplinary care including local regional staging (2 studies, both reporting an association), metastatic disease staging (3 studies, 2 reporting an association), overall treatment (1 study) and receipt of radiation (4 studies, 2 reporting an association). Three outcomes were not associated with multidisciplinary care including, including CEA staging (1 study), adherent chemotherapy (1 study) and appropriate surgery (1 study). Only two multivariable analyses were identified assessing any of the adherence outcomes and multidisciplinary care, which included the overall treatment adherence (an association was identified) and receipt of adherent radiation therapy (no association identified).

Table 4-16 Summary of narrative synthesis of the associations between multidisciplinary care and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	2	Univariable Only	Increased adherence with Multidisciplinary Care (2 of 2 Studies)
Metastatic Disease Assessment	3	Univariable Only	Increased adherence with Multidisciplinary Care (2 of 3 Studies)
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	1	Univariable Only	Not associated
Treatments			
Overall Treatment	1	Multivariable	Increased adherence with multidisciplinary care
Radiation Therapy	4	1 of 4 multivariable	Increased adherence with multidisciplinary care (2 of 4 studies, all univariable)
Chemotherapy	1	Univariable Only	Not associated
Surgery	1	Univariable Only	Not associated
Surveillance			
Overall Surveillance			
Colonoscopy	None		
Metastatic Disease Assessment	None		
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	None		

Due to the low number of publications with multivariable analyses reported, a quantitative analysis was not possible.

4.5.3.8 Patient Co-morbidity as a predictor of guideline adherent care

The association between comorbidity and adherence outcomes, based on the narrative synthesis, are summarized in Table 4 – 17, with detailed study results available in Appendix Chapter 4 – 3. No study assessed the association between comorbidity with any of the staging outcomes (overall, colonoscopy, local-regional, metastatic, CEA), or the association with surgery adherence. The rest of the reported outcomes all demonstrated a negative association with increasing comorbidities. The most common method to describe comorbidity was Charlson Co-morbidity Score (CCS), or one of its variants (i.e. the Charlson – Deyo Score)). Other studies categorized comorbidities in other ways, including: "High" vs. "Low" (3 Studies); "High" vs. "Moderate" vs. "Low" (1 Study); Number of Comorbidities (1 vs. 2 vs. 3+) (2 Studies); Extent of Functional Disability (2 Studies); Diabetes Status (1 Study).

Table 4-17 Summary of the narrative synthesis of the associations between co-morbidities and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	None		
Metastatic Disease Assessment	None		
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	2	1 of 2 Multivariable	Less adherence with higher score (2 of 2 Studies)
Radiation Therapy	17	16 of 17 Multivariable	Less adherence with higher score (10 of 17 Studies)
Chemotherapy	11	11 of 11 Multivariable	Less adherence with higher score (7 of 11 Studies)
Surgery	None		
Surveillance			
Overall Surveillance	2	2 of 2 Multivariable	Less adherence with higher score (2 of 2 Studies)
Colonoscopy	5	3 of 5 Multivariable	Less adherence with higher score (3 of 5)
Metastatic Disease Assessment	4	4 of 4 Multivariable	More adherent with higher score (1 of 4 Studies)
Clinic Assessment	2	Univariable Only	Less adherence with higher score (2 of 2 Studies)
Carcinoembryonic Antigen (CEA)	3	1 of 3 multivariable	Less adherence with higher score (1 of 3 studies)

Meta-analysis was possible for two adherence outcomes, adherent radiation and adherent chemotherapy. For both outcomes, meta-analysis of comorbidity score of 1 vs. 0 and comorbidity score of 2+ vs. 0 was completed. For the association between comorbidity score and chemotherapy, a meta-analysis of comorbidity score of 3+ vs. 0 was able to be completed. These categories were selected as they were the ones which satisfied the requirement for meta-analysis (i.e. at least 2 studies performing a multivariable analysis). One study assessed the association

between CCS 3+ vs. CCS 0 for receipt of radiation using a multivariable analysis. (54) The Forest plots appears in Appendix Chapter 4 – 4 (Figures 8 – 28 to Figure 8 – 34). A summary of the pooled results can be found in Table 4 – 18.

Table 4-18: Summary of Pooled estimates of the association between comorbidity score and outcomes

Outcome	Number of Studies	Odds Ratio	[95% Conf.	Interval]	Significant Testing	I^2
Adherent Radiation						
CCS 1 vs. 0 (Ref)	13	0.90	0.84	0.96	P = 0.002	45%
CCS 2+ vs 0 (Ref)	11	0.65	0.55	0.77	P = 0.045	78%
Adherent Chemotherapy						
CCS 1 vs. 0 (Ref)	9	0.88	0.798	0.97	P = 0.01	40%
CCS 2+ vs. 0 (Ref)	5	0.75	0.65	0.86	P < 0.001	0%
CCS 3+ vs. 0 (Ref)	2 (4 analyses)	0.38	0.27	0.53	P < 0.001	0%

CCS Charlson Comorbidity Score

In each of the meta-analyses, higher comorbidity score was negatively associated with receiving adherent treatment. A dose-response was observed in that the magnitude of effect was larger as the comorbidity score group increased (as compared with CCS 0 as the reference group). The analysis of co-morbidity score (2+ vs. 0) and adherent radiation demonstrated considerable heterogeneity (I^2 = 78%). All studies did report the same direction of effect, in which increased co-morbidity was associated with less adherence to radiation. The Forest plot demonstrated two obvious outliers (25, 51) which reported a much lower odds of receiving adherent radiation with a higher co-morbidity score. Both studies were from Northern Europe, whereas all other studies were from the United States (9 studies) or Southern Europe (1 study). Excluding these two from the meta-analysis substantially reduces the heterogeneity (OR 0.71, 95%CI 0.67 – 0.76, I^2 = 4%). (Figure 8 – 31, Appendix Chapter 4 – 4).

The results of the narrative synthesis and Meta-analyses were consistent in demonstrating a negative association between increasing co-morbidity score and the available adherence outcomes.

4.5.3.9 Marital Status as a predictor of guideline adherent care

Narrative synthesis of the association between marital status and the following adherence outcomes was possible: Overall treatment adherence (1 study); adherent radiation (3 studies, 4 analyses); adherent chemotherapy (3 studies, 5 analyses); overall surveillance adherence (1 study); adherent colonoscopy (3 studies); adherent metastatic surveillance (1 study) (Table 4 – 19). No studies tested the association between any of the staging adherence outcomes and marital status. Being married was positively associated with overall treatment adherence, adherent radiation, and adherent colonoscopy surveillance in at least one included study. No association was reported in any of the studies assessing marital status and adherent chemotherapy, overall surveillance or metastatic disease surveillance.

Table 4-19 Summary of the narrative synthesis of the associations between Marital status and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	None		
Metastatic Disease Assessment	None		
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	1	Multivariable	Married associated with increased adherence
Radiation Therapy	3 (4 analyses)	All multivariable	Associated with marital status in 1 of 4 analyses
Chemotherapy	3 (5 analyses)	All multivariable	No association in 5 of 5 analyses
Surgery	None		
Surveillance			
Overall Surveillance	1	Multivariable	No association
Colonoscopy	3	All multivariable	Married associated with increased adherence in 1 of 3 studies
Metastatic Disease Assessment	1	Multivariable	No association
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	None		

The associations with adherent radiation and with adherent chemotherapy were suitable for meta-analysis (Table 4 -20). In both cases, married status was included as the referent value, while unmarried was included as the exposure. In both adherent radiation (OR 0.81, 95%CI 0.61 – 1.09, $I^2 = 48\%$, 4 analyses) and adherent chemotherapy (OR 0.94, 95%CI 0.78 – 1.14, $I^2 = 1\%$, 5 analyses), no association was found. (Figure 8 – 33 and Figure 8 – 34, Appendix Chapter 4 – 4)

Table 4-20 Summary of meta-analyses testing the association between marital status (unmarried vs. married as the referent) and adherence outcomes

Outcome	Number of Studies	Odds Ratio	[95% Conf.	Interval]	Significant Testing	I^2
Adherent Radiation	3 (4 analyses)	0.813	0.608	1.089	0.165	48%
Adherent Chemotherapy	3 (5 analyses)	0.942	0.776	1.144	0.548	1%

The narrative synthesis and meta-analysis were inconsistent in their findings. The narrative synthesis identified a potential positive association between being married and adherence to radiation, while the meta-analysis did not identify an association. The narrative synthesis results were based on a single study's result, while 2 other studies (3 analyses) did not report an association. Both narrative synthesis and quantitative assessments found no association between chemotherapy and marriage status.

4.5.3.10 Insurance Type as a predictor of guideline adherent care

Narrative synthesis of the association between insurance type and adherence outcomes was possible for Staging Colonoscopy (1 Study), Staging CEA (1 Study), Overall Treatment Adherence (2 studies), Adherent Radiation (7 Studies), and Adherent Chemotherapy (3 studies, 4 analyses). Insurance was typically categorized as "Private" vs. "Public", "Private" vs. government provided vs. uninsured, or government provided vs. not. Insurance type was associated with adherent care in most assessed outcomes (Colonoscopy, 1 study; CEA, 1 Study; Radiation, 5 of 7 studies; Chemotherapy, 3 studies), with the exception being Overall Treatment. In the studies reporting an association, private insurance (vs. public, non insured and/or government provided) was consistently found to be positively associated with adherence. For overall treatment adherence, private vs. public insurance (1 study, univariable analysis, P = 0.51) and Veteran-Affairs insurance vs non-Veteran-Affairs insurance (1 study, univariable analysis, P

= 1.0) were compared and no association was reported. (Table 4 – 21, detailed study results Appendix Chapter 4 - 3)

Table 4-21 Summary of narrative synthesis of the associations between Health Insurance Type and Adherence Outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	None		
Metastatic Disease Assessment	None		
Colonoscopy	1	Multivariable	Public Insurance associated with lower adherence
Carcinoembryonic Antigen (CEA)	1	Multivariable	Public Insurance associated with lower adherence
Treatments			
Overall Treatment	2	Univariable Only	No association
Radiation Therapy	7	5 of 7 multivariable	Insurance Type associated with adherence in 6 of 7 studies
Chemotherapy	3 (4 analyses)	All multivariable	Insurance Type associated with adherence in 4 of 4 analyses
Surgery	None		
Surveillance			
Overall Surveillance	None		
Colonoscopy	None		
Metastatic Disease Assessment	None		
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	None		

Of the identified adherence outcomes, only adherent radiation was suitable for meta-analysis. In this meta-analysis, no insurance was compared to private insurance (referent). This analysis did not demonstrate an association between the exposure and outcome. (OR 0.875,

95%CI 0.69 – 1.12, I^2 = 71%, 3 Studies, P = 0.282). All three included studies were from the United States and categorized insurance status in the same way (Private vs. Medicaid vs. Medicare vs. Uninsured). Two of the studies (66, 72) were larger population based studies, had similar effect estimates and were much more precise from the third study.(68) This third study from Wong et al. was smaller, had an imprecise finding and reported a much different effect estimate than the other two. The Forest plot can be found in Figure 8 – 35, Appendix Chapter 4 – 4.

4.5.3.11 Hospital Volume as a potential predictor of guideline adherent care

A summary of the association between hospital volume and adherence outcomes, based on narrative synthesis, can be found in Table 4 – 22 (detailed study results in Appendix Chapter 4 – 3). Hospital volume was capture either as a continuous variable (per 1 case/year increase) or as a categorical variable. When assessed as a categorical variable, the threshold for high vs. mid vs. low (or high vs. low) was inconsistent. High volume was categorized as (1) >80 cases per year, (2) > 40 cases per year or (3) > 30 cases per year. Three staging outcomes and four treatment outcomes were evaluated, while no surveillance outcomes were available. A positive association was identified between higher volume and adherent local regional staging (in 1 of 2 studies assessing this outcomes), adherent overall treatment (1 study) and adherent surgery (1 study). No association was reported between hospital volume and adherent metastatic disease assessment (1 study, 2 analyses) or adherent staging colonoscopy (1 study). Notably, an unclear association between hospital volume and both adherent radiation and adherent chemotherapy was found. Seven studies reported the analysis of the association between hospital volume and adherent radiation. Four of these studies found a positive association between higher volume

and adherence to radiation (39, 55, 57, 66), 1 study found a positive association between *lower volume* and adherence to radiation (25), and 2 studies did not find an association (16, 51). Of the 4 studies that found higher volume associated with radiation adherence, 3 used population based data from the United States (39, 57, 66) , and included patients with overlapping years of diagnosis or treatment (2006 – 2011, 1992 – 2009, 2005 – 2010). The single study that found an association between lower volume and adherence was from the Netherlands and included patients from 2008 – 2010 only. (25) In the studies assessing adherence to chemotherapy, 2 studies found a positive association between higher volume and adherence (46, 55), while one found a positive association between lower volume and adherence. (57). Interestingly, two of these studies were large population level studies from the United States, from the same time period (2006 – 2011), but found different direction of the association.

Table 4-22: Summary of the narrative synthesis of the association between hospital volumes and adherence outcomes.

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	2	1 of 2 multivariable	Higher Volume associated with higher adherence in 1 (multivariable) of 2 studies
Metastatic Disease Assessment	1 study (2 analyses)	Multivariable	No Association
Colonoscopy	1	Multivariable	No Association
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	1	Univariable	Higher volume associated with higher adherence
Radiation Therapy	7 studies	6 of 7 multivariable	Unclear, higher adherence with higher volume in 4 studies, higher adherence with lower volume in 1 study, no association in 2 studies
Chemotherapy	4	3 of 4 multivariable	Unclear, higher adherence with higher volume in 2 studies, higher adherence with lower volume in 1 study, no association in 1 study
Surgery	1	Multivariable	Higher quality associated with higher volume
Surveillance			
Overall Surveillance	None		
Colonoscopy	None		
Metastatic Disease Assessment	None		
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	None		

Unfortunately, the study results could not be combined in a meta-analysis, due to inconsistency in how the exposure variable was categorized. Two studies used a continuous variable (per case/year), one study reported volume as a dichotomous variable (High 40+/year vs. low <40), and 4 studies reported volume as a categorical variable with different thresholds/cutoffs.

4.5.3.12 Hospital Type as a potential predictor of guideline adherent care

Hospital type was captured in a variety of ways, typically based on either the available resources (i.e. Comprehensive Cancer Hospital, National Cancer Institute designated hospital), associations with training programs or universities, or hospital size. A summary of the associations between hospital type and adherence outcomes, based on narrative synthesis, can be found in Table 4 – 23 (detailed study results are available in Appendix Chapter 4 – 3). There was an association between higher resourced hospitals and adherence to local regional staging (2 studies, 4 analyses), metastatic disease assessment (3 studies, 8 analyses), staging CEA (1 study, 3 analyses), overall treatment (2 studies, 4 analyses) and radiation (8 studies). In all cases, hospitals with higher levels of resources (regardless of how it was categorized) were associated with increased adherence. There was no association between hospital type and adherent chemotherapy (4 studies). No surveillance adherence outcomes were assessed. Of the included studies, several provided more than one analyses based on how hospitals were categorized. For instance Charlton et al. (89) separately compared national cancer institute designation vs. not; presence of a residency program vs. not; and medical affiliation vs. not. Similarly, Schroen et al. (45) provided separate analysis of American College of Surgeon approved vs not; and Hospital teaching status.

Table 4-23 Summary of the narrative synthesis of the associations between hospital type and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	2 studies (4 analyses)	All Multivariable	Increased adherence in higher resource hospitals (1 of 2 studies, 3 of 4 analyses)
Metastatic Disease Assessment	3 Studies (8 analyses)	7 of 8 were multivariable analyses	Increased adherence in higher resource hospitals (1 of 8 analyses)
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	1 study (3 analyses)	Multivariable	Increased adherence in higher resource hospitals (3 of 3 analyses)
Treatments			
Overall Treatment	2 studies (4 analyses)	Multivariable Only	Increased adherence in higher resources hospitals (1 of 4 analyses)
Radiation Therapy	8	6 of 8 multivariable	Increased adherence with higher resource hospitals (5 of 8 studies, 4 multivariable analyses)
Chemotherapy	4	Multivariable only	No Association with higher resource hospitals
Surgery	None		
Surveillance			
Overall Surveillance	None		
Colonoscopy	None		
Metastatic Disease Assessment	None		
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	None		

For hospital type, numerous inconsistent hospital classification were used, which precluded meta-analysis.

4.5.3.13 Physician Specialty as a potential predictor of guideline adherent care

The association between physician specialty and adherence outcomes were evaluated in only a limited number of studies, including one staging outcome (metastatic disease assessment), no treatment outcomes and 3 surveillance outcomes (Colonoscopy, Metastatic Disease

Assessment, CEA). A summary of the narrative synthesis is found in Table 4 – 24, with detailed study results in Appendix Chapter 4 – 3. The association between diagnosing physician and adherence to metastatic disease staging was assessed in 1 study. This study compared gastroenterologists to all other specialties (as one group) and found an association between lower adherence and gastroenterology specialty (OR 0.40, 95%CI 0.21 – 0.77). For the surveillance outcomes (surveillance colonoscopy, metastatic disease surveillance and CEA surveillance), physician specialty was determined based on which health care provider was providing the surveillance. In all three of these outcomes, physician specialty was associated with adherence, with specialists (oncologist, surgeon) being positively associated with adherence when compared with primary care physicians.

Table 4-24 Summary of the narrative synthesis of the associations between Physician Specialty and adherence outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	None		
Metastatic Disease Assessment	1	Multivariable	Physician Specialty (gastroenterologist vs. all others) associated with adherence
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	None		
Radiation Therapy	None		
Chemotherapy	None		
Surgery	None		
Surveillance			
Overall Surveillance	None		
Colonoscopy	4	3 of 4 multivariable	Physician Specialty associated with adherence in 4 of 4 studies
Metastatic Disease Assessment	3	2 of 3 multivariable	Physician Specialty associated with adherence in 2 of 3 studies
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	2	1 of 2 multivariable	Physician Specialty associated with adherence in 2 of 2 studies

Due to the inconsistency in the physician types being assessed as exposures, meta-analysis was not possible for any of the adherence outcomes.

4.5.3.14 Physician Volume as a potential predictor of guideline adherent care

A number of studies assessed physician volume and outcomes and were included in the narrative synthesis (Table 4 – 25, detailed study results in Appendix Chapter 4 - 3). Despite the intention to include any type of physician (i.e. Medical Oncologist, Radiation Oncologist, Surgeon), the identified studies only included surgeons. Thus all results described below describe the association between surgeon volume and outcomes. Surgeon volume as a predictor was evaluated in 2 staging adherence outcomes (local regional staging and metastatic disease assessment) and 3 treatment adherence outcomes (radiation, chemotherapy, surgery). No surveillance outcomes were evaluated in any of the identified studies. Most of the studies used volume as a continuous variable (per additional case), while two studies (22, 36) dichotomized volume into "high" vs. "low". Of the included studies, most found that higher volume was positively associated with adherence. The exception was adherence to metastatic staging. The study by Comber et al. (16) was a large study from Italy which found that higher surgeon volume was associated with an increase in adherence to abdominal imaging, but a decreased adherence to chest imaging, based on Multivariable analysis. The other study assessing metastatic staging found a positive association between increasing surgeon volume and adherence. Adherence to two of the three treatment outcomes (radiation and high quality surgery) were found to be positively associated with increased surgeon volume, while no association was found between surgeon volume and adherent chemotherapy.

Table 4-25 Summary of the association between Physician Volume and Adherence Outcomes

Outcome	Number of Included Studies	Type of Analysis	Type of Association
Staging Investigations			
Overall Staging	None		
Local Regional Staging	2	1 Multivariable	Higher Volume associated with increased adherence in 2 of 2 studies
Metastatic Disease Assessment	2 (3 analyses)	2 Multivariable	Unclear, 2 analyses found higher volume associated with reduced adherence (Multivariable) and 1 analysis found higher volume associated with increased adherence
Colonoscopy	None		
Carcinoembryonic Antigen (CEA)	None		
Treatments			
Overall Treatment	None		
Radiation Therapy	2	Multivariable only	Higher Volume associated with increased adherence in 2 of 2 studies
Chemotherapy	1	Multivariable only	No association
Surgery	1	Multivariable only	Higher quality surgery associated with increased volume
Surveillance			
Overall Surveillance	None		
Colonoscopy	None		
Metastatic Disease Assessment	None		
Clinic Assessment	None		
Carcinoembryonic Antigen (CEA)	None		

Meta-analysis was not possible to assess surgeon volume, as few outcomes were assessed by more than one study, and in those that did, the classification of the exposure was not consistent enough to perform a meta-analysis.

4.5.3.15 Immigration Status and Employment status as predictors of guideline adherent care

Only a single study assessed the association between immigration status and adherence outcomes. (60) This study found a negative association between being foreign born and overall

treatment adherence, with those born outside of the United States less likely to be guideline adherent (OR 0.35, 95%CI 0.12 – 0.99).

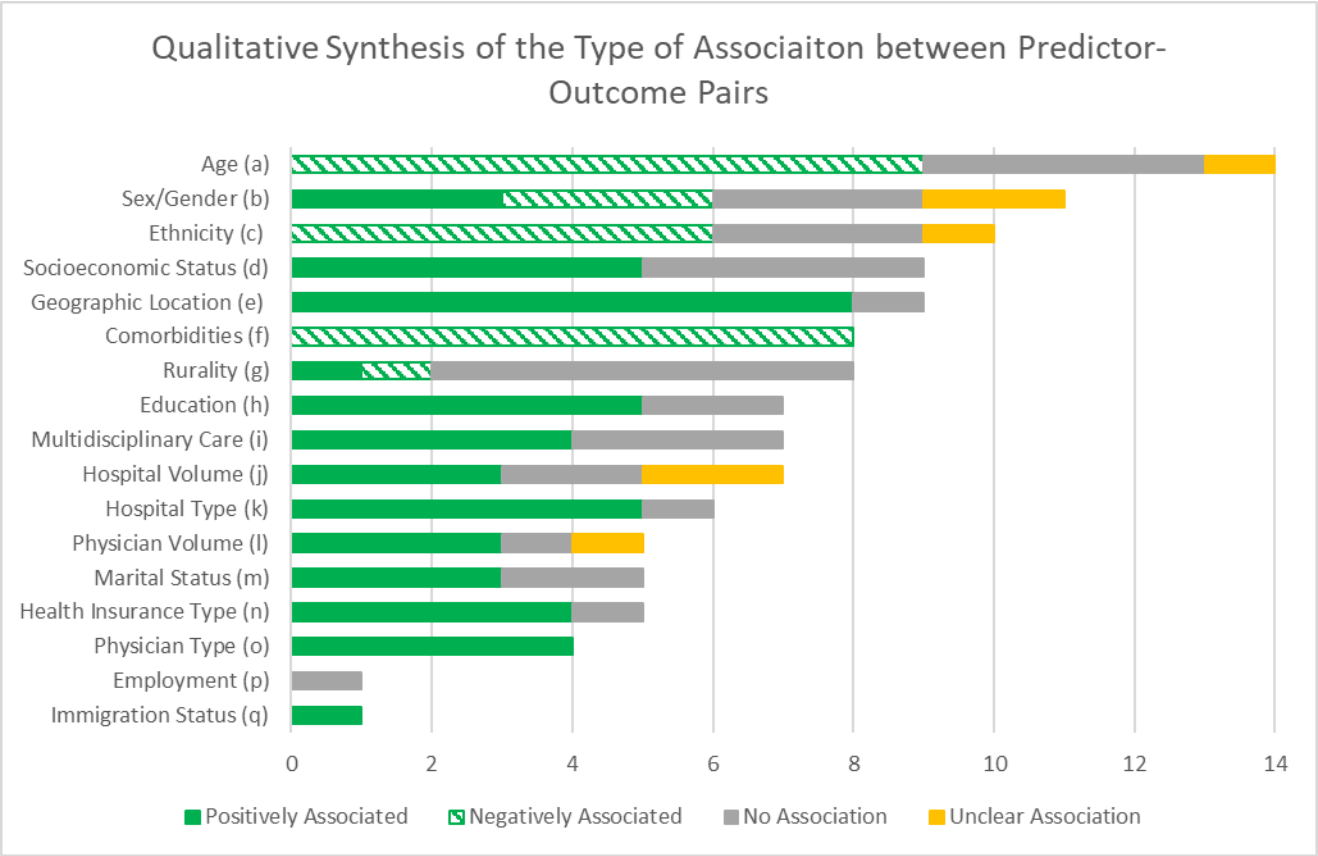
A single study also assessed the association between employment status and adherence outcomes. (74) This study did not find an association between employment status and adherence surveillance colonoscopy (Unemployed OR 0.58, 95%CI 0.3 – 1.12 vs. Employed [ref]).

4.5.4 Summary of Results

4.5.4.1 narrative synthesis Summary

A summary of the type of association between potential barriers or facilitators and aspects of guideline adherent care can be found in Figure 4 - 5. This figure presents the type of association (Associated/potentially associated, not associated, unclear association) between the predictor and the number of guideline adherent care outcomes assessed based on the narrative synthesis methods described in section 4.4.8. A total of 118 predictor-outcome pairs were included in this review. It should be noted that the determination of the type (associated vs. not) and direction of association (positive or negative) was based on the findings of a single study in 52 of the 118 predictor-outcome pairs. Tables 4 – 26 (Staging Adherence Outcomes), 4 – 27 (Treatment Adherence Outcomes), and 4 – 28 (Surveillance Adherence Outcomes) provide a summary of the type of associations based on each phase of treatment and includes the number of unique studies assessing each predictor-outcome pair.

Figure 4-5 Summary of the type of association (positive or negative association, no association, unclear association) between predictors and number of assessed adherence outcomes based on the narrative synthesis



Direction of association with adherence determined based on the following: a) increasing age; (b) female sex/gender; c) black ethnicity; d) increasing socioeconomic status; e) geographic location; f) increasing comorbidity; g) urban location; h) increasing education; i) use of multidisciplinary care; j) increasing hospital volume; k) increasing hospital resources; l) increasing physician volume; m) married status vs. not; n) increasing insurance coverage; o) specialist training; p) increasing employment status; q) non-foreign born

Table 4-26 Type of Association between predictors and Staging Adherence Outcomes, with number of included studies (Based on narrative synthesis)

	Overall Staging	Local Regional	Metastatic	Colonoscopy	CEA
Age (a)	1	1	2	1	1
Sex/Gender (b)	1	1	1		
Ethnicity (c)	1		1		
Socioeconomic Status (d)			1	1	
Geographic Location (e)		1	1	2	1
Comorbidities (f)					
Rurality (g)			1	1	1
Education (h)		1	1	1	
Multidisciplinary Care (i)		2	3		1
Hospital Volume (j)		2	1	1	
Hospital Type (k)		2	3		1
Physician Volume (l)		2	2		
Marital Status (m)					
Health Insurance Type (n)				1	1
Physician Type (o)			1		
Employment (p)					
Immigration Status (q)					
Association Type	Positive	Negative	Unclear	None	

Table 4-27 The association between predictors and treatment adherence outcomes, with number of included studies (Based on narrative synthesis)

	Overall Treatment	Radiation	Chemotherapy	Surgery
Age (a)	6	24	8	1
Ethnicity (c)	2	18	7	2
Sex/Gender (b)	5	20	8	1
Socioeconomic Status (d)		2	12	3
Geographic Location (e)		1		
Comorbidities (f)	2	17	11	
Rurality (g)		2	6	5
Education (h)			5	
Multidisciplinary Care (i)	1	4	1	1
Hospital Volume (j)	1	7	4	1
Hospital Type (k)	2	8	4	
Physician Volume (l)		2	1	1
Marital Status (m)	1	3	3	
Health Insurance Type (n)	2	7	3	
Physician Type (o)				
Employment (p)				
Immigration Status (q)	1			
Association Type	Positive	Negative	Unclear	None

Table 4-28 The association between predictors and Surveillance Adherence Outcomes, with number of included studies (Based on narrative synthesis)

	Overall Surveillance	Colonoscopy	Metastatic	Clinic	CEA
Age (a)	6	11	6	3	5
Sex/Gender (b)	5	10		4	5
Ethnicity (c)	4	7		2	4
Socioeconomic Status (d)	1	5		1	2
Geographic Location (e)	1	4		1	2
Comorbidities (f)	2	5	4	2	3
Rurality (g)	1	1			
Education (h)	1	3			1
Multidisciplinary Care (i)					
Hospital Volume (j)					
Hospital Type (k)					
Physician Volume (l)					
Marital Status (m)	1	3	1		
Health Insurance Type (n)					
Physician Type (o)		4	3		2
Employment (p)		1			
Immigration Status (q)					
Association Type	Positive	Negative	Unclear	None	

The predictors with the most assessed adherence outcomes were non-modifiable, such as Age (14 adherence outcomes assessed), Sex/Gender (11 adherence outcomes), Ethnicity (10 adherence outcomes), Socioeconomic Status (9 adherence outcomes) and comorbidity (8 adherence outcomes). Care provider factors such as hospital volume (7 adherence outcomes), hospital type (7 adherence outcomes), physician volume (5 adherence outcomes), and physician type (4 adherence outcomes) were less available.

Of the available predictor – outcome pairs, a total of 77 were found to demonstrate an association based on narrative synthesis, while 34 predictor-outcome pairs did not demonstrate an association. In general, the direction of association (i.e. positive or negative), if present, was

consistent across each adherence domain. For example, increasing age and increasing co-morbidity score was negatively associated with adherence in all outcomes in which an association was identified. The exception being sex/gender, in which half of the associations were positively associated with female sex/gender and half of the associations were negatively associated with female/sex gender. The other exception was rurality, in which adherent radiation was more likely to occur in more rural settings, while adherent chemotherapy was more likely in urban settings.

There were few conflicting directions of associations reported between predictor-adherence outcome pairs (i.e. "Unclear Associations"), in which at least one study reported a positive association and at least one study reported a negative association between the same predictor-outcome pair. This did occur in 7 of the 117 analyses. The unclear associations included those between age and clinical surveillance, between sex/gender and chemotherapy, between sex/gender and overall surveillance, between ethnicity and appropriate radiation, between physician volume and metastatic, between hospital volume and use of radiation, between hospital volume and use of chemotherapy. These conflicts were discussed in detail in the preceding chapter sections.

Finally, it should be noted that almost than half (120 of 238) of the potential predictor-outcome pairs were not assessed by any study.

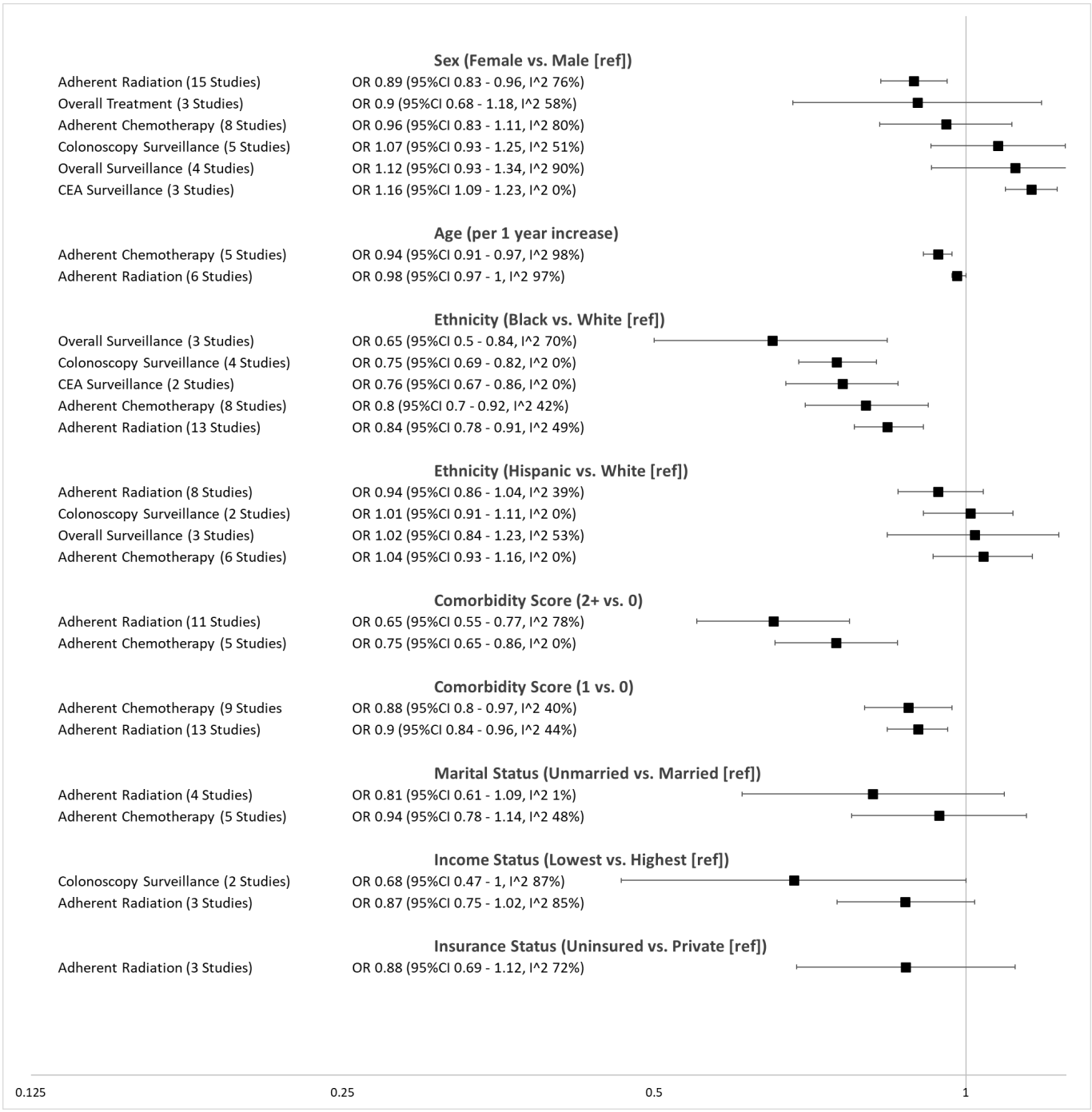
4.5.4.2 Quantitative Analysis Summary

A summary of the meta-analyses can be found in Figure 4 – 6. Of the meta-analyses, 14 demonstrated a significant association between the predictor and adherence outcome.

Generally, the exposure – outcome relationship was consistent across outcomes. For instance, increasing age, or increased co-morbidity score, were associated with decreased adherence in all assessed outcomes. Co-morbidity score also showed a "dose-response" in that those with a higher score (i.e. 2+) had a large magnitude of effect than those with a moderate score (i.e. 1), when compared to those without co-morbidities. The one area of inconsistency in the direction of effect was the associations between sex/gender and outcomes. Being female was associated with a *lower odds* of receiving adherent radiation (OR 0.89, 95%CI 0.83 – 0.96), while having a *higher odds* of CEA surveillance adherence (OR 1.16, 95%CI 1.09 – 1.23). Although not all statistically significant, it is interesting to note that females had a lower odds of adherence to treatment, but higher odds of adherence to surveillance in the other evaluated adherence outcomes.

Another interesting finding was the association between ethnicity and outcomes. Black ethnicity (when compared to white ethnicity) was associated with decreased adherence for all adherence outcomes, while Hispanic ethnicity (compared to white ethnicity) was not associated with any of the adherence outcomes. This contradicts a number of previous studies that have generally identified Hispanic Ethnicity as a risk for receiving poorer quality care or poorer access to care, compared with white ethnicity. (90, 91)

Figure 4-6 Summary of Meta-analyses, by exposure type



4.5.4.3 Heterogeneity within the Quantitative Analyses

Of the 27 included meta-analyses, 8 (30%) had considerable heterogeneity ($I^2 > 75\%$) and 6 (22%) had substantial heterogeneity ($I^2 = 50 - 75\%$). The analyses are organized by type of heterogeneity and are summarized in Table 4 – 29.

Table 4-29 Level of Heterogeneity of included Meta-Analyses

Exposure	Outcome	Effect Estimate and I^2
Considerable Heterogeneity ($I^2 > 75\%$)		
Sex	Adherent Chemotherapy	OR 0.96 (95%CI 0.83 - 1.11, I^2 80%)
Sex	Overall Surveillance	OR 1.12 (95%CI 0.93 - 1.34, I^2 90%)
Age	Adherent Chemotherapy	OR 0.94 (95%CI 0.91 - 0.97, I^2 98%)
Age	Adherent Radiation	OR 0.98 (95%CI 0.97 - 1, I^2 97%)
Co-morbidity Score (2+ vs. 0)	Adherent Radiation	OR 0.65 (95%CI 0.55 - 0.77, I^2 78%)
Income Status	Colonoscopy Surveillance	OR 0.68 (95%CI 0.47 - 1, I^2 87%)
Income Status	Adherent Radiation	OR 0.87 (95%CI 0.75 - 1.02, I^2 85%)
Education Status	Adherent Radiation	OR 0.99 (95%CI 0.79 - 1.23, I^2 91%)
Substantial Heterogeneity (I^2 50 - 75%)		
Sex	Overall Treatment	OR 0.9 (95%CI 0.68 - 1.18, I^2 58%)
Sex	Adherent Radiation	OR 0.9 (95%CI 0.84 – 0.97, I^2 = 74%)
Sex	Surveillance Colonoscopy	OR 1.07 (95%CI 0.93 - 1.25, I^2 51%)
Ethnicity (Black vs. White)	Overall Surveillance	OR 0.65 (95%CI 0.5 - 0.84, I^2 70%)
Ethnicity (Hispanic vs. White)	Overall Surveillance	OR 1.02 (95%CI 0.84 - 1.23, I^2 53%)
Insurance Status	Adherent Radiation	OR 0.88 (95%CI 0.69 - 1.12, I^2 72%)
Moderate or Low Heterogeneity ($I^2 < 50\%$)		
Sex	CEA Surveillance	OR 1.16 (95%CI 1.09 - 1.23, I^2 0%)
Ethnicity (Black vs. White)	Colonoscopy Surveillance	OR 0.75 (95%CI 0.69 - 0.82, I^2 0%)
Ethnicity (Black vs. White)	CEA Surveillance	OR 0.76 (95%CI 0.67 - 0.86, I^2 0%)
Ethnicity (Black vs. White)	Adherent Chemotherapy	OR 0.8 (95%CI 0.7 - 0.92, I^2 42%)
Ethnicity (Black vs. White)	Adherent Radiation	OR 0.84 (95%CI 0.78 - 0.91, I^2 49%)
Ethnicity (Hispanic vs. White)	Adherent Radiation	OR 0.94 (95%CI 0.86 - 1.04, I^2 39%)
Ethnicity (Hispanic vs. White)	Colonoscopy Surveillance	OR 1.01 (95%CI 0.91 - 1.11, I^2 0%)
Ethnicity (Hispanic vs. White)	Adherent Chemotherapy	OR 1.04 (95%CI 0.93 - 1.16, I^2 0%)
Co-morbidity Score (2+ vs. 0)	Adherent Chemotherapy	OR 0.75 (95%CI 0.65 - 0.86, I^2 0%)
Marital Status	Adherent Radiation	OR 0.81 (95%CI 0.61 - 1.09, I^2 1%)
Co-morbidity Score (1+ vs. 0)	Adherent Chemotherapy	OR 0.88 (95%CI 0.8 - 0.97, I^2 40%)
Co-morbidity Score (1+ vs. 0)	Adherent Radiation	OR 0.9 (95%CI 0.84 - 0.96, I^2 44%)
Marital Status	Adherent Chemotherapy	OR 0.94 (95%CI 0.78 - 1.14, I^2 48%)

High levels of heterogeneity within these analyses was expected for two primary reasons. The first and most important, is that the study populations within the included studies were highly variable. For example, in the meta-analysis assessing age and receipt of guideline adherent radiation (Figure 8 – 1, Appendix Chapter 4 – 4), 6 studies were included.(37, 39, 52, 57, 63, 68) Of these studies, two included only patients over age 65 (52, 63), two studies included patients from hospitals in a single municipality (52, 68), four studies included patients from a national databases (37, 39, 57, 63), and the studies drew patients over different time periods (1988 – 2006 vs. 2005 – 2010 vs. 2006 – 2011 vs. 2005 – 2014 vs. 1995 – 2005). These differences resulted in different study populations including differences in the proportion of female patients (range 37% - 44%), mean/median age (range 59 – 73) and cancer stage (Stage III proportion 30 – 80%). Differences in study populations was a common theme across all the meta-analyses.

The second contributor to heterogeneity in some of the meta-analyses was how the variable was defined. Socio-economic Status and Co-morbidity Score were particularly affected. As an example, the association between socio-economic status and adherent radiation had considerable heterogeneity (I^2 = 85%) (Figure 8 – 22, Appendix Chapter 4 – 4). In this analysis, 9 studies were included. (35, 37, 48, 63-66, 72) Of these, 1 study used 5 SES categories (48), 5 studies used 4 SES categories(37, 63, 64, 66, 72) and 2 studies (3 analyses) used 3 SES categories (35, 65). Co-morbidity score was categorized in a number of ways as well: 1+ vs. 0; 2+ vs. 1 vs. 0; 3+ vs. 2 vs. 1 vs. 0.

Finally, heterogeneity was also likely impacted by the statistical models used within the included studies. A requirement for inclusion in the meta-analyses was that the original study

reported a multivariable adjusted model. Although the models were multivariable models, the co-variates included in the model varied. In addition, the included variables were often categorized in different ways. For instance, age was a common co-variate for multivariable models and was included in these models as a continuous variable, a binary variable (i.e. <65 vs. 65+) or a categorical variable (i.e. Age < 65, Age 65 – 80; Age 85+).

4.5.4.4 Comparison of the Narrative Syntheses and Quantitative Analyses

A summary of the comparison of the narrative synthesis and quantitative analyses, when available, is presented in table 4 – 30. Some key differences were identified when comparing the two types of analyses. Most of these differences was a change from a finding of an association to a finding of no association. This occurred in 7 predictor outcome pairs, including sex/gender and overall treatment, sex/gender and colonoscopy surveillance, Hispanic ethnicity and colonoscopy surveillance, socioeconomic status and adherent radiation, marriage status and adherent radiation and insurance type and adherent radiation. Three of the unclear association on narrative synthesis were found to have no association on quantitative analysis, including sex/gender and chemotherapy, sex/gender and overall surveillance, and Hispanic ethnicity and adherent radiation. One unclear association, black ethnicity and adherent radiation, was found to have a negative association on meta-analysis. This was expected, as the unclear designation was based on a single study, which was in contrast to numerous other studies finding black ethnicity was negatively associated with adherent radiation.

Table 4-30 Comparison of Narrative Synthesis Findings and Meta-Analysis Results by Predictor-Outcome Pairs

Predictor-Outcome Pair	Narrative Synthesis Findings	Meta-Analysis Results
Age - Radiation	Negatively Associated	Negatively Associated
Age - Chemotherapy	Negatively Associated	Negatively Associated
Sex/Gender - Overall Treatment	Females negatively associated	No Association
Sex/Gender - Radiation	Females negatively associated	Females negatively associated
Sex/Gender - Chemotherapy	Unclear Association	No Association
Sex/Gender - Combined Surveillance	Unclear Association	No Association
Sex/Gender - Colonoscopy Surveillance	Females positively associated	No Association
Sex/Gender - Surveillance CEA	Females positively associated	Females positively associated
Black Ethnicity - Radiation	Unclear Association	Black Ethnicity negatively associated
Black Ethnicity - Chemotherapy	Black Ethnicity negatively associated	Black Ethnicity negatively associated
Black Ethnicity - Overall Surveillance	Black Ethnicity negatively associated	Black Ethnicity negatively associated
Black Ethnicity - Colonoscopy Surveillance	Black Ethnicity negatively associated	Black Ethnicity negatively associated
Black Ethnicity - CEA Surveillance	Black Ethnicity negatively associated	Black Ethnicity negatively associated
Hispanic Ethnicity - Radiation	Unclear Association	No Association
Hispanic Ethnicity - Chemotherapy	No Association	No Association
Hispanic Ethnicity - Overall Surveillance	No Association	No Association
Hispanic Ethnicity - Colonoscopy Surveillance	Hispanic negatively associated	No Association
Socioeconomic Status - Radiation	High SES positively associated	Trend towards High SES positively associated
Socioeconomic Status - Colonoscopy Surveillance	High SES positively associated	High SES positively associated
Education - Radiation	Higher Education positively associated	No Association
Comorbidity Score - Radiation	Increase Comorbidity negatively associated	Increase Comorbidity negatively associated
Comorbidity Score - Chemotherapy	Increase Comorbidity negatively associated	Increase Comorbidity negatively associated
Marriage Status - Radiation	Married positively associated	No Association
Marriage Status - Chemotherapy	No Association	No Association
Insurance Type - Radiation	Private Insurance positively associated	No Association

4.6 Discussion

This chapter presents the results of a large systematic review and meta-analysis which reviewed the associations between potential predictors and adherence outcomes. A total of 16 potential predictors were identified, which were tested for an association with a total of 14 different adherence outcomes. A total of 72 studies were identified which assessed at least one predictor – outcome pair, with 39 studies included in at least one of the 27 completed meta-analyses.

Some predictors were tested frequently, such as age, socioeconomic status, sex/gender and ethnicity, while others were tested rarely, such as immigration status and employment. Many more studies tested for associations between potential predictors and treatment adherence outcomes (48 studies) compared with staging adherence outcomes (15 studies) or surveillance adherence outcomes (14 studies). Of the total of 118 predictor – outcome pairs, 77 (65%) demonstrated an association or potential association between the predictor and outcome on narrative synthesis. Meta-analyses demonstrated a lower proportion of predictor-outcome pairs with an association. Of the 26 meta-analyses, 12 (46%) were found to have an association between the predictor and outcome. It should be noted that only a single study was identified for 52 of 118 (44%) predictor-outcome pairs.

In general, many of the associations identified were predictable. For instance, younger age, less comorbidity, higher socioeconomic status and white ethnicity were associated with increased adherence in many domains. Increasing age and co-morbidity scores are important predictors of non-adherent care. Elderly patients and those with high co-morbidity scores require careful consideration when discussing care options, due to their complexities in underlying health, goals of care and patient priorities. (92) These issues are the likely explanation for why many in these groups are not offered adherent cancer treatments. A number have studies have demonstrated that the elderly can tolerate recommended treatments, benefit from these treatments, but are not commonly offered these treatments. (93, 94) The reasons for lack of adherence to recommended care are most probably related to both patient preferences, and care provider biases. Neither of these concepts were explored in detail within the studies included in this review. Providing the role of patient and care provider preferences would have allowed for a fuller understanding of adherent care in these high risk groups.

Ethnicity was another important non-modifiable predictor of adherent care. Both in the narrative synthesis and quantitative synthesis, black ethnicity was negatively associated with adherent care. This finding was reported even in the studies that completed multivariable analyses which included age and/or co-morbidity scores. Implicit bias on behalf of health care providers is well described as a contributing factor in the delivery of health care to different ethnicities. (95, 96) This bias may partially explain the findings in the analyses presented in this chapter.

Sex/Gender as a non-modifiable risk factor deserves discussion as there were opposite directions of effect, based on the adherence outcome. Female sex/gender was associated with lower ***treatment adherence*** but higher ***surveillance adherence***. Although the reasons for sex/gender differences in adherence to cancer care is not well described, a number of studies have assessed sex/gender difference in adherence to medications for chronic conditions. (97-99) In these studies, female gender was found to be associated with higher rates of non-adherence. The publications found that when non-adherent, females tended to be so due to purposefully not taking prescribed medications or having adverse events (and stopping the medication), while men tended to be non-adherent due to forgetting to take the medication, or feeling they had recovered and no-longer needed it. It is clear from these publications that the reasons for non-adherence between males and females are different. Similar to other non-modifiable risk factors, it would have been helpful for the included studies to report patient preferences and/or care provider preferences and how these directed adherence to care. The reasons for non-adherence may have been purposeful (i.e. patients refusing the recommendation) or not (i.e. not being offered the care at all).

Socio-economic status as a predictor of adherent care was anticipated, based on the settings of many of the included studies. The largest number of studies came from the United States, which has challenges in providing access to cancer care for those without private insurance and who are not-eligible for government provided insurance. (100) This review did identify public insurance and no-insurance as predictors of non-adherence to care, but not all of the identified studies included both insurance status and socioeconomic status in their analyses. Insurance status likely only partially explains non-adherence in this group, as even in settings with universal health care insurance, lower social economic status has been associated with worse access to care. (101, 102) Access to care and/or adherence in those in the lower socioeconomic status groups may also be explained through the interaction with a number of other factors such as gender, education, race and residential segregation. (103)

It is noteworthy that non-modifiable risk factors (Age, Sex/Gender, Ethnicity, Co-morbidity Score) were much more frequently assessed than modifiable risk factors (Hospital Type or Volume, Physician Specialty or Volume, Use of Multidisciplinary Teams). Understanding the impact of these modifiable risk factors on adherence to care allows for targeted interventions to improve the delivery and access of high quality cancer care. This review identified that receiving care at higher resourced hospitals and receiving care in a multidisciplinary setting resulted in increased adherence to recommended care. However, these findings are based on a small number of studies, but if valid, would support centralization of care as an intervention in improving adherence to care.

4.6.1 Strengths and Limitations

The strengths of this chapter include the comprehensive search strategy, the inclusive definition of potential predictors and adherence outcomes, the assessment of study quality using a well described and commonly used tool (the Newcastle-Ottawa Scale) and the use of both narrative and quantitative methods to synthesize study results. Prior to this review, there has not been an attempt to summarize the relationship between all potential predictors with each aspect of guideline adherent care.

The search terms used to find potentially eligible studies was broad, with close to 7000 studies identified for screening. The primary constraint placed on the search was publication period which was limited to the modern era of rectal cancer treatment. During this time period multimodal treatment (radiation, chemotherapy, surgery) and modern diagnostic imaging (MRI, CT and Transrectal Ultrasound) were available. This period of time is also one in which clinical practice guidelines were first widely available, which further justified the time limits placed.

Studies were selected, only if they referenced a clinical practice guideline, to ensure that "adherence" could be determined. Studies were included if any potential predictor was reported, whether they were an *a priori* selected predictor, or those of interest to study authors. This review also included adherence outcomes across all aspects of the care spectrum including the diagnostic/staging phase, the treatment phase and the surveillance/follow up phase. Including all phases of care allows for a complete assessment of a patient's cancer journey. In addition to specific adherence outcomes, this chapter included "overall" (or composite) adherence from studies that reported these. Overall adherence is a helpful outcome as it includes a number of specific investigation or treatments, each of which may have different directions of association (or no association) with a potential predictor. When considering the impact of a predictor, it is

helpful to understand the relationship with both specific adherence outcomes, as well as the bigger picture described by the "overall adherence". The inclusive approach to eligible predictors and eligible outcomes allowed for the assessment of 16 predictors and 14 outcomes, resulting in 118 predictor-outcome pairs included in the narrative synthesis and the ability to complete meta-analyses in 26 predictor-outcome pairs.

An additional strength was the use of a well described tool to assess study quality, the Newcastle-Ottawa Scale. This tool allows the reader of this work to understand the weaknesses of the studies included in the review and how these could impact the reported findings. Although there have been some questions regarding the validity and reproducibility of this scale (104), at the present time there is no "gold standard" for evaluating the quality of observational studies. A recent publication reported the use of quality assessment tools for non-randomized controlled studies in systematic review protocols (N = 471 protocols). (105) This study identified the Newcastle-Ottawa Scale (39%) as the most commonly used tool, followed by the ROBINS-I (33%). Nine other tools were identified, none of which were used in > 10% of included protocols.(105) The ROBINS-I tool was developed for use in observational studies that assessed at least two different interventions. As the systematic review is assessing risk factors, the Newcastle-Ottawa Scale was selected as ROBINS-I was not deemed appropriate for this work.

Narrative synthesis of the included study results was conducted to provide a general determination of the associations between potential predictors and adherence outcomes, while quantitative methods (meta-analysis) was used when appropriate. The narrative synthesis was purposely reported as a summary, with the detailed study results available in the appendix. Summarizing the findings of the large number of studies which assessed numerous predictors-outcome pairs, allows for a general understanding of the predictor as a barrier or facilitator of

guideline adherent care. When used, meta-analysis included only those studies reporting multivariable results to help reduce the risk of known confounders within these analyses. By using both narrative and quantitative methods, the impact of the identified predictors on adherence outcomes could be summarized, contrasted and discussed.

The primary limitation of this review is the type of studies included in the reviews. All studies were observational studies, with few being prospective in nature. Although many were rated as having high quality on the Newcastle-Ottawa Scale, by their nature, these studies are at risk of selection bias, confounding and misclassification.

Comparability of study results between studies was problematic. Studies included in the reviews varied based on publication year (and/or treatment years), setting (country, health care systems), source data (single centre vs. multicentre vs. population based) and clinical practice guideline referenced. In some cases, the types of patients included in the studies also varied substantially. For instance a number of studies only included patients over a specific age, or of a specific ethnicity.

Even in those studies that had similar settings and inclusion criteria, there was inconsistency in how the predictors and/or adherence outcomes were defined, categorized and reported. For instance, age was reported as a continuous variable or in a variety of age groupings, comorbidity scores were grouped in a number of different ways (1+ vs. 0; 2+ vs. 1 vs. 0; 3+ vs. 2 vs. 1 vs. 0), hospital were inconsistently categorized (Arbitrary and inconsistent volumes, number of beds, resources in place). A lack of consistency in defining these predictors limits the conclusions that can be drawn. For instance, hospital volume was categorized differently in most identified studies. This likely resulted in an inconsistent direction of effect for the association between volume and adherence outcomes. In addition, a quantitative analysis could not be

performed due to a lack of a uniform exposure definition. The inconsistencies in some of the predictor-outcome pairs may have been resolved with more consistent definitions and/or the ability to combine results into a meta-analysis.

The quantitative assessment provides a summary of the associations between the predictor and the adherence outcomes. Although only those reporting a multivariable model's results were included, there is a substantial risk of confounding due to the observational nature of the included studies. In addition, the multivariable models included a variety of co-variates, and there were inconsistencies in which ones were included in each model. Many of the meta-analyses suffered from considerable or substantial heterogeneity. This heterogeneity was driven by several factors, including different study population, different categorizations of exposures and differences in the study models. High levels of heterogeneity were expected based on the types of studies included. These limitations due impact the confidence in the effect estimates and confidence intervals reported in the included meta-analyses. This issue needs to be interpreted in the context of the aims of this chapter. The chapter aimed to identify which factors were potentially associated with adherence to rectal cancer care recommendations. The aim was not to determine the precise effect these factors may have had on adherence outcomes.

Another limitation is that although a large number of studies were identified and included, many of the potential predictor – adherence outcome associations were assessed in only a limited number of studies. For instance, more than a third of reported associations were based on a single study only. This issue was much more common in the assessment of staging and surveillance adherence outcomes than the treatment outcomes.

The themes and findings of this chapter must be taken in the context of the included study settings, patient populations and treatment years. For example, the importance of ethnicity on

receipt of guideline adherent care was only assessed in studies from the United States. Although ethnicity seemed to be an important predictor of a number of adherence outcomes, these results may not be generalizable to other settings. Similar issues arise when interpreting the importance of socio-economic status and insurance status. In some settings, such as the United States, insurance status is highly correlated with socio economic status and is a potentially important predictor of adherent care. In other settings such as the United Kingdom and Canada, socio-economic status and/or insurance status are less predictive of adherent care.(106) Finally, the infrastructure providing rectal cancer care can differ substantially between settings. In some settings, such as in Europe and the United Kingdom, the delivery of complex cancer care is determined based on national policy, while other settings, such as the United States, there is little national oversight in how or where complex care is provided.(107) This has implications for the importance of hospital types as a predictor of adherent care.

Finally, the purpose of this review was to provide a general understanding of numerous predictors and adherence outcomes. Although the individual study characteristics and study results can be found in the appendices, this chapter primarily reports a summary of the findings for each of the available predictor-outcome pairs. Thus, the review presented in this chapter provides the reader a "big picture" assessment of the literature.

4.6.2 Implications for Clinical Practice

The results of this chapter provide clinicians and those in health policy a summary of predictors of guideline adherent care. Despite previously being identified in a number of settings, several non-modifiable risk factors consistently were associated with worse adherence. Older age, Ethnicity, Socio-economic Status and Gender continue to be important risk factors for

lower adherence to recommended care. Awareness of these potentially vulnerable groups could allow for interventions to improve the quality of care in high risk groups. In addition, several modifiable risk factors, including higher resourced hospitals and multidisciplinary teams, were associated with increased adherence to care across the spectrum of rectal cancer management. This result potentially justifies centralization of care to these types of settings.

4.6.3 Implications for Research

This systematic review and meta-analysis identified a number of commonly assessed predictors of guideline adherent care. These predictors, when available, were included in the Ontario Rectal Cancer Cohort ("OntaReCC), described in ***Chapter 5,*** as they are potentially important barriers or facilitators to guideline adherent care in Ontario. This systematic review also identified where deficits in the evidence describing predictors of guideline adherent rectal cancer care existed. For instance, few studies assessed overall adherence to each phase of care (staging, treatment, surveillance), and only a small number of studies assessed important modifiable risk factors such as hospital resources or physician volume. These findings informed the design and conduct of ***Chapter 6***, which aimed to determine which factors were important predictors of guideline adherent care, as well as the impact of guideline adherent care.

4.7 How this chapter fits into the thesis as a whole

This chapter aimed to identify commonly assessed predictors of guideline adherent rectal cancer care, as well as summarize the relationship between these predictors and aspects of guideline adherent care. In doing so, this chapter informed how the Ontario Rectal Cancer

Cohort was constructed (described in ***Chapter 5***), by providing which factors and outcomes should be included. In addition, this chapter identified a number of gaps in our understanding of the predictors and impact of guideline adherent care, which were addressed in ***Chapter 6.***

4.8 Chapter 4 Summary

- A systematic review and meta-analysis of predictors of guideline adherent care was completed
- A large number of predictor-adherent outcomes pairs were identified, with the relationship summarized in a narrative synthesis and, when appropriate, quantitative analysis.
- There were a number of non-modifiable (age, sex, comorbidity score, socioeconomic status) and modifiable (hospital resource, physician volume) predictors identified, which were included in the Ontario Rectal Cancer Cohort

4.9 Chapter 4 References

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Chapter 5 The Ontario Rectal Cancer Cohort

5.1 Chapter Overview

This chapter describes the creation and description of the Ontario Rectal Cancer Cohort ("OntaReCC"). OntaReCC is a comprehensive database of those with rectal cancer in Ontario between 2010 – 2019. OntaReCC contains all those initially diagnosed with rectal cancer, as well as the "curative intent" cohort which included those who underwent either local excision or radical resection for rectal cancer. Surgical treatment (local excision or radical resection) was a requirement for curative intent treatment as described in ***Chapter*** 3 which reviewed all Canadian Clinical Practice guidelines. OntaReCC uses a number of provincially maintained administrative databases and other data sources and is the first and only resource available to assess all aspect of rectal cancer care in a Canadian population. This chapter provides the methods used to create the OntaReCC, as well as provides descriptive results of the delivery of rectal cancer care and outcomes in Ontario during the study period. Prior to the creation of the OntaReCC, there was no dataset available to researchers to specifically assess rectal cancer care in Ontario.

5.2 Chapter Aims and Objectives

This chapter describes the creation of the Ontario Rectal Cancer Cohort and provides summary data describing the management of rectal cancer in Ontario between 2010 - 2019. The overall aim of the Ontario Rectal Cancer Cohort was to create a comprehensive and contemporary resource that can be used for population level research assessing the delivery and outcomes of those with rectal cancer. This cohort was specifically created to determine the

adherence to the minimum recommended care (described in Chapter 3), which would allow for an assessment of the impact of adherence on other important outcomes, which is described in Chapter 6. The specific objectives of this chapter are to describe the methodology used to create the Ontario Rectal Cancer Cohort, as well as to summarize the practice patterns and outcomes of those with rectal cancer over the study period.

5.3 Background

As described in ***Chapter 2***, Management of those with rectal cancer often requires a number staging investigation, multimodality treatment, and ongoing surveillance or follow up. With this level of complexity, fragmentation of care can occur (1) and inconsistent delivery of treatments may be observed.(2) In addition, due to the nature of the treatment, rectal cancer patients often experience high rates of short- and long-term morbidity.

Chapter 4 describes a systematic review and meta-analysis of studies assessing the predictors of guideline adherent care in those with rectal cancer. A number of limitations were identified within this systematic review. First, modifiable predictors such as hospital type or surgeon volume were infrequently assessed as potential predictors of guideline adherent care. Second, there was great inconsistency in how predictors (and outcomes) were defined, which makes comparability between studies problematics. Third, the included publications varied greatly in terms of study setting and inclusion criteria, with few Canadian specific studies identified. Thus the generalizability of the systematic review findings to a Canadian context is questionable. Finally, many predictor - adherence outcome pairs were assessed in a single study, calling into question the reproducibility and generalizability of the study findings.

The ability to overcome these limitations would substantially improve the ability to assess the predictors of guideline adherent care, and how receipt of guideline adherent care affects

outcomes such as survival, especially within a Canadian context. The Ontario Rectal Cancer Cohort, described below, is a resource that can be used to address the limitations of the current evidence.

5.4 Chapter Methods

Below describes the methods used to create the Ontario Rectal Cancer Cohort. Unless explicitly stated otherwise, all work in this chapter was completed by the primary author of this thesis (Sunil Patel).

5.4.1 Study Setting

Individuals from Ontario, Canada were included in the Ontario Rectal Cancer Cohort. Ontario is Canada's most populous province (estimated population 14.6 million in 2019) and is a large and diverse region. The demographics include a wide range of socioeconomic backgrounds, a large number of first and second generation Canadians and indigenous populations. (3)

The province includes large metropolitan areas, as well as sparsely populated rural communities. Fourteen "Local Health Integration Networks" (LHINS) are responsible for the regional delivery of health care. (Figure 5 – 1) The delivery of cancer care is provided through the province's cancer centres. (Figure 5 – 2) These cancer centres are designated as "Regional Cancer Centres" (Level 1 & 2), Affiliate Cancer Centres (Level 3), "Satellite Cancer Centres" (Level 4) and "Non-designated Hospitals" based on the complexity of treatment offered and resources available. (Table 5 – 1) These designation were created by Cancer Care Ontario.

Figure 5-1: Ontario Health Regions (4)

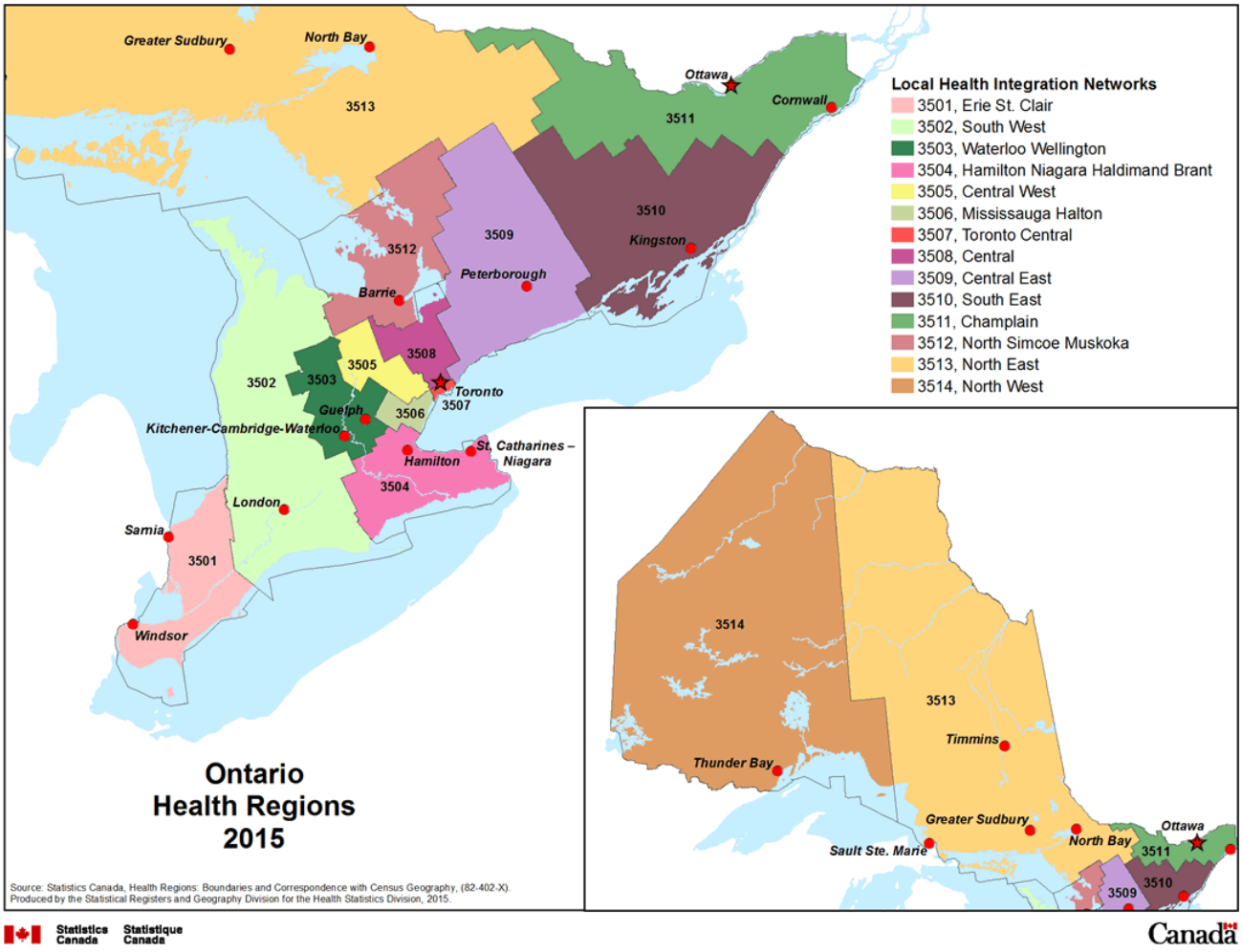


Figure 5-2: Cancer Centre Locations, Ontario (5)

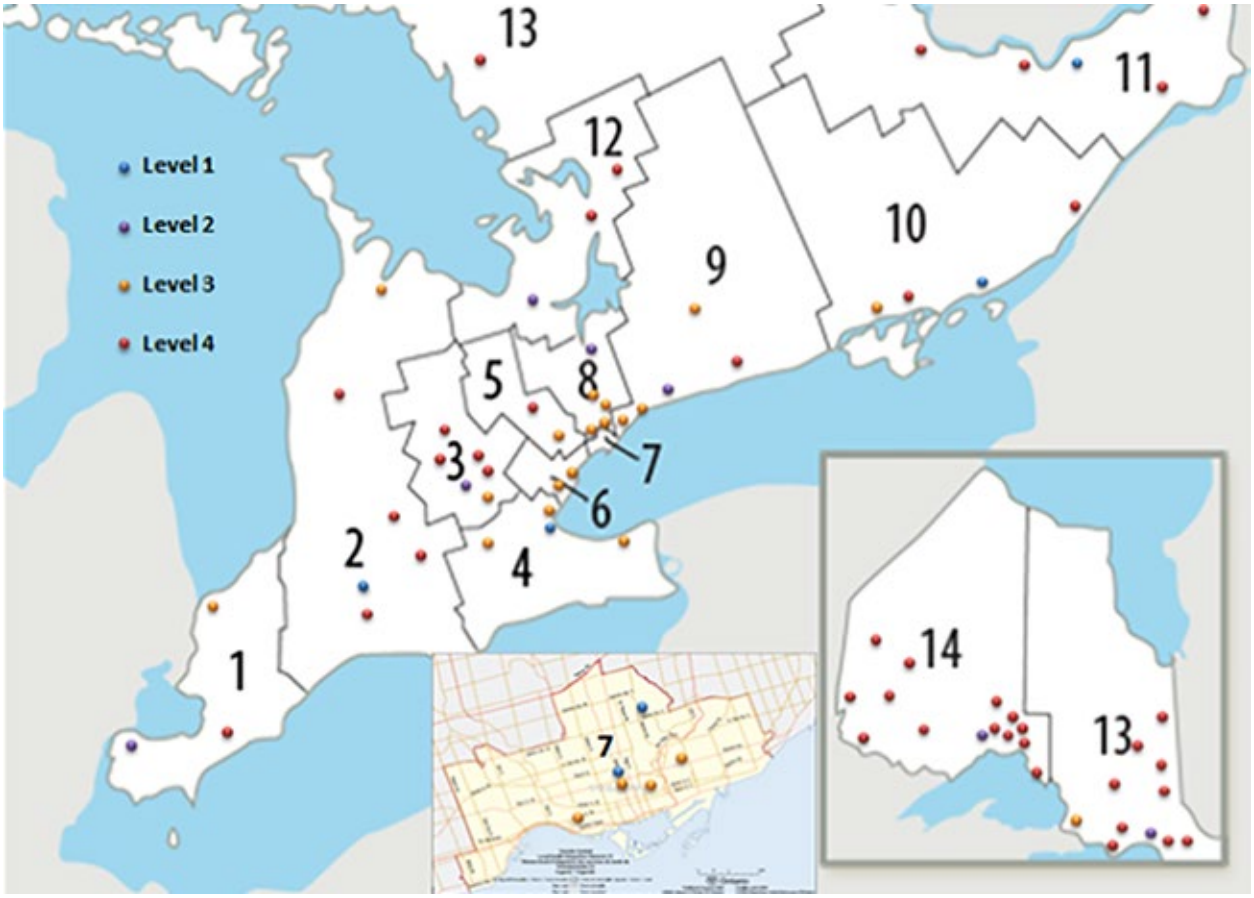


Table 5-1: Cancer Centre Designation and the types of treatments offered (adapted from Cancer Care Ontario)

Services offered	Level 1 - "Regional"	Level 2 - "Regional"	Level 3 "Affiliate"	Level 4 "Satellite"	Non-Designated
Surgery					
Non Complex	Yes	Yes	Yes	Yes/No (a)	Yes/No (a)
Complex/ Multi-visceral Resection	Yes	Yes	No	No	No
Systemic/Chemotherapy					
Investigation of New Drugs	Yes	No	No	No	No
Complex Procedures	Yes	Yes	No	No	No
On Site Medical Oncologist	Yes	Yes	Yes	No	No
1st Dose high risk chemotherapy	Yes	Yes	Yes	No	No
All Other Systemic Chemotherapy	Yes	Yes	Yes	Yes	No
Radiation (b)	Yes	Yes	No (b)	No	No
Number of Hospitals	6	9	20	38	

(a) Based on local surgeon expertise
(b) Radiation is delivered in the 15 regional cancer centres (Level 1&2) and 2 affiliated cancer centres

Residents of Ontario are eligible for a government run universal, single payer health insurance plan (OHIP). This plan covers the cost of doctor visits, diagnostic investigations, hospital stays, surgical services, and cancer services (including radiation therapy and chemotherapy). Although individual patients are not charged for services provided, Physicians "bill" the provincial health insurance plan for each patient encounter, which includes clinical assessment, procedures, interpretation of diagnostic imaging and pathology reports. Physicians do not have the ability to charge individual patients (or private insurance) for these services.

5.4.2 Data Sources

The Ontario Rectal Cancer Cohort combines data from provincially maintained, administrative databases. A full listing of the administrative datasets used for the creation of the Ontario Rectal Cancer Cohort can be found in Table 5 – 2. These databases include health administrative data that is generated whenever a health care service is delivered to an individual, which is utilized for billing, registration, transactions, or record keeping by health care providers. The heath administrative datasets are linked to other provincially maintained datasets which provide vital statistics, census information and other demographic data. Linkages occur through unique patient identification numbers (the Ontario Health Insurance Plan). It should be noted that before the creation of the Ontario Rectal Cancer Cohort, the combined data contained within each database was not available in a single, comprehensive database.

Table 5-2: Summary of Administrative Databases used in the Ontario Rectal Cancer Cohort

Data Source	Summary	Details
Ontario Cancer Registry (OCR)	The Ontario Cancer Registry is the provincial database of information for all Ontario residents who have been diagnosed with cancer (incidence) or who have died of cancer (mortality). Data are collected from hospitals, regional cancer centres, pathology reports and death certificates, and cover the entire province of Ontario.	- Hospital admission and discharge information from the Canadian Institute for Health Information - Pathology reports from public hospitals and community laboratories - Consultation and treatment records of patients who have been referred to one of 14 regional cancer centres or their associated hospitals - Death certificates from the Ontario Registrar General
Cancer Activity Level Reporting (ALR)	The data elements constitute patient level activity within the cancer system focused on radiation and systemic therapy services and outpatient oncology clinic visits. The dataset contains clinical, patient level data.	- OH-CCO requires all activity from the cancer centre and its related outreach clinics, if any. - Activity-level reporting database, containing data from Ontario's 14 regional cancer centres and their associated hospitals, for selected systemic therapy and all radiation treatment
Canadian Institute of Health Information - Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD captures administrative, clinical and demographic information on hospital discharges (including deaths, sign-outs and transfers). Includes demographic, administrative and clinical data for inpatient discharges (including surgery) and day surgery interventions.	- The DAD contains demographic, administrative and clinical data for: Hospital inpatient discharges; and Day surgery encounters. - Data available from 1993-1994 to 2023-2024
Registered Persons Database (RPDB)	A listing of all persons insured under the Ontario Health Insurance Plan. The data is used to ensure that individuals in other data sources are identified correctly, and to support analysis by demographic groups and geography.	- The RPDB (database) provides basic demographic information about anyone who has ever received an Ontario Health Insurance Plan (OHIP) card - It links physician and hospital payments for interventions

The Ontario Cancer Registry (OCR) is the province's cancer registry and is maintained by Cancer Care Ontario – Ontario Health. It captures incident cancer cases through mandatory reporting, and is estimated to include > 95% of newly diagnosed cancers, in which >94% of colorectal cancers were microscopically confirmed. (6, 7) The OCR captures the detailed histology (i.e. adenocarcinoma), site of cancer (i.e. colon vs. rectal), and stage of disease at

diagnosis. The OCR also houses biopsy and surgical pathology reports. Institutions are mandated to provide the OCR with a copy of the biopsy and surgical pathology reports for every incident case. The OCR also captures vital statistic, demographics, date and cause of death.

The Cancer Activity Level Reporting Database includes data generated at every one of the province's cancer centres. It includes routinely captured data on radiation treatment, including: the days of treatment, the body region treated, the size and number of doses given, and the intent of treatment. Similarly, chemotherapy data is routinely captured and includes: the date and type of chemotherapy delivered, the dose of chemotherapy, and the duration of chemotherapy. The data is collected prospectively and released for research purposes twice a year.

The Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD) captures data on every patient hospital admission as mandated by provincial and federal legislation. The CIHI-DAD provides detailed information on patient diagnoses, treatments, procedures, and all other relevant hospital delivered care. Finally, the registered person's database includes data on physician billings and payments provided through the Ontario Health Insurance Plan.

These datasets provide comprehensive data on individual characteristics (i.e. demographics, co-morbidities, socioeconomic status), diagnostic details (date of diagnosis, histologic variant and cancer cite), and treatment details. In addition, health care provider details and institution details are captured within these data sets. Using the above mentioned datasets, important factors or characteristics could be derived, including: the completeness of preoperative investigations; the type, extent and completeness of treatments (including surgery, radiation and chemotherapy); treating clinician characteristics (volumes, practice setting); institution

characteristics (volumes, level of care, presence of multidisciplinary cancer centre); cancer related outcomes (overall and cancer specific survival, treatment of metastatic disease, use of palliative treatments, symptom burden).

5.4.3 Data Management and Security

I worked closely with two data analysts (Chad McClintock and Weidong Kong) to create this cohort. Both analysts are employees of Cancer Care and Epidemiology (Queen's Cancer Research Institute) and have experience in population health research. My role was to define all inclusion criteria, variables and outcomes, and to provide the relevant diagnostic and treatment codes to the analysts. Once the study inclusion criteria were provided, the data analyst would use a common patient identification number (i.e. their Ontario Health Insurance Plan number) to link data from the numerous potential data sources. Due to restrictions on data access, only the employed data-analysts at Cancer Care and Epidemiology were permitted to access the raw data. Through an iterative and collaborative process, I worked with the data analysts to review the initial data and resolve any sources of error or inconsistency. Once the cohort was established, all data was housed on the systems at Cancer Care and Epidemiology. Below describes Cancer Care and Epidemiology's process for securing the data:

"The Department of Cancer Care and Epidemiology (CCE), who receives data transfers from Ontario Health-Cancer Care Ontario (OH-CCO), is responsible for the protection and security of this data. Once all permissions are obtained from OH-CCO to conduct a research project, a CCE statistician accesses the data holdings to obtain a study cohort, which remains on the isolated network server. The data holdings are encrypted and stored on an isolated network server, located behind a firewall at the Kingston Health Sciences Centre-Kingston General

Hospital site. Access to these data holdings are restricted to 4 personnel. The Manager, the 2 statisticians/data-analysts and a Kingston Health Science Centre IT Technologist, when necessary updates are required. These team members are set up with their own secured network drive that is only accessible by the individual when using the data.

Histopathology report files, provided by Ontario Health – Cancer Care Ontario, are accessed and downloaded by a team member from the secured Ontario – Health – Cancer Ontario site onto a secured network drive. Any and all paper study material are locked in cabinets that are located in locked offices and all doors into the CCE are locked 24 hours/day, 7 days a week and require a programmed proximity key to enter. Office doors are locked except when the principal investigator or team member is present and all rooms are locked outside of regular office hours. The processes described above are consistent with the DCCE policies, which have been in use for more than 20 years, and to date, there has not been a breach of confidentiality or security."

5.4.4 Permissions and Ethics Approval

Permission to use the provincially maintained linked administrative databases, as well as obtain the raw histopathology data was granted by Ontario Health-Cancer Care Ontario (OH-CCO).

Ontario Health – Cancer Care Ontario and the Division of Cancer Care and Epidemiology (CCE) at Queen's University, where I have an appointment, have a pre-existing relationship, which includes a Memorandum of Understanding and a Data-Sharing Agreement. This agreement allows for the transfer of OH-CCO's provincial registry data and access, for work that is completed on behalf of OH-CCO. Although this agreement is in place, researchers

must submit requests to access this data for their individual research and must be a member in CCE, thus there are restrictions on who can access the data.

The anonymization of the data, through removal of identifying date and replacing with a unique code, occurs after all data from OH-CCO are linked. Linkage occurs using a unique patient identifier (the patient's Ontario health insurance plan ID number). Data reporting was also restricted to aggregates of less than 5. An application requesting access to the CCE data holdings was submitted to Ontario Health-Cancer Care Ontario, and a fully executed agreement to access data was granted on November 17, 2020 (Appendix Chapter 5 - 3). Research ethics approval was obtained from the Queen's University Health Sciences Research Ethics Board prior to data access. (Appendix Chapter 5 – 4).

5.4.5 Study Population and Years of Inclusion

The Ontario Rectal Cancer Cohort includes all individuals diagnosed with adenocarcinoma of the rectum in Ontario between 2010 and 2019, and includes follow up data to the end of 2022. The start date of the study was selected based on several factors. The first is that radiation and chemotherapy data (available through the Cancer Activity Level Reporting Database) were completely captured beginning in 2010. Between 2007 – 2009, the data is partially complete and prior to 2007, incomplete. In addition, the use of preoperative radiation therapy and the addition of post-operative chemotherapy became the standard of care and appeared in most clinical practice guidelines at the end of the 2000's. (8, 9) Prior to this time, postoperative radiation was commonly recommended and routine chemotherapy was often omitted. Between 2010 and 2019, clinical practice guidelines have been consistent in general treatment recommendations, with no substantial variations between subsequent versions, as

described in ***Chapter 3***. (10) The diagnosis end date (2019) was selected as this was the latest time in which complete treatment data was available at the time of the creation of the Ontario Rectal Cancer Cohort. Follow up data was available until the end of 2022.

Individuals with adenocarcinoma of the rectum were identified from the Ontario Cancer Registry using the International Classification of Diseases (ICD) codes for rectal cancer. Which included C20 (ICD 10 code, in use from 2015 – 2019) and 154.1 (ICD 9 code, in use from 2010 – 2014). Adenocarcinoma histology was identified through the Ontario Cancer Registry.

Several exclusions were applied. This included age < 18 at time of diagnosis, previous rectal cancer resection, or a concurrent cancer diagnosis. Few individuals < 18 were expected over the study period, and additional permissions are required when accessing children's data. Those with recurrent rectal cancer were excluded if the index (or first) cancer diagnosis was prior to 2010. "Recurrent" cancer was defined as occurring < 5 years between diagnoses. This group was excluded as the original intent of the OntaReCC was to evaluate those with an index rectal cancer diagnosis. In those with an index rectal cancer diagnosis after 2010 and a subsequent recurrence, only the first diagnosis was included in the database.

Those with a 2nd primary cancer diagnosis were excluded if this cancer was diagnosed < 5 years prior to the rectal cancer diagnosis or < 1 year after the rectal cancer diagnosis. The reason for exclusion was that the competing risk of the concurrent cancer can influence treatment decision, and care is individualized. In addition, differentiating investigations and treatments for each cancer is often not possible due to the common use of investigations and treatment which are not distinguishable from the available population health data.

The inclusion and exclusion criteria were applied using an iterative process between myself and one data-analyst (Chad McClintock). This left a cohort of individuals with an index diagnosis of rectal cancer.

The cohort included anyone diagnosed with rectal cancer during the study period, which was further refined to identify those with "curative intent" treatments. This group was defined in the following way:

1. Underwent either Local Excision or Radical Resection for Rectal Cancer
2. Did not have Stage IV disease

Thus, the "curative intent" cohort must have undergone a surgical treatment and not have evidence of metastatic disease. This definition of "curative intent" was based on the clinical practice guideline review which recommended, at a minimum, that Stage I - III patients undergo some form of surgery (or local excision) as part of the standard of care. Although some individuals with Stage IV disease may have been eligible for curative intent treatments (i.e. resection of the metastatic disease in addition to treatment of the primary rectal cancer), this group of patients would have their care "individualized" as per the available clinical practice guidelines. This group would thus not be assessable for "adherence" to the minimum recommended care as no standard exists.

5.4.6 Patient Related, Care Provider Related and Disease Related Variables

Variables included in the Ontario Rectal Cancer Cohort included those readily available from the administrative databases (such as date of birth) and those that were derived specifically for this work (such as age at time of diagnosis). A summary of pre-existing and derived

variables can be found in Table 5 - 3. A description of the source and definition of each variable follows.

Table 5-3: Summary of Pre-existing vs. Derived Variables

Pre-existing Variables	Derived Variables
Age	Age at Surgery
Sex	Rurality
Date/Cause of Death (if applicable)	Neighborhood Income Quintile
Cancer Centre Level Designation	Charlson Co-Morbidity Score
Stage of Disease	Hospital Volume
Physician Billing Codes	Surgeon Volume
Raw Surgical Codes	Diagnosis Date
	Early vs. Locally Advanced Stage
	Histopathology Data
	Type of Surgery
	Physician Specialty Consultation
	Radiation Received
	Chemotherapy Received
	Time between investigations and/or treatments
	"Fragmented Care"
	Guideline Adherent Staging
	Guideline Adherent Treatment
	Guideline Adherent Surveillance
	Overall Guideline Adherent Care

5.4.6.1 Patient Related Variables

Age, sex and rurality were identified through the Ontario Cancer Registry. Age was defined based on the date of surgery for those who underwent curative intent treatments. In those who did not undergo curative intent treatments, age was determined based on date of diagnosis. Rurality was identified through postal code, where the 2nd digit of Canadian postal codes is "0" in rural locations. Sex was determined based on how it was defined in the administrative databases. Sex (based on biologic attributes) and not gender (based on socially constructed roles) is available through these administrative databases.

Charlson Co-morbidity score was identified using the CIHI-DAD database and based on the co-morbidities present in the 2 years prior to diagnosis. Income quintile was based on neighborhood income using census data included in the Ontario Cancer Registry. A number of

relevant patient related barriers or predictors were unavailable within the linked data sets, such as education level, race/ethnicity, marital status and immigration status.

5.4.6.2 Care Provider Variables

Care provider characteristics included surgeon volume, hospital volume and cancer centre level designation. Each physician has a unique physician identification number used for physician billing within the Ontario Health Insurance Plan and available in the RPDB. This identification number was used to capture all applicable rectal cancer surgeries performed. Although a number of studies have previously defined "High" volume or "sufficient" volume for rectal cancer, there is no existing agreed upon definition. A previously published systematic review demonstrates this issue well. (11) A total of 47 articles were included, with little consistency between articles. The definition of a "Low" volume surgeon ranged from less than 1 operation per 5 years to less than 108 annual operations. "High" volume had cut offs of 5 surgeries per year to more than 500 operations per year. For the purposes of the Ontario Rectal Cancer Cohort, the surgeons mean annual volume, in the preceding two years, was used. Surgical procedures were identified using the physician OHIP billing code. Selection of surgical codes is described in detail in section 5.3.5 (Guideline Adherent Care). Surgeons were then categorized into "low", "medium" and "high" volume based on the tertiles within the province.

Hospital Volume was identified using the hospital code required for submission of a physician billing code. Similar to surgeon volume, the hospital volume was based on the average number of procedures completed over the preceding 2 years, based on rectal cancer surgical codes. Both physician OHIP billing codes and the Canadian Classification of Interventions (CCI) codes were used, and are described in section 5.3.5. Similar to surgeon

volume, there is no agreed upon definition of "low" or "high" volumes. The same review described above found a range of "low" volume from less than 5 operations over 5 years to less than 530 operations per year and "high" volume ranged from more than 6 per year to more than 2600 per year. (11) Hospitals were then categorized in tertiles to "low", "medium" and "high" volume centres.

Cancer Centre Level Designation was determined using hospital codes found in the CIHI-DAD database. Hospitals are categorized by Cancer Care Ontario. In those who had treatment at more than one hospital, the location of surgery was used. Due to similarities in the services offered and resources (as described above in Table 5-1) hospitals were grouped: Level 1 and Level 2 (regional cancer centres) vs. Level 3 (affiliated cancer centres) vs. Level 4 (satellite cancer centres) and Non-Designated.

5.4.6.3 Diagnosis Date and Cancer Related Variables

Although the Ontario Cancer Registry identifies "diagnosis" date in the registry, there was reluctance to rely on this date for the Ontario Rectal Cancer Cohort, as no validation studies have been completed demonstrating the accuracy of this variable. Direct visualization through colonoscopy or flexible sigmoidoscopy (i.e. "endoscopy") continues to be the gold standard method for diagnosing rectal cancer in most cases. The exception is the up to 15% of individuals who have an emergency presentation, in which few undergo colonoscopy prior to intervention.(12) Thus, the diagnosis date for the Ontario Rectal Cancer Cohort was defined as (1) the date of endoscopy, which preceded any treatment or (2) In those without endoscopy, the diagnosis date as recorded in the Ontario Cancer Registry. Within Ontario, Cancer Care Ontario (through the regional Colorectal Cancer Diagnostic Assessment Program) recommends referral

to a specialist for rectal cancer management when a highly suspicious mass is seen on endoscopy and does not require pathologic confirmation and thus endoscopy date was selected as the anchor date for diagnosis, when available.

Year of surgery was included as both the specific year, as well as grouped into three periods: 2010 – 2013; 2014 – 2016; 2017 – 2019. The grouping was used in subsequent analyses.

The stage of disease was determined using the Ontario Cancer Registry's "Best Stage". This classification of stage is based on the stage at diagnosis, and is determined using a number of sources within the available administrative databases. (6) For the purposes of the Ontario Rectal Cancer Cohort, stage was further categorized into early stage (Stage I), locally advanced (Stage II & III), metastatic (Stage IV) and unknown (stage not available in the OCR). Stage II and III were grouped together due to the similarities in recommendations for treatment, and the difficulty in discriminating between stage II and III disease, as described in ***Chapter 2***.

Although the American Joint Commission on Cancer (AJCC) describes rectal cancer stage based on Tumor Stage ("T" Stage), Nodal Stage ("N" Stage) and Metastatic Stage ("M" Stage), the Ontario Cancer Registry did not capture this data well during the study period. It was expected that there would be a large number of missing values. For this reason, stage of disease was defined based on the OCR "best stage" and was not derived from the available "T", "N" and "M" Stage. Other disease related characteristics were identified from histopathology reports which are detailed below.

5.4.7 Histopathology Variables

A separate histopathology database of those with rectal cancer was created to enhance the available administrative data and validate the data from these administrative databases. The pathology database was created using histopathology reports acquired from the Ontario Cancer Registry. As mandated by provincial legislation, the registry receives a copy of the histopathology report following any surgical resection for cancer. This histopathology report is sent directly from the institution in which the procedure was completed. Although the Ontario Cancer Registry warehouses these reports, data contained within the reports is not comprehensively abstracted or curated. For these reasons, the individual elements contained within each individual histopathology needed to be abstracted to be included in the OntaReCC.

To do so, an application to the Ontario Cancer Registry was made on May 25, 2017 to obtain individual histopathology reports for all those undergoing resection for rectal cancer. At the time of request, histopathology was at least partially available for those who had surgery prior to December 31, 2015. Thus the original request was for histopathology from January 1, 2007 to December 31, 2015. All available histopathology reports for those with a diagnosis of adenocarcinoma of the rectum were received from the Ontario Cancer Registry on February 22, 2018. An audit of the reports determined that 2007 – 2009 and 2015 were only partially available. Thus, the histopathology database contained reports from 2010 – 2014.

The histopathology variables abstracted were based on the College of American Pathologists protocol for the "Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum". (13) Dr. David Hurlbut (Professor of Pathology at Queen's University) assisted with determining which variable should be included in the database. A summary of the data elements for "Major Excisions" can be found in Table 5 – 4.

Table 5-4: Abstracted Elements from Histopathology Reports

Quality of Reporting	Synoptic Report Completeness of Reporting
Quality of Excision	Intactness of the Mesorectum (Complete, Near Complete, Incomplete) for major resection or Completeness of Excision (piecemeal vs. not) for local excision Margin Status (Major Resection - Proximal, Distal, Circumferential; Local Excision – lateral, deep) Nodal Harvest (>= 12)
Histology	Adenocarcinoma and its variants Degree of Differentiation Lympho-vascular Invasion, Perineural Invasion
Stage of Disease	Tumor Stage, Nodal Stage, Metastatic Disease (if applicable)
Neoadjuvant Treatment Response	Complete Response, Partial Response, No Response (if applicable)
Mutations and Immunohistochemistry	BRAF, KRAS Status Microsatellite Instability and Mismatch Repair Proteins

An abstraction database was then created with these variables, the screenshot of which can be found in Appendix Chapter 5 – 1. In addition, a full "Data Dictionary" was created to guide abstraction and ensure reproducibility and validity of this process. (Appendix Chapter 5 - 2) An experience data abstractor (Ms. Sarah Pickett) performed the data abstraction between March 1, 2018 and August 30, 2018. Random audits of abstracted variables were completed by myself to ensure the accuracy of the data. This occurred in 10% (i.e. 10 of each group of 100) of the first 1000 reports. Random audits then occurred for 2 – 3% of the subsequent reports. Elements in the histopathology database were uploaded to the Ontario Rectal Cancer Cohort based on the individual's unique identification number.

A comparison between those with and without available histopathology reports was conducted. The purpose was to determine whether important differences between these groups could be identified. Patient demographics (sex, age, rurality, income quintile), treatment and cancer characteristics (surgery year, cancer stage) and survival were included in this comparison.

5.4.8 Investigations and Treatments

5.4.8.1 Staging and Surveillance Investigations

There is substantial overlap between the types of staging (i.e. pre-treatment) investigation and surveillance (or post-treatment) investigations. For that reason, this section describes the methods used for both periods. Investigations were broadly organized in the following way: Colonic Assessment; Local-Regional Assessment; Metastatic Disease Assessment.

Colonic Assessment included both colonoscopy as well CT Colonography. Local Regional Assessment included MRI and Transrectal Ultrasound. Metastatic disease assessment included the assessment for lung metastases (CT Chest, Chest Xray), and assessment of abdominal metastases (CT Abdomen, MRI Abdomen, Ultrasound Abdomen). It was the intent to also include Carcinoembryonic Antigen (CEA), which is the recommended tumor marker for colorectal cancer. Lab data, including CEA, was unavailable for the study dates, thus not included in this cohort.

The above mentioned investigations were identified using physician billing codes as described in Table 5 – 5. These billing codes are used by the colonoscopist or radiologist whenever the service is provided, and captured in the linked administrative databases. Assistance in identifying the appropriate diagnostic radiology codes was provided by Dr. Alex Menard (Associate Professor of Radiology, Queen's University).

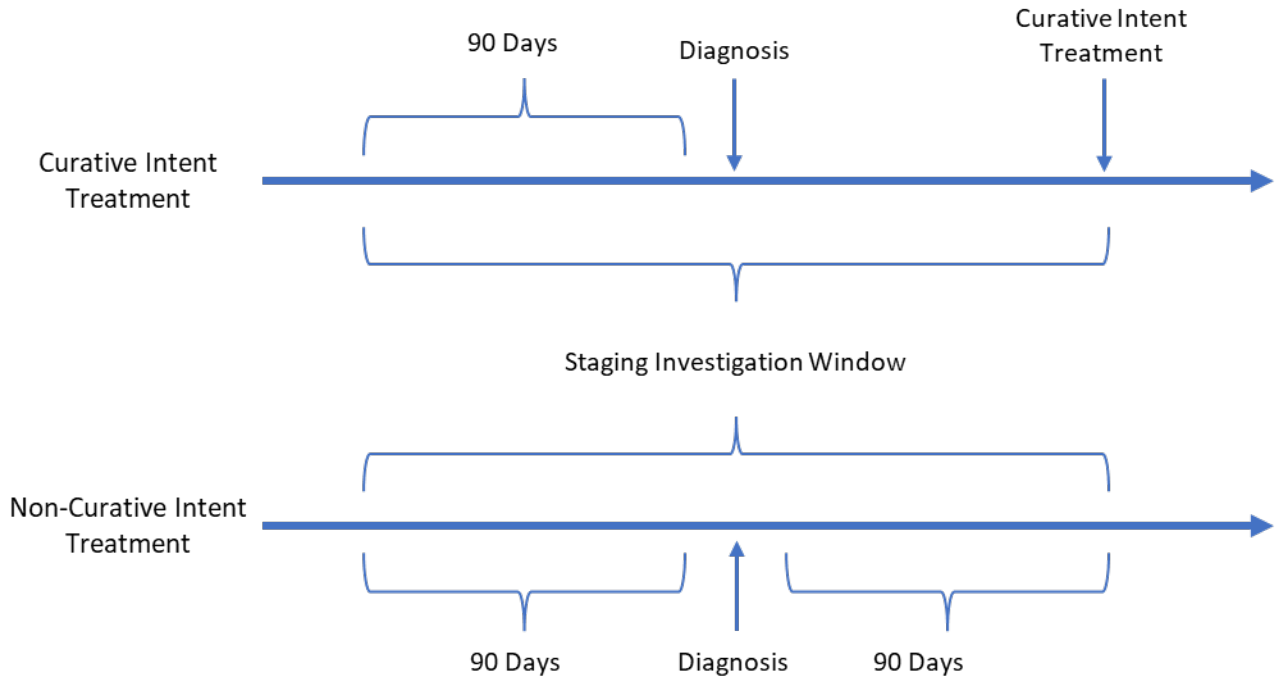
Table 5-5: Physician OHIP billing codes used to identified Staging and Surveillance Investigations

Assessment of Synchronous or Metachronous Colorectal Cancer (or local recurrence)	
Colonoscopy	Z491; Z492; Z493; Z494; Z495; Z496; Z497; Z498; Z499; Z555
CT Colonography	X234
Flexible Sigmoidoscopy	Z580
Local-Regional Assessment	
Pelvic MRI	X461; X465
Transrectal Ultrasound	Z580 with E800; J138; J161; J162
Metastatic Assessment	
CT Chest	X406; X407; X125
Chest Xray	X090; X091; X092
CT Abdomen	X409; X410; X126
Abdominal Ultrasound	J135; J128
Abdominal MRI	X451; X455

CT Computed Tomography; MRI magnetic resonance imaging;

To be considered a "staging investigation", an investigation must have been completed between 90 days prior to diagnosis and up to the first date of any treatment. Investigations completed prior to diagnosis were included, as some individuals have tests done for symptoms (or other reasons) which demonstrates an abnormal finding and thus leads to the confirmatory test. Staging Investigations must have occurred prior to the first treatment date, as treatment decisions are made based on clinical stage which is only available as a result of these investigations. The exception to this case is where the diagnosis and treatment date occurred at the same time, which could occur for local excision for early stage disease or when an emergency intervention is required due to symptoms or complications. In this circumstance, an investigation performed up to 90 days after the diagnosis date was included. Finally, in those who did not have curative intent treatment, investigations were included if they occurred 90 days before or after diagnosis. (Figure 5 – 3).

Figure 5-3: Staging Investigation Window



In the case that the diagnostic imaging test occurred more than once prior to the first treatment date, the test occurring closest (but not after) the first treatment date was considered the "Staging Investigation".

Investigations which occurred between 6 months and 18 months after surgery were considered "Surveillance Investigations". Date of surgery (or local excision) was used as the anchor date, as clinical practice guidelines recommend timing of these investigations based on this date, as described in ***Chapter 3***. Investigations that occurred sooner than 6 months after surgery were excluded, as no CPG recommends early surveillance investigations, and the presumption is that these tests were used for other purposes, such as investigating a treatment related complications, or follow up of abnormalities identified on previous investigations.

I provided the appropriate codes to the data analysts (Chad McClintock, Weidong Kong), who queried the relevant administrative databases. Using an iterative process and applying the

above described methods, all relevant diagnostic and staging investigations were identified and included.

5.4.8.2 Clinical Assessment

Clinical assessment by surgeons, medical oncologist and radiation oncologist was captured, including date of assessment. These were further classified as pre-operative or post-operative. Assessments were included if they occurred between 6 months prior to first treatment date and 6 months after surgery. Clinical assessment was identified using physician OHIP billing codes. Each specialty has a specific code, which is available from the RPDB (Table 5 – 6). Similar to the diagnostic and staging investigations, I provided the data-analysts (Chad McClintock, Weidong Kong) the appropriate billing codes and rules. Using an iterative process, all relevant clinic visits were identified and included.

Table 5-6: Physician OHIP billing codes used to identify a clinical assessment

Description	Medical Oncology	Radiation Oncology	Surgery
Consultation	A445	A345	A035
Limited Consultation	A845	A745	
Repeat Consultation	A446	A346	A036
Medical/Surgical Specific Assessment	A443	A343	A033
Medical Specific Reassessment	A444	A340	
Complex Medical Specific reassessment	A441	A341	
Partial Assessment	A448	A348	A034
Inpatient Consultation	C445	C345	C035
Inpatient Limited Consult	C845	C745	
Inpatient repeat consult	C446	C346	C036
inpatient assessment	C443	C343	C033
inpatient reassessment	C444	C344	C034
inpatient complex med reassessment	C441	C341	
Special Surgical Consultation			A935 or C935

5.4.8.3 Surgery for Rectal Cancer

Surgery details were captured using the physician OHIP billing codes, available from the RPDB, and the Canadian Classification of Intervention Codes available from the CIHI-DAD database. The surgical codes were identified *a* priori based on expert opinion. The date and type of surgery were included. Surgery was broadly classified as local excision or major resection (as described in ***Chapter 2***). Major resections were further classified based on type of resection. A major resection was considered to have occurred if either a relevant CCI code or OHIP code was identified during their treatment. The relevant codes are presented in table 5-7.

Table 5-7 Canadian Classification of Interventions (CCI) and Ontario Health Insurance Plan (OHIP) Procedure Codes

CCI	OHIP	CCI	OHIP
Local Excision		**Hartmann's Procedure**	
1NM87LA	Z753, Z794	1NQ87DX	S217
1NQ87DA	Z784, Z785	1NQ87TF	S188
1NQ87BA	Z755, Z761	1NM91TF	
1NM87DA	E685	1NM87TG	
1NQ87DA	Z571	1NM91TF	
1NM87BA	Z764 or Z765	1NM87DY	
	E685	1NM91TF	
Low Anterior Resection		**Proctocolectomy**	
1NQ89GV	S213	1NQ89RSXXG	S172
1NQ89KZ		1NQ89RS	S170
1NQ89KZXXG		1NQ89SFXXG	S173 & S174
1NQ89SF			
1NQ87RD		**Other Major Colorectal Resections**	
1NQ87DE		1NM89TF	S168
1NQ87CA		1NM89DX	
1NQ87LA		1NM89RN	S169
1NQ87PB		1NM89DF	
1NM91RD		1NM87RE	S166
		1NM87RN	S167
Abdominoperineal Resection		1NM87DF	
1NQ89AB	S214	1NM87DN	
1NQ89LH	S215 & S216	1NM91RE	
1NQ89LHXXG		1NM91RN	

Both OHIP and CCI codes, based on the surgical resection category, were provided to the data analysts (Chad McClintock, Weidong Kong). Using a collaborative and iterative process, all relevant surgical procedures were identified and included in the OntaReCC. Some surgical details were not sought, such as use of temporary stomas and/or multi-visceral resection. Multi-visceral resections (i.e. pelvic exenteration) are captured in both OHIP and CCI using multiple codes, which would include the rectal resection code (i.e. Low Anterior Resection or Abdominal Perineal resection) as well as the code for resection of the adjacent organ (i.e. hysterectomy, cystectomy, sacrectomy). The use of a permanent colostomy (abdominoperineal resection, hartmann's procedure or proctectomy) was captured, but the use of a temporary ileostomy was not. Clinical practice guidelines did not specifically recommend for or against temporary ileostomies.

5.4.8.4 Radiation Therapy

Radiation treatment details were available from the Cancer Activity Level Reporting Database (ALR). This database provides the date of treatment, the dose of radiation, the body region treated, and the intent of treatment. This database does not provide summary data such as total number of doses, duration of treatment or completeness of treatment, which needed to be derived for the Ontario Rectal Cancer Cohort.

The ALR was queried for all radiation therapy related encounters for each included individual. These encounters were restricted to those between 1 year prior to surgical resection to 1 year after surgical resection. Time constraints were placed based on clinical practice guidelines (***Chapter 3***) and in consultation with clinical experts (Dr. Timothy Hanna and Dr. Maria Kalyvas, Radiation Oncologists at Queen's University), to avoid including unrelated

radiation treatments or those used for non-curative purposes. Radiation details from each encounter were identified which included: Date of Treatment, Dose, and Body Region.

The radiation details were then derived, including the total number of fractions (i.e. number of radiation treatments) delivered, the total dose delivered, the most common dose delivered, and treatment delays. The "course" was then defined as either short course or long course, based on the pertinent details. By definition, short course radiation included 5 fractions or less, given sequentially at a dose of 4 – 6 gy/fraction. Long course radiation was defined as 5+ fractions at a dose of 1.5 – 2.5 gy/fraction. A maximum of one fraction per day was allowed. Interruptions of > 14 days between sequential fractions were considered to represent two separate "courses". Complete treatment was defined as receiving 5 fractions (short course) or 25+ fractions (long course). These definition were created based on clinical practice guidelines and in consultation with clinical experts. During the initial data analysis, several issues with the data were encountered. These included: Inconsistent body region description through a course (i.e. multiple body regions described); More than 1 fraction recorded in a single day; Misclassified or missense doses; discordant courses (i.e. course could not be classified as either short course or long course based on dosing and duration). The following solutions were applied, based on consultation with Dr. Timothy Hanna:

Table 5-8: Radiation Errors and Solutions

Error Encountered	Solution
More than 1 body region throughout a course	Included, if at least 1 fraction given to an eligible body region
> 1 fraction delivered in 1 day	Classified as 1 fraction only
>1 fraction delivered in 1 day to 2 body regions	Include fraction given to rectal cancer body region
> 1 fraction delivered in 1 day to same body region	Include fraction with the highest dose
Suspected Misclassified Doses	Dose of "1" - Reclassify based on mode fraction dose for course
	Dose of "1" for all fractions in course: >5 fractions reclassify as 1.8 gy; <=5 fractions reclassify as 5 gy (a)
	Missense dose due to suspected input error (i.e. 0.18gy, 18 gy, etc.) reclassify based on mode fraction dose for course (b)

(a) A Dose of 1 gy is not used in radiation treatment for rectal cancer, the suspicion of the group was that this dose was indicated based on 1 fraction being given
(b) Input errors suspected as the dosing was a factor of 10 off expected (i.e. missed decimal point).

Working with the data analysts (Chad McClintock, Weidong Kong), summaries of the derived radiation data were reviewed. The above mentioned methodology and rules were applied to capture and classify relevant radiation treatments.

5.4.8.5 Chemotherapy

Details of chemotherapy treatments were identified through the Cancer Activity Level Database (ALR). Similar to radiation treatment, the ALR captures dates of treatment, the name of the chemotherapy drug administered, the dose of the chemotherapy drug and the name of the chemotherapy "regimen". "Regimen" is the combination of specific chemotherapy drugs used, and is standardized. Similar to radiation data, chemotherapy data is not summarized in a meaningful way in the ALR. Clinical experts (Dr. Chris Booth and Dr. Adam Fundytus, Medical Oncologists, Queen's University) were engaged to interpret ALR data to ensure that appropriate treatments were captured.

The ALR was queried for encounters between 1 year prior to surgery and 1 year after surgery. These time constraints were used based on clinical practice guideline review (***Chapter 3)*** and in consultation with the clinical experts. Encounters where colorectal applicable chemotherapy regimens or drugs were delivered were included. The ALR does include a label for which regimen is was used at each encounter, and also which individuals drugs were delivered at each encounter. Chemotherapy was categorized as preoperative or postoperative based on the date of surgery and date of chemotherapy receipt. Chemotherapy was also further categorized as "Chemo-radiation" if given concurrently with radiation. Regimen was categorized as "Single Agent", "Chemoradiation", "FOLFOX/XELOX" and "Palliative". The ALR does identify chemotherapy delivered concurrently with radiation through a specific regimen code. In the case that ALR regimen value was missing, the regimen was classified based on the specific drugs delivered. If not indicated in the regimen code, chemo-radiation was identified based on whether the chemotherapy was delivered within 14 days of the radiation treatment dates. A summary can be found in table 5 – 9. Note, palliative codes are not included.

Table 5-9: Cancer Activity Level Reporting Database Regimen Definition

Regimen	ALR Code
Single Agent (5-Fluoruouracil or Capecitabine)	CAPE; CAPEC; FU; FU(CIV); FU (IV-CIV)LCVR; FU*CIV; FU*CIVFA; FULCV; FU-LEV; FUV; 5FU; FLUCVR; FUFA; FULCVR
Chemoradiation	FU+RT; CAPE (RT); FU (CIV-RT); FU (IV-CIV-RT-IV); FU*CIV+RT; FUCVR (RT); FU (CIV-RT)
FOLFOX or XELOX	FOLFOX; FOLFOX (MODIFIED); FU-OX; MFOLFOX; XELOX
Derived Regiment	ALR Drug Name
Single Agent	Capecitabine OR Fluorouracil OR Capecitabine Trial
Chemoradiation	Capecitabine OR Fluorouracil Plus Radiation
FOLFOX or XELOX	[Capecitabine OR Fluorouracil] AND Oxaliplatin

Similar to the radiation data, summaries of the raw chemotherapy data were provided by the data-analysts (Chad McClintock, Weidong Kong). These were reviewed, and working in

collaboration with the clinical experts, appropriate chemotherapy was identified, classified and included in the OntaReCC.

5.4.9 Survival

Date and cause of death was available from the Ontario Cancer Registry as part of mandatory reporting. Overall survival was used as a time dependent outcome in the survival analysis. In addition, both 3 and 5 year survival was also calculated, to allow for comparison with previous studies.

5.4.10 Statistical Analyses

Means with standard deviations were calculated for continuous variables, and count and proportions were tabulated for categorical variables. Medians and inter-quartile ranges were also calculated for continuous variables. Statistical comparisons of means between groups were performed with one-way analysis of variance, comparison of medians with Wilcoxon Rank Sum Test, and comparisons of proportions with the chi-square test. Date of Diagnosis was used to determine both three and five year overall survival. Kaplan Meier Analysis was also used to assess survival, anchored by date of diagnosis. Individuals were categorized as having the event (i.e. death) or censored at the end of this follow up. Univariable analysis was completed and reported.

Missing data for patient demographics was anticipated to be very low. Ultimately, the data was near complete, with only postal code missing in < 1% of patients in the entire cohort. The missing group was included in the most common category within the two variables which used postal code, including neighborhood income quintile (missing included in the middle

income group) and rurality (missing included in the urban group). For overall stage of disease, missing stage data (from Best Stage in the OCR) was included as a separate category. For the derived variables, missing data was found for surgeon volume and cancer centre designation. In both cases, missing was included as a separate category.

As described in section 5.4.3 (Data management), a data analyst was required for the raw statistical analyses, due restrictions as to who can work with raw data. After I selected the appropriate tests/analyses, the data analysts (Chad McClintock and Weidong Kong) applied the raw statistical testing. I reviewed the raw outputs and directed any refinement of the statistical testing required. I then combined the raw output into the tables presented in this chapter. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC)

5.4.11 Addressing Logistical Challenges in the Creation of the Ontario Rectal Cancer Cohort

Creating a new provincial database of those with Rectal Cancer required overcoming a number of logistical challenges. To begin with, permission to access data holdings curated by the Ontario Cancer Registry required the submission of a data-access application. Permission to access this data was ultimately granted, but did require a number of meetings with the data curators at the Ontario Cancer Registry to ensure that the purposes of the research aligned with the priorities of the Ontario Cancer Registry/Cancer Care Ontario. In addition, extensive discussions were required to ensure that compliance with the Ontario Cancer Registry's data security and curation policies were met. Specific protocols were established based on these discussions.

Once permission was granted, I had to recruit a team of individuals who would support the work. This included data-analysts (Mr. Wiedong Kong and Mr. Chad McClintock) who had permission to access provincially maintained data, which contained personal and sensitive information. I also needed to recruit a program manager (Ms. Tina Dyer) who had experience with ensuring compliance with the Ontario Cancer Registry's policies and had experience in communicating with the Ontario Cancer Registry/Cancer Care Ontario. Finally, I recruited an individual with experience in pathology data abstraction (Ms. Sarah Pickett).

After the team was recruited, the early period of the research was spent ensuring that the correct data-sources were accessible and that the correct time periods were available. For example, pathology data was initially available until the end of 2015, but was only complete to the end of 2014. Additionally, the Cancer Activity Level Reporting Database is updated at the end of the fiscal year, while the CIHI-DAD database is updated at least quarterly. The data for this thesis was eventually available for a 10 year period (January 1, 2010 – December 31, 2019), and updating the data within the Ontario Rectal Cancer Cohort required regular maintenance and oversight.

Some other challenges that were faced included incomplete data within the databases. For instance, the Cancer Activity Level Reporting Database, which was the primary source of radiation and chemotherapy treatment details, was incomplete prior to 2009. Similarly, the "e-Path" database, which ultimately was not included in this work, was unavailable prior to 2015, and was incomplete between 2016 – 2019. "E-path" would have been a very helpful resource as the current version provides information on surgical pathology specimens such as completeness of resection and positive margins. This data would have been helpful to validate the pathology

data I abstracted for this thesis, as well as allowing for a more efficient way of update pathology data for the 2nd half of the study period.

Finally, the creation and maintenance of the Ontario Rectal Cancer required funding from a variety of sources. This funding was necessary as there were significant costs associated with seeking permissions and accessing data from the Ontario Cancer Registry, costs associated with importing data into the Ontario Rectal Cancer Cohort, costs with the initial cleaning and validation of the data, and costs with data-analysts. There are ongoing costs related to maintaining the database, including maintenance of ethics, program management, and updating the database for the future work described in Chapter 7. Acquiring funding for the Ontario Rectal Cancer required me to obtain funding from a number of sources including the Canadian Institutes of Health Research, Interdisciplinary Grants through the Department of Oncology at Queen's University and other sources of internal funding.

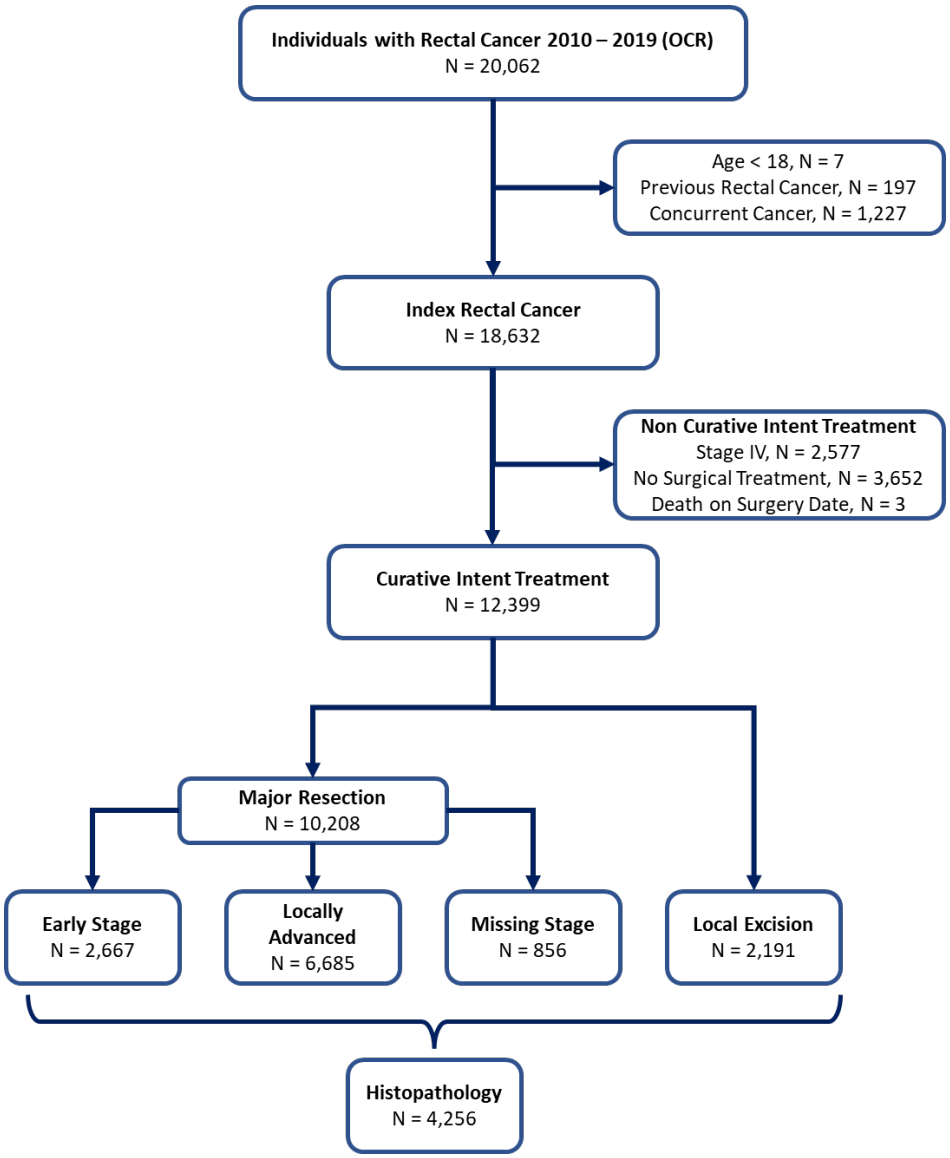
5.5 Chapter Results – Profile of the Ontario Rectal Cancer Cohort

A total of 20,062 individuals with a rectal cancer diagnosis were identified from the Ontario Cancer Registry between 2010 – 2019. A total of 7 individuals were < 18 years of age at diagnosis and were excluded. A total of 197 individuals had a previous colorectal cancer (diagnosed prior to 2010), while 1,227 had a concurrent or recent diagnosis of a 2nd primary cancer. Both groups were excluded for reasons described above. This left 18,632 individuals with a new diagnosis of rectal cancer.

The cohort was then further divided into "curative intent" and "non-curative intent" groups. A total of 2,577 individuals had Stage IV (metastatic) cancer at diagnosis, while 3,652 individuals did not undergo any surgical treatment. These two groups were combined to form the

"non-curative intent" group. Of the remaining individuals, 3 died on the date of surgery and were excluded from the curative intent treatment group. Those with "curative intent treatment" (n = 12,399) were further categorized based on type of surgery (local excision vs. major resection). Finally, those undergoing major resection were classified as Early Stage (Stage I), Locally Advanced (Stage II and III) and Missing Stage. (Figure 5 – 4) From these groups, 4,256 had histopathology data available.

Figure 5-4: Flowsheet of Included Individuals in the Ontario Rectal Cancer Cohort



5.5.1 Diagnosis Date

The diagnosis date was determined using the endoscopy date (colonoscopy or flexible sigmoidoscopy) in 97.5% of individuals. The remaining did not have a linked endoscopy date on or preceding treatment, and the OCR date was used. The endoscopy and OCR diagnoses dates were compared. This comparison found 70.2% of individuals had the endoscopy date and OCR diagnosis date as the same date, and a total of 89.4% of individuals had a diagnosis date within 30 days of the endoscopy date.

5.5.2 Baseline Characteristics

Table 5 – 10 describes the available patient related variables for the entire cohort (N = 18,632) and by intent of treatment (curative intent treatment, n = 12,399; non-curative intent, n = 6,232). Overall, the average age was 65.5 (Standard Deviation 13.4), with the majority of included patients being male (61.9%). There was no missing data for age or sex within the cohort. Most individuals lived in urban settings (82%) with slightly less individuals from the highest income quintile (18.8%) compared with the lowest income quintile (20.7%). A total of 188 individuals (1% of the total; n<10, <0.05% in the curative intent group) had a missing postal code and could not be categorized. For the purposes of analyses, those with missing postal code were added to those in the urban setting and mid-income quintile. Lowest co-morbidity score group (Charlson Comorbidity Score of 0 – 2) was the most common, with no missing values. Based on the Ontario Cancer Registry's "Best Stage", 23.4% of individuals had early stage disease, 43.9% had locally advanced disease, 13.8% had metastatic disease, and 18.9% did not

have an assigned stage at time of diagnosis. A comparison of the OCR best stage and the available TNM data appears in appendix Chapter 5 – 5. This demonstrated that OCR best stage had more complete data vs. the TNM staging based on available data. Using the TNM staging would have resulted in an additional 1,368 (7.3%) missing stage patients, but would have allowed for identification of 6 patients in the missing group to have staging assigned.

The median age (67 vs. 65, $P < 0.0001$) and mean age (66.6 vs. 64.9, $P < 0.0001$) of the non-curative intent cohort was higher than those in the curative intent cohort. There were a similar proportion of males and females in the two groups ($P = 0.107$). Most individuals with early stage (87%) or locally advanced disease (86.3%) underwent curative intent treatment. More than half (55.8%) of those with missing stage did not receive curative intent treatment.

Table 5-10: Characteristics of Individuals with an Index Rectal Cancer (2010 - 2019), by treatment intent

	Curative Intent Cohort N = 12,399	Not Curative Intent N = 6,232	Total N = 18,631	Significant Testing
Age, Mean (SD)	64.9 (12.9)	66.6 (14.4)	65.5 (13.4)	P < 0.0001
Age, Median (IQR)	65.0 (56.0, 74.0)	67.0 (56.0, 78.0)	66.0 (56.0, 75.0)	P < 0.0001
Age Range	18.0 - 97.0	19.0 - 102.0	18.0 - 102.0	
Age Group				
18-29	62 (0.5%)	35 (0.6%)	97 (0.5%)	P < 0.0001
30-39	306 (2.5%)	172 (2.8%)	478 (2.6%)	
40-49	1024 (8.3%)	526 (8.4%)	1550 (8.3%)	
50-59	2790 (22.5%)	1294 (20.8%)	4084 (21.9%)	
60-69	3544 (28.6%)	1506 (24.2%)	5050 (27.1%)	
70-79	2926 (23.6%)	1334 (21.4%)	4260 (22.9%)	
80+				
Sex	1747 (14.1%)	1365 (21.9%)	3112 (16.7%)	
Female	4676 (37.7%)	2426 (38.9%)	7102 (38.1%)	P = 0.11
Male				
Income quintile (a)	7723 (62.3%)	3806 (61.1%)	11529 (61.9%)	
1 (lowest)	2466 (19.9%)	1395 (22.4%)	3861 (20.7%)	P < 0.0001
2-4	7505 (60.5%)	3763 (60.4%)	11268 (60.5%)	
5 (highest)				
Residential Region (a)	2428 (19.6%)	1074 (17.2%)	3502 (18.8%)	
Rural	2337 (18.8%)	1012 (16.2%)	3349 (18.0%)	P < 0.0001
Urban				
Charlson Comorbidity Score	10062 (81.2%)	5220 (83.8%)	15282 (82.0%)	
0 - 2	7320 (59.0%)	3842 (61.6%)	11162 (59.9%)	P < 0.0001
3	1784 (14.4%)	506 (8.1%)	2290 (12.3%)	
> 3	3295 (26.5%)	1884 (30.2%)	5179 (27.8%)	
Mean(SD)	3.1 (1.9)	2.8 (2.5)	3.0 (2.1)	P < 0.0001
Median(IQR)				
Cancer Stage	2.0 (2.0, 4.0)	2.0 (0.0, 6.0)	2.0 (2.0, 4.0)	P < 0.0001
Early (Stage I)	3785 (30.5%)	568 (9.1%)	4353 (23.4%)	P < 0.0001
Locally Advanced (Stage II/III)	7055 (56.9%)	1117 (17.9%)	8172 (43.9%)	
Metastatic (Stage IV)	0 (0.0%)	2577 (41.4%)	2577 (13.8%)	
Missing				

(a) A total of 188 individuals had a missing postal code and thus had missing residential region and missing neighbourhood income quintile. These individuals were included in the "Urban" and mid income quintile.

5.5.3 Staging Investigations

A summary of the completed staging investigations can be found in table 5 – 11. Overall, 46.2% of individuals received all recommended staging investigations. Local regional staging (Pelvic MRI or TRUS) was the least frequently completed staging investigation at 51.8%. Those undergoing curative intent treatment had higher rates of each individual staging investigation, as well as a higher rate of overall complete staging. Notably, only a small proportion of individuals in the non-curative group completed local regional staging through Pelvic MRI or Transrectal Ultrasound.

Table 5-11: Completed Staging Investigations, by treatment intent

Staging Investigation	Curative Intent Cohort N = 12,399	Not Curative Intent N = 6,232	Total N = 18,631	
Colonic Assessment	10768 (86.8%)	3459 (55.5%)	14227 (76.4%)	P < 0.0001
Chest CT or CXR	10473 (84.4%)	3244 (52.1%)	13717 (73.6%)	P < 0.0001
Abdominal CT, U/S or MRI	10660 (85.9%)	3071 (48.3%)	13731 (73.7%)	P < 0.0001
Pelvic MRI or TRUS	8441 (68.1%)	1204 (19.3%)	9645 (51.8%)	P < 0.0001
Complete Staging	7813 (63.0%)	792 (12.7%)	8605 (46.2%)	P < 0.0001

In those who completed all required staging investigations, the median time from diagnosis to last investigation was 35 days (IQR 21 – 56). Chest imaging was completed at a median of 20 days (IQR 8 – 43), abdominal imaging at a median of 15 days (IQR 7 – 32) and local regional staging at a median of 21 days (IQR 12 – 35). (Figure 5 – 5 to 5 – 8). The presented figures include staging investigations completed up to 1 year after diagnosis, for illustrative purposes only. Only investigations completed prior to first treatment date (or up to 90 days after diagnosis in those with non-curative intent treatments) were included in analyses of completed (or adherent) staging investigations. Although investigations completed up to 90 days prior to diagnosis were eligible for inclusion as “Staging Investigations”, only a small proportion

fit this description. For instance, <5% of Chest Imaging or abdominal imaging was completed prior to diagnosis and <2% of local-regional staging was completed prior to diagnosis.

Figure 5-5: Time from diagnosis to last staging investigation in those with complete staging

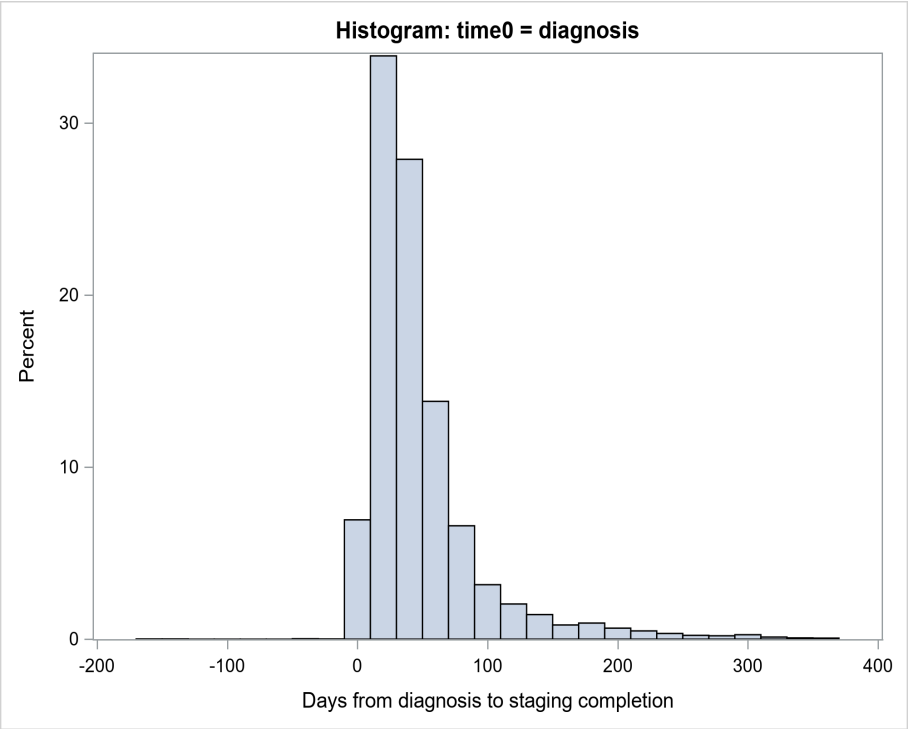


Figure 5-6: Time from diagnosis to chest staging completion

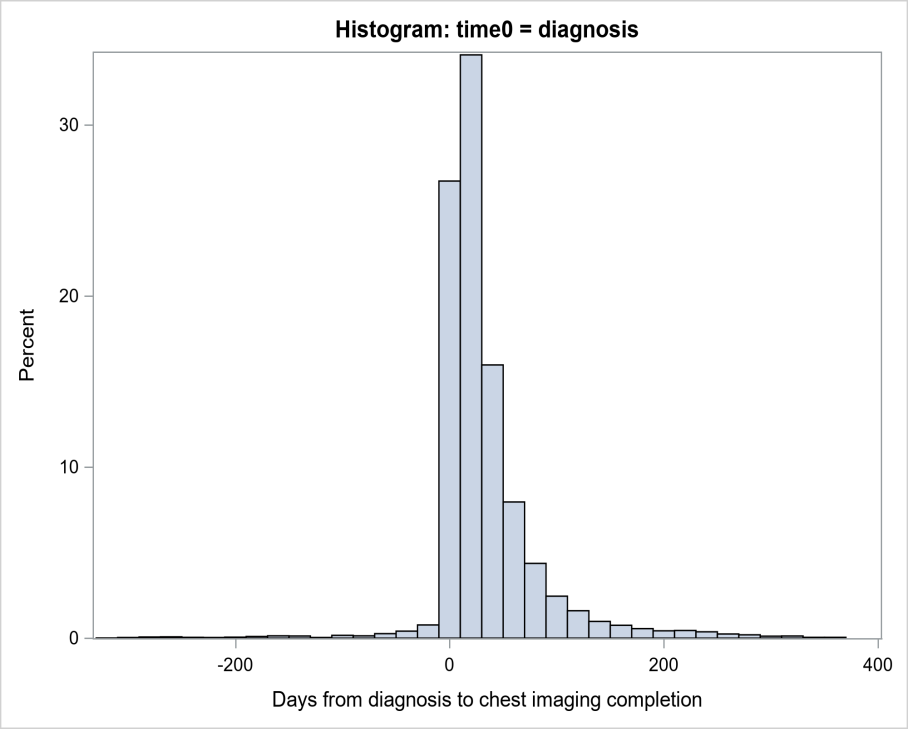


Figure 5-7: Time from diagnosis to abdominal imaging completion

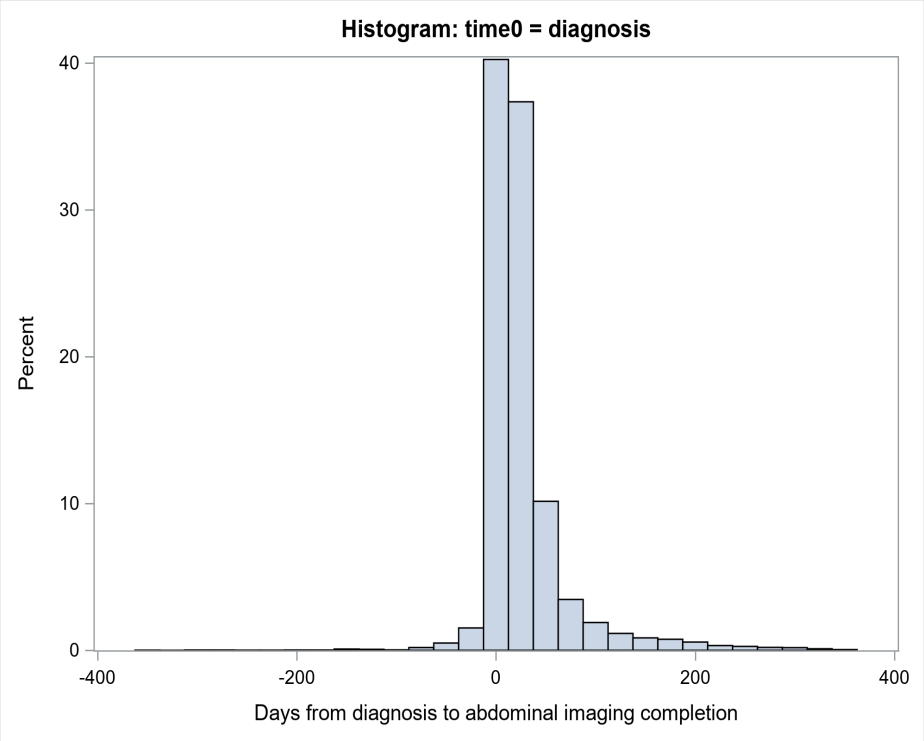
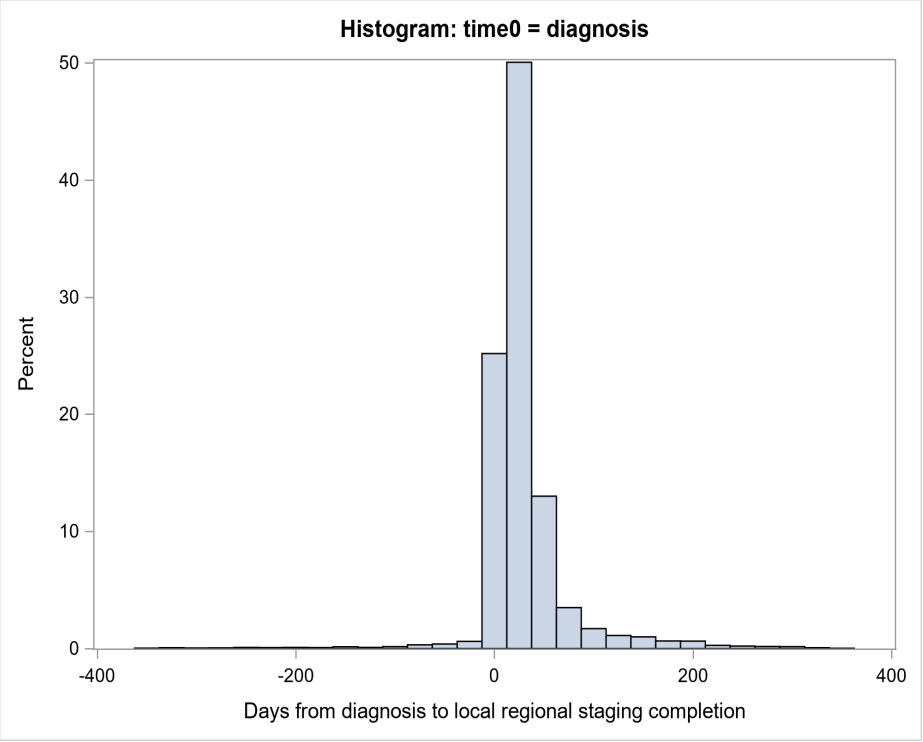


Figure 5-8: Time from diagnosis to local regional staging completion



5.5.4 Clinical Assessments

Clinical assessments are presented for the entire cohort (Table 5 - 12) and for those undergoing curative intent treatment (Table 5 – 13). Surgical Assessment was the most common type of clinical assessment, occurring in > 90% of the cohort. Only a small number of individuals undergoing major surgical excision did not have a surgical assessment captured within the available databases. Radiation Oncology assessment occurred in 64% of all individuals in the cohort, and was most common in those with locally advanced disease (86.2%). Medical oncology assessment occurred less frequently (53% of the total cohort), with those with locally advanced disease most commonly assessed (71.0%).

Table 5-12: Clinical Assessments by Specialty, Full Cohort

	Curative Intent N = 12,399	**Non-Curative N = 6,232**	**Total N = 18,631**
Medical Oncology Assessment	6696 (54.0%)	3115 (50.0%)	9811 (52.7%)
Radiation Oncology Assessment	7936 (64.0%)	3993 (64.1%)	11929 (64.0%)
Surgical Assessment	12024 (97.0%)	5676 (91.1%)	17700 (95.0%)

Table 5-13: Clinical Assessments, by Specialty based on Type of Surgery and Stage of Disease

		Major Resection		
	Local Excision Only N = 2,191	**Early Stage N = 2,667**	**Locally Advanced N = 6,685**	**Missing Stage N = 856**
Medical Oncology Assessment	557 (25.4%)	927 (34.8%)	4745 (71.0%)	467 (54.6%)
Radiation Oncology Assessment	662 (30.2%)	1031 (38.7%)	5762 (86.2%)	481 (56.2%)
Surgical Assessment	1844 (84.1%)	2657 (99.6%)	6672 (99.8%)	851 (99.4%)

5.5.5 Surgical Treatment

A total of 12,399 individuals underwent either local excision or major resection for curative intent. This included local excision only (N = 2,191), resection for early stage disease (N = 2,667), resection for locally advanced disease (N = 6,685) and resection in those with missing stage (N = 856). Surgeon volume tertile was not applicable for those undergoing local excision only (n = 2,191), as volume was defined based on number of major resections performed and not local excisions performed. Less than 10% of those undergoing a major resection had missing surgeons volume (n=892/10,208). Cancer Centre Designation was missing in <1% of individuals.

Characteristics based on type of surgical excision and stage of disease are reported in table 5 – 14. There were small differences noted between these groups for all included characteristics. Not included in table 5 – 14 were those with Stage IV disease. This group was included in the "non-curative" treatment group which included 24.3% (n = 627/2577) who underwent a major surgical resection. The type of resections included in this group were: Low Anterior Resection, n = 306, 49%; Abdominoperineal Resection or Hartmann's Procedure, n = 262, 42%; or Other Major Colorectal Resection, n = 59, 9%.

Table 5-14: Characteristics of those undergoing surgical excision, by type of surgery and cancer stage

	Local Excision Only N = 2,191 (17.6%)	Major Surgical Excision			Total	
		Early Stage N = 2,667 (21.5%)	Locally Advanced N = 6,685 (53.9%)	Missing Stage N = 856 (6.9%)	N = 12,399	
Surgery Type					**2,191 (17.6%)**	
Low Anterior Resection		**1,554 (58.2%)**	**3,206 (48.0%)**	**455 (53.2%)**	**5,215 (42.1%)**	
Abdominal Perineal Resection or Hartmann's Procedure		**680 (25.5%)**	**2,457 (36.7%)**	**233 (27.2%)**	**3,370 (27.2%)**	
Other Major Resection		**433 (16.2%)**	**1,022 (15.3%)**	**168 (19.6%)**	**1,623 (13.1%)**	
Age Group						
19-39	87 (24.4%)	52 (14.6%)	196 (55.1%)	21 (5.9%)	356 (2.9%)	P < 0.0001
40-49	165 (16.1%)	193 (18.8%)	592 (57.8%)	74 (7.2%)	1024 (8.3%)	
50-59	535 (19.2%)	554 (19.9%)	1511 (54.2%)	190 (6.8%)	2790 (22.5%)	
60-69	547 (15.4%)	773 (21.8%)	1986 (56.0%)	238 (6.7%)	3544 (28.6%)	
70-79	453 (15.5%)	733 (25.1%)	1524 (52.1%)	216 (7.4%)	2926 (23.6%)	
80+	403 (23.1%)	358 (20.5%)	869 (49.7%)	117 (6.7%)	1747 (14.1%)	
Mean Age (SD)	65.0 (14.3)	65.8 (12.2)	64.5 (12.7)	65.0 (12.6)	64.9 (12.9)	P < 0.0001
Female	882 (18.9%)	1046 (22.4%)	2444 (52.3%)	304 (6.5%)	4676 (37.7%)	P = 0.003
Male	1309 (16.9%)	1621 (21.0%)	4241 (54.9%)	552 (7.1%)	7723 (62.3%)	
1 (lowest income)	437 (17.7%)	505 (20.5%)	1376 (55.8%)	148 (6.0%)	2466 (19.9%)	P = 0.009
2-4	1301 (17.3%)	1606 (21.4%)	4078 (54.3%)	520 (6.9%)	7505 (60.5%)	
5 (highest income)	453 (18.7%)	556 (22.9%)	1231 (50.7%)	188 (7.7%)	2428 (19.6%)	
Rural	365 (15.6%)	521 (22.3%)	1287 (55.1%)	164 (7.0%)	2337 (18.8%)	P = 0.04
Urban	1826 (18.1%)	2146 (21.3%)	5398 (53.6%)	692 (6.9%)	10062 (81.2%)	
Comorbidity Score 0 - 2	1666 (22.8%)	1766 (24.1%)	3410 (46.6%)	478 (6.5%)	7320 (59.0%)	P < 0.0001
Comorbidity Score 3	287 (16.1%)	490 (27.5%)	875 (49.0%)	132 (7.4%)	1784 (14.4%)	
Comorbidity Score > 3	238 (7.2%)	411 (12.5%)	2400 (72.8%)	246 (7.5%)	3295 (26.6%)	
Mean Score (SD)	2.1 (1.5)	2.6 (1.3)	3.6 (2.1)	3.2 (1.8)	3.1 (1.9)	P < 0.0001
Median Score (IQR)	2.0 (2.0, 2.0)	2.0 (2.0, 3.0)	2.0 (2.0, 6.0)	2.0 (2.0, 4.0)	2.0 (2.0, 4.0)	P < 0.0001
Cancer Centre Level 1-2	763 (12.3%)	1361 (22.0%)	3634 (58.7%)	437 (7.1%)	6195 (50.0%)	P < 0.0001
Cancer Centre Level 3	849 (19.9%)	894 (21.0%)	2196 (51.6%)	317 (7.4%)	4256 (34.3%)	
Cancer Centre level 4-5	571 (29.6%)	411 (21.3%)	848 (43.9%)	102 (5.3%)	1932 (15.6%)	
Missing	8 (50.0%)	1 (6.3%)	7 (43.8%)	0 (0.0%)	16 (0.1%)	
Surgeon Volume/year						
Missing or Not Applicable	2191 (71.1%)	390 (12.7%)	377 (12.2%)	125 (4.1%)	3083 (24.9%)	P < 0.0001
Q1 (Low-3.5)	0 (0.0%)	861 (26.3%)	2185 (66.7%)	231 (7.0%)	3277 (26.4%)	
Q2 (>3.5-14.5)	0 (0.0%)	711 (23.3%)	2082 (68.4%)	252 (8.3%)	3045 (24.6%)	
Q3 (>14.5)	0 (0.0%)	705 (23.5%)	2041 (68.2%)	248 (8.3%)	2994 (24.1%)	
Index Surgery Year						
2010-2013	694 (14.4%)	1147 (23.7%)	2729 (56.5%)	261 (5.4%)	4831 (39.0%)	P < 0.0001
2014-2016	610 (16.6%)	856 (23.4%)	2101 (57.3%)	97 (2.6%)	3664 (29.6%)	
2017-2019	887 (22.7%)	664 (17.0%)	1855 (47.5%)	498 (12.8%)	3904 (31.5%)	

In those whose first treatment was major resection, the median and mean time from diagnosis to surgery was longer in those with early stage disease compared with those with locally advanced disease. The time from completion of the last preoperative staging investigation to surgery in this group was relatively short in both early and locally advanced disease. (Table 5 – 15)

Table 5-15: Days until surgery, in those who did not receive preoperative radiation, major resection only

	Early Stage Disease N = 2,210	Locally Advanced Disease N = 2,477
Diagnosis to Surgery		
Mean Days (SD)	83.5 (61.6)	58.4 (50.5)
Median Days (IQR)	67 (45 - 102)	47 (29 - 71)
Last Staging Investigation to Surgery		
Mean Days (SD)	24.0 (26.2)	17.4 (21.2)
Median Days (IQR)	17 (5 - 35)	10 (1 - 26)

5.5.6 Radiation Treatment

A total of 6,277 individuals received rectal cancer specific radiation with curative intent. Of those who received radiation, 87.2% (n = 5548) received long course radiation and 12.0% (n = 764) received short course radiation based on the previously established definitions (section 5.4.6.4). The majority of individuals received radiation prior to surgical resection (n = 5326, 85%) with fewer receiving radiation after surgery (n = 969, 15%). Initially, 745 courses did not meet the criteria for either short course or long course radiation. The most common reason was due to a dose outside the defined dose range for long course (1.5 to 2.5 gy) or short course (4 – 6 gy). Within this group, 669 courses had a dose of "1" gy. Individual chart review of these cases was completed to allow for categorization. Ultimately, a dose of "1" (which is not a dose used in rectal cancer) was considered to be an input error, as this represented one dose given (as opposed to the actual dose). These doses were then recoded as 5 gy (for short course as defined as 5 or

less fractions received) or 1.8 (for long course, as defined as more than 5 fractions received) based on standard doses. Additional criteria were then applied including: (i) Surgery <= 14 days following last dose of radiation (Short Course Radiation) (ii) Chemotherapy given <=14 days from first dose of radiation (Long course Chemoradiation). This left 52 courses (0.8% of the total) that were unable to be categorized and labelled as "discordant (Table 5 – 16)

Table 5-16: Preoperative vs. Postoperative Radiation and Type. Note, includes early stage, locally advanced and missing stage.

	Preoperative Radiation (n = 5378, 83.6%)	Postoperative Radiation (n = 986, 16.4%)	Total (N = 6364)
Long Course	4653 (86.5%)	895 (90.8%)	5548 (87.2%)
Short Course	703 (13.1%)	61 (6.2%)	764 (12.0%)
Discordant	22 (0.4%)	30 (3.0%)	52 (0.8%)

5.5.7 Chemotherapy

A total of 5,947 (48%) individuals received chemotherapy in the curative intent cohort. This included 3,867 (31.8%) who received chemotherapy before surgery, and 4,794 (38.6%) after surgery. In those who underwent major resection and had a known stage (N = 9,352), 55.6% received chemotherapy, including 3,559 (35.9%) who received preoperative chemotherapy and 44.3% who received post operative chemotherapy. The majority of chemotherapy received preoperatively was part of long course chemoradiation (Curative Intent Cohort n = 2,592/3,867, 65.7%; Major Excision n = 2,395/3,359, 72.1%), while the majority of postoperative chemotherapy was systemic chemotherapy (Curative Intent Cohort n = 4,109/4,794, 85.7%; Major Excision n = 3,745/4,148, 90.2%). Only a small number of those who received chemotherapy had an unknown type of chemotherapy (Preoperative: Curative Intent Cohort n = 106/3,867, 2.7%; Postoperative: Curative Intent n = 291/4794, 6.1%). (Table 5 – 17)

Table 5-17: Chemotherapy received in the Curative Intent Cohorts

	Curative Intent Cohort	Major Surgical Excision with Known Stage
	N = 12,399	N = 9,352
Preoperative Chemotherapy	**3,867 (31.8%)**	**3,359 (35.9%)**
Chemoradiation	2,592 (20.9%)	2,395 (25.9%
Systemic Chemotherapy	1,169 (9.4%)	1,080 (11.5%)
Unknown Chemotherapy	106 (0.8%)	84 (0.9%)
Postoperative Chemotherapy	**4,794 (38.6%)**	**4,148 (44.3%)**
Chemoradiation	394 (3.1%)	187 (2.0%)
Systemic Chemotherapy	4,109 (33.1%)	3,745 (40.0%)
Unknown Chemotherapy	291 (2.3%)	216 (2.3%)
Any Chemotherapy (Pre or Post Operative)	**5,947 (48%)**	**5,196 (55.6%)**

5.5.8 Surveillance following Treatment

Surveillance following treatment was determined for those who underwent curative intent treatment only. There are no specific recommendations for those with non-curative intent treatment, and thus were excluded. Overall, 47.8% (n = 5,929/12,399) had completed surveillance within 18 months following surgical treatment. Of the recommended surveillance investigations, colonic assessment was completed the least frequently (6,561/12,399, 52.9%). Chest, Abdominal and Pelvic imaging were completed in more than 80% of patients. (Table 5 – 18)

Table 5-18 Surveillance Completions, by modality of investigation

	Colonic Assessment		Any Chest Imaging		Any Abdominal Imaging		Any Pelvic Imaging		Complete Surveillance	
Local Excision Only (n = 2,191)	784	35.7%	1511	69.0%	1595	72.8%	1526	69.6%	646	29.5%
Major Resection										
Early Stage (n = 2,667)	1680	63.0%	2115	79.3%	2066	77.5%	1925	72.2%	1229	46.1%
Locally Advanced (n = 6,685)	3704	55.4%	6409	95.9%	6274	93.9%	6177	92.4%	3734	55.9%
Missing Stage (n = 856)	393	45.9%	689	80.5%	701	81.9%	680	79.4%	320	37.4%
Total (n = 12,399)	**6561**	**52.9%**	**10724**	**86.5%**	**10636**	**85.8%**	**10308**	**83.1%**	**5929**	**47.8%**

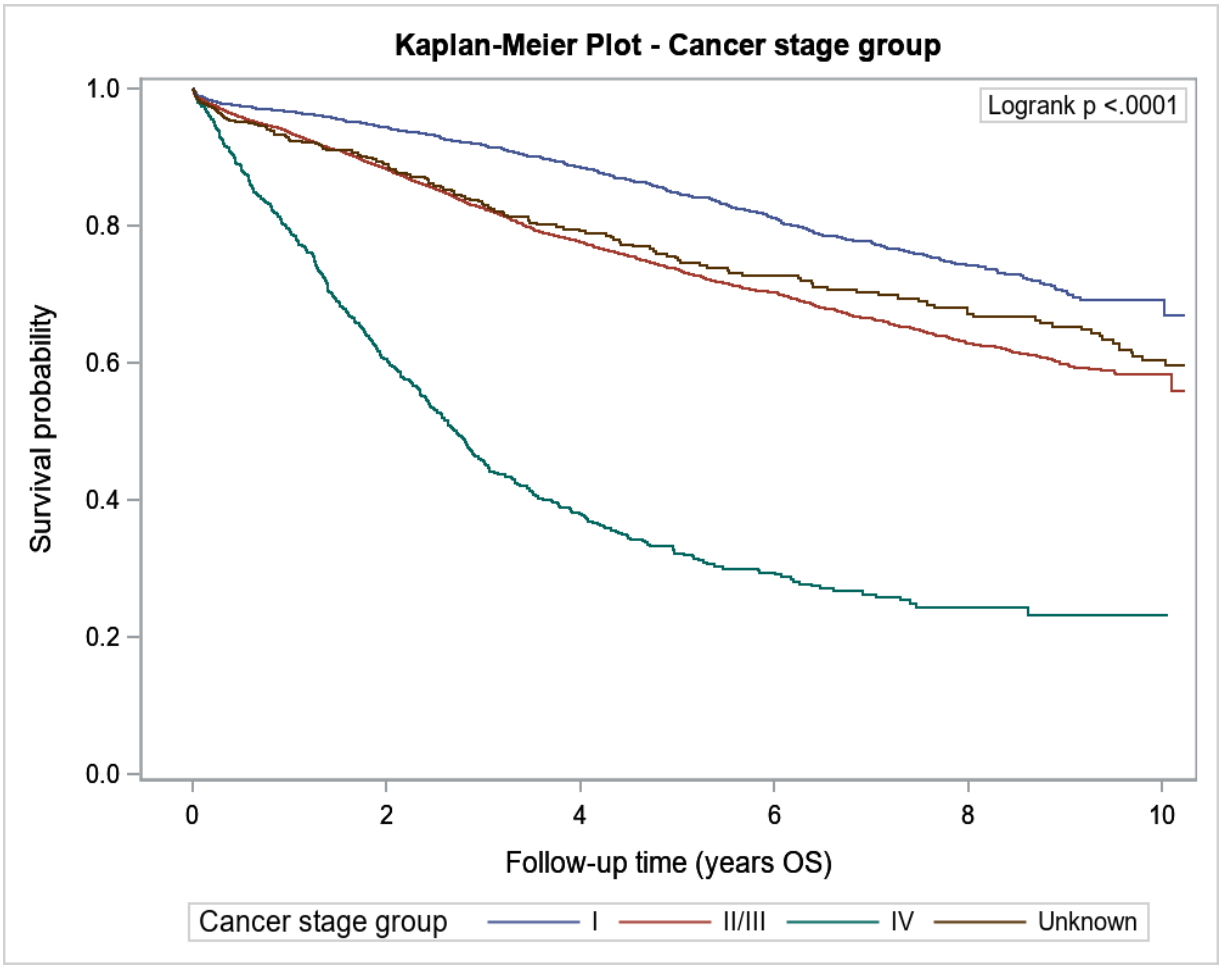
5.5.9 Survival

The overall 5 year survival for the entire cohort was 68.0%. Those who underwent curative intent treatment had a higher 5 year survival (82.0%) compared with the non curative intent cohort (40.2%, $P < 0.001$). In those undergoing curative intent treatment, the highest survival was found in those undergoing major resection with early stage disease (88.2%) followed by those undergoing major resection with unknown stage (86.6%), those undergoing a local excision only (81.3%) and those with locally advanced disease (79.1%). In the non-curative intent cohort, those with stage IV disease had a low 5 year overall survival (23.7%). (Table 5 – 19, Figure 5 – 9)

Table 5-19: Overall 5 Year Survival of those included in the Ontario Rectal Cancer Cohort

	Overall 5 Year Survival
All Individuals (N = 18,631)	**68.0%**
Curative Intent (N = 12,399)	**82.0%**
Local Excision Only (n = 2,191)	81.3%
Major Resection, Early Stage (n = 2,667)	88.2%
Major Resection, Locally Advanced (n = 6,685)	79.1%
Major Resection, Unknown Stage (n = 856)	86.6%
Non-Curative Intent (N = 6232)	**40.2%**
Stage IV Disease (n = 2,577)	23.7%
"Other" non curative (n = 3,655)	51.8%

Figure 5-9 Kaplan Meier Survival Curve by Stage of Disease at Diagnosis



Note: Stage I – Early Stage; Stage II/III - Locally Advanced; Stage IV - Metastatic; Stage Unknown – Missing; OS Overall Survival.

5.5.10 Histopathology Data

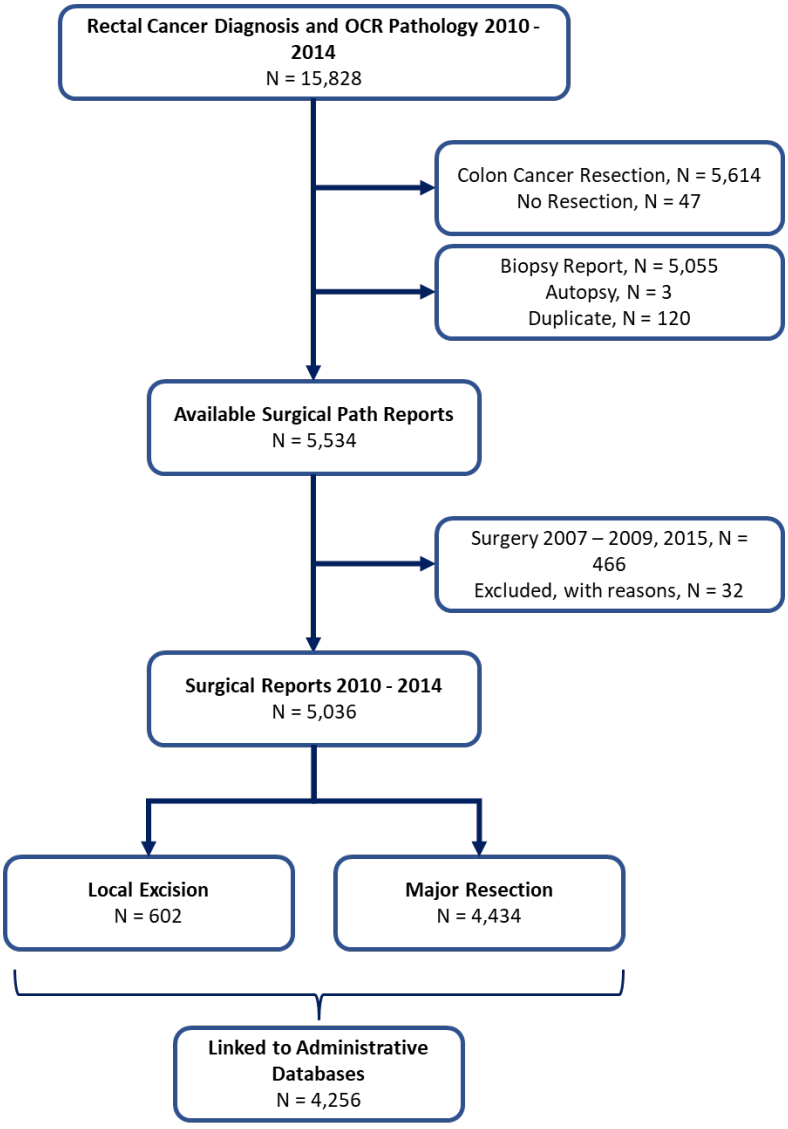
A total of 15,828 individuals had a rectal cancer diagnosis code and an available pathology report between 2007 and 2015. Excluding those with a colon cancer resection surgical code, or no resection, left 10,167 individuals with a suspected major or local excision for rectal cancer. Those with a biopsy report only (n = 5,055), autopsy (n = 3) or consult/2nd opinion (n = 120) were excluded. The Ontario Cancer Registry was unable to send reports from 2007 – 2009. In addition, at the time of request, the 2015 reports were incomplete (~399 of an expected ~1000 reports). For these reasons, the histopathology database was restricted to those between 2010 –

2014. Finally, 32 pathology reports were excluded for a variety of reasons. (Table 5 – 20) This resulted in a total of 5,036 reports which underwent full data abstraction, of which 4,433 had a major surgical resection and 602 had a local excision. (Figure 5 – 10) Of these reports, a total of 4,256 (84.5%) could be linked to individuals within the full dataset. It should be noted that those with stage IV disease were included in the histopathology database.

Table 5-20: Reasons for Exclusion of Histopathology Reports

Exclusion Reason	Number of Cases (%)
Ancillary Studies	12 (38%)
Autopsy	2 (6%)
Biopsy Only	1 (3%)
Colon Cancer	4 (13%)
Dysplasia Only	3 (9%)
Metastatic Disease	2 (6%)
Other Histology	3 (9%)
Non-colorectal Procedure	4 (13%)
Local Recurrence	1 (3%)

Figure 5-10: Flowsheet of Included Histopathology Data



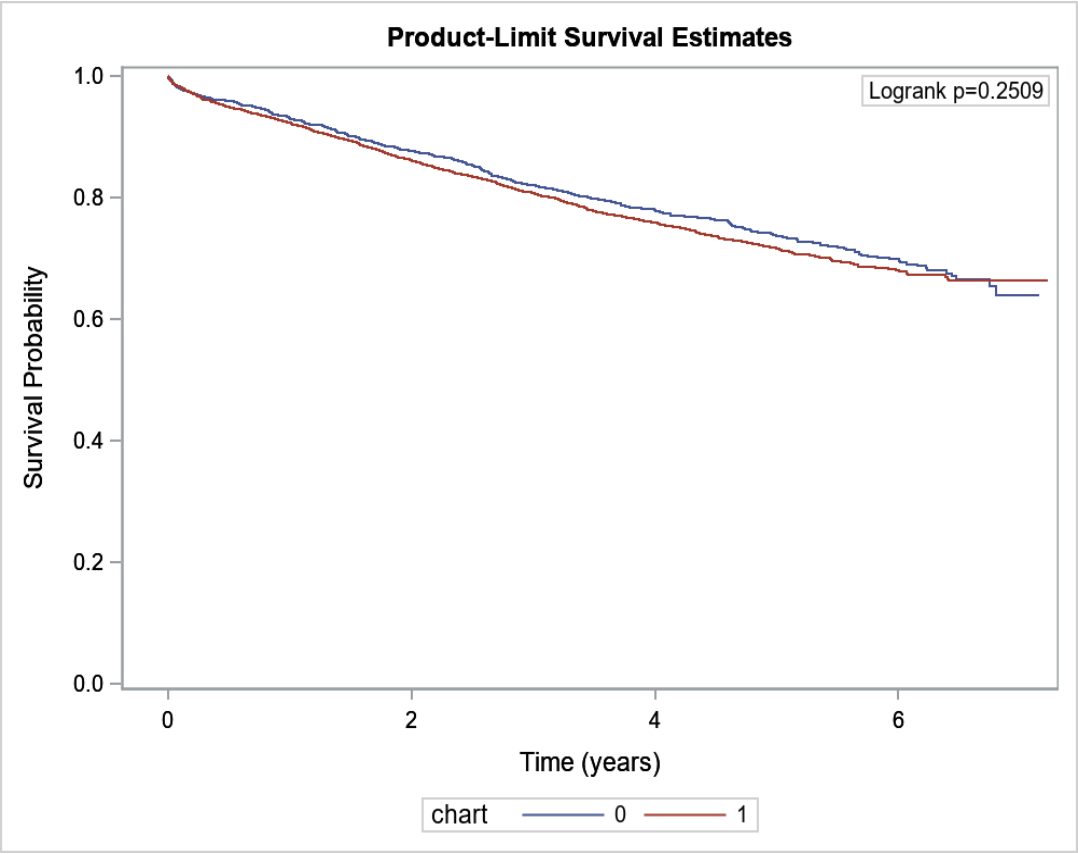
Individuals with available histopathology data were compared to those without histopathologic data (during the same period) to determine whether important differences existed between these two groups. Comparison of baseline characteristics between these groups is presented in Table 5 – 21. This table includes those undergoing a major surgical excision, with stage IV disease excluded (n = 245). The two groups were similar in terms of baseline characteristics (age, sex, rurality, socio-economic status). Missing stage was more common in those without surgical pathology (15.7% vs. 3.8%). The likely explanation is that the Ontario

Cancer Registry assigns cancer stage based on a number of sources, including the histopathology report. When those with missing stage are excluded, similar distribution of cancer stage was observed (Stage I 34.4% vs. 35.6%; Stage II 23.6% vs. 25.4%; Stage III 41.9% vs. 39.0%). The other significant difference between the groups was surgical year. Those in later years were more likely to have path data available. Survival was similar between groups, as demonstrated by the Kaplan-Meier Analysis (Figure 5 – 11).

Table 5-21 Comparison of Baseline Characteristics between those with and without available histopathology data (2010 -2014) in those undergoing major resection (curative intent cohort)

	Major Resections, 2010 – 2014 (N = 6,102)	**Pathology Data Available (N = 4,256)**	**Pathology Data Not Available (N = 1,846)**	**Statistical Testing**
Sex				
Female	2,255 (37.0%)	1,549 (36.4%)	706 (38.2%)	P = 0.17
Male	3,847 (63.0%)	2,707 (63.6%)	1,140 (61.8%)	
Age				
< 30	25 (0.4%)	15 (0.4%)	10 (0.5%)	P = 0.23
30 - 39	125 (2.0%)	82 (1.9%)	43 (2.3%)	
40 - 49	451 (7.4%)	321 (7.5%)	130 (7.0%)	
50 - 59	1,262 (20.7%)	892 (21.0%)	370 (20.0%)	
60 - 69	1,720 (28.2%)	1,201 (28.2%)	519 (28.1%)	
70 - 79	1,513 (24.8%)	1,056 (24.8%)	457 (24.8%)	
80+	1,006 (16.5%)	689 (16.2%)	317 (17.2%)	
Surgery Year				
2010	1,099 (18.0%)	717 (16.8%)	382 (20.7%)	P < 0.0001
2011	1,323 (21.7%)	877 (20.6%)	446 (24.2%)	
2012	1,280 (21.0%)	919 (21.6%)	361 (19.6%)	
2013	1,338 (21.9%)	976 (22.9%)	362 (19.6%)	
2014	1,062 (17.4%)	767 (18.0%)	295 (16.0%)	
Cancer Stage				
I	1,964 (32.1%)	1,410 (33.1%)	554 (30.0%)	P < 0.001
II	1,362 (22.3%)	967 (22.7%)	395 (21.4%)	
III	2,326 (38.1%)	1,719 (40.4%)	607 (32.9%)	
Missing	450 (7.4%)	160 (3.8%)	290 (15.7%)	
Residential Area				
Urban	4,825 (79.1%)	3,377 (79.3%)	1,448 (78.4%)	P = 0.64
Rural	1,175 (19.3%)	811 (19.1%)	364 (19.7%)	
Missing	102 (1.7%)	68 (1.6%)	34 (1.8%)	
SES Quintile				
1 (poorest)	1,020 (16.7%)	709 (16.7%)	311 (16.8%)	P = 0.97
2	4,012 (65.7%)	2,803 (65.9%)	1,209 (65.5%)	
5 (richest)	986 (16.2%)	684 (16.1%)	302 (16.4%)	
missing	84 (1.4%)	60 (1.4%)	24 (1.3%)	

Figure 5-11: Kaplan Meier Analysis, comparing those with histopathology data (Chart = 1) and without histopathology data (Chart = 0)



The completeness of the histopathology was assessed based on the recommended reporting requirements provided by the College of American Pathologists. (13) In those with an available pathology report, the majority had a synoptic report (n = 4459/5036, 88.5%) or synoptic-like report (n = 33/5036, 0.7%). In those undergoing a major resection (N = 4434), there was near complete reporting of most of the required elements. The exception was the quality of the total mesorectal excision (n=3532/4434, 79.7%). In those undergoing local excision (n = 602), there was wide variation in the reporting of the required elements. Overall, 59.5% (n = 358) of those undergoing local excision had the minimum required elements reported, while 46.8% (n = 282) had all suggested elements reported. (Table 5-22)

Table 5-22: Completeness of Pathology Reporting in the available histopathology reports

Synoptic Report (Resection and Local Excision, N = 5,036)		
Yes	4,459	88.5%
No	544	10.8%
Some Features	33	0.7%
Reporting of Required Elements - Major Resection (N = 4434)		
Quality of Total Mesorectal Excision	3,595	81.1%
Distal Margin Status	4,379	98.8%
Circumferential Margin Status	4,277	96.5%
"T" Stage	4,341	97.9%
"N" Stage	4,308	97.2%
Grade (Differentiation)	4,363	98.4%
Lymphatic Invasion	4,051	91.4%
Vascular Invasion	4,110	92.7%
Perineural Invasion	4,108	92.6%
Reporting of Required Elements - Local Excision (N = 602)		
Piecemeal Excision Status	598	99.3%
Deep Margin Status	411	68.3%
Grade (Differentiation)	449	74.6%
Lymphatic Invasion	353	58.6%
Vascular Invasion	363	60.3%
Piecemeal, Margin, Grade (a)	358	59.5%
Piecemeal, Margin, Grade AND Lymph, Vascular Invasion (b)	282	46.8%

a Minimal Requirements to determine need for Major Resection

b Recommended requirement to determine need for Major Resection

The quality of surgical resection was determined. Adequate total mesorectal excision (i.e. complete or near complete resection) occurred in 88.1% (n = 3158/3595) of pathology reports that reported this variable. It should be noted that 18.9% of reports did not describe this variable. Margin positivity was rare, with distal margin positivity occurring in 36 cases (0.8%) and circumferential radial margin positivity occurring in 310 cases (7.0%). A successful resection, which is defined as having a complete/near complete total mesorectal excision and negative margins (both circumferential and distal), was found in 2961 cases. This represented

66.8% of all cases or 82.5% (n = 2961/3588) of those with reports that could be fully assessed (i.e. reported all three data elements). (Table 5-23)

Table 5-23: Quality of Surgical Excision (Major Resections)

Mesorectum Status		
Complete	2505	56.5%
Near Complete	653	14.7%
Incomplete	364	8.2%
Indeterminate	73	1.6%
Not Reported	839	18.9%
Adequate (Complete or Near Complete)	3158	88.1% (a)
Distal Margin		
Positive	36	0.8%
Negative	4268	96.3%
Indeterminate	75	1.7%
Not Reported	55	1.2%
Circumferential Margin		
Positive	310	7.0%
Negative	3936	88.8%
Indeterminate	31	0.7%
Not Reported	157	3.5%
Successful Resection (a)		
Adequate	2961	66.8%
Inadequate	627	14.1%
Insufficient Reporting to assess	846	19.1%

a Proportion of those with reported TME quality

b Complete/Near Complete TME, Negative Distal and Radial Margin

The associations between adequate mesorectal excision and positive circumferential margin was determined. Those with an inadequate mesorectal excision were more likely to have a positive circumferential margin compared to those with an adequate mesorectal excision (20.8% vs. 5.1%, $P < 0.001$). This relationship was also observed when stratified by receipt of neoadjuvant therapy. (Table 5-24)

Table 5-24: Association adequate mesorectal excision and circumferential radial margin in those undergoing major resection

	Negative CRM	Positive CRM	
All those with complete data elements (N = 3318)			
Adequate TME	2975, 94.3%	180, 5.1%	P < 0.001
Inadequate TME	343, 79.2%	90, 20.8%	
Neoadjuvant Therapy (N = 1,611)			
Adequate TME	1323, 93.7%	89, 6.3%	P < 0.001
Inadequate TME	154, 77.4%	45, 22.6%	
No Neoadjuvant Therapy (1,977)			
Adequate TME	1652, 94.8%	91, 5.2%	P < 0.001
Inadequate TME	189, 80.7%	45, 19.2%	

5.6 Discussion

The Ontario Rectal Cancer Cohort is the first comprehensive database of individuals with rectal cancer diagnosed and treated in Ontario, Canada. The database was created by linking a number of provincially maintained administrative databases to allow for a complete description of the practice patterns and outcomes of those with rectal cancer. In addition, comprehensive histopathology was included for those undergoing surgery between 2010 – 2014. This combination of administrative data and histopathology allows for additional analyses not possible with administrative data only.

A total of 18,632 individuals had a new diagnosis of rectal cancer between 2010 – 2019 in Ontario, Canada. Within the database, there is little missing data, with complete capture of most patient characteristics (i.e. age, sex, income quintile, co-morbidities) and near complete capture of treatment details (such as surgical details, diagnostic imaging). The most common missing data element was cancer stage, which was missing in 18% of all those identified and 7% (n = 856) of those who underwent curative intent treatment. The 5 year overall survival for all those

included was 68% and ranged from 88% (early stage) to 24% (metastatic/Stage IV). Those within the Ontario Rectal Cancer Cohort compared favourably to other settings (Table 5 – 25).

Table 5-25: Comparison of 5 year survival, Ontario vs. United States vs. United Kingdom

	Ontario Rectal Cancer Cohort (2010 - 2019)	United States (2013- 2019)(14)	United Kingdom (2013- 2017)(15)
All Stages	68%	68%	60%
Early Stage	88%	90%	90%
Locally Advanced	79%	73%	70 - 80%
Metastatic (Stage IV)	24%	16%	10%

5.6.1 Strengths and Limitations of the Ontario Rectal Cancer Cohort

A strength of the Ontario Rectal Cancer Cohort is the quality and completeness of the data sources used. The province of Ontario has mandatory reporting of incident cancer cases, with the data maintained at the Ontario Cancer Registry. Within the registry, there is near complete capture of incident cases, with approximately 94% of colorectal cancer cases being microscopically confirmed. Other reliable data sources, such as the Canadian Institute of Health Information Discharge Database, the Cancer Activity Level Reporting Database, and the Ontario Health Insurance Plan Physician Billing Database, were used to determine patient characteristics, care provider characteristics and treatment details. The data contained within these databases is routinely audited.

Another strength of the Ontario Rectal Cancer Cohort is that it brings together data from a number of different databases to allow for a description of the practice patterns (investigations and treatments) and outcomes for each included individual. Residents of Ontario receive all cancer related care through the single-payer Ontario Health Insurance Plan, which allows for near complete capture of investigations and interventions a patient receives. Although this data existed prior to establishing the Ontario Rectal Cancer Cohort, no data source had previously

made available the specific details as it related to rectal cancer care. For instance, diagnostic imaging and procedure codes were available, but which of these were relevant to rectal cancer care were not previously identified. In addition, some treatments (such as radiation and chemotherapy) were only available at the individual visit level (i.e. the date and dose of treatment), but a summary of the treatments (i.e. start/end date, completeness of treatment, timing in relation to other investigations and treatment) were not available. Thus, OntaReCC is the first (and only) resource that allows researchers to fully assess the delivery of specific aspects of rectal cancer care.

There are a number of important limitations to the Ontario Rectal Cancer Cohort which must be considered, which are summarized below.

Selection Bias

The OntaReCC used the Ontario Cancer Registry (OCR) to identify incident cases of rectal cancer. As described above, it has a high rate of capture of these cases with most of these being histo-pathologically confirmed. A potential limitation is that the OCR was the only source for this information. There may be important and systematic reasons why certain individuals were not captured within the OCR. For instance, the following may not have been captured by the OCR: those who died as a consequence of treatment or disease complications, prior to histopathology being available; those receiving care at institutions with poor compliance with mandatory reporting; or those who were diagnosed outside of Ontario but received treatment in Ontario.

Individuals were selected for inclusion if a diagnosis of rectal cancer was identified in the Ontario Rectal Cancer registry, based on international classification of diseases codes. As described in Chapter 2, there is an inherent difficulty in distinguishing between recto-sigmoid

cancers (considered colon cancer) and rectal cancers. The OntaReCC may have excluded those with rectal cancer (but were classified as colon cancer in the OCR). There is the potential that certain groups are over/under represented in the OntaReCC for this reason. For instance, one way to distinguish rectal cancer from colon cancer is based on the height of the cancer in relation to the "anal verge", which is an external landmark. Those with a longer anal canal, typically males, can have the height overestimated, and thus misidentified as colon cancers and excluded.

An additional potential source of selection bias is through the exclusions that were applied. The goal of the OntaReCC was to identified incident rectal cancer to understand guideline adherent care, which cannot be applied uniformly to those with recurrent cancers. A small number of individuals were identified as having recurrent rectal cancer and were excluded. There is the potential that some in this group were misclassified and excluded inappropriately. Those with other concurrent cancer were also excluded for pragmatic reasons. This group will have a number of investigations or treatments that, at the population level, are indistinguishable from rectal cancer care. Identifying which aspects of their care were related specifically to rectal cancer is thus not possible.

There is a group of individuals with genetic pre-disposition to cancers (i.e. Lynch Syndrome) who may be especially at risk for this form of selection bias. This group of patients have a high risk of both concurrent other cancers as well as recurrent cancers. Future work is planned to specifically add those with recurrent rectal to understand the practice patterns and outcomes in this unique group.

Unavailable Information

The Ontario Rectal Cancer Cohort is a population based database, and thus is limited to data available from provincially maintained, linked databases. Unavailable data could not be

included. The databases lack specific diagnostic or investigation details, which are pertinent to rectal cancer care. Examples of unavailable information include:

- Carcinoembryonic antigen: CEA (a tumor marker) is required by all CPGs for both staging and surveillance and was not available.
- Diagnostic Investigations Indications and Results: The indication for the diagnostic investigations included in the OntaReCC is unavailable. The assumption made was that the purpose of the investigation was related to rectal cancer care, but this may not have been the case. In addition, the OntaReCC captures whether an investigation occurred or not, but did not have the results of the diagnostic investigation. This information would have been helpful in confirming the clinical stage and the presence/absence of metastatic disease.
- Specific Pre-Treatment Tumor Characteristics: A number of tumor characteristics are used to determine treatment and were unavailable. These include the height of the tumor above the pelvic floor and relationship to the peritoneal reflection, and the proximity of the tumor to the proposed resection margin (circumferential radial margin). Favourable characteristics could explain treatment decisions. For instance, early stage II disease and/or those with upfront resectable cancers may not have been offered neoadjuvant therapy, despite being recommended by most CPGs.
- Multidisciplinary Cancer Conference Discussion or Details: As described in Chapter 3, these discussions are a recommended and important aspect in determining the appropriate treatments. There is the possibility of re-interpretation of diagnostic imaging, re-classification of staging, and/or a change in the proposed treatment.(16) The decisions

made at these conferences could explain why an individual appeared to be "under-treated" or non-adherent.

- Endoscopic or Operative Findings: Detailed endoscopic and operative findings were not available. These details provide important clinical context in determining next steps in care and/or treatment. For instance, technical complexities due to the cancer or previous surgeries could explain an incomplete mesorectal excision or positive margin.
- Purpose of Clinic Visits: The purpose of clinic visits after treatment was unknown. Clinic visits are a recommended component of surveillance, and may be provided by a number of different health professionals, including the surgeon, radiation oncologist, medical oncologist or primary care physician.
- Histopathology data from 2015 – 2019: This data was only available for half of the cohort (2010 – 2014). At the time of request (May 2017), the latest complete year of available pathology reports was 2014. Pathology reports for the period 2015 – 2019 were requested in April 2021. At that time (and currently) the Ontario Cancer Registry was not providing new pathology reports for research purposes based on significant human resources constraints at Cancer Care Ontario (who oversees the Registry). As of 2019, many details available in the pathology reports are being included in a new administrative database, "E-path". This database includes the following variables: completeness of resection (total mesorectal excision quality), number of lymph nodes resected, tumor stage, nodal stage, margin status (both circumferential and distal). Updated versions of the OntaReCC will include this newly available data, which will address some of the missing pathology data for more recent cohorts of patients.

Incorrect Data and Misinformation

As the Ontario Rectal Cancer Cohort uses population level databases, the potential for incorrect data and misinformation exists. Some specific areas include:

- Incorrect Diagnosis Date: Diagnosis was defined as the date of endoscopy, which preceded any treatment or in those without endoscopy, the date as recorded in the OCR. Date of diagnosis is an important variable as it provides the requisite information to determine timeliness of care as well as to perform survival analyses. It is also a date that could be incorrect in the available databases. Unlike some cancers, pathologic confirmation of rectal cancer is not required prior to arranging staging investigations, referrals to specialists and/or starting treatment. A highly suspicious physical exam finding or diagnostic imaging test could similarly trigger the management of rectal cancer even prior to colonoscopy. Thus the true diagnosis date may be different from the endoscopy date and/or the OCR diagnosis date which would result in incorrect determination of timeliness of care and/or survival analyses. Finally, discrepancies in the true diagnosis date and how it relates to endoscopy and pathology dates may reflect systemic issues that could also be related to other aspects of care. For instance, significant delays between date of endoscopy (and biopsy) and pathologic confirmation may be associated with other delays in treatments not fully captured in this work.
- Misdiagnosis: As described in the selection bias section, distinguishing recto-sigmoid cancers (i.e. colon cancer) from rectal cancer is challenging. This may have led to the inclusion of colon cancer patients, who undergo more limited staging investigations and offered fewer treatments. I attempted to mitigate this issue through validating part of the cohort (2010 – 2014) with histopathology reports, as well as determining the proportion

of patients undergoing surgery only offered to those with rectal cancer (i.e. Low Anterior Resection or Abdominoperineal Resection).

- Misclassification of Predictors/Characteristics: The source of the majority of data included in the Ontario Rectal Cancer Cohort was linked administrative databases maintained provincially or nationally. Some variables (such as age, sex and postal code of residence) are unlikely to be misclassified due to the multiple data sources, while others (such as Cancer Stage, Co-morbidity Score) are taken from one or few data sources. In addition, socio-economic status, is based on average neighborhood income and not individual income.
- Misclassification of Investigations, Treatment, Surveillance: Relevant investigations, treatments and surveillance were derived from the available data sources using a number of methods. When possible, multiple sources were used (i.e. type of surgery), but in some cases, a single source was used (Diagnostic Imaging, Clinic Visits). In addition, for radiation and chemotherapy treatment, the details were derived from a single source (The Cancer Activity Level Reporting Database) using novel algorithms. Due to the nature of the data source, a number of "rules" were used to overcome conflicts within the database (i.e. inconsistent labelling of "palliative" vs. "curative" treatment intent). These algorithms have not be externally validated.

Incomplete Confounder information

The use of population level data does limit the completeness and availability of potential confounders needed for analysis of associations. For instance, histo-pathology data was available only in those diagnosed between 2010 – 2014, and can include important cancer

characteristics that are associated with the types of treatment an individual would receive and/or prognosis. For instance, those with a positive margin or incomplete total mesorectal excisions may be more likely to receive post operative radiation or chemotherapy. Other important (and unavailable confounders) includes specific details about the individual, such as functional status or frailty, and personal beliefs or personal circumstances. These details would be important in understanding why specific treatments or investigations were or were not pursued. Frail patients are generally not eligible for chemotherapy, while personal circumstances may limit the ability of an individual to travel for numerous radiation treatments.

Generalizability

The Ontario Rectal Cancer cohort contains data from the province of Ontario in Canada. The population is large, diverse and spread out over a large geographic area. Individuals have access to single-payer universal health care (i.e. there are no "out of pocket" expenses), but all care is delivered through this "public" system, with no option for "privatized" care. This health care system has limited, and often strained resources. For these reasons, the results from the Ontario Rectal Cancer Cohort may not be generalizable to very different settings. For instance, settings with large number of uninsured individuals, those with significantly different available resources, settings with small geographic distribution and/or centralized care or settings with homogenous populations.

The purpose of the Ontario Rectal Cancer Cohort was to provide a comprehensive resource that would provide an understanding of the practice patterns and outcomes in a Canadian setting. Ontario is Canada's largest, but not its sole province. There are important differences in the demographics, population distribution and cancer risk factors between

provinces, which may make the findings from OntaReCC less generalizable to other provinces. (17) Some key differences between Ontario and the other provinces:

- Population Density (2022): Ontario 15.9 per square kilometer; Canada 4.2 per square kilometer (Range 1.4 – 27.2 per square kilometer). (18)
- Proportion of Population > 65 (2023): Ontario 18.3%; Canada 18.9% (Range 15.1% – 24.4%). (19)
- Health Care Spending (per capita, 2023): Ontario $8,245; Canada $8,740 (Range $8,245 - $10,333). (20)
- Rectal Cancer Incidence (per 100,000, 2019): Ontario 18.3; Canada 18.6 (Range 14.4 – 32.2). (21)

Establishing a pan-Canadian cohort, which would have included individuals across Canada's 10 provinces and 3 territories, is desirable and was considered. Ultimately, an Ontario only cohort was created, for pragmatic reasons. As described earlier in this thesis, health care is administered by the provincial or territorial government, with funding from both provincial and federal sources. The primary source of cancer related data (the cancer registries) is thus available at a provincial, not federal, level. Combining data from across the provinces is feasible, but requires an additional layer of approvals, requires the data to be housed in different institutions and is much more costly. Thus, a provincial approach was taken. ***Chapter 7*** describes future work, which includes adding data from other Canadian provinces.

5.6.2 Implications for Practice

The Ontario Rectal Cancer Cohort is a resource that can be used, for example, to determine the performance of the cancer system, determine the appropriateness of treatment and

follow-up, and assess disparities in care and outcomes. This resource has several clinical practice implications. The first would be to allow those in health policy and planning the ability to determine the effectiveness of previous quality improvements. For instance, there was an initiative by Cancer Care Ontario to improve routine use of MRI for all rectal cancers. The OntaReCC can be used to determine whether this initiative improved the provincial, regional and/or institution specific use of MRI. The OntaReCC can also be a resource to identify institutions or regions that are outliers in terms of quality metrics. Cancer Care Ontario has identified several metrics that are routinely audited at a regional level, and include the quality of surgical excision, whether MRI was done prior to treatment, 90 day mortality, and time between diagnosis and first treatment. OntaReCC provides institutional level data for each of these outcomes which would complement the available regional level data, as well as provide a number of other potential metrics not available at Cancer Care Ontario.

In addition to the health policy and health system implications, OntaReCC is a resource that can be used by clinicians as it provides real world outcomes for patients treated for rectal cancer. This data can help with informed discussions regarding the benefits and risks of treatments based on real world data and available at specific local-regional locations.

5.6.3 Implications for Research

OntaReCC allows researchers to address a number of questions regarding practice patterns and outcomes for those with rectal cancer. For example, the subsequent chapter uses the OntaReCC to determine predictors and impact of guideline adherent care. OntaReCC could be used as a data-source to evaluate the impact of exposures on other real world outcomes,

OntaReCC is also a useful research tool in that it can be updated as additional administrative data and additional years of patients information is made available. The methods and algorithms used are well described and easily reproduced at Cancer Care and Epidemiology (at the Queens Cancer Research Institute, Queen's University, Kingston, Canada). This ability will allow researchers to use the OntaReCC to assess new or evolving challenges in the delivery of rectal cancer care. Due to the large number of included individuals, rare exposures or events can be assessed using the OntaReCC. Assessing the very young with rectal cancer, those treated with local excision only and/or those who require emergency surgery, have often been challenging due to small sample sizes. OntaReCC allows researchers to overcome this issue and determine practice patterns and outcomes in these groups.

5.7 How this chapter fits into the thesis as a whole

This chapter describes the creation of the Ontario Rectal Cancer Cohort. The creation of the OntaReCC was informed by the clinical practice guideline review, described in ***Chapter 3***, as we well as the systematic review described in ***Chapter 4***. The data contained within the OntaReCC is used in the ***Chapter 6*** which evaluates potential predictors and impact of guideline adherent care. Without the OntaReCC, the analyses presented in Chapter 6 would not have been possible.

5.8 Chapter 5 Summary

- The methods pertaining to the Ontario Rectal Cancer Cohort were described, including the data sources, study population, how study variables were identified or derived, and the statistical methods used.
- The OntaReCC identified 18,632 incident rectal cancer cases, with 12,399 undergoing curative intent treatment (the majority of which underwent Major Surgical Resection)
- Some pre-treatment investigations, such as CT Chest and Abdominal CT were completed frequently, while others, such as MRI pelvis were not.
- Medical oncology and radiation oncology assessments occurred frequently in those with locally advanced disease, but not in those with early stage disease or those who underwent local excision only.
- Long Course Chemo-radiation was the most common form of neoadjuvant therapy (87%)
- Major Surgical Resection was the most common form of surgical treatment, regardless of stage of disease.
- Chemotherapy was given to approximately half of the study cohort
- Five year overall survival was 68% for all comers, and was 82% in those undergoing curative intent treatment.
- In those treated between 2010 – 2014, the majority (70%) had histopathology data available to be linked to the rest of the database. Those with and without histopathology were similar in most baseline characteristics except stage at diagnosis.

5.9 Chapter 5 References

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Chapter 6 Predictors and Impact of Guideline Adherent Care in Ontario

6.1 Chapter Overview

This chapter uses the OntaReCC (described in ***Chapter 5***) to assess potential predictors as barriers or facilitators to the receipt of the minimum requirements of guideline adherent care (defined in ***Chapter 3***). Important modifiable and non-modifiable risk factors were identified in ***Chapter 4*** and informed the selection of potential predictors for this chapter. The type of association (negative, positive, none) and magnitude of the associations were determined.

6.2 Chapter Aims and Objectives

The overall aim of this chapter was to use data from the Ontario Rectal Cancer Cohort (***Chapter 5***) to determine the predictors of the minimum requirements guideline adherent care in those with Rectal Cancer in Ontario. This chapter also aimed to address the knowledge gaps identified in ***Chapter 4***, and to better understand the delivery of rectal cancer care in Ontario, Canada.

The specific aims are:

- Report the adherence to specific components of guideline recommended care as well as overall adherence to care in Ontario between 2010 – 2019 for those with rectal cancer.
- Determine which factors were acting as predictors of the minimum requirements of guideline adherent care

- Determine the association between receipt of one aspect of guideline adherent care and subsequent care

6.3 Background

As previously described, the management of rectal cancer is multidisciplinary and requires a number of investigations and treatments. Clinical practice guidelines have been developed to aid clinicians in providing consistent, high quality care based on current evidence, and a Canadian definition of the minimum requirements of recommended care (i.e. "Guideline Adherent Care") has been created (***Chapter 3***).

Chapter 4 provided a systematic review of potential barriers and facilitators (i.e. predictors) of guideline adherent care. Notably, most assessed associations were between adherence outcomes and non-modifiable risk factors (such as age, sex, comorbidities), with much fewer modifiable risk factors. There were a number of gaps in the evidence where no or few studies assessed the relationship between a given predictor and a specific adherence outcome. Of the potential predictor – outcomes pairs around half (53%) have been evaluated, with, > 40% assessed in a single study. Of specific concern, few studies evaluated the predictors of "overall" adherence to phases of care, including overall staging adherence, overall treatment adherence, overall surveillance adherence or adherence to all aspects of guideline adherent care. Determining how different predictors impact adherence to specific recommendations, as well as adherence to broad recommendations provides additional context and allows for great understanding about how cancer care is delivered.

The term "Adherence" to the minimum requirements of recommended care was chosen as the most appropriate one for this chapter. "Adherence" to care implies a collaborative decision

between a patient and their care provider in the choice of a treatment, while "compliance" implies a patient is a passive participant in the treatment decision. (1) In the modern age of cancer treatment, "adherence" is a more appropriate term as it signifies a patient centred approach to decision making.

6.4 Chapter Methods

Below describes the methods used to analyse the predictors of guideline adherent care, and determine the impact of adherent care on important outcomes. Unless explicitly stated otherwise, all work in this chapter was completed by the primary author of this thesis (Sunil Patel)

6.4.1 Design, Setting, Participants

This is a retrospective, population-based cohort study of individuals within the Ontario Rectal Cancer Cohort, described in detail in chapter 5. This group includes all those with a diagnosis of rectal cancer between 2010 – 2019 in Ontario, Canada. All individuals, both curative and non-curative, were included in the analyses of guideline adherent staging investigations. Only those with curable disease (i.e. stage I – III) were included in the analyses of guideline adherent treatment and guideline adherent surveillance. Those with stage IV (metastatic) disease were excluded from the treatment and surveillance analyses, as guidelines recommend individualized care and thus a standard cannot be defined. Those with missing stage were included in some analyses (such as staging investigations) but excluded in others (such as treatment), as guideline adherent treatment is determined by knowing the stage of disease.

6.4.2 Outcomes

6.4.2.1 Guideline Adherent Care

Receipt of guideline adherent care, including guideline adherent staging investigations, guideline adherent treatment and guideline adherent surveillance was assessed as both an outcome and as an exposure. The definition of the minimum requirements of guideline adherent care for those with curative intent disease is described in ***Chapter 3*** and summarized in Table 6 – 1. ***Chapter 5*** (Section 5.4.8) reports the methodology of how each aspect of guideline adherent care was determined, including diagnostic imaging, radiation receipt, chemotherapy receipt, type of surgery, and colonoscopic evaluation.

Table 6-1: Minimum Requirements of Guideline Adherent Care for Stage I – III Rectal Cancer Summary

<table>
<tr><th></th><th>Early Stage (Stage I)</th><th>Locally Advanced (Stage II & III)</th></tr>
<tr><td>Staging Investigations</td><td colspan="2">Colonoscopy or CT Colonography
Carcinoembryonic Antigen
CT Chest or Chest Xray
CT Abdomen/Pelvis
MRI Pelvis or Endorectal Ultrasound</td></tr>
<tr><td>Treatment</td><td>Major Surgical Resection or Local Excision</td><td>Preoperative Short Course Radiation or Long Course CRT
Major Surgical Resection
Postoperative Systemic Chemotherapy (Fluoropyrimidine-based therapy)</td></tr>
<tr><td>Surveillance/ Follow-up</td><td colspan="2">History and Physical Exam at least q6months x 3 years
Carcinoembryonic Antigen with each History and Physical Visit
Colonoscopy at 1 year following surgery then every 3 - 5 years
Chest (CT or CXR) and Abdominal (CT) imaging every year x at least 2 years</td></tr>
</table>

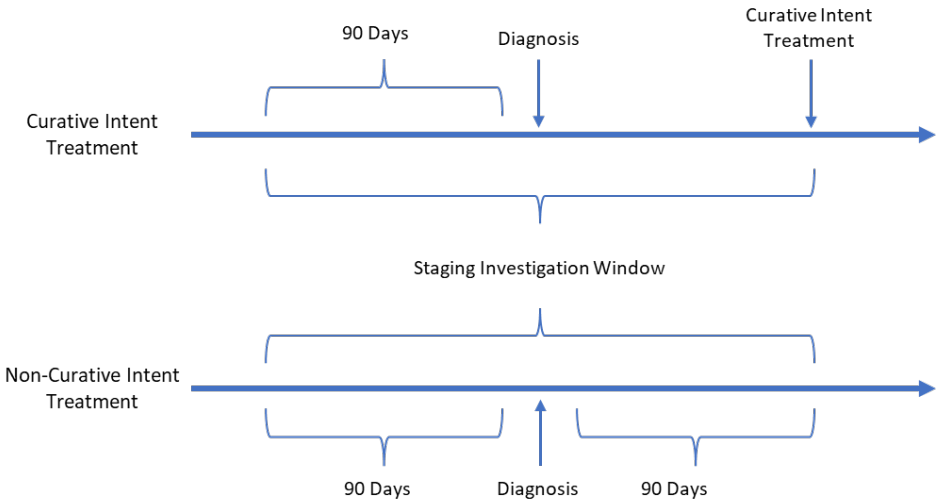
As described in ***Chapter 3***, Locally advanced disease included those with Stage II and Stage III rectal cancer. Stage II and Stage III patients were combined for two reasons. The first is that discriminating between Stage II and Stage III disease prior to treatment can be challenging. Magnetic Resonance Imaging (MRI) is the currently the best modality to do so, but

does have its limitations. MRI is 80 – 90% accurate in identifying Stage III disease. Unlike other cancers, including colon cancer, confirmation of stage through histopathology is not possible for locally advanced disease as clinical practice guidelines recommend preoperative treatment in this group (radiation or chemoradiation) which results in downstaging and unreliable pathology stage. The other justification for combing Stage II and Stage III disease is that all guideline identified in ***Chapter 3*** recommended the same treatment for both stages. As distinguishing between Stage II and Stage III disease can be challenging and the fact that treatment recommendations are the same for both stage of disease, the two groups were combined throughout this chapter.

Chapter 5 provided the definitions of the eligible investigations. Staging investigations must have occurred < 90 days prior to diagnosis and up the first date of treatment (in those with curative intent treatment) or 90 days after diagnosis (in those with non-curative intent treatment, or those with diagnosis and 1st treatment on the same day). (Figure 6 – 1) In those undergoing a specific investigation more than once, the investigations closest to the 1st treatment date (curative intent treatment) or diagnosis date (non-curative intent treatment) was included. Staging investigations included diagnostic imaging (CT, MRI, U/S, Chest Xray) and endoscopy (colonoscopy). A detailed description of the data sources and how these variables were identified can be found in section 5.4.8. It should be noted that the association between potential predictors and staging adherence outcomes was done using the entire cohort of rectal cancer patients, including those who underwent curative intent treatment and those who did not have curative intent treatment. The reason this approach was selected was that all individuals with a new diagnosis require staging investigations to determine their eligibility of curative intent treatments. Identifying a patient as “incurable” can only be done once these tests have been

completed. In addition to the entire cohort, predictors of guideline adherent staging for the "curative intent" group was explored separately. This group includes those undergoing either local excision only, or major resection. Although treatment occurs after staging investigations are to occur, the type of treatment and the physician providing treatment can influence whether these investigations are completed. For instance, preoperative radiation or specific surgical treatments may not be offered until local regional staging is completed.

Figure 6-1: Staging Investigation Definition



Treatment for early-stage disease (Stage I) includes local excision or surgical resection only, while those with locally advanced disease (Stage II, III), require preoperative radiation followed by major surgery and postoperative systemic chemotherapy. Since treatment adherence is dependent on stage of disease, treatment adherence outcomes were assessed separately for the early stage and locally advanced patient groups. Those with Stage IV disease (i.e. metastatic disease) and those with missing stage of disease were not included in these analyses, as guideline adherent treatment is either individualized (Stage IV) or unknown (Missing Stage). Receiving at least one dose of radiation and/or chemotherapy was considered adherent in those with locally advanced disease. Completeness of radiation and/or chemotherapy was not used to determine

adherence. The justification for this decision is that radiation and chemotherapy treatments may be incomplete for a number of reasons, most commonly being intolerance to the treatment due to toxicity and/or other adverse events. Receiving at least one dose implies the intent of being adherent to recommendations and thus is the minimum required care. Treatments were identified using the Cancer Activity Level Reporting Database (chemotherapy and radiation) and the CIHI-DAD and registered persons database (for surgery). A detailed description of how these were identified appear in Section 5.4.8.

Surveillance following major resection included colonic assessment (colonoscopy or CT colonography) and assessment for metastatic disease (Chest, Abdominal and Pelvic Imaging). For the purposes of this chapter, only first surveillance was included. This was defined as receipt of colonic assessment and completion of metastatic imaging within 18 months of surgery. Those undergoing local excision only or those with non-curative treatments were not included in the analyses assessing surveillance adherence. Local excision surveillance was not well defined in the assessed clinical practice guidelines, and routine surveillance in those with metastatic disease is not generally recommended. (***Chapter 3***)

6.4.2.2 "Opportunity for Treatment"

Both radiation therapy and systemic chemotherapy are recommended for the treatment of locally advanced disease. In addition to the receipt of treatment, the "opportunity" to receive treatment was determined. This was done through identification of radiation oncology assessment and medical oncology assessment, as described in detail in ***Chapter 5*** (Section 5.4.8) using Ontario Health Insurance Plan physician billing codes. There may be reasons why an individual does not receive adherent treatments, and could be explained by contraindications to

the treatment or patient preference. Capturing the "opportunity" for treatment in addition to receipt of treatment, allows for a more comprehensive assessment of predictors of care.

6.4.2.3 Timeliness of Treatment

Timeliness of care was included as an outcome. The definition of timely care was adapted from recommendations made by Cancer Care Ontario and defined in Table 6 – 2.

Table 6-2: Timeliness of Treatment Definition

Treatment	Timeliness Definition
Receipt of 1st dose of Radiation	< 35 days from last completed staging investigation
Receipt of Surgery	< 35 days from last completed staging investigation (a) < 84 days from last dose radiation
Receipt of Chemotherapy	< 84 days from surgery date

(a) in those who did not receive radiation first

6.4.2.4 Survival

Overall survival was identified using vital statistics maintained by the Ontario Cancer Registry based on death date. This outcome was used when assessing the impact of receipt of guideline adherent care on survival.

6.4.3 Predictors

A number of patient related, care provider related and disease related factors were included as potential predictors of receiving guideline adherent care. Patient related variables included age, sex, income quintile, rurality, and Charlson co-morbidity score. Age and sex were identified from the Ontario Cancer Registry. Income quintile and rurality were determined based on postal code (available through the Ontario Cancer Registry). Rurality was determined based

on the 2nd digit in the patients postal code ("0" signified a rural location). Income quintile was determined based at the neighborhood level and was available from CIHI. Care provider variables included hospital type (i.e. Cancer Centre Designation) and surgeon volume. (Table 6 – 3) and were determined from the CIHI database (which included the hospital identification number) and the Ontario Health Insurance Plan physician billing code for procedures (available through the Registered Person Database. A detailed description of these variables, the data source and how they were defined appears in Chapter 5 (section 5.4.6).

Table 6-3: Care Provider Characteristic Definitions

Care Provided Characteristics	**Levels**
Hospital Type (a)	Regional Cancer Centre (Level 1&2) Affiliated Cancer Centre (Level 3) Satellite or Non-Designated Cancer Centre (Level 4)
Surgeon Volume (b)	Tertile 1, Low Volume (< 3.5 resections/year) Tertile 2, Mid Volume (3.5 - < 14.5 resections/year) Tertile 3, High Volume (14.5+ resections/year)

a) Based on Cancer Care Ontario's definition
b) Major Surgical Resection

Disease related variables included year of diagnosis and stage of disease, as described in Chapter 5. The OCR provides the stage of disease and diagnosis date. In addition, receipt of earlier components of guideline adherent care (i.e. receipt of a staging investigation) was assessed as a predictor of receiving a later component of guideline adherent care (i.e. appropriate radiation therapy). The definition and source of these variables can be found in ***Chapter 5***.

6.4.4 Data-sources

The data source for all variables and outcomes was the Ontario Rectal Cancer Cohort (OntaReCC). The OntaReCC was built using the following provincially maintained databases:

Ontario Cancer Registry: The Ontario Cancer Registry is the provincial database of information for all Ontario residents who have been diagnosed with cancer (incidence) or who have died of cancer (mortality). Data are collected from hospitals, regional cancer centres, pathology reports and death certificates, and cover the entire province of Ontario.

Cancer Activity Level Reporting Database: The data elements constitute patient level activity within the cancer system focused on radiation and systemic therapy services and outpatient oncology clinic visits. The dataset contains clinical, patient level data.

Canadian Institute of Health Information – Discharge Abstract Database: The CIHI-DAD captures administrative, clinical and demographic information on hospital discharges (including deaths, sign-outs and transfers). Includes demographic, administrative and clinical data for inpatient discharges (including surgery) and day surgery interventions.

Registered Persons Database (RPDB): A listing of all persons insured under the Ontario Health Insurance Plan. The data is used to ensure that individuals in other data sources are identified correctly, and to support analysis by demographic groups and geography.

The detailed methodology describing how the OntaReCC can be found in ***Chapter 5*** (section 5.4.2).

6.4.5 Statistical Analysis

Descriptive statistics were used to describe the cohort. Proportions, means with standard deviations and medians with interquartile range were reported, based on the type of variable. Patient related (age, sex/gender, comorbidity score, socioeconomic status, rurality, year of diagnosis/surgery) and care provider factors (Cancer Centre Designation, Surgeon Volume Tertile) were included as predictors based on *a priori* decisions based on the evidence based review and availability of the data. The association between the potential predictor and the adherence outcome was determined based on the appropriate statistical test, including: Chi-Squared Test (differences in proportions), Analysis of Variance (ANOVA, differences in means) and Wilcoxon Rank Test (differences in medians).

Both univariable and multivariable models of the association between the potential predictors and adherence outcomes were created. Logistic Regression Analysis was used to assess the associations between dichotomous outcomes and potential predictors, while Cox Regression Analysis was used to report the association between time dependent outcomes and potential predictors. The univariable (unadjusted) and multivariable (adjusted) analyses were both reported for each of the outcomes. Multivariable models were creating using all potential predictors, regardless of whether the univariable model demonstrated an association or not. This approach was taken to allow for a determination of whether each of these variables were acting as a predictor (i.e. associated with) of the assessed adherence outcome. Each of the selected potential predictors have been assessed in previous publications and thus were of interest within this chapter.

Confounding was assessed by comparing the of univariable and multivariable outputs. Substantial differences in the effect estimate were described in the results section. It is important

to note that as a population level study, a number of potential confounders and/or important predictors were not available for assessment. For example, specific findings from diagnostic imaging were not available. Histopathology data was available for only those treated between 2010 – 2014. Both histopathology results and diagnostic imaging findings can provide important information on prognosis and/or aggressiveness of disease which can influence the treatments received. In addition, care provider factors (hospital type, surgeon volume) are crude measures of the expertise of those involved in the care of this group of patients. Ultimately, the multivariable models included all available variables that have been previously determined to be potentially important predictors or possible confounders (as discussed in ***Chapter 4***).

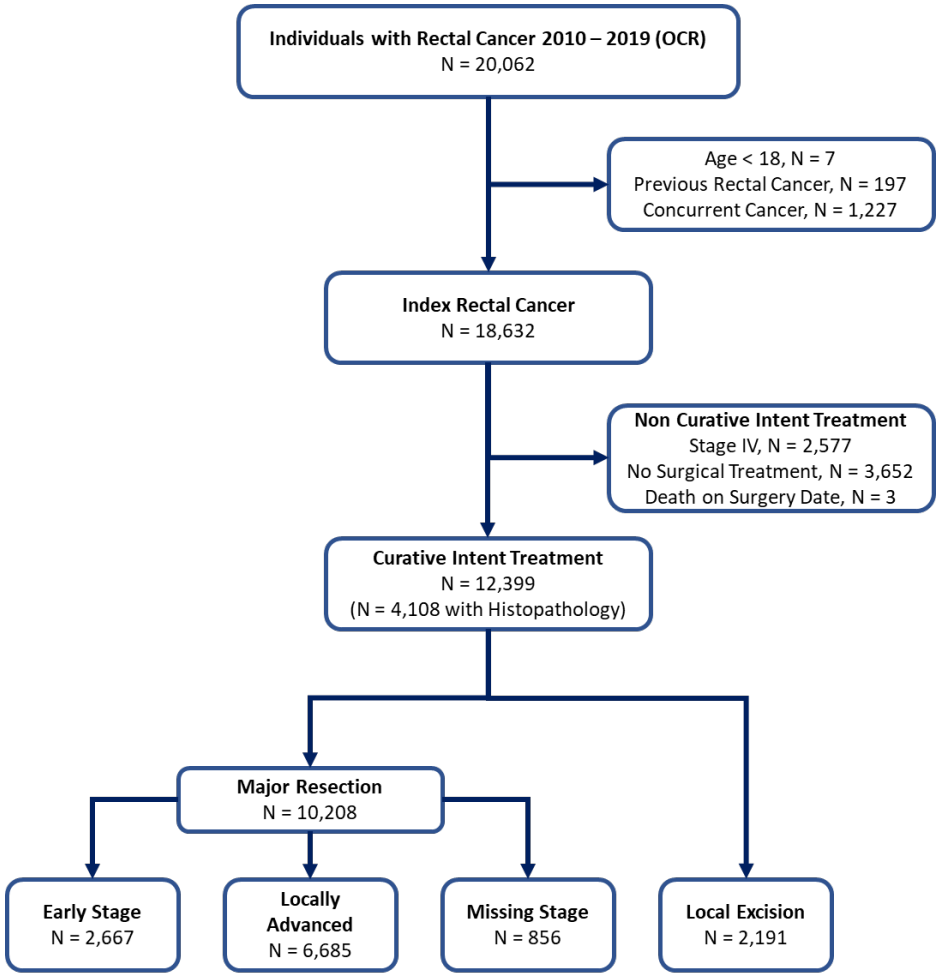
As described in ***Chapter 5*** (Section 5.4.3), there are restriction as to who was permitted to access raw data from the linked administrative databases. Based on previous data-sharing agreements between Cancer Care Ontario and Cancer Care and Epidemiology (CCE), access is primarily limited to data-analysts at CCE. I worked closely with two data analysts (Chad McClintock, Weidong Kong) to produce the results presented in this chapter. ***Chapter*** 5 provides the detailed methods describing how the variables were identified and/or derived. I determined the inclusion criteria for the OntaReCC, including the diagnostic codes required, the study dates and the exclusions (including how these were determined from the data). I selected which variables would be included with OntaReCC. If available from the available databases, I determined which diagnostic or intervention codes were needed to identify these variables. If the variables were not available, I defined the process for which these variables were derived. I worked closely with the data-analysts to ensure that the requisite variables were included within the OntaReCC. For ***Chapter 6***, I determined which exposures and outcomes were to be evaluated and selected the appropriate statistical models. The data-analysts then created the

statistical files and completed the analyses and provided me with the raw statistical output. Using an iterative and collaborative process, the final results were produced. I then created the tables presented in this chapter with the raw statistical output provided by the data-analysts. All statistical analyses were completed in SAS v9.4 (SAS Institute, Cary, North Carolina, USA)

6.5 Results

A total of 20,062 individuals had a diagnosis of rectal cancer in the Ontario Cancer Registry between 2010 – 2019. After exclusion were applied, which were described in ***Chapter 5***, a study cohort of 18,632 individuals was created. This cohort was used in the analyses of staging adherence. Within the study cohort a total of 12,399 individuals underwent curative intent treatment through either local excision (n = 2,191) or major resection (n = 10,208). This "curative intent" cohort was used in the analyses of treatment adherence and surveillance adherence. (Figure 6 – 2)

Figure 6-2: Flowsheet of included individuals with rectal cancer



6.5.1 Predictors of Guideline Adherent Staging Investigations

6.5.1.1 Adherence to Colonic Staging

Of those included in the cohort, a total of 14,363 (77.1%) had a colonic assessment prior to first treatment (curative intent cohort) or within 90 days of diagnosis (non-curative intent cohort). Those who underwent colonic assessment were younger than those who didn't (Mean age 64.6 vs. 68.6, $P < 0.0001$). The proportion of males who were adherent were higher than those who were female (77.9% vs. 75.8%, $P = 0.01$). Those in the highest income quintile were

more adherent (79.9%) than those in the mid-tier (77.6%) or those in the lowest tier (72.9%, $P < 0.0001$). Colonic assessment was also more common in those in the lowest co-morbidity score category (80.2%) compared with those in the mid-tier (79.1%) and those in the lowest tier (69.6%, $P < 0.0001$). Notably, rurality (77.4%) and urban (77.0%, $P = 0.61$) had similar proportions of individuals undergoing a colonic assessment. (Appendix Chapter 6 – 1, Table 8 - 45)

The univariable and multivariable analyses are presented in table 6 – 4. Both analyses identified that older age, female sex, lower income quintile, and higher co-morbidity score were associated with worse adherence to colonic assessment. Rurality was not associated, while the mid period of year of diagnosis (2014 – 2017) was the period with the highest adherence.

Table 6-4 The association between predictors and receipt of staging colonoscopy, Univariable and Multivariable analysis

Characteristic	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	Significant Testing	OR (95% CI)	Significant Testing
Age, per 10 year increase	0.79 (0.77, 0.81)	<.0001	0.80 (0.78, 0.83)	P <.0001
Sex				
Female	0.89 (0.83, 0.96)	P = 0.0012	0.88 (0.82,0.95)	P = 0.0008
Male	Referent		Referent	
Diagnosis Year				
2009-2013	Referent	P = 0.0035	Referent	P = 0.0011
2014-2016	1.12 (1.03, 1.22)		1.12 (1.03, 1.22)	
2017-2019	0.96 (0.88, 1.04)		0.94 (0.86, 1.02)	
Income Quintile				
1 (lowest)	0.72 (0.65,0.81)	P <.0001	0.72 (0.65,0.81)	P <.0001
2 - 4	0.89 (0.81, 0.98)		0.89 (0.81, 0.98)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.02 (0.94, 1.12)	P = 0.61	1.00 (0.92, 1.10)	P = 0.93
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P <.0001	Referent	P <.0001
Mid (3)	0.94 (0.84, 1.05)		1.05 (0.94, 1.18)	
High (> 3)	0.56 (0.52, 0.61)		0.60 (0.55, 0.65)	

6.5.1.2 Adherence to recommended metastatic disease staging

Adherence to recommended chest staging and abdominal staging was high in the cohort. Overall, 85.2% (15,884/18,631) of individuals completed chest staging while 88.7% (16,358/18,631) completed abdominal staging. For both chest and abdominal staging, older mean age, male sex, later diagnostic period and increasing co-morbidity score were associated with a high proportion of adherence. Income quintile was not associated with a higher proportion of adherence for either staging test, while rurality was associated with higher proportion of adherence to chest staging only. (Appendix Chapter 6 – 1, Table 8 - 46).

Univariable and Multivariable analyses are presented in Table 6 – 5 (chest staging) and Table 6 – 6 (abdominal staging). Univariable and multivariable analyses were consistent across each predictor for both chest and abdominal imaging. In both types of staging (chest and abdominal), the following predictors were positively associated with adherence: Increasing age, male sex, later diagnosis year, and higher comorbidity score. Income quintile was not associated with adherence in either modality, while geography was associated with chest imaging only (Rural more adherent).

Table 6-5 Univariable and Multivariable analysis of the associations between predictors and adherent chest staging

	Chest Imaging			
Characteristic	**Univariable Analysis**		**Multivariable Analysis**	
	OR (95% CI)	**Significant Testing**	**OR (95% CI)**	**Significant Testing**
Age, per 10 year increase	1.18 (1.14, 1.21)	P <.0001	1.14 (1.10, 1.17)	P <.0001
Sex				
Female	0.82 (0.75, 0.89)	P <.0001	0.85 (0.78, 0.92)	P = 0.0001
Male	Referent		Referent	
Diagnosis Year				
2009-2013	Referent	P = 0.0017	Referent	P = 0.0003
2014-2016	1.03 (0.93, 1.13)		1.01 (0.91, 1.12)	
2017-2019	1.19 (1.08, 1.32)		1.21 (1.10, 1.34)	
Income Quintile				
1 (lowest)	1.06 (0.93, 1.21)	P = 0.48	1.06 (0.93, 1.21)	P = 0.48
2 - 4	1.00 (0.89, 1.11)		1.00 (0.89, 1.11)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.34 (1.20, 1.50)	P <.0001	1.31 (1.17, 1.47)	P <.0001
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P <.0001	Referent	P <.0001
Mid (3)	1.74 (1.53, 2.00)		1.61 (1.41, 1.85)	
High (> 3)	3.53 (3.13, 3.99)		3.37 (2.99, 3.82)	

Table 6-6 Univariable and Multivariable analyses of the association between predictors and adherent abdominal staging

Characteristic	Abdominal Imaging			
	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	Significant Testing	OR (95% CI)	Significant Testing
Age, per 10 year increase	1.11 (1.07, 1.15)	P <.0001	1.07 (1.04, 1.11)	P <.0001
Sex				
Female	0.83 (0.76, 0.91)	P = 0.0001	0.86 (0.79, 0.95)	P = 0.002
Male	Referent		Referent	
Diagnosis Year				
2009-2013	Referent	P = 0.59	Referent	P = 0.014
2014-2016	1.07 (0.96, 1.20)		1.06 (0.94, 1.18)	
2017-2019	1.17 (1.05, 1.31)		1.18 (1.06, 1.32)	
Income Quintile				
1 (lowest)	1.06 (0.93, 1.21)	P = 0.48	0.98 (0.85, 1.14)	P = 0.73
2 - 4	1.00 (0.89, 1.11)		0.96 (0.85, 1.08)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.11 (0.98, 1.25)	P = 0.10	1.08 (0.96, 1.23)	P = 0.21
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P <.0001	Referent	P <.0001
Mid (3)	1.60 (1.38, 1.86)		1.54 (1.32, 1.79)	
High (> 3)	3.24 (2.84, 3.72)		3.15 (2.76, 3.62)	

6.5.1.3 Adherence to recommended local-regional staging

Of all the staging modalities, local regional staging was least likely to be adherent. Only 65.4% (n = 12,195/18,631) of those in the cohort were adherent. A higher proportion of those diagnosed in the later period and those in the highest income group underwent local regional staging. (Appendix Chapter 6 – 1, Table 8 - 47).

Univariable and multivariable analyses are presented in Table 6 – 7. Of the assessed predictors, older age, later diagnosis period, and comorbidity score were positively associated with local regional staging adherence. Co-morbidity score did not follow a trend, as those in the mid-tier score had the highest odds of completing local regional staging prior to treatment (OR

1.21, 95% CI 1.10 – 1.33 vs. Highest OR 1.08, 95%CI 1.01 – 1.16 vs. Lowest Ref, P = 0.0003). Later diagnosis period had a larger effect on adherence compared with any other predictor, as the later period was associated with more than a 1.5x increase in the odds of completing local regional staging compared with the earlies period (OR 1.66, 95%CI 1.54 – 1.79). Income quintile, sex and geographic location did not seem to be important predictors, while increasing age (per 10 year increase) was associated with decreased odds of adherence.

Table 6-7 Univariable and Multivariable analyses of the association between predictors and adherent local regional staging

Characteristic	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	Significant Testing	OR (95% CI)	Significant Testing
Age, per ten year increase	0.88 (0.86, 0.91)	P <.0001	0.88 (0.86, 0.90)	P <.0001
Sex				
Female	0.97 (0.91, 1.03)	P = 0.31	0.98 (0.92, 1.04)	P = 0.53
Male	Referent		Referent	
Diagnosis Year				
2009-2013	Referent	P < 0.001	Referent	P <.0001
2014-2016	1.52 (1.41, 1.64)		1.51 (1.40, 1.63)	
2017-2019	1.68 (1.56, 1.80)		1.66 (1.54, 1.79)	
Income Quintile				
1 (lowest)	0.89 (0.81, 0.98)	P = 0.048	0.90 (0.82, 0.99)	P = 0.081
2 - 4	0.97 (0.89, 1.05)		0.97 (0.89, 1.05)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.02 (0.95, 1.11)	P = 0.58	1.02 (0.94, 1.10)	P = 0.70
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P = 0.041	Referent	P = 0.0003
Mid (3)	1.12 (1.02, 1.24)		1.21 (1.10, 1.33)	
High (> 3)	1.05(0.98, 1.12)		1.08 (1.01, 1.16)	

6.5.1.4 Adherence to compete staging investigations

The receipt of all guideline adherent staging, by predictor, was determined (Table 6 – 8). Overall, 59.6% of individuals (n = 11,103/18,631) received all recommended pre-treatment staging investigations (Colonic Assessment, Metastatic Disease Assessment, Local Regional

Assessment). Mean age was older in those who received all guideline adherent staging investigations (mean 66.4 vs. 64.8, P < 0.0001). There was low adherence (i.e. < 50%) in the elderly (age 80+), those undergoing local excision only and those with metastatic or incurable disease.

Table 6-8: Association between predictors and guideline adherent staging

Predictor	Adherent (Completed all staging) N = 11103	59.6%	Non Adherent (Did not complete all staging) N = 7528	40.4%	Significance Testing (χ^2, ANOVA)
Age Group (Years), N %					
18-39	325	56.5%	250	43.5%	P < 0.0001
40-49	973	62.8%	577	37.2%	
50-59	2480	60.7%	1604	39.3%	
60-69	3164	62.7%	1886	37.3%	
70-79	2648	62.2%	1612	37.8%	
80+	1513	48.6%	1599	51.4%	
Mean Age	66.4 (14.2)		64.8 (12.8)		P< 0.0001
Sex, N %					
Female	4141	58.3%	2961	41.7%	P = 0.005
Male	6962	60.4%	4567	39.6%	
Cancer Diagnosis Year, N %					
2009-2013	4344	52.9%	3866	47.1%	P < 0.0001
2014-2016	3192	63.4%	1839	36.6%	
2017-2019	3567	66.2%	1823	33.8%	
Income Quintile, N %					
1 (lowest)	2252	58.3%	1609	41.7%	P = 0.19
2-4 (mid)	6746	59.9%	4522	40.1%	
5 (highest)	2105	60.1%	1397	39.9%	
Residential Region					
Rural	2040	60.9%	1309	39.1%	P = 0.09
Urban	9063	59.3%	6219	40.7%	
Charlson Co-Morbidity Score, Tertile					
Low (0-2)	6476	58.0%	4686	42.0%	P< 0.0001
Mid (3)	1438	62.8%	852	37.2%	
High (>3)	3189	61.6%	1990	38.4%	
Surgery Type					
Local Excision	763	34.8%	1428	65.2%	P< 0.0001
Major Surgery	7504	73.5%	2704	26.5%	
None or Stage IV	2836	45.5%	3396	54.5%	

In those who underwent major surgery, Cancer Centre Designation and Surgeon Volume could be assessed as potential predictors. Those who underwent treatment at a regional cancer

centre and those who had a high volume surgeon had much higher proportions of complete staging when compared to lower level cancer centres or lower volume surgeons. (Table 6 – 9)

Table 6-9 Care Provider Factors and Proportion receiving guideline adherent staging investigations

	Adherent		Non Adherent		X^2 Test
Cancer Centre Level Designation of Surgical Treatment (if applicable), N % (a)					
	N = 8767	65.1%	N = 4709	34.9%	
Regional Cancer Centre	4880	72.3%	1870	27.7%	P<.0001
Affiliated Cancer Centre	2822	61.3%	1778	38.7%	
Satellite or Non-Designated	1065	50.1%	1061	49.9%	
Surgeon Volume per year (Major Resections only, if applicable), N %					
	N = 7441	74.7%	N = 2511	25.2%	
Low Volume, Q1 (min-3.5)	2262	65.1%	1214	34.9%	P<.0001
Mid Volume, Q2 (>3.5-14.5)	2480	76.3%	772	23.7%	
Highest Volume, Q3 (>14.5)	2699	83.7%	525	16.3%	

(a) Local Excision or Major Resection

Multivariable analysis was completed to determine the associations between potential predictors and receipt of guideline adherent staging investigations (Table 6 – 10). The analyses were completed for the entire cohort (N = 18,631) and those undergoing major resection (N = 10,208) with the results presented separately. (Table 6 – 10) The major resection group was included in this table which allowed for an assessment of cancer centre designation of major surgery and surgeon volume (major surgery) in the model. For the entire cohort, young age, male sex, and later diagnosis year were positively associated with receipt of complete guideline adherent staging on multivariable analysis. Charlson Co-morbidity score was also associated with guideline adherent staging, with the lowest score positively associated with guideline adherent staging. There was no observed association between rurality or income quintile and overall staging adherence on this analysis. It should be noted that Cancer Centre Level Designation and Surgeon Volume were not tested for the entire cohort, as only those with curative intent treatment had this variable available defined.

Table 6-10 Multivariable analysis of predictors of guideline adherent staging in the entire cohort and in those undergoing major resection

	Entire Cohort (N = 18,631)		Major Resection (N = 10,208)	
Predictor	**Multivariable Analysis OR (95%CI)**		**Multivariable Analysis OR (95%CI)**	
Age, per 10 year increase	0.91 (0.89, 0.93)	P<0.0001	0.92 (0.88, 0.95)	P<.0001
Sex, N %				
Female	0.93 (0.87, 0.99)	P = 0.019	0.97 (0.88, 1.06)	P = 0.50
Male	Referent		Referent	
Cancer Diagnosis Year, N %				
2009-2013	Referent	<.0001	Referent	P<.0001
2014-2016	1.53 (1.42, 1.65)		1.68 (1.51, 1.88)	
2017-2019	1.73 (1.61, 1.86)		2.03 (1.81, 2.29)	
Income Quintile, N %				
1 (lowest)	0.93 (0.84, 1.02)	P = 0.222	1.04 (0.90, 1.20)	P = 0.74
2- 4	0.99 (0.91, 1.07)		1.05 (0.93, 1.18)	
5 (highest)	Referent		Referent	
Residential Region				
Rural	1.06 (0.98, 1.15)	P = 0.145	0.91 (0.81, 1.02)	P = 0.10
Urban	Referent		Referent	
Charlson Co-Morbidity Score, Tertile				
Low (0 - 2)	Referent	P <.0001	Referent	P = 0.36
Mid (3)	1.29 (1.18, 1.42)		1.04 (0.91, 1.19)	
High (> 3)	1.19 (1.11, 1.27)		1.08 (0.97, 1.20)	
Cancer Centre Designation				
Regional Cancer Centre (Level 1&2)			Referent	P<.0001
Affiliated Cancer Centre (Level 3)	Not Applicable		0.80 (0.72, 0.89)	
Satellite Cancer Centre (Level 4) or non-designated			0.64 (0.56, 0.74)	
Surgeon Volume				
Low Volume, Q1 (min-3.5)			0.48 (0.42, 0.55)	P<.0001
Mid Volume, Q2 (>3.5-14.5)	Not Applicable		0.70 (0.61, 0.80)	
Highest Volume, Q3 (>14.5)			Referent	
Missing			0.28 (0.24, 0.33)	

In those undergoing major resection, younger age and later year of diagnosis were positively associated with adherence. This was the case in the entire cohort as well. Those diagnosed in the latest years were more than twice as likely to receive guideline adherent staging investigations than those in the earlier groups. Unlike in the full cohort neither female sex nor

Charlson co-morbidity score were associated with guideline adherent staging investigations in the major resection cohort. Both higher resourced hospitals and higher volume surgeons were positively associated with guideline adherent staging in this major resection group. There was a large magnitude of effect in the association with surgeon volume and with cancer centre level designation. For instance, patients undergoing surgery with low volume surgeons were less than half as likely to have completed guideline adherent staging, compared with those undergoing surgery with high volume surgeons.

6.5.2 Predictors of Guideline Adherent Treatment

6.5.2.1 Guideline Adherent Surgery – Early Stage Disease

In those with early stage disease, guideline adherent treatment includes timely surgery only, without radiation or chemotherapy. As described in the methods (Section 6.4.2.3), timely surgery was defined as local excision or major surgery within 35 days of completion of last staging investigation.

Of the 3,785 with early stage disease, 68,1% (n = 2608) met the definition of timely surgery. The proportion adherent vs. non adherent, by predictor, can be found in Appendix Chapter 6 – 1 (Table 8 – 48).

All assessed patient related characteristics (Age, Sex, Income Quintile, Geographic Location, Co-morbidity score) were either not associated or weakly associated with timely surgery on multivariable analysis (Table 6 – 11). More strongly associated with timely surgery were care provider characteristics or surgery type. Those undergoing local excision (vs. major resection) were more likely to have timely surgery (OR 2.75, 95%CI 2.14 – 3.53), as were those who had surgery during the early years of the study (2010 – 2013). Those having surgery at

regional cancer centres were less likely to have timely surgery. Of note, only 60.2% of the included individuals had a surgeon volume variable available as this was defined based on number of major resections performed by the surgeon in the preceding two years. For those undergoing local excision, the physician performing the procedure could include non surgeons (i.e. gastroenterologist) who perform endoscopic removal only.

Table 6-11 Univariable and Multivariable analysis of the association between predictors and timely surgery in those with early stage disease

Characteristic	Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis OR (95%CI), Significant Testing	
Surgery Type				
Local Excision	1.88 (1.60, 2.21)	P <.0001	2.75 (2.14, 3.53)	P <.0001
Major Resection	Referent		Referent	
Age, per 10 year increase	0.97 (0.92, 1.02) (a)	P = 0.28	0.94 (0.89, 1.00) (a)	P = 0.051
Sex				
Female	1.02 (0.88, 1.17)	P = 0.81	1.00 (0.87, 1.16)	P = 1.00
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P <.0001	Referent	P <.0001
2014-2016	0.68 (0.58, 0.80)		0.69 (0.59, 0.82)	
2017-2019	0.48 (0.40, 0.57)		0.51 (0.42, 0.61)	
Cancer Centre Designation				
Regional	Referent	<.0001	Referent	P = 0.0001
Affiliate	1.27 (1.09, 1.48)		1.05 (0.89, 1.24)	
Satellite/Non-Designated	2.27 (1.84, 2.81)		1.63 (1.30, 2.05)	
Surgeon Volume (cases/year)				
Missing	0.87 (0.67, 1.13)	P<.0001	0.87 (0.67, 1.13)	P<.0001
Low (<3.5)	1.75 (1.39, 2.21)		1.75 (1.39, 2.21)	
Mid (3.5 - 14.5)	1.66 (1.32, 2.08)		1.66 (1.32, 2.08)	
High (>14.5)	Referent		Referent	
Income Quintile				
1 (lowest)	1.01 (0.80, 1.27)	P = 0.79	1.01 (0.80, 1.27)	P = 0.79
2 – 4 (mid)	0.95 (0.80, 1.14)		0.95 (0.80, 1.14)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	0.98 (0.82, 1.17)	0.8421	0.97 (0.80, 1.17)	P = 0.75
Urban	Referent		Referent	

Charlson Co-morbidity Score				
Low (< 3)	Referent	0.0108	Referent	P = 0.016
Mid (3)	1.18 (0.97, 1.44)		1.29 (1.06, 1.58)	
High (> 3)	0.80 (0.66, 0.98)		0.90 (0.73, 1.12)	

(a) per 10 year increase

6.5.2.2 Guideline Adherent Surgery - Locally Advanced Disease

Guideline adherent surgery for those with locally advanced disease is major surgical resection, as opposed to local excision only. The vast majority of those with locally advanced disease had guideline adherent surgery (94.8%), while only a small number of individuals underwent local excision (5.2%, n = 370/7055). . The proportion of those adherent vs. not, by predictor can be found in Appendix Chapter 6 – 1 (Table 8 – 49).

The univariable and multivariable analyses reporting the association between predictors and adherent surgery in those with locally advanced disease are presented in Table 6 – 12. Older patient and patients with higher co-morbidities score were less likely to undergo major (i.e. adherent) surgery. In terms of care provider characteristics, those treated at non-regional cancer centres were less likely to have a major resection, as were those treated in the later years of the study (2017 – 2019).

Table 6-12 Univariable and Multivariable analyses of the association between predictors and adherent surgery (major surgery) in those with locally advanced disease

Characteristic	Univariable Analysis (a) OR (95%CI), Significant Testing		Multivariable Analysis (a) OR (95%CI), Significant Testing	
Age, per 10 year increase	0.69 (0.63, 0.75) (b)	P <.0001	0.68 (0.62, 0.75) (b)	P<.0001
Sex				
Female	1.22 (0.97, 1.52)	P = 0.0874	1.33 (1.06, 1.68)	P = 0.017
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P <.0001	Referent	P<.0001
2014-2016	0.73 (0.55, 0.97)		0.61 (0.45, 0.82)	
2017-2019	0.39 (0.30, 0.50)		0.30 (0.23, 0.39)	
Cancer Centre Designation				
Regional	Referent	P <.0001	Referent	P<.0001
Affiliate	0.52 (0.41, 0.67)		0.50 (0.39, 0.65)	
Satellite/Non-Designated	0.25 (0.19, 0.33)		0.23 (0.17, 0.30)	
Income Quintile				
1 (lowest)	0.86 (0.60, 1.22)	P = 0.70	0.86 (0.60, 1.22)	P = 0.70
2 - 4	0.94 (0.69, 1.26)		0.94 (0.69, 1.26)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.08 (0.83, 1.43)	P = 0.59	1.20 (0.91, 1.61)	P = 0.21
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P <.0001	Referent	P<.0001
Mid (3)	1.00 (0.75, 1.34)		1.18 (0.88, 1.60)	
High (> 3)	2.78 (2.11, 3.72)		3.13 (2.36, 4.22)	

(a) Non adherent = local excision

(b) Per 10 year increase

6.5.2.3 Guideline Adherent Radiation – Locally Advanced Disease

A total of 4,150 (58.8%) of those with locally advanced disease received guideline adherent radiation, which was defined as receipt of preoperative radiation. The proportion adherent vs. not can be found in Appendix Chapter 6 – 1 (Table 8 – 50).

Univariable and multivariable analyses are presented in Table 6 – 13. A number of factors were negatively associated with adherent radiation on multivariable analysis, including:

Increasing age, earlier surgery date, treatment at a lower level cancer centre, and lower volume surgeon. High surgeon volume was strongly protective, as those with a low volume surgeon were less than half as likely to receive preoperative radiation. Female sex was not associated with radiation receipt, which is notable as many previous publications have identified female sex as a risk factor for non-adherence. Similarly, co-morbidity score was not an important predictor of radiation adherence despite previous reports describing older age as a risk factor for non-adherence.

Table 6-13 Univariable and Multivariable analyses of the association between predictors and adherent radiation in those with locally advanced disease

Characteristic	Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis OR (95%CI), Significant Testing	
Age, per 10 year increase	0.75 (0.72, 0.78) (a)	P <.0001	0.78 (0.75, 0.81) (a)	P<.0001
Sex				
Female	0.98 (0.88, 1.08)	P = 0.63	0.97 (0.87, 1.08)	P = 0.56
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P = 0.0002	Referent	P = 0.002
2014-2016	1.19 (1.07, 1.34)		1.16 (1.03, 1.31)	
2017-2019	1.26 (1.12, 1.41)		1.24 (1.09, 1.40)	
Cancer Centre Designation				
Regional	Referent	P <.0001	Referent	P<.0001
Affiliate	0.65 (0.59, 0.72)		0.82 (0.72, 0.92)	
Satellite/Non-Designated	0.42 (0.37, 0.49)		0.73 (0.62, 0.86)	
Surgeon Volume (cases/year)				
Missing	0.08 (0.06, 0.09)	P<.0001	0.09 (0.07, 0.11)	P<.0001
Low (<3.5)	0.35 (0.31, 0.40)		0.42 (0.36, 0.48)	
Mid (3.5 - 14.5)	0.59 (0.51, 0.67)		0.64 (0.56, 0.74)	
High (>14.5)	Referent		Referent	
Income Quintile				
1 (lowest)	1.02 (0.90, 1.15)	P = 0.95	1.15 (0.97, 1.35)	P = 0.25
2 - 4	Referent		1.05 (0.92, 1.20)	
5 (highest)	1.00 (0.89, 1.14)		Referent	
Geographical Location				
Rural	0.95 (0.84, 1.07)	P = 0.41	0.95 (0.83, 1.08)	P = 0.41
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P = 0.38	Referent	P = 0.56
Mid (3)	0.94 (0.81, 1.09)		1.08 (0.92, 1.27)	
High (> 3)	1.04 (0.94, 1.16)		1.04 (0.93, 1.17)	

(a) per 10 year increase

6.5.2.4 Guideline Adherent Chemotherapy – Locally Advanced Disease

A total of 4,068 (57.7%) of those with locally advanced disease received guideline adherent chemotherapy, which was defined as systemic chemotherapy started within 90 days

after surgery. The proportion of adherence vs. not can be found in Appendix Chapter 6 – 1 (Table 8 – 51)

Univariable and multivariable analyses can be found in Table 6 – 14. All assessed predictors were associated with postoperative chemotherapy on multivariable analysis. Adherence was found to be negatively associated with the following: Older age, male sex, earlier year of surgery, treatment at an affiliated cancer centre, lower surgeon volume, lower income quintile, Urban Residence and higher comorbidity score. Age as an important predictor of adherence was clearly demonstrated. The magnitude of effect, per 10 year increase, was larger than that observed for receipt of adherent radiation or adherent surgery. Geographic and socioeconomic status all were found to be important predictors of adherent chemotherapy, which was not the case for adherent radiation. Finally, co-morbidity score demonstrated an association with adherent chemotherapy. Those with highest co-morbidity score were most likely to be adherent, while those in the mid level score were least likely to be adherent. This is an unusual finding in that most of the previous literature identified increasing co-morbidities to be strongly associated with less adherence to chemotherapy.

Table 6-14 Univariable and Multivariable analyses of the association between predictors and adherent chemotherapy in those with locally advanced disease

Characteristic	Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis OR (95%CI), Significant Testing	
Age, per 10 year increase	0.51 (0.49, 0.53)	P <.0001	0.51 (0.48, 0.53) (a)	P<.0001
Sex				
Female	0.87 (0.79, 0.96)	P = 0.006	0.89 (0.80, 0.99)	P = 0.031
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P<.0001	Referent	P<.0001
2014-2016	1.63 (1.46, 1.83)		1.71 (1.51, 1.93)	
2017-2019	1.64 (1.46, 1.84)		1.66 (1.46, 1.89)	
Cancer Centre Designation				
Regional	Referent	P<.0001	Referent	P<.0001
Affiliate	0.66 (0.60, 0.73)		0.71 (0.63, 0.81)	
Satellite/Non-Designated	0.76 (0.66, 0.87)		1.09 (0.92, 1.29)	
Surgeon Volume (cases/year)				
Missing	0.60 (0.51, 0.71)	P<.0001	0.87 (0.71, 1.05)	P = 0.0042
Low (<3.5)	0.62 (0.55, 0.71)		0.76 (0.66, 0.88)	
Mid (3.5 - 14.5)	0.76 (0.67, 0.86)		0.86 (0.74, 0.98)	
High (>14.5)	Referent		Referent	
Income Quintile				
1 (lowest)	0.64 (0.55, 0.74)	P<.0001	0.70 (0.59, 0.83)	P = 0.0002
2 - 4	0.80 (0.71, 0.91)		0.84 (0.73, 0.96)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.35 (1.20, 1.53)	P<.0001	1.31 (1.14, 1.50)	P = 0.0001
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P<.0001	Referent	P <.0001
Mid (3)	0.66 (0.57, 0.77)		0.86 (0.74, 1.01)	
High (> 3)	1.03 (0.93, 1.14)		1.25 (1.11, 1.40)	

(a) per 10 year increase

6.5.2.5 Overall Treatment Adherence – Locally Advanced Disease

A total of 2,626 (37.3%) of those with locally advanced disease received all guideline adherent treatments, which included preoperative radiation, major surgical resection and

postoperative systemic chemotherapy. The association between potential predictors and treatment adherence can be found in table 6 – 15.

Table 6-15 The association between overall treatment adherence and potential predictors for those with locally advanced disease

Characteristic	Treatment Adherent (Preop Radiation, Major Surgery, Postop Chemotherapy)			
	No (N=4429, 62.7%)	Yes (N=2626, 37.3%)	Total (N=7,055)	Significant Testing (χ^2, ANOVA)
Mean Age, year (STD)	68.0 (12.8)	60.2 (11.2)	65.1 (12.8)	P<.0001
Age Group				
18-39	96 (46.8%)	109 (53.2%)	205 (2.9%)	P<.0001
40-49	271 (46.1%)	317 (53.9%)	588 (8.3%)	
50-59	758 (49.6%)	769 (50.4%)	1527 (21.6%)	
60-69	1179 (57.1%)	885 (42.9%)	2064 (29.3%)	
70-79	1180 (71.6%)	467 (28.4%)	1647 (23.3%)	
80+	945 (92.3%)	79 (7.7%)	1024 (14.5%)	
Sex				
Female	1634 (63.8%)	929 (36.2%)	2563 (36.3%)	P = 0.20
Male	2795 (62.2%)	1697 (37.8%)	4492 (63.7%)	
Year of Surgery				
2010-2013	1926 (68.2%)	900 (31.8%)	2826 (40.1%)	P<.0001
2014-2016	1293 (58.7%)	910 (41.3%)	2203 (31.2%)	
2017-2019	1210 (59.7%)	816 (40.3%)	2026 (28.7%)	
Cancer Centre Designation				
Regional	2108 (56.2%)	1646 (43.8%)	3754 (53.2%)	P<.0001
Affiliate	1612 (68.8%)	730 (31.2%)	2342 (33.2%)	
Satellite/Non-Designated	709 (73.9%)	250 (26.1%)	959 (13.6%)	
Surgeon Volume (cases/year)				
Missing	676 (90.5%)	71 (9.5%)	747 (10.6%)	P<.0001
Low (<3.5)	1533 (70.2%)	652 (29.8%)	2185 (31.0%)	
Mid (3.5 - 14.5)	1227 (58.9%)	855 (41.1%)	2082 (29.5%)	
High (>14.5)	993 (48.7%)	1048 (51.3%)	2041 (28.9%)	
Income Quintile				
1 (lowest)	969 (66.1%)	496 (33.9%)	1465 (20.8%)	P = 0.008
2 - 4	2676 (62.2%)	1625 (37.8%)	4301 (61.0%)	
5 (highest)	784 (60.8%)	505 (39.2%)	1289 (18.3%)	
Geographical Location				
Rural	809 (59.7%)	545 (40.3%)	1354 (19.2%)	P = 0.010
Urban	3620 (63.5%)	2081 (36.5%)	5701 (80.8%)	
Charlson Co-morbidity Score				
Low (< 3)	2263 (61.9%)	1392 (38.1%)	3655 (51.8%)	P<.0001
Mid (3)	649 (69.2%)	289 (30.8%)	938 (13.3%)	
High (> 3)	1517 (61.6%)	945 (38.4%)	2462 (34.9%)	

Age was found to be an important predictor of overall adherence. Increasing age was negatively associated with adherence for each of the treatment modalities (surgery, radiation, chemotherapy), and this negative association was demonstrated with overall treatment adherence as well. More recent year of surgery also continued to be an important predictor of overall adherence. This was primarily driven by large improvements in adherence to chemotherapy and modest improvements in adherence to radiation over the study period, whereas adherence to surgery, which was negatively associated with increasing time period, imposed less of an effect on the analysis. Those who were non adherent to surgery represented only a small proportion of the cohort (~5%) compared with much larger proportions of non-adherence to chemotherapy (~40%) and non-adherence to radiation (~40%). Cancer centre designation and surgeon volume were both also important predictors of overall treatment adherence. Co-morbidity score was a less important predictor, with a modest effect identified. Rurality was positively associated with overall adherence, primarily as a result of the association with adherent chemotherapy. This is somewhat unexpected in that those further from the site of chemotherapy delivery would presumably be less inclined to accept treatment. (Table 6 – 16)

Table 6-16 Univariable and Multivariable analyses of the association between predictors and guideline adherent treatment (preoperative radiation, systemic chemotherapy and major surgical resection) in those with locally advanced disease

Characteristic	Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis OR (95%CI), Significant Testing	
Age, per 10 year increase	0.60 (0.58, 0.63) (a)	P<.0001	0.61 (0.58, 0.64) (a)	P<.0001
Sex				
Female	0.94 (0.85, 1.04)	P = 0.20	0.93 (0.83, 1.03)	P = 0.17
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P<.0001	Referent	P<.0001
2014-2016	1.51 (1.34, 1.69)		1.51 (1.33, 1.71)	
2017-2019	1.44 (1.28, 1.63)		1.41 (1.23, 1.60)	
Cancer Centre Designation				
Regional	Referent	P<.0001	Referent	P<.0001
Affiliate	0.58 (0.52, 0.65)		0.69 (0.61, 0.78)	
Satellite/Non-Designated	0.45 (0.39, 0.53)		0.79 (0.66, 0.95)	
Surgeon Volume (cases/year)				
Missing	0.10 (0.08, 0.13)	P<.0001	0.12 (0.09, 0.16)	P<.0001
Low (<3.5)	0.40 (0.36, 0.46)		0.50 (0.43, 0.58)	
Mid (3.5 - 14.5)	0.66 (0.58, 0.75)		0.76 (0.66, 0.86)	
High (>14.5)	Referent		Referent	
Income Quintile				
1 (lowest)	0.79 (0.68, 0.93)	P = 0.0076	0.89 (0.75, 1.06)	P = 0.24
2 - 4	0.94 (0.83, 1.07)		1.00 (0.87, 1.15)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.17 (1.04, 1.32)	P = 0.010	1.16 (1.01, 1.32)	P = 0.033
Urban	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P<.0001	Referent	P = 0.051
Mid (3)	0.72 (0.62, 0.84)		0.91 (0.77, 1.08)	
High (> 3)	1.01 (0.91, 1.12)		1.11 (0.99, 1.25)	

(a) per 10 year increase

6.5.2.6 Timely and Adherent Treatment, Locally Advanced Disease

Timely and adherent treatment was assessed for those with locally advanced disease. As described in the methods, timely radiation was defined as receiving first dose of radiation < 35 days after diagnosis, timely surgery was defined as undergoing resection < 84 days following the

last dose of radiation and timely chemotherapy was defined as receiving first dose of chemotherapy < 84 days after surgery. Timely and Adherent treatment required that each treatment was received in a timely manner. For those with locally advanced disease, 20% (n = 1350/6888) had timely and adherent treatments. (Table 6 – 17) Being timely and adherent was less common than being adherent to treatments only (37%) for this group.

Table 6-17 Timely and Adherent Treatment (Radiation < 35 days after diagnosis, Surgery < 84 days after last dose of radiation, Chemotherapy < 84 days after surgery), by predictor, in those with locally advanced disease

Timely Adherent Treatment (a)				
Characteristic	**Non-Adherent (n = 5338, 79.9%)**	**Adherent (n = 1350, 20.1%)**	**Total (N = 6888)**	**Significant Testing (χ^2, ANOVA)**
Mean Age, year (STD)	66.2 (12.6)	59.1 (11.5)	64.8 (12.7)	P < .0001
Age Group				
18-39	127 (64.8%)	69 (35.3%)	196 (2.8%)	P < .0001
40-49	375 (65.9%)	194 (34.1%)	569 (8.5%)	
50-59	1084 (73.4%)	393 (26.6%)	1477 (22.1%)	
60-69	1539 (77.5%)	447 (22.5%)	1986 (29.7%)	
70-79	1342 (86.2%)	214 (13.8%)	1556 (23.3%)	
80+	871 (96.3%)	33 (3.7%)	904 (13.5%)	
Sex				
Female	1974 (80.7%)	473 (19.3%)	2447 (36.6%)	P = 0.19
Male	3364 (79.3%)	877 (20.7%)	4241 (63.4%)	
Year of Surgery				
2010-2013	2202 (80.7%)	527 (19.3%)	2729 (40.8%)	P = 0.028
2014-2016	1637 (77.9%)	465 (22.1%)	2102 (31.4%)	
2017-2019	1499 (80.7%)	358 (19.3%)	1857 (27.8%)	
Cancer Centre Designation				
Regional	2788 (76.1%)	876 (23.9%)	3664 (54.8%)	P < .0001
Affiliate	1843 (83.9%)	353 (16.1%)	2196 (32.8%)	
Satellite/Non-Designated	702 (85.5%)	119 (14.5%)	821 (12.3%)	
Surgeon Volume (cases/year)				
Missing	340 (90.2%)	37 (9.8%)	377 (5.6%)	P < .0001
Low (<3.5)	1869 (85.5%)	318 (14.5%)	2187 (32.7%)	
Mid (3.5 - 14.5)	1667 (80.1%)	415 (19.9%)	2082 (31.1%)	
High (>14.5)	1462 (71.6%)	580 (28.4%)	2042 (30.5%)	
Income Quintile				
1 (lowest)	1144 (82.6%)	241 (17.4%)	1385 (20.7%)	P = 0.0059
2 - 4	3206 (79.5%)	826 (20.5%)	4032 (60.3%)	
5 (highest)	988 (77.7%)	283 (22.3%)	1271 (19.0%)	
Geographical Location				
Rural	1017 (79.0%)	271 (21.0%)	1288 (19.3%)	P = 0.40
Urban	4321 (80.0%)	1079 (20.0%)	5400 (80.7%)	
Charlson Co-morbidity Score				
Low (< 3)	2686 (78.7%)	725 (21.3%)	3411 (51.0%)	P < .0001
Mid (3 - 4)	1022 (86.0%)	167 (14.0%)	1189 (17.8%)	
High (> 4)	1630 (78.1%)	458 (21.9%)	2088 (31.2%)	

Univariable and Multivariable analysis was completed (Table 6 – 18). Age continued to be an important predictor, with the elderly much less likely to receive timely and adherent care. Both cancer centre designation and surgeon volume were also important predictors. This is consistent with the analysis reported in 6.5.2.5 which assessed overall treatment adherence without the timeliness variable. Those treated at a regional cancer centre and those treated by high volume surgeons were much more likely to receive timely and adherent treatments. Co-morbidity score was the other predictor found to be associated with timely and adherent treatment. Similar to the analysis without the timeliness variable, those with the lowest and highest co-morbidity scores were more adherent than those in the mid scores. (Table 6 – 18).

Table 6-18 Univariable and Multivariable analysis of the association between predictors and timely adherent treatment in those with locally advanced disease

Characteristic	Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis OR (95%CI), Significant Testing	
Age Group				
18-39	1.66 (1.18, 2.31)	P <.0001	1.58 (1.10, 2.23)	P <.0001
40-49	1.78 (1.45, 2.18)		1.78 (1.44, 2.20)	
50-59	1.25 (1.07, 1.46)		1.23 (1.05, 1.45)	
60-69	referent		referent	
70-79	0.55 (0.46, 0.66)		0.57 (0.47, 0.68)	
80+	0.13 (0.09, 0.18)		0.15 (0.10, 0.21)	
Sex/Gender				
Female	0.92 (0.81, 1.04)	P = 0.19	0.93 (0.82, 1.06)	P = 0.30
Male	referent		referent	
Year of Surgery				
2010-2013	1.00 (0.86, 1.16)	P = 0.028	0.72 (0.45, 1.17)	P = 0.12
2014-2016	1.19 (1.02, 1.39)		1.02 (0.72, 1.46)	
2017-2019	referent		referent	
Cancer Centre Designation				
Regional	referent		referent	
Affiliate	0.61 (0.53, 0.70)	P <.0001	0.72 (0.62, 0.84)	P = 0.002
Satellite/Non-Designated	0.54 (0.44, 0.66)		0.85 (0.67, 1.08)	
Surgeon Volume (cases/year)				
Missing				
Low (<3.5)	0.43 (0.37, 0.50)	P <.0001	0.51 (0.43, 0.61)	P <.0001
Mid (3.5 - 14.5)	0.63 (0.54, 0.72)		0.70 (0.60, 0.82)	
High (>14.5)	referent		referent	
Income Quintile				
1 (lowest)	0.74 (0.61, 0.89)	P = 0.0059	0.82 (0.67, 1.01)	P = 0.11
2 - 4	0.90 (0.77, 1.05)		0.96 (0.82, 1.13)	
5 (highest)	referent		referent	
Geographical Location				
Rural	1.07 (0.92, 1.24)	P = 0.40	0.99 (0.84, 1.16)	P = 0.91
Urban	referent		referent	
Charlson Co-morbidity Score				
Low (< 3)	0.96 (0.84, 1.10)	P <.0001	0.88 (0.77, 1.02)	P = 0.0014
Mid (3 - 4)	0.58 (0.48, 0.70)		0.69 (0.56, 0.84)	
High (> 4)	referent		referent	

6.5.3 Predictors of Guideline Adherent Surveillance

Guideline adherent surveillance was determined in those who underwent major surgical resection only. As described in the methods, those that did not undergo surgery or who had a local excision were excluded from this analysis, as guideline recommendations are either inconsistent or not available. Overall, 5283 (51.7%) individuals undergoing major surgery were adherent to surveillance, which was defined as receipt of colonoscopy, chest imaging, abdominal imaging and pelvic imaging within 18 months of surgery. Those with locally advanced disease had the highest proportion adherent (55.9%), followed by early stage (46.1%) and missing stage (37.3%). Of the assessed surveillance investigations, chest imaging (90.3%), abdominal imaging (88.6%) and pelvic imaging (86.0%) were all performed commonly, while colonoscopy was performed least frequently (56.6%). (Table 6 – 19)

Table 6-19 Guideline Adherent Surveillance within 18 months of major resection

	Early Stage (N=2,667)	Locally Advanced (N=6,685)	Missing Stage (N=856)	All (N = 10,208)	X^2 Test
Colonoscopy	1680 (63.0%)	3704 (55.4%)	393 (45.9%)	5777 (56.6%)	P<0.0001
Chest Imaging (CT, CXR)	2115 (79.3%)	6409 (95.9%)	689 (80.5%)	9213 (90.3%)	P<0.0001
Abdominal Imaging (CT, US, MRI)	2066 (77.5%)	6274 (93.8%)	701 (81.9%)	9041 (88.6%)	P<0.0001
Pelvic Imaging (CT, MRI)	1925 (72.2%)	6177 (92.4%)	680 (79.4%)	8782 (86.0%)	P<0.0001
Guideline Adherent Surveillance	1229 (46.1%)	3734 (55.9%)	320 (37.3%)	5283 (51.7%)	P<0.0001

Predictors of adherent surveillance were determined for those undergoing major surgery and who lived at least 18 months after major surgery. (Table 6 – 20) Although mean age was younger in those who were adherent, notably the youngest age group was less adherent than many of the older age groups. Lower co-morbidity score, higher income quintile, and surgery by higher volume surgeons were all associated with increased adherence.

Table 6-20 Potential Predictors and Overall Surveillance, Major Resection and Survived > 18 months

Characteristic	Major Surgery, Survived >18 months		
	Adherent (N = 4737, 54.1%)	**Non-Adherent (N = 4011, 45.9%)**	**X^2 Test or ANOVA**
Mean Age, year (STD)	62.9 (11.7)	65.9 (13.2)	P< 0.0001
Age Group			
18-39	155 (52.5%)	140 (47.5%)	P < 0.0001
40-49	545 (60.5%)	356 (39.5%)	
50-59	1226 (58.1%)	883 (41.9%)	
60-69	1503 (57.9%)	1093 (42.1%)	
70+	1308 (45.9%)	1539 (54.1%)	
Sex			
Female	1730 (52.6%)	1558 (47.4%)	P = 0.026
Male	3007 (55.1%)	2453 (44.9%)	
Year of Surgery			
2010-2013	2109 (52.7%)	1892 (47.3%)	P = 0.028
2014-2016	1640 (54.8%)	1353 (45.2%)	
2017-2019	988 (56.3%)	766 (43.7%)	
Cancer Centre Designation			
Regional	2504 (54.3%)	2111 (45.7%)	P = 0.16
Affiliate	1579 (54.2%)	1333 (45.8%)	
Satellite/Non-Designated	651 (53.9%)	557 (46.1%)	
Income Quintile			
1 (lowest)	879 (51.0%)	844 (49.0%)	P = 0.0005
2 - 4	2882 (54.1%)	2449 (45.9%)	
5 (highest)	976 (57.6%)	718 (42.4%)	
Geographical Location			
Rural	926 (54.7%)	767 (45.3%)	P = 0.61
Urban	3811 (54.0%)	3244 (46.0%)	
Surgeon Volume			
Missing	280 (36.9%)	479 (63.1%)	P < 0.0001
Low (< 3.5/year)	1531 (53.9%)	1311 (46.1%)	
Mid (3.5 - <14.5/year)	1465 (56.3%)	1135 (43.7%)	
High (> 14.5/year)	1461 (57.4%)	1086 (42.6%)	
Charlson Co-morbidity Score			
Low (< 3)	2731 (56.8%)	2076 (43.2%)	P < 0.0001
Mid (3)	636 (51.6%)	596 (48.4%)	
High (> 3)	1370 (50.6%)	1339 (49.4%)	

Univariable and multivariable analyses were completed to determine which predictors were associated with guideline adherent surveillance. (Table 6 - 21) Age, comorbidity score and income quintile were associated with adherent surveillance. Notably (and unlike staging or treatment), cancer centre designation did not show an association with adherent surveillance. Only a modest association with surgeon volume was identified, which is different than the large magnitude of effect surgeon volume had on many of the staging and treatment adherence outcomes.

Table 6-21 Univariable and Multivariable analyses of the association between predictors and adherent surveillance (Colonoscopy and Chest, Abdominal, Pelvic imaging) within 18 months of major surgery, in those who were alive at 18 months

Characteristic	Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis OR (95%CI), Significant Testing	
Mean Age, year (STD)	0.83 (0.80, 0.85) (a)	P<.0001	0.83 (0.80, 0.85) (a)	P <0.0001
Sex				
Female	0.91 (0.83, 0.99)	P= 0.025	0.92 (0.84, 1.01)	P = 0.071
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P = 0.028	Referent	P = 0.036
2014-2016	1.09 (0.99, 1.20)		1.09 (0.98, 1.20)	
2017-2019	1.16 (1.03, 1.30)		1.16 (1.03, 1.30)	
Cancer Centre Designation				
Regional	Referent	P = 0.97	Referent	P = 0.17
Affiliate	0.99 (0.90, 1.09)		1.08 (0.98, 1.19)	
Satellite/Non-Designated	0.99 (0.87, 1.12)		1.12 (0.97, 1.29)	
Income Quintile				
1 (lowest)	0.77 (0.67, 0.88)	P = 0.0006	0.80 (0.69, 0.92)	P = 0.0055
2 - 4	0.87 (0.78, 0.97)		0.88 (0.79, 0.99)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.03 (0.92, 1.14)	P = 0.62	1.01 (0.91, 1.13)	P = 0.81
Urban	Referent		Referent	
Surgeon Volume				
Missing	0.43 (0.37, 0.51)	P<.0001	0.42 (0.35, 0.49)	P<.0001
Low (< 3.5/year)	0.87 (0.78, 0.97)		0.88 (0.78, 0.99)	
Mid (3.5 - <14.5/year)	0.96 (0.86, 1.07)		0.95 (0.85, 1.07)	
High (> 14.5/year)	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P <.0001	Referent	P<.0001
Mid (3)	0.81 (0.72, 0.92)		0.84 (0.74, 0.96)	
High (> 3)	0.78 (0.71, 0.85)		0.77 (0.70, 0.84)	

(a) Per 10 year increase

6.5.4 Predictors of Overall Guideline Adherent Care

The associations between potential predictors and overall guideline adherent care can be found in table 6 – 22. For early stage disease, overall adherence included complete staging investigations (local regional staging, metastatic disease assessment, colonic assessment), timely surgery and complete surveillance within 18 months of surgery. For locally advanced disease, overall adherence included the same elements as for early stage disease, but also included preoperative radiation and post operative chemotherapy. The timeliness variable was not included in this analysis. Overall, only a minority of those with early stage disease (21.4%, n = 570/2,667) and locally advanced disease (23.0%, n = 1,535/6,685) were adherent to all aspects of guideline recommended care.

Table 6-22 Adherence vs. non adherence to overall guideline adherence (Staging, Treatment, Surveillance) for early stage and locally advanced disease, by predictor

Characteristic	Early Stage (N = 2667)			Locally Advanced (N = 6685)		
	Adherent (N = 570, 21.4%)	Non-Adherent (N = 2097, 78.6%)	X^2 Test or ANOVA	Adherent (N = 1535, 22.9%))	Non-Adherent (N = 5150, 77.1%)	X^2 Test or ANOVA
Mean Age, year (STD)	64.3 (11.6)	66.5 (12.3)	P = 0.0001	59.8 (11.0)	66.3 (12.8)	P<.0001
Age Group						
18-39	12 (23.1%)	40 (76.9%)	P<.0001	59 (30.1%)	137 (69.9%)	
40-49	53 (27.5%)	140 (72.5%)		190 (33.4%)	379 (66.6%)	
50-59	116 (21.5%)	424 (78.5%)		471 (31.9%)	1,006 (68.1%)	
60-69	183 (23.8%)	587 (76.2%)		524 (26.4%)	1,460 (73.6%)	
70 - 79	164 (22.1%)	579 (77.9%)		249 (16.0%)	1,306 (84.0%)	
80+	42 (11.4%)	327(88.6%)		42 (4.6%)	862 (95.4%)	
Sex						
Female	220 (21.0%)	826 (79.0%)	P = 0.73	563 (23.0%)	1,881 (77.0%)	P = 0.91
Male	350 (21.6%)	1,271 (78.4%)		972 (22.9%)	3,269 (77.1%)	
Year of Surgery						
2010-2013	234 (20.4%)	913 (79.6%)	P = 0.39	524 (19.2%)	2,205 (80.8%)	P<.0001
2014-2016	196 (22.9%)	660 (77.1%)		560 (26.7%)	1,541 (73.3%)	
2017-2019	140 (21.1%)	524 (78.9%)		451 (24.3%)	1,404 (75.7%)	
Cancer Centre Designation						
Regional	292 (21.5%)	1,069 (78.5%)	P = 0.97	963 (26.5%)	2,671 (73.5%)	P<.0001
Affiliate	189 (21.1%)	706 (78.9%)		423 (19.2%)	1,780 (80.8%)	
Satellite/Non-Designated	89 (21.7%)	322 (78.3%)		149 (17.6%)	699 (82.4%)	
Income Quintile						
1 (lowest)	113 (22.4%)	392 (77.6%)	P = 0.15	267 (19.4%)	1,109 (80.6%)	P = 0.0007
2 - 4	324 (20.2%)	1,282 (79.8%)		955 (23.4%)	3,123 (76.6%)	
5 (highest)	133 (23.9%)	423 (76.1%)		313 (25.4%)	918 (74.6%)	
Geographical Location						
Rural	108 (20.7%)	413 (79.3%)	P = 0.69	295 (22.9%)	992 (77.1%)	P = 0.97
Urban	462 (21.5%)	1,684 (78.5%)		1,240 (23.0%)	4,158 (77.0%)	
Surgeon Volume						
Missing	45 (11.5%)	345 (88.5%)	P <.0001	33 (8.8%)	344 (91.2%)	P <.0001
Low (< 3.5/year)	195 (22.6%)	666 (77.4%)		379 (17.3%)	1,806 (82.7%)	
Mid (3.5 - <14.5/year)	176 (24.8%)	535 (75.2%)		495 (23.8%)	1,587 (76.2%)	
High (> 14.5/year)	154 (21.8%)	551 (78.2%)		628 (30.8%)	1,413 (69.2%)	
Charlson Co-morbidity Score						
Low (< 3)	382 (21.6%)	1,384 (78.4%)	P = 0.58	837 (24.5%)	2,573 (75.5%)	P = 0.0005
Mid (3)	108 (22.0%)	382 (78.0%)		162 (18.5%)	713 (81.5%)	
High (> 3)	80 (19.5%)	331 (80.5%)		536 (22.3%)	1,864 (77.7%)	

Univariable and multivariable analysis is reported in Table 6 – 23 for early stage disease. In this group, age was negatively associated with overall adherence. The only other factor demonstrating an association with overall adherence in early stage disease was surgeon volume. This was driven primarily by those with "missing" surgeon, which occurred frequently in those undergoing local excision only

Table 6-23 Univariable and Multivariable analyses of the association between predictors and overall adherence in those with early stage disease

Characteristic	Univariable		Multivariable	
	OR, 95% CI	Significant Testing	OR, 95% CI	Significant Testing
Age (a)	0.86 (0.80, 0.93)	P = 0.0001	0.86 (0.80, 0.94)	P = 0.0003
Sex				
Female	0.97 (0.80, 1.17)	P = 0.73	0.98 (0.80, 1.18)	P = 0.80
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P = 0.39	Referent	P = 0.38
2014-2016	1.16 (0.93, 1.44)		1.16 (0.93, 1.44)	
2017-2019	1.04 (0.82, 1.32)		1.02 (0.80, 1.30)	
Cancer Centre Designation				
Regional	Referent	P = 0.97	Referent	P = 0.95
Affiliate	0.98 (0.80, 1.20)		1.00 (0.80, 1.25)	
Satellite/Non-Designated	P = 1.01 (0.77, 1.32)		1.05 (0.77, 1.41)	
Income Quintile				
1 (lowest)	0.92 (0.69, 1.22)	P = 0.15	0.95 (0.71, 1.27)	P = 0.17
2 - 4	0.80 (0.64, 1.01)		0.82 (0.65, 1.03)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	0.95 (0.75, 1.20)	P = 0.69	0.96 (0.75, 1.21)	P = 0.71
Urban	Referent		Referent	
Surgeon Volume				
Missing	0.47 (0.32, 0.66)	P <.0001	0.49 (0.33, 0.70)	P <.0001
Low (< 3.5/year)	1.05 (0.82, 1.33)		1.10 (0.84, 1.45)	
Mid (3.5 - <14.5/year)	1.18 (0.92, 1.51)		1.22 (0.94, 1.58)	
High (> 14.5/year)	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P = 0.58	Referent	P = 0.74
Mid (3)	1.02 (0.80, 1.30)		1.08 (0.84, 1.38)	
High (> 3)	0.88 (0.67, 1.14)		0.95 (0.72, 1.25)	

(a) per 10 year increase

. For those with locally advanced disease, a number of predictors were identified based on univariable and multivariable analyses (Table 6 – 24). Age was negatively associated with adherence, while higher cancer centre level designation, higher income quintile and higher surgeon volume were positively associated with overall adherence. Year of surgery was also associated with adherence, but a trend was not established. Those in the middle time period had the highest odds of adherence, followed by the latest time period and then the earliest time period. Interestingly, co-morbidity score was not associated with overall adherence. There were conflicting direction of association between comorbidity score and staging investigations and comorbidity score and treatment adherence, which likely explains this result. Finally, there was no association between overall adherence and sex or between overall adherence and geographic location.

Table 6-24 Univariable and Multivariable analyses of the association between predictors and overall adherence in those with locally advanced disease

Characteristic	Univariable		Multivariable	
	OR, 95% CI	Significant Testing	OR, 95% CI	Significant Testing
Age (a)	0.66 (0.63, 0.70)	P<.0001	0.67 (0.64, 0.71)	P <.0001
Sex				
Female	1.01 (0.89, 1.13)	P = 0.91	1.01 (0.89, 1.14)	P = 0.93
Male	Referent		Referent	
Year of Surgery				
2010-2013	Referent	P<.0001	Referent	P <.0001
2014-2016	1.53 (1.34, 1.75)		1.50 (1.30, 1.73)	
2017-2019	1.35 (1.17, 1.56)		1.24 (1.06, 1.44)	
Cancer Centre Designation				
Regional	Referent	P<.0001	Referent	P = 0.0004
Affiliate	0.66 (0.58, 0.75)		0.75 (0.65, 0.87)	
Satellite/Non-Designated	0.59 (0.49, 0.71)		0.93 (0.75, 1.15)	
Income Quintile				
1 (lowest)	0.71 (0.59, 0.85)	P = 0.0007	0.75 (0.62, 0.91)	P = 0.008
2 - 4	0.90 (0.77, 1.04)		0.93 (0.80, 1.09)	
5 (highest)	Referent		Referent	
Geographical Location				
Rural	1.00 (0.86, 1.15)	P = 0.97	0.96 (0.82, 1.12)	P = 0.60
Urban	Referent		Referent	
Surgeon Volume				
Missing	0.22 (0.15, 0.31)	P<.0001	0.25 (0.17, 0.36)	P <.0001
Low (< 3.5/year)	0.47 (0.41, 0.55)		0.56 (0.48, 0.66)	
Mid (3.5 - <14.5/year)	0.70 (0.61, 0.81)		0.78 (0.67, 0.90)	
High (> 14.5/year)	Referent		Referent	
Charlson Co-morbidity Score				
Low (< 3)	Referent	P = 0.0005	Referent	P = 0.40
Mid (3)	0.70 (0.58, 0.84)		0.88 (0.72, 1.06)	
High (> 3)	0.88 (0.78, 1.00)		0.99 (0.87, 1.13)	

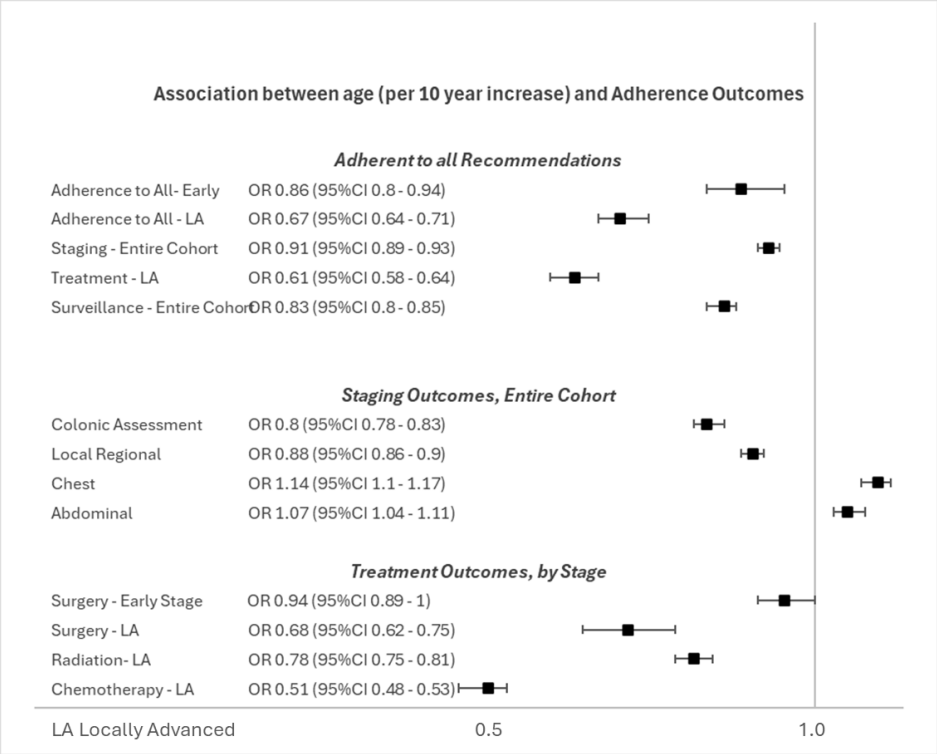
(a) per 10 year increase

6.5.5 Summary of Predictors of Guideline Adherent Care

The results of the multivariable analyses for each predictor and outcome were summarized in the figures below. This was done to allow for a determination of the consistency of effect direction across outcomes. As described in the methods, and in the preceding chapter sections, each analysis including the following co-variates: Age; Sex; Diagnosis Year; Socioeconomic Status; Charlson Comorbidity Score; Rurality. For the treatment adherence outcomes and surveillance outcomes, cancer centre designation and surgeon volume were also included. The treatment adherence outcomes were restricted to those with a known stage of disease (early stage or locally advanced), while surveillance was restricted to those who underwent a major resection only. The justification for these decision appears in the methods section.

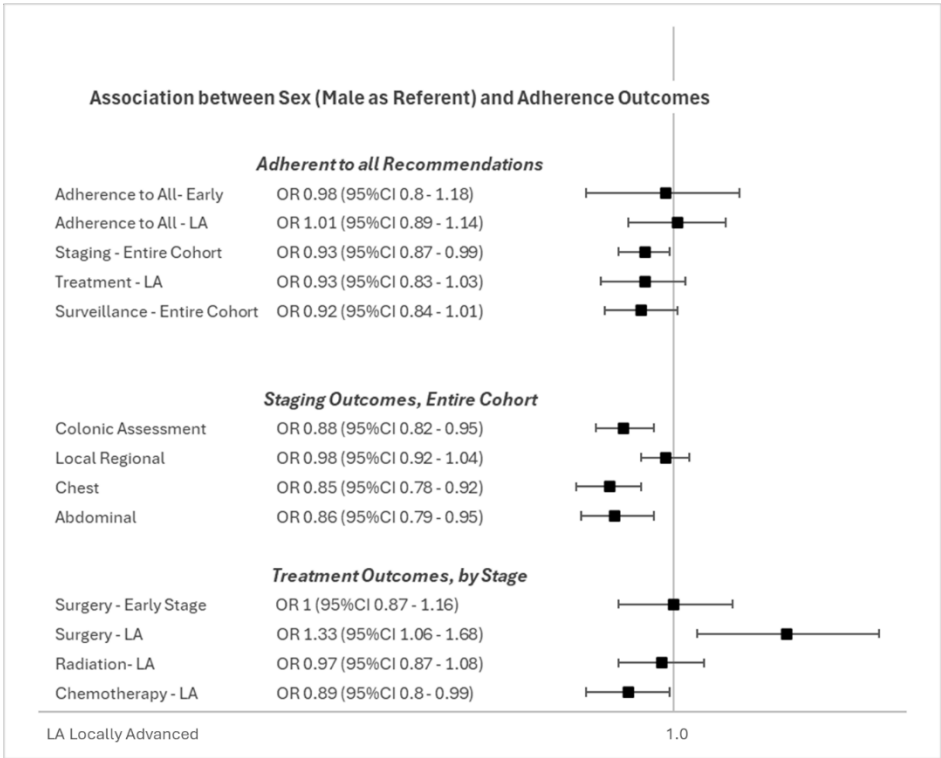
Age, per 10 year increase, was associated with guideline adherent care for all adherence outcomes. The majority of these (n = 11/13) demonstrated that increasing age was negatively associated with the outcome. The exception was for Chest and Abdominal Staging in which increasing age was positively associated with adherence. (Figure 6 – 3) The largest magnitude of effect was with the receipt of adherent chemotherapy (OR 0.51, 95%CI 0.48 – 0.53) and receipt of overall treatment (OR 0.61, 95%CI 0.58 – 0.64) in those with locally advanced disease.

Figure 6-3 Summary of the Associations between age and adherence outcomes, multivariable analyses



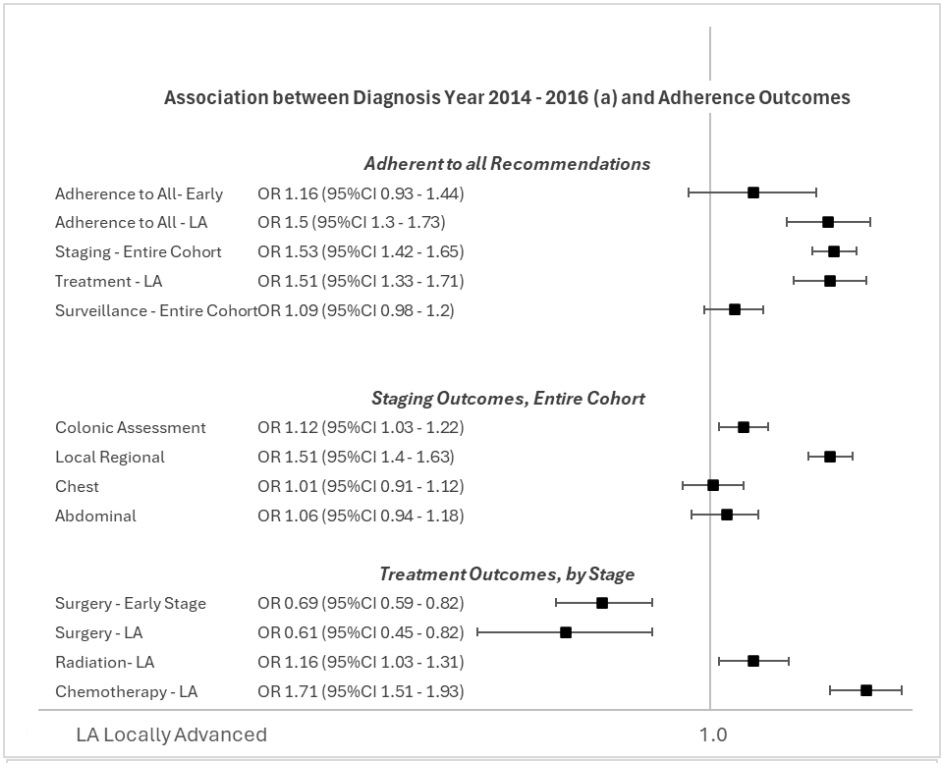
The association between sex and adherence outcomes are summarized in Figure 6 – 4. Female sex was negatively associated with overall staging, as well as colonic staging, chest staging and abdominal staging. It was also negatively associated with receipt of chemotherapy. Female sex was positively associated with receipt of adherent surgery (i.e. major resection) in those with locally advanced disease. The rest of the analyses did not demonstrate an association between sex and outcomes. Notably, overall adherence was very similar between the sexes.

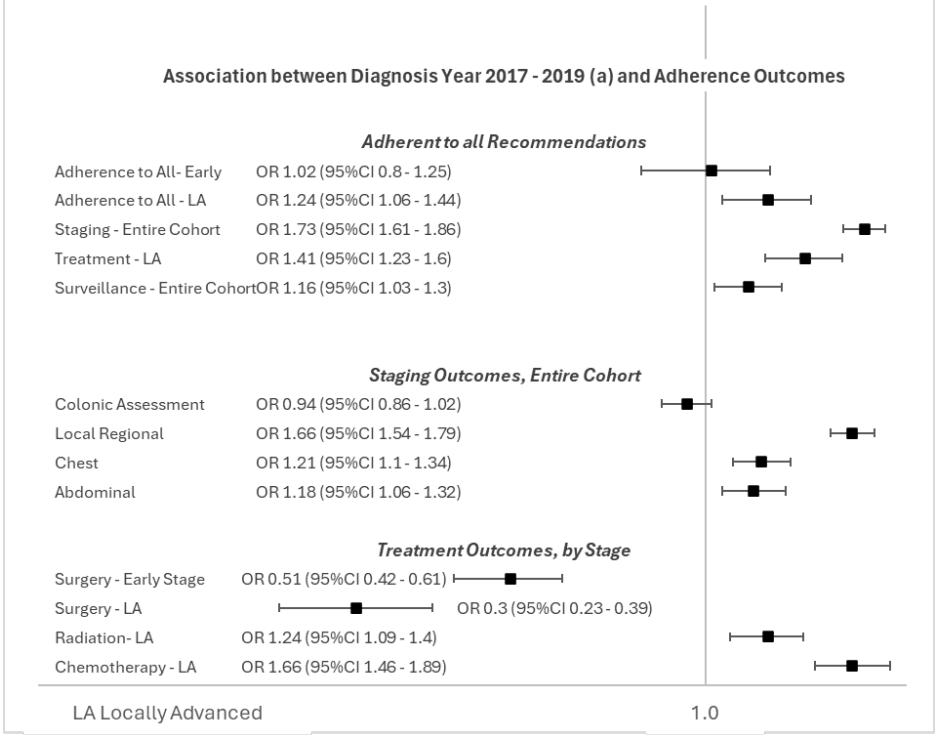
Figure 6-4 Summary of the Association between Sex and Adherence Outcomes, multivariable analyses



The summary of diagnosis year and adherence outcomes are presented in Figure 6 – 5 (a, b). In general, later diagnosis year was associated with increased adherence, including: Overall Adherence (locally advanced); Staging Adherence; Treatment Adherence (locally advanced); Surveillance Adherence; Local Regional Staging; Chest Staging; Abdominal Staging; Radiation Adherence; Chemotherapy Adherence. The exception was adherence to staging, including adherence to timely surgery for early stage disease or adherence to major resection for locally advanced disease. In both cases, later diagnosis year was associated with worsening adherence.

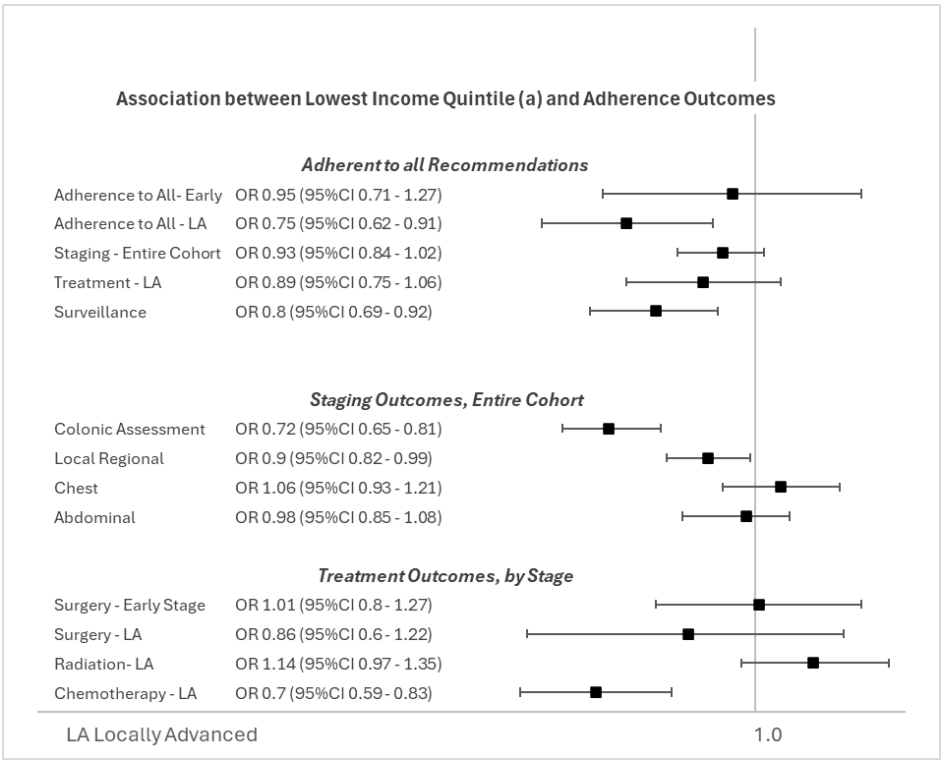
Figure 6-5 (a, b) Summary of the associations between Diagnosis Year and Adherence Outcomes, multivariable analysis: (a) – Diagnosis Year 2009 – 2013 was the referent group

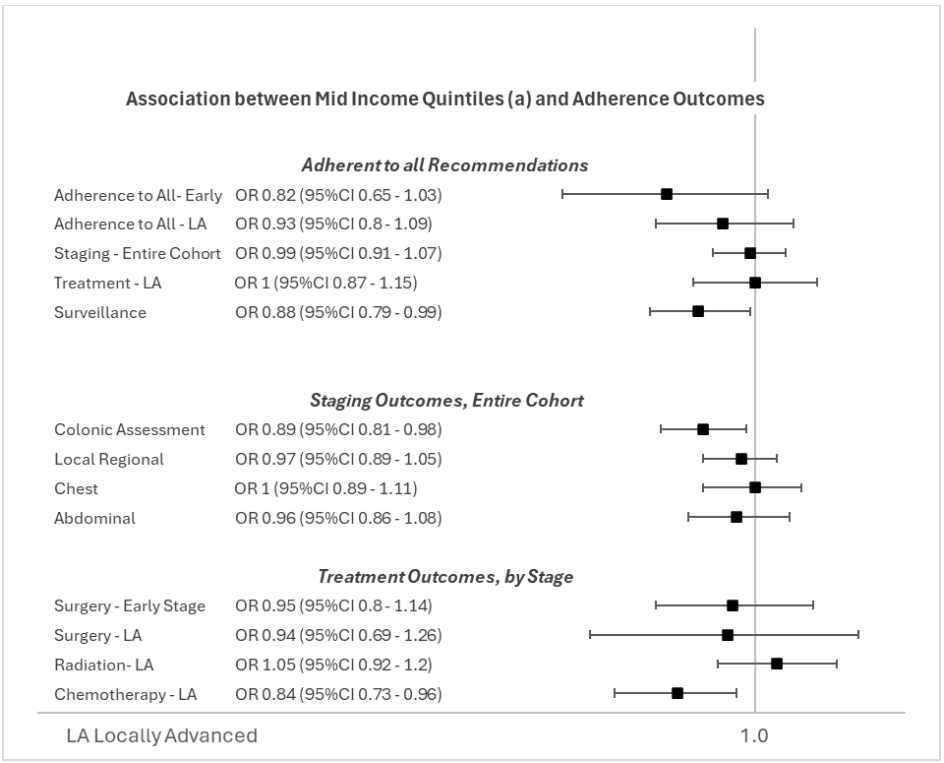




A summary of the associations between income quintile and adherence outcomes appears in Figure 6 – 6 (a, b). Lowest income quintile (with highest as the referent group) was associated with some adherence outcomes. For instance, adherence to all recommendation in those with locally advanced disease, adherence to surveillance, local regional staging, colonic staging and chemotherapy receipt were all negatively associated with the lowest income quintile. Only two association between the mid tier quintiles and adherence was identified, with those in this group negatively associated with receipt of adherent chemotherapy and overall surveillance.

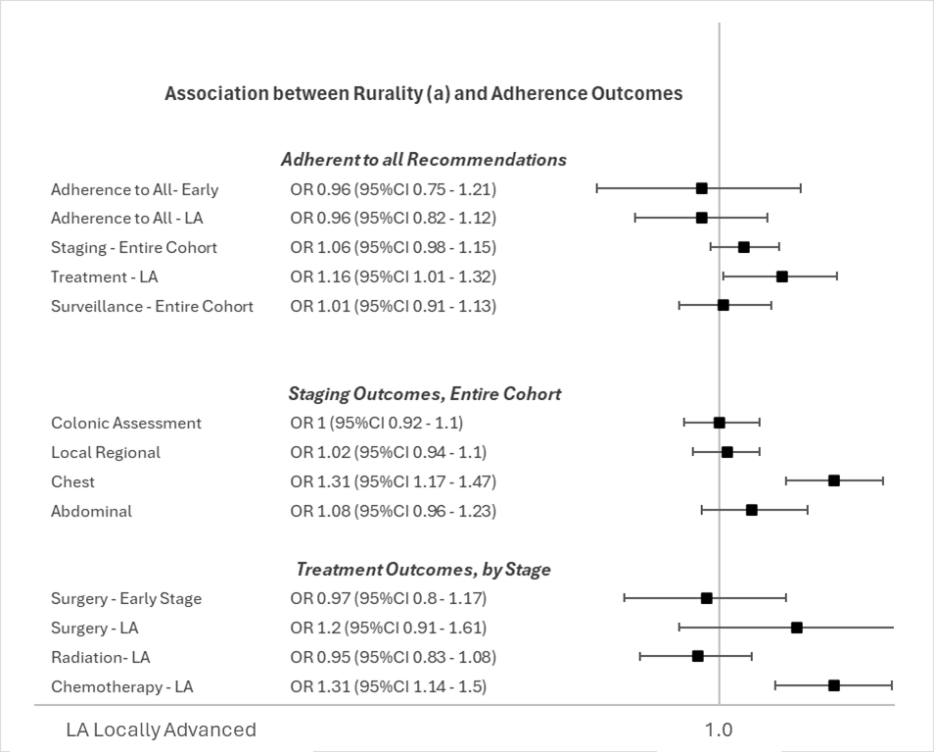
Figure 6-6 (a, b) Summary of the associations between Income Quintile and Adherence Outcomes, multivariable analysis: (a) Highest Income Quintile is Referent Group





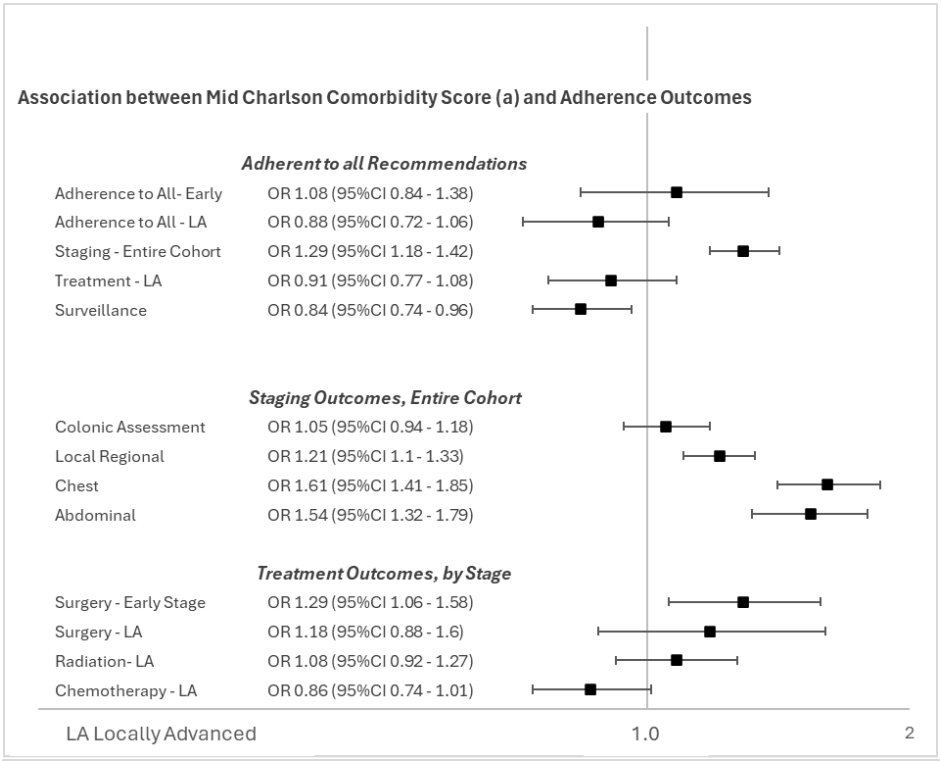
Rurality (with Urban residence as referent) and its associations with adherence outcomes is summarised in Figure 6 – 7. Rurality was positively associated with three adherence outcomes, including overall treatment (locally advanced), chest staging and receipt of chemotherapy. Interestingly, radiation adherence was not associated with rurality, despite the hypothesized impact of increased travel and/or distance on receipt of radiation.

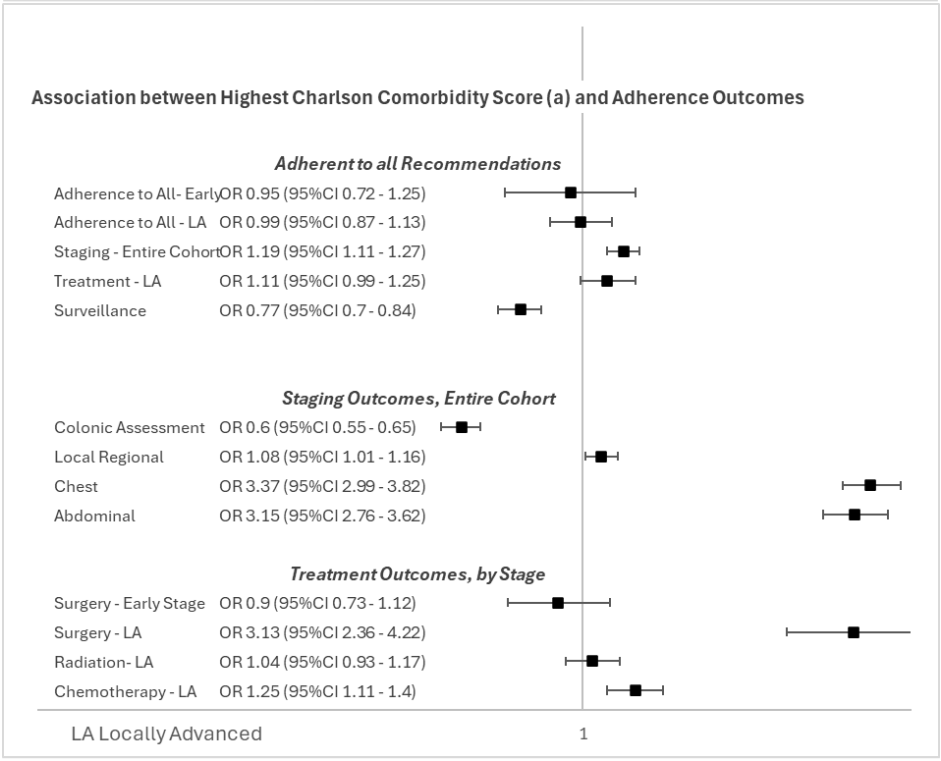
Figure 6-7 Summary of the association between Rurality and adherence outcome, multivariable analyses: a) Urban is referent



The associations between Charlson Comorbidity Score and adherence outcomes are presented in Figure 6 – 8 (a, b). The figure presents the mid tier group (Score = 3) and the highest comorbidity group (Score > 3), with the lowest comorbidity score group as the referent. No consistent patterns of association were found. For instance, a number of adherence outcomes were positively associated with highest comorbidity score (overall staging, local regional staging, chest and abdominal staging, adherent surgery in locally advanced, adherent chemotherapy), while other adherence outcomes were negatively associated with comorbidity score (colonic staging and surveillance).

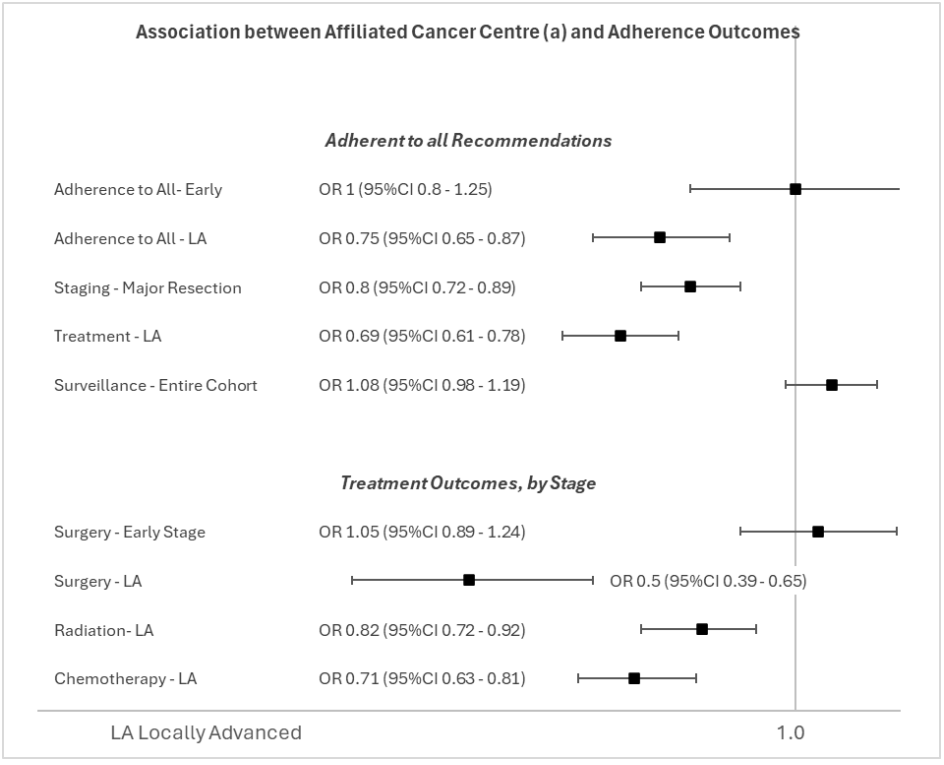
Figure 6-8 (a, b) Summary of the associations between Charlson Comorbidity Score and adherence outcomes, multivariable analysis: a) Lowest Score is Referent

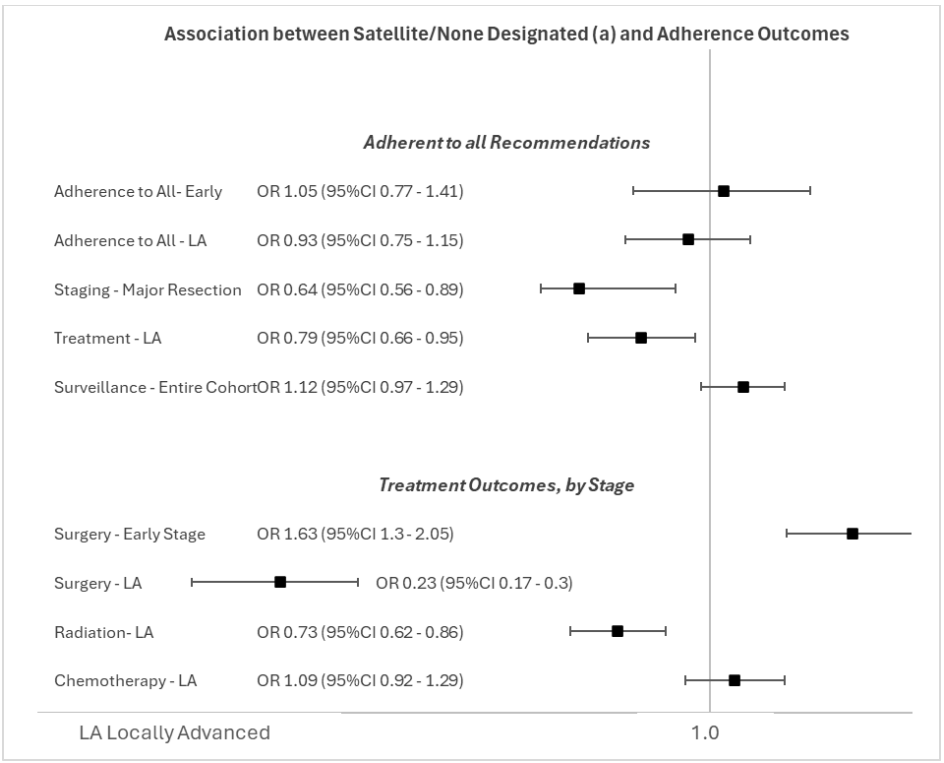




The summary of the associations between cancer centre designation and adherence outcomes can be found in Figure 6 – 9 (a, b). Only overall staging for those undergoing major resection were included as cancer centre designation was defined based on where a patient underwent surgery. Treatment adherence in those with locally advanced disease was negatively associated with both affiliated cancer centres and satellite/non-designated cancer centres. Notably, in both types of centres, radiation adherence was less likely than in regional cancer centres. Affiliated Cancer Centres were negatively associated with chemotherapy receipt in this group, while Satellite/Non-Designated Centres were not associated. Both types of cancer centres were negatively associated with completing staging prior to surgery and undergoing adherent surgery in locally advanced disease. Satellite/Non-designated Centres were positively associated with adherent (i.e. timely) surgery in those with early stage disease.

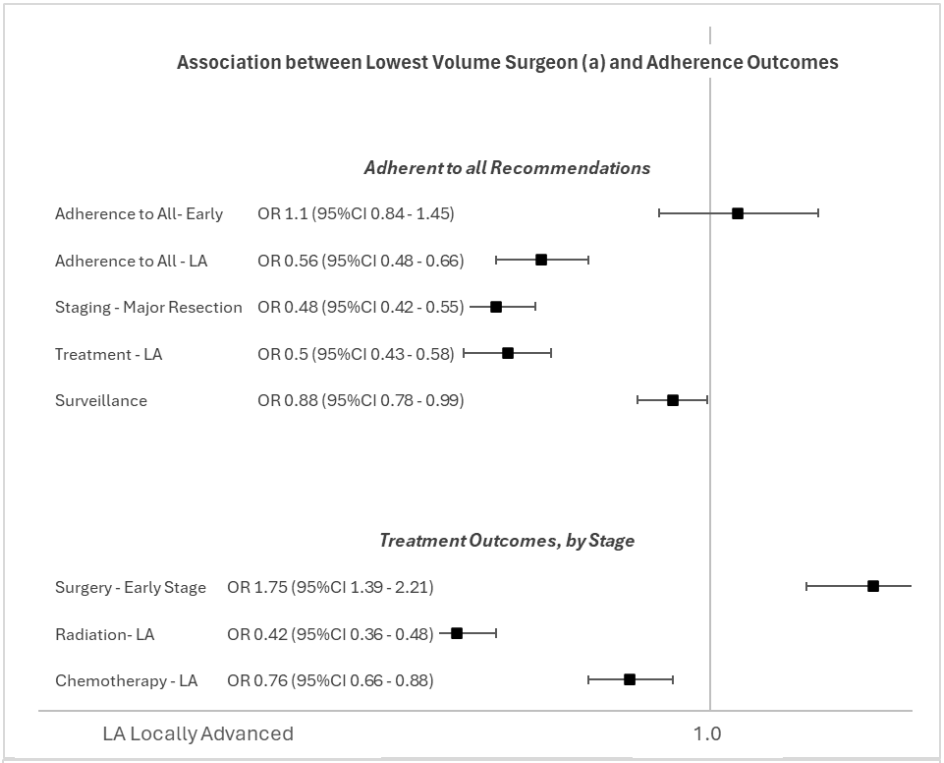
Figure 6-9 (a, b) Summary of associations between Cancer Centre Designation and adherence outcomes, multivariable analysis: (a) Regional Cancer Centre is Referent

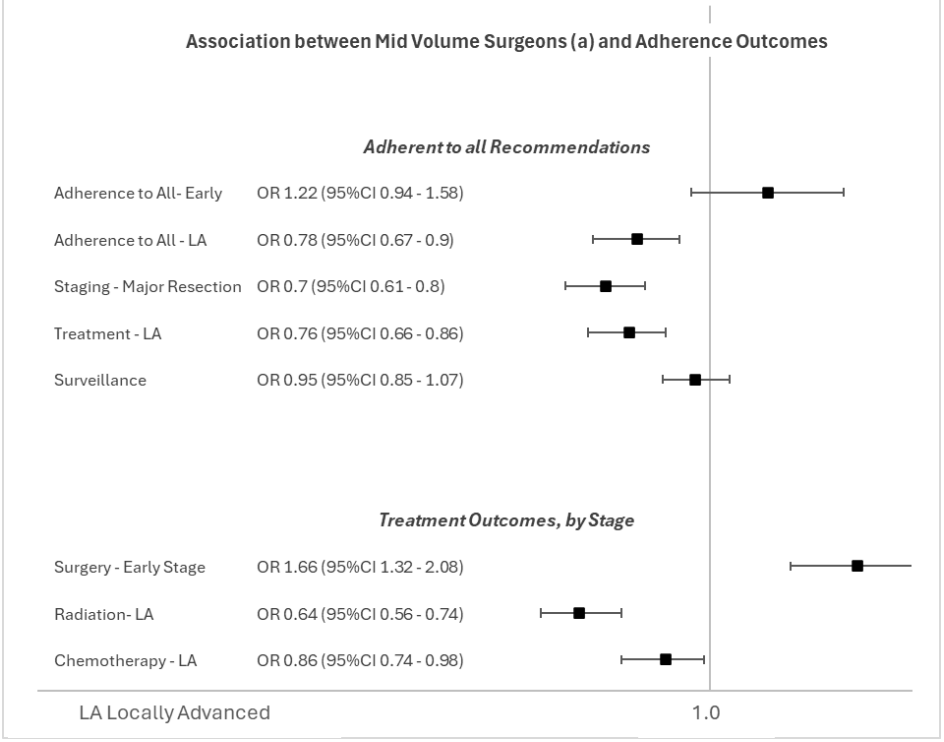




Finally, a summary of the associations between surgeon volume and adherence outcomes are found in Figure 6 – 10 (a, b). The impact of lower volumes was most obvious in those with locally advanced disease. In this group, lower surgeon volume was negatively associated with overall adherence, adherence to all treatments and adherence to staging (in those undergoing major surgical resection). Radiation adherence and Chemotherapy adherence were both negatively associated with lower surgeon volume. In addition a dose-response was identified, with a larger magnitude of effect in those undergoing surgery with the lowest volume surgeons, and a more modest magnitude of effect in those undergoing surgery with the mid-volume surgeons.

Figure 6-10 (a, b) Summary of the associations between Surgeon Volume and adherence outcomes, multivariable analyses: (a) High Volume is referent





6.5.6 Impact of Guideline Adherent Care on Subsequent Care and Outcomes

6.5.6.1 Guideline Adherent Staging Investigations and Radiation Oncology Care

As described in Chapters 2 and 3, appropriate pre-treatment investigations ("staging investigations") are required to provide a "clinical" or pre-treatment stage, which is used to guide treatments. Eligible patients should be assessed by a radiation oncologist to discuss radiation therapy, which represents an "opportunity" to receive guideline adherent radiation. Those who did not receive a preoperative assessment (or preoperative radiation) may be offered post operative radiation based on surgical histopathology. Postoperative radiation is considered "non-adherent" as no guideline recommends for this approach. (Chapter 3)

The association between adherent preoperative staging investigations and radiation oncology assessment, receipt of preoperative radiation (i.e. adherent) and receipt of post operative radiation (i.e. non-adherent) are presented in table 6 – 25. This analysis was for those with locally advanced disease only, as those with early stage disease are not recommended to have radiation. Those who had guideline adherent staging were assessed by radiation oncology much more frequently than those without guideline adherent staging (80.2% vs. 26.9%, $p < 0.001$). Similarly, those with guideline adherent staging more frequently received preoperative radiation (73.9% vs. 22.1, $P < 0.0001$) and less frequently received postoperative radiation (8.2% vs. 23.4%, $P < 0.001$). Multivariable logistical regression analysis was then completed to determine the association between staging adherence and these three outcomes, while adjusting for other predictors of treatment. (Table 6 – 25) Non-adherence to staging recommendations was strongly associated with not being assessed by radiation oncology (OR 0.10, 95%CI 0.08 – 0.11), not receiving guideline recommended preoperative radiation (OR 0.11, 95% CI 0.09 – 0.13) and

receiving postoperative radiation (i.e. non-adherent radiation) (OR 2.74, 95%CI 2.32 – 3.24). (Table 6 – 25)

Table 6-25 Analysis of the association between Staging Adherence and Preoperative Radiation Oncologist Assessment, Preoperative Radiation Therapy, Postoperative Radiation Therapy, in those with locally advanced disease

Preoperative Radiation Oncology Assessment					
	Yes (N = 4549, 68.0%)	No (N = 2,136, 32.0%)		Univariable Analysis OR (95%CI), Significant Testing	Multivariable Analysis (a) OR (95%CI), Significant Testing
Non-Adherent Staging	410 (26.9%)	1117 (73.1%)	P<.0001	0.09 (0.08, 0.10) P<.0001	0.10 (0.08, 0.11) P<.0001
Adherent Staging	4139 (80.2%)	1019 (19.8%)		Referent	Referent
Preoperative Radiation Therapy (i.e. Adherent Radiation)					
	Yes (N = 4549, 68.0%)	No (N = 2,136, 32.0%)		Univariable Analysis OR (95%CI), Significant Testing	Multivariable Analysis (a) OR (95%CI), Significant Testing
Non-Adherent Staging	337 (22.1%)	1190 (77.9%)	P<.0001	0.10 (0.09, 0.11) P<.0001	0.11 (0.09, 0.13) P<.0001
Adherent Staging	3813 (73.9%)	1345 (26.1%)		Referent	Referent
Post Operative Radiation Therapy (i.e. Non-adherent Radiation)					
	Yes (N = 4549, 68.0%)	No (N = 2,136, 32.0%)		Univariable Analysis OR (95%CI), Significant Testing	Multivariable Analysis (a) OR (95%CI), Significant Testing
Non-Adherent Staging	357 (23.4%)	1170 (76.6%)	P<.0001	2.80 (2.37, 3.31) P<.0001	2.74 (2.32, 3.24) P<.0001
Adherent Staging	422 (8.2%)	4736 (91.8%)		Referent	Referent

(a) Adjusted for: Age, Sex, Surgery Year Group, Surgeon Volume Group, Cancer Centre Designation, Income Quintile, Co-morbidity Score Group

6.5.6.2 Guideline Adherent Staging Investigations and Medical Oncology Care

Those with locally advanced disease were analysed to determine the association between adherent staging investigations and medical oncology assessment or chemotherapy receipt. (Table 6 – 26) Of those eligible for chemotherapy, 71.0% were assessed by a medical oncologist. Those who had adherent staging had a higher frequency of medical oncology assessment compared to those who did no have adherent staging (74.9% vs 57.9%, P < 0.0001). On multivariable analysis, those with non-adherent staging were less likely to have a medical oncology assessment (OR 0.56, 95%CI 0.49 – 0.64). Similarly, those with adherent staging more frequently received chemotherapy (60.6% vs. non adherent 49.7%, P < 0.0001). On

multivariable analysis, non-adherent staging was associated with receipt of chemotherapy (OR 0.83, 95%CI 0.73 – 0.95).

Table 6-26 The association between Staging adherence and medical oncology assessment and systemic chemotherapy, in those with locally advanced disease

	Medical Oncology Assessment					
	Yes (N = 4745, 71.0%)	No (N = 1940, 29.0%)		Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis (a) OR (95%CI), Significant Testing	
Non-Adherent Staging	884 (57.9%)	643 (42.1%)	<.0001	0.46 (0.41, 0.52)	<.0001	0.56 (0.49, 0.64)	<.0001
Adherent Staging	3861 (74.9%)	1297 (25.1%)				Referent	
Systemic Chemotherapy Receipt (i.e. Adherent Chemotherapy)							
	Yes (N = 3883, 58.1%)	No (N = 2802, 41.9%)		Univariable Analysis OR (95%CI), Significant Testing		Multivariable Analysis (a) OR (95%CI), Significant Testing	
Non-Adherent Staging	759 (49.7%)	768 (50.3%)	<.0001			0.83 (0.73, 0.95)	0.0069
Adherent Staging	3124 (60.6%)	2034 (39.4%)				Referent	

(a) Adjusted for: Age, Sex, Surgery Year Group, Surgeon Volume Group, Cancer Centre Designation, Income Quintile, Co-morbidity Score Group

6.6 Chapter Discussion

Chapter 6 describes the associations between potential predictors and guideline adherent staging investigations, guideline adherent treatments and guideline adherent surveillance investigations. In addition, the associations between guideline adherent care and other outcomes was reported. Some important findings were identified.

Perhaps most strikingly was that the proportion of those who received adherent care was low, regardless of stage of disease. In those with early stage disease, only 21% were adherent to all staging investigations, treatment (i.e. timely surgery) and surveillance. This was similar in those with locally advanced disease with 23% being adherent to all staging investigations, treatments (neoadjuvant therapy, surgery and adjuvant therapy) and surveillance. Despite the importance of staging in determining the intent of treatment (curative vs. not) and the clinical

stage (which dictates appropriate treatment), only 60% of all those included received the recommended staging investigations. Interestingly, the low proportion of adherence staging was not driven solely by adherence to local regional staging. A previous report out of Ontario, from a single region, found low rates of MRI use between 2010 and 2014 (~50%). (2) This chapter found that MRI adherence was higher than this previous study (65%) but lower than other required staging investigations including colonoscopy (77%), chest imaging (85%) and abdominal imaging (89%). It is unclear what is driving the poor adherence to staging investigations, as these tests are relatively non-invasive, have low risks, are widely available and not particularly costly.

Treatment adherence in those with locally advanced disease was quite poor (37%), but the causes clearer. A large proportion of those who were non-adherent in staging were also non-adherent in treatment. It can be assumed that the local regional stage of disease was either unknown or not clearly defined prior to surgical resection. Only after surgical resection was completed, and pathologic stage available, was locally advanced disease identified. At that point, the patient would have already missed the opportunity for adherent (preoperative) radiation. Non-adherence to post-operative chemotherapy may have been driven by perioperative complications or changes in clinical status rendering the patient unsuitable for chemotherapy. This issue has been highlighted in a number of previous publications. (3, 4) The relatively poor adherence to surveillance (52%) was driven largely by a lack of adherence to surveillance colonoscopy (57%). The reason for this is not clear. Adherence to diagnostic imaging was > 85% for chest, pelvic and abdominal imaging. Colonoscopy is an invasive test, but one that was completed in nearly all those diagnosed with rectal cancer prior to treatment.

In terms of predictors of guideline adherent care, there were a number of important themes identified. First, regardless of the adherence outcome, younger age was associated with higher adherence. This is consistent with the results from Chapter 4, which reported the narrative synthesis and quantitative analyses of from a review of previous publications. A notable difference between the results of the current chapter and those of previous studies is the way age was categorized. Most previous publications dichotomized age (i.e. <65 vs. 65+), or used 4 or less groups and/or restricted the cohorts based on age (i.e. including age >65 or < 80). The current chapters includes 6 different age groups in the univariable analyses, and uses age as a continuous variable (per 10 year increase) in the multivariable analysis. This was possible due to the large number of included patients, which allowed for sufficient sample size to assess the extremes of age.

The second theme identified was that increasing co-morbidity score was positively associated with some outcomes and negatively associated with others. This is in contrast to the qualitative and quantitative analyses from previous publications, which were reported in Chapter 4. These analyses found that all assessed adherence outcomes were negatively associated with higher comorbidity score. The current chapter reports no association between co-morbidity score and overall staging adherence or adherent radiation, while increasing co-morbidity score was negatively associated with guideline adherent colonic staging and overall surveillance. These results may be explained by the differences in risks posed. Staging investigations pose very low risks to the patients, and thus may be regularly offered to co-morbid patients. This group of patients likely benefit from high adherence to pre-treatment investigations to ensure accurate staging and reducing the risks of overtreatment with potentially toxic interventions. Although not comprehensively studied in those with rectal cancer, there is some evidence that

radiation, more so than chemotherapy, can be reasonably well tolerated in frail patients, which may explain the association with one, but not both of these treatments (5, 6). Although this may be a plausible explanation for our results, it should be noted that both adherent radiation and adherent chemotherapy were negatively associated with even small increases in co-morbidity score in previous publications, including the results of meta-analyses of studies reporting multivariable analyses (reported in Chapter 4).

Thirdly, both adherent staging (in those undergoing major resection) and adherent treatment were positively associated with both higher cancer centre level designation, and high surgeon volume. The magnitude of the effect between these care provider factors and adherence outcomes was amongst the highest observed of any of those assessed. The association between surgeon volume and adherence outcomes was reported in few previous studies. In Chapter 4, narrative synthesis found that local regional staging (2 studies) and receipt of preoperative radiation (2 studies) were both associated with increasing volume, while metastatic disease assessment (2 studies) and receipt of chemotherapy (1 study) were not. It should be noted that the association between surgeon volume and adherence to (i) overall treatment, (ii) overall staging, or (iii) any aspect of surveillance have not been reported previously. The associations between higher resourced hospital and adherence outcomes were commonly reported previously, although the definition of the exposure was highly variable.

The next theme to emerge was that those diagnosed in later years were more likely to have adherent staging investigations, adherent radiation, adherent chemotherapy and overall treatment adherence. These findings may partially be explained by a concerted effort by Cancer Care Ontario to improve utilization of appropriate pre-treatment local-regional staging, and appropriate use of radiation. (7, 8) Although the effectiveness of knowledge translation in this

domain has been challenged (9), there has been a clear trend to increasing use of MRI staging in Ontario. Increasing adherence to preoperative staging allows for a pre-treatment stage to be assigned and allows for those eligible for neoadjuvant therapy to be identified to allow for the opportunity to receive adherent radiation.

Later diagnosis or treatment year may have provided clinicians more time to become aware of and accept clinical practice guidelines recommendations. Clinical Practice Guidelines were first published by Provincial health authorities in the mid 1990's, with comprehensive guidelines appearing throughout the 2000's. During the study period, numerous guidelines were updated based on emerging evidence. Additionally, evidence supporting much of adherence care continued to mature early in the study period. (10-13) These factor may have influenced care providers in the delivery of rectal cancer care.

It is important to note that later diagnosis year was negatively associated with timely surgery in those with early stage disease, and associated with reduced use of major resection in those with locally advanced disease (i.e. "Surgery Adherence"). The reasons for less timely surgery are multifactorial, but may be explained by a reduction in health care spending by the provincial government and a reduction in operating room capacity. Wait time in Ontario were increasing prior to the COVID pandemic and have likely worsened since that time. (14, 15) The increased use of local excision (i.e. surgery "non-adherence") in those with locally advanced disease is another interesting finding. Local excision avoids the risks of a major resection and reduces the long term functional implications of treatments, thus is an attractive option. The use in locally advanced disease is not recommended, but there has been research interest in this approach. Several trials, including the "NEO" Trial, GRECCAR Trial and CARTS Trial all explored local excision in combination with chemotherapy or chemoradiation therapy. (16-18)

A number of regional cancer centres, including my own, recruited patients to the NEO trial between 2017 and 2019, which corresponds to the latest time period group. There were a very low number (N = 58) of patients recruited to this trial, but other patients may have been offered this approach outside of the trial.

Another theme to emerge was that income quintile was inconsistently associated with adherence outcomes. For instance, overall treatment adherence, overall staging adherence, most of the specific staging investigations, adherent surgery and adherent radiation were not associated with income quintile, while adherence to surveillance and adherence to chemotherapy were. These findings are contrary to what has been reported in other settings, which consistently demonstrated a negative association between lower socio-economic status and adherence (Chapter 4), with increased socio-economic status being associated with better access to care. (19) The chapter results may reflect the cancer system organization within Ontario. Unlike many other settings, cancer care in Ontario is provided by a public, universal health care system without a private option. As reported in Chapter 4, in settings with both public and private options, those with private insurance are more likely to be adherent to recommended care. Those with private insurance are more likely to be in a higher socioeconomic status and have better access to care.(20, 21) Another factor is the relative lack of choice for Canadians in choosing their care provider or treating institution, which results in similar care provided to the affluent and non-affluent alike. (22)

The impact of adherence on subsequent treatment is worth reviewing. This chapter reports that adherence to staging investigations was an important predictor of adherence to treatment recommendations. For instance, those who did not have adherence staging were very unlikely to have a preoperative assessment by a Radiation Oncologist or receive adherent preoperative

radiation. This finding was predictable, as pre-operative treatments are entirely dependent on accurate clinical staging.

6.6.1 Strengths and Limitations

Chapter 6 provides a comprehensive assessment of the receipt and impact of guideline adherent care in those with a new diagnosis of rectal cancer. The data source for this chapter is from the Ontario Rectal Cancer Cohort, described in detail in Chapter 5. Chapter 5 also describes the limitations and included a discussion of (i) Selection Bias; (ii) Unavailable Information; (iii) Incorrect Data and Misinformation; (iv) Incomplete Confounder Information; and (v) Generalizability to other/different populations. Below is a specific discussion about how each of these limitations potentially influenced the findings from this chapter.

Selection Bias

As described in Chapter 5, those selected for inclusion were identified through the Ontario Cancer Registry (OCR). This registry has a high rate of capture of incident cases. Institutions where the diagnosis is made are mandated to submit to the Ontario Cancer Registry and there may be instances where an institution had poor reporting. These institutions may also have been those that were less likely to have adherent care, as both are quality indicators. This selection bias could impact the association between cancer centre designation and the outcomes assessed, in that the true adherence to care may have been overestimated. As >95% of incident cancers are captured within the registry, the impact of selection bias on the chapter results is likely low.

The difficulties in distinguishing recto-sigmoid cancer (i.e. colon cancer) from rectal cancer is another potential source of selection bias. There is an inherent limitation in distinguishing rectal cancer from recto-sigmoid (i.e. colon) cancer when using population level data. Those designated as having colon cancer in the OCR, but treated as a rectal cancer clinically would have been excluded from this analysis. Males have a higher risk due to the anatomic differences, when compared with females and may be under-represented in this work, although the reported proportion of males in the Ontario Rectal Cancer Cohort (63%) is similar to those described previously. (23)

Unavailable Information

Several components of guideline adherent care, such as the tumor marker (Carcinoembryonic antigen, CEA) and surveillance clinic visits, were not available. CEA is a laboratory value and was unavailable, while identifying surveillance clinic visits was not possible. Ideally, both would have been included when describing guideline adherent staging (CEA) and guideline adherent surveillance (CEA and Clinic Visits). Without this information, the results above may have overestimated the proportion of guideline adherence in both phases.

The specific results from diagnostic imaging were also not available. Ideally, favourable disease characteristics of those with locally advanced disease, including proximal tumors and those with an uninvolved circumferential margin, would have been included. There is emerging evidence that those with favourable characteristics found on MRI could avoid pre-operative radiation. (24, 25) Although this option doesn't appear on any of the Canadian Clinical Practice Guidelines, it would explain why some individuals did not receive adherent preoperative

treatments. Having this data would thus provide context in discussing predictors of guideline adherent care.

A similar issue existed with a lack of information regarding the use and results of multidisciplinary cancer conference (MCC) discussion. MCC discussions are recommended in all Canadian guidelines, the purpose of which is to review diagnostic and clinical information. Previous research has demonstrated that this discussion often leads to a change of stage and/or change in proposed treatment (i.e. guideline adherent treatment). (26) Understanding the outcomes of these discussions would have provided valuable information on the true adherence to treatments. In some cases, individuals may have had a change in assigned stage (i.e. from early to locally advanced, or vis-versa), which may have not been captured within the assigned stage available in the OntaReCC. Not capturing when a lower stage was assigned would result in an individual appearing to not undergo adherent treatments for locally advanced disease (i.e. receiving radiation prior to surgery).

Incorrect Data or Misinformation

There is an inherent limitation in distinguishing rectal cancer from recto-sigmoid (i.e. colon) cancer when using population level data. The recommended management of colon and rectal cancer differ in important ways, with rectal cancer patients needing more diagnostic tests (MRI and/or TRUS) and more treatments (i.e. radiation therapy). Thus, those with colon cancer who were incorrectly included in this cohort would be more likely to be identified as having "non-adherent" care. As described in chapter 5, this issue was partly mitigated by validating the diagnostic codes with histopathology characteristics, when available, as well as including those

with procedures typically reserved for treatment of rectal cancer (low anterior resection and abdominoperineal resection).

Another potentially significant issue is misclassification of stage. Rectal Cancer is especially prone to misclassification of stage (in comparison with colon cancer), as clinical stage relies on pre-treatment diagnostic investigations and clinical impression, and not histopathologic staging. There are inherent limitations with pre-treatment investigations in terms of accuracy of stage, as discussed in Chapter 2. Those who ultimately had locally advance disease and were initially "under-staged" (i.e. assigned an early clinical stage, but found to have a locally advanced pathologic stage) would not have been offered preoperative radiation. This group would thus be classified as "non-adherent" based on treatments offered using the best available information.

There is also the possibility of misclassification of other patient related characteristics, such as socio-economic status and co-morbidity score. Socioeconomic status was determined based on neighborhood income quintile and not based on individual or household income. Using neighborhood income may correlate poorly with individual socioeconomic status, especially in rural settings. (27, 28) The OntaReCC was limited to neighborhood income quintile as a measure of socioeconomic status as individual (or household) income or other measures were not available. Co-morbidity score was determine based on health care contacts in the 2 years prior to diagnosis of rectal cancer. Those who had infrequent contact with health care providers may have been misclassified as having a lower co-morbidity score. These variables were included in the adjusted models and misclassification of these variables would likely result in underestimating the effect estimates as it is assumed this is non-differential misclassification.

Finally, there may have been misclassification of components of guideline adherent care (i.e. diagnostic tests and treatments) which were used to create these outcomes. Some examples include:

- Surgery Type – Individuals may have undergone major surgery which wasn't captured through the physician billing code or the procedure code submitted by the institution.
- Radiation type, dose and completeness – Radiation details were derived from the ALR using a number of novel algorithms and rules. It is unlikely that an individual was mistakenly labelled as receiving (or not receiving) radiation, but the specifics may be erroneous. For instance, the intent (palliative vs. curative), the type (short vs. long course), or the specific start and end dates may have been incorrect. To counteract this, receipt of radiation was categorized as a binary variable (yes/no) based on when it was given (pre or post operatively). Although this allows for a general assessment of guideline adherence, is does limit our ability to assess completeness of radiation received.
- Chemotherapy type, dose and completeness – Similar to radiation, chemotherapy details were derived from the ALR. The date, drug/regiment and dose for each treatment was available, and novel rules and algorithms were applied to determine intent (palliative vs. curative) and type (chemo-radiation vs. systemic chemotherapy). Similar to radiation, individuals were labelled as having received systemic chemotherapy (Yes/no) which allowed for a general assessment of guideline adherent treatment but not a detailed one.

Incomplete Confounder Information

The use of population level data does limit the completeness and availability of potential confounders needed for analysis of associations. For instance, histopathology data was available only in those diagnosed between 2010 – 2014, and can include important cancer

characteristics that are associated with the types of treatment an individual would receive and/or prognosis. Other important (and unavailable confounders) includes specific details about the individual, such as functional status, frailty, personal beliefs and other personal circumstances. For instance, those with severe claustrophobia or metal implants would not be eligible for MRI, those with very poor baseline function (not well captured via comorbidity scores) may not be offered a major resection, and those who have specific contraindications to radiation or chemotherapy (such as previous neuropathy, connective tissue disorders, females wishing to maintain fertility or ovarian function) may not be offered neoadjuvant or adjuvant therapies. In these circumstances, lack of receipt of "guideline adherent" care could be explained.

Another potential issue are individuals unwilling to consider certain aspects of care. For instance, some patients are unwilling or unable to travel for radiation (which can include 25 consecutive days of treatment at the radiation centre), are unwilling to accept a permanent or temporary colostomy, or unwilling to accept chemotherapy under any circumstance. To address some of the patient related preference, I reported both receipt of the applicable treatment (i.e. radiation or chemotherapy) as well whether an applicable assessment occurred (with the radiation oncologist or medical oncologist). Oncologist assessment provides an individual the opportunity to learn about potential treatment as well as for the clinician to determine whether contraindications to treatment are present. A limitation to this approach would be if an individual refuses to meet with a clinician at all.

Other potential incomplete confounder information includes resource availability and clinical expertise at the treating institution. For instance, there may have been a lack of access to MRI or transrectal ultrasound as a reason for incomplete staging investigations, or a lack of expertise in delivering certain aspects of treatment. Due to the limitations in the availability

and/or completeness of confounder information, the true effects may be different than those reported in this population health research study.

Treatment Completion and Interruptions

Treatment adherence was determined based on whether a patient received at least one dose of either radiation and/or chemotherapy, in those eligible. Treatment completion, in which an individual received the full dose of recommended radiation and/or chemotherapy was not assessed. Similarly, treatment interruptions were not assessed. Within this work, it is assumed that if an individual started treatment (i.e. received at least one dose), the intent was to complete treatment. Incomplete treatment and interruptions in treatment occur due to a number of reasons, most commonly being toxicity caused by the treatment and other adverse events. This does not reflect "non-adherence" but likely reflects "non-tolerance" to the treatment itself. For these reasons, predictors of completion of treatment was not assessed.

6.6.2 Implications for Practice

The results of this chapter have several implications for practice. The first is the importance of completing all recommended staging investigations. These investigations allow clinicians to assign a "clinical" stage, which determines the most appropriate treatments. Over the study period, up to 1/3 of individuals did not complete the requisite investigations prior to starting treatments. Improving the rates of adherence in this phase of care would likely have the biggest impact in ensuring that most appropriate treatments are received, as demonstrated by the poor adherence to treatment recommendations in those who did not complete staging.

Centralizing care to regional cancer centres and/or high volume surgeons may also be an important quality improvement intervention to ensure adherence to recommended care. Those

receiving care from a low volume surgeon were half as likely to complete all staging investigations and half as likely to receive all recommended treatments. A similar negative association between lower resourced cancer centres and adherence was also observed. Mandated centralization of care to high resourced and high volume surgeons has previously occurred in Ontario for pancreatic cancer surgery. (29) The motivating factor was to improve post operative mortality, which was extremely high in some settings. A similar mandate has not been implemented for rectal cancer care. This chapter makes a compelling argument for why it should be considered.

Finally, this chapter identified that local-regional staging and receipt of radiation and chemotherapy were positively associated with later diagnosis year. This finding demonstrates the success of provincial interventions to improve adherent care. Cancer Care Ontario, through the Surgical Quality Improvement Program, provides quality performance reviews of hospitals performing rectal cancer surgery. The metrics used include pre-treatment MRI and use of neoadjuvant therapy. Outlier hospitals are identified and quality improvement initiatives occur. This program begun during the study period which may explain some of the improvements identified in this chapter.

6.6.3 Implications for Research

The chapter provides an overview of the predictors and impact of guideline adherent care. The are a number of implications for future research as a result of this work. These are discussed in detail in Chapter 7. Broadly speaking, the following areas should be further evaluated:

- Predictors and Outcomes when alternative treatments can be offered: For example, comparison of local excision and radical resection in those with early stage disease,

comparison of short course radiation vs. long course chemoradiation in those with locally advanced disease, comparison of specific chemotherapy regimens in those with locally advance disease

- Predictors and outcomes of incomplete or interrupted treatments: For example, the impact of interruptions, delay or incomplete neoadjuvant treatment or adjuvant treatment.
- Evaluation of high risk patients in the receipt of adherent care: For example, evaluating those at the extremes of age (<40 or 80+), or those with significant co-morbidities.
- Determining the cause and impact of variability in the delivery of adherent care: Assessing which regions or institutions provide highly variable care vs. those that do not. Does care provider (surgeon, oncologist) or treating institutions (cancer centre designation) explain variability>
- Updating the assessment of adherence based on new guidelines or emerging treatments: Determining the correlation between guideline release and time to steady state adoption. Assessment of the introduction of total neoadjuvant therapy, non-operative management and local excision.

6.7 How this chapter fits into the thesis as a whole

Chapter 6 makes use of the Ontario Rectal Cancer Cohort ("OntaReCC"), described in ***Chapter 5***. This chapter utilizes the population based data available in the OntaReCC to determine predictors of guideline adherent care in those with rectal cancer in Ontario. This chapter also makes use of the findings from ***Chapter 3***, which defined what constituted "Guideline Adherent" in Ontario during the study period. This chapter also used the results of

Chapter 4 (Systematic Review and Meta-Analysis) to provide context and inform which potential predictors should be considered in the analyses.

6.8 Chapter 6 Summary

- The associations between potential predictors and guideline adherent care were determined. This included the association with each specific aspect of guideline adherent care, overall guideline adherent care based on phase of care, and overall guideline adherent care
- A number of modifiable and non-modifiable risk factors were assessed and some common themes were identified, including:
    - Increasing age was negatively associated with most adherence outcomes
    - Female sex was negatively associated with staging adherence outcomes and chemotherapy adherence, while being positively associated with adherent surgery in locally advanced disease
    - Later diagnosis year was positively associated with most adherence outcomes, the exception being timely surgery (negatively associated)
    - Socioeconomic status was associated with few adherence outcomes
    - Rurality was not associated with adherence to treatments, despite the hypothesized impact of travel on treatments received
    - Comorbidity was inconsistently associated with adherence outcomes, which was different than the findings from the systematic review and meta-analyses presented in Chapter 4

    - Cancer Centre Designation and Surgeon Volume were both important predictors of adherent care, with high surgeon volume and higher cancer centre designation positively associated with adherence
- Adherence to staging positively predicted adherence to subsequent treatment

6.9 Chapter 6 References

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Chapter 7 Discussion

7.1 Chapter Overview

This chapter provides a discussion of the content contained within this thesis and the implications of the work.

7.2 Chapter Aims and Objectives

This final chapter aims to summarize the content of this thesis, explores the strengths and limitations, and describes the implications of this work on policy and future research.

7.3 Summary of Findings

This thesis began with an overview of Rectal Cancer (***Chapter 2***), which provides the reader an understanding of rectal cancer as a complex disease requiring multidisciplinary care. Colorectal cancer, of which rectal cancer represents approximately one-third, is the 2nd most diagnosed malignancy in males and 3rd most diagnosed cancer in females. Ultimately, 1 in 14 Canadians will be diagnosed with colorectal cancer, with males representing the majority of new cases. (1, 2) After a diagnosis of rectal cancer, pre-treatment investigations are required to provide clinicians with the "Clinical Stage" and allow for the selection of appropriate treatments. The investigations include Magnetic Resonance Imaging (MRI) or transrectal ultrasound, computed tomography (CT), colonoscopy and the tumor marker, "Carcinoembryonic Antigen"

(CEA). Those with clinical early-stage disease will typically be treated with surgery only, while those with locally advanced disease may be offered chemotherapy and/or radiation therapy in addition to surgery. Those with metastatic disease are generally offered treatments based on the extent of disease, underlying co-morbidities and possibility of cure. Following the completion of treatment, a number of follow up investigations are typically completed to assess for recurrence of disease or the development of distant metastases. (3)

Due to the complexity of disease, and the need for multidisciplinary treatment, numerous clinical practice guidelines are available. (3-5) These guidelines have been developed by societies, national or international organizations and by government cancer authorities. Prior to this thesis, there was no Canada wide guideline available to clinicians. ***Chapter 3*** addressed the lack of a common Canadian definition of guideline adherent care through identification of all available provincial guidelines. A review of agreements and disagreements was conducted. A total of 7 provincial health authorities had published a clinical practice guideline between 2010 - 2019. Several of these had more than one available version. In general, there was good agreement between these guidelines, although there were disagreements in specific aspects of treatment (i.e. when to use short course radiation vs. long course chemoradiation). These disagreements were explored in detail within the chapter. Chapter 3 concludes by proposing a common, general definition of the minimum requirements of guideline adherent care in Canada. The proposed definition of guideline adherent care was used in ***Chapter 6*** both as an important outcome and important exposure.

An exhaustive systematic review and meta-analysis of the literature was then completed, which was described in ***Chapter 4***. The objective was to review the previous literature describing barriers and facilitators to guideline adherent care. The direction and magnitude of

the associations between potential predictors and adherence outcomes were presented based on both qualitative and quantitative analyses. Important predictors were identified, and the consistency of the associations discussed. The systematic review identified more than 70 publications which were included in the qualitative synthesis, with 39 included in the meta-analyses. More than 120 predictor – adherence outcome pairs were assessed, with 27 predictor-adherence outcomes able to be quantitatively assessed. Non-modifiable predictors (such as age, gender/sex, ethnicity, socioeconomic status and geographical location) were most commonly evaluated within the identified studies, while modifiable predictors (such as physician volume and type, hospital volume and type) were much less commonly evaluated. The impact of many of the predictors on adherence was anticipated, such as improved adherence in: Younger Age; Lower Comorbidity Score; Higher Socioeconomic Status; Private Insurance. The results of this chapter were then used to inform the creation of the Ontario Cancer Cohort (***Chapter 5***), to ensure that important variables were included. The results were also used to provide context when discussing the results of ***Chapter 6,*** which describes the associations between predictors and adherence outcomes in Ontario.

The methodology and justification for the creation of the Ontario Rectal Cancer Cohort was described in detail in ***Chapter 5***. The Ontario Rectal Cancer Cohort was created using data available from provincially maintained administrative databases and data abstracted from available histopathology reports. The Ontario Rectal Cancer Cohort is the first comprehensive resource that brings together data from these various sources in a way that allows researchers to determine the practice patterns and outcomes of those with rectal cancer from pre-diagnosis to death (or end of follow up, 2022). A number of algorithms and rules were created to allow for a detailed description of the care an individual received. This included defining and validating the

relevant investigations, treatments and outcomes. The Ontario Rectal Cancer Cohort ultimately included cancer care details on more than 18,000 individuals with a new diagnosis of rectal cancer during the study period. The demographics of those with rectal cancer, the initial stage at time of diagnosis and the details of the provided care were described. There was little missing data within the Ontario Rectal Cancer Cohort, with complete capture of most patient characteristics (i.e. age, sex, income quintile, co-morbidities) and near complete capture of the care provided (such as investigations, treatments and surveillance). The overall 5 year survival was 68% for the entire cohort, and ranged from 24% (metastatic or incurable disease) to 88% (early stage disease). This survival compared favourably with other similar jurisdictions such as the United Kingdom (All Stages, 60% 5 year survival) and the United States (All Stages, 68% 5 year survival). (6, 7)

Chapter 6 used the data contained within the Ontario Rectal Cancer cohort to determine which factors were acting as predictors of guideline adherent care, as well as to determine whether guideline adherent care was associated with subsequent care. Guideline adherent care was defined using the definition created in ***Chapter 3***, while the potential predictors were identified from the systematic review described in ***Chapter 4***. The methodology in ***Chapter 6*** describes how the adherent variables were determined, as well as how the predictors were identified and classified. Each aspect of guideline adherent care was described in this chapter. A total of 60% of included individuals were adherent to all staging investigations, while treatment adherence was observed in 37% of those with locally advanced disease and 68% in those with early stage disease. Just over half (52%) of those who underwent curative intent treatments were adherent to all surveillance recommendations. This resulted in a very low overall adherence (i.e.

adherence to staging, treatment and surveillance) in both early stage disease (21%) and locally advanced disease (23%).

When assessing the potential predictors, there were a number of expected and some unexpected findings. As expected, younger age was positively associated with most of the adherence outcomes. Unexpectedly, co-morbidity was not associated with a number of adherence outcomes. Co-morbidity was not an important predictor adherent radiation or adherent chemotherapy, which is in contrast to the systematic review which found that all assessed adherence outcomes were negatively associated with increasing comorbidity.

One of the more notable findings from this chapter was the magnitude of association between care provider factors (Hospital type and Surgeon Volume) and adherence to staging and treatment. Those treated at a regional cancer centre and those cared for by a high volume surgeon were much more likely to receive guideline adherent care. The association between hospital type and adherence has been observed in several other studies, while the associations between higher volume surgeons and increased adherence is unique to this thesis, largely due to a dearth of previous studies assessing this association. Later diagnosis date was another important predictor of guideline adherent care. Those diagnosed later in the study period were much more likely to be adherent to all recommendations, especially in those with locally advance disease.

The positive impact of being guideline adherent was also demonstrated in ***Chapter 6***. Adherence to all recommended staging investigations resulted in higher adherence to treatment recommendations. This finding was largely driven by the "opportunity" to receive treatment. Those who completed all staging investigations were more likely to be seen by a radiation oncologist and/or a medical oncologist, regardless of whether they received treatment or not.

7.4 Strengths and Limitations of the Thesis

The specific strengths and limitations were discussed in detail within each chapter. Below I describe the strengths and limitations of this thesis as a whole, focusing on the most important aspects.

The primary strength of this thesis lies in the quality of the methodology used to: (i) review previously published research; (ii) create a novel, comprehensive rectal cancer cohort; (iii) determine predictors of adherence in Ontario; (iv) determine the impact of adherence on subsequent care.

I have included a robust systematic review and meta-analysis of the predictors of guideline adherent care which allows for an understanding of the current evidence available. A first of its kind, this review was rigorous in its design, adhering to the principals described by the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" group. The search for relevant articles was exhaustive with more than 70 studies included. Both qualitative and quantitative analyses were completed and the results compared allowing for a fuller understanding of the literature. The review identified a number of predictable associations (i.e. increasing age and worsening adherence), inconsistent associations (i.e. female sex/gender positively associated with some adherence outcomes, and negatively associated with others) and infrequently assessed associations (i.e. between care provider factors and adherence outcomes). This review was thus able to provide an understanding of which predictors were important in predicting guideline adherent care, as well as which predictors warranted further investigations. This information was essential in the construction of the Ontario Rectal Cancer Cohort.

To understand the current Canadian landscape of clinical practice guidelines, a thorough review of available guidelines was completed. All provincial clinical practice guidelines,

available during the study period, were identified and assessed. A definition of adherent staging, treatment and surveillance was then created. The overall objective of this work was to assess guideline adherence in a Canadian setting, and defining this variable for use in the subsequent chapters was essential.

The Ontario Cancer Cohort was then constructed based on a thorough understanding of the available literature. By using linked administrative datasets, OntaReCC had near complete capture of incident rectal cancer patients. As almost all cancer related health care is delivered through the publicly funded system, this population based dataset also had near complete capture of the available variables and outcomes. The cohort was created using well described methods with input from clinical experts, allowing it to be reproduced and updated regularly. The Ontario Rectal Cancer Cohort is thus a valid and robust resource for researchers to interrogate the delivery and outcomes of those with rectal cancer in Ontario.

Finally, using sound methodologic approaches, the associations between potential predictors and guideline adherent care was determined. The association between guideline adherent care and other outcomes was determined, which included adherence to subsequent care. These analyses were completed using a large sample size which included nearly everyone diagnosed with rectal cancer over the study period, had near complete capture of the available exposures and outcomes, and used multivariable analyses to determine the independent associations between exposure and outcomes.

Despite the strengths described above, there are a number of limitations that should be highlighted. To begin with, the primary objective of this work was to assess adherence to Canadian clinical practice guidelines. The assumption being that a goal of health care providers is to deliver adherent care. In this context, adherence represents “high quality” and desirable

care. Some providers may strive to provide care consistent with other, non-Canadian recommendations that could be in conflict with local ones. In addition, some clinicians may be offering care that is new or innovative, and has yet to appear in contemporary clinical practice guidelines. A good example of both of these issues is the avoidance of neoadjuvant therapy in low risk Stage II disease. This would be "non-adherent" base on Canadian guidelines, but is supported by recent publications (8) and other available guidelines (4). Although non-adherent based on the thesis definition, this care could still be considered "high quality" or "standard of care".

Another related assumption is that the available clinical practice guidelines represent a consensus opinion of what is considered high quality care based on strong levels of evidence. We reviewed the quality of the available clinical practice guidelines, with 3 provincial guidelines scoring well (based on the Appraisal of Guidelines for Research & Evaluation II instrument), 2 scoring moderately and 2 scoring poorly. (9) Despite the differences in quality, there were few major differences between guidelines suggesting that these guidelines are generally accepted and do represent a consensus opinion. Although care providers on the whole may accept the recommended care as "standard of care", there has been well described reasons why some individual providers do not follow or accept clinical practice guidelines. (10) Failure to follow clinical practice guidelines may be explained by a lack of awareness or familiarity with the guideline, disagreement with the guideline's recommendations, inability to overcome the inertia of previous practices and/or a lack of consequences in delivery non-recommended care. Understanding which of these issues is driving non-adherence by providers is challenging when using population health research methods, and would be better explored with qualitative methodologies.

Another limitation is that the source of the data was entirely from the province of Ontario and the thesis results may not be generalizable to other Canadian settings. The selection of Ontario as the sole source of data was pragmatic, based on availability, feasibility and cost. As discussed previously, the delivery of health care is the responsibility of the provinces and there can be important difference in how the cancer systems deliver this care between provinces. Provincial cancer systems may be constructed differently based on demographics, population distribution, funding, health care resources and access to care. Although differences exist, provinces are far more similar to each other, than other commonly assessed settings, such as the United States or United Kingdom. Despite these similarities, some of the findings described in this thesis may be only relevant to the Ontario population and not generalizable across provinces. As the focus of this work was to understand guideline adherent care from the Canadian perspective, this limitation needs to be acknowledged, and future research work is planned to incorporate other provincial data into the a combined Canadian Rectal Cancer Cohort.

Next, this thesis relies on data from a cancer registry and linked administrative databases, which were used to create the Ontario Rectal Cancer Cohort. Despite the numerous advantages of this type of data there are well described limitations. The source of the data was not created for the purpose of research, but instead for the administration and funding of Ontario's publicly funded health care system. In using these sources, I was restricted to including the data available within these databases. Several helpful variables were not included, while there was a lack of details in others. Stage data was determined from the Ontario Cancer Registry only. Confirmation of stage using detailed diagnostic imaging results was not possible due to unavailability of this data. As stage determines recommended care, validation of this variable would have provided more confidence in determining whether adherent care was provided.

Another limitation is that treatment details were derived, using novel methods. These methods have not been validated externally, and often relied on data from a single source such as the Cancer Activity Level Reporting (ALR) database. Finally, although multivariable analyses were completed, using population level data results in residual confounding from both known and unknown confounders.

The purpose of the systematic review was to provide a general overview of the current evidence regarding predictors of guideline adherent care to inform the creation of the OntaReCC and provide context for the findings in Chapter 6. The review was limited based on the quality and comprehensiveness of the included studies Many predictors and outcomes were not evaluated frequently (or at all) in the included publications and thus the thesis results could not be comprehensively compared to other settings or time periods. One of the objectives of this work was to address these gaps in evidence, which was accomplished. In addition, the review provides the reader of this thesis a "big-picture" view of the current evidence describing predictors of guideline adherent care. Detailed reporting of each study was not provided, but instead included in the appendices.

Finally, the common definition of guideline adherent care in Canada was developed for research purposes. It was meant to be inclusive and provide general recommendation for rectal cancer care. This definition lacked specific details that may be necessary for care providers. For example, the common definition recommends for adjuvant 5-FU based chemotherapy in those with locally advanced disease, but does not provide recommendations on the specific chemotherapy regimen, dose or duration. Similarly, the common definition recommends for neoadjuvant therapy in this group, but does not provide the exact doses, body regions, role of "Boost" or other specific radiation details. Care providers thus would need to supplement the

developed common definition with other local clinical practice guidelines for the specific treatment delivery.

7.5 Implications of the Thesis

This doctoral thesis advances the understanding of guideline adherent rectal cancer care. There are several primary implications of the work presented.

Guideline adherent care in Ontario for those with rectal cancer is poor. Less than a quarter of those with early or locally advanced disease were adherent to all recommendations. Within each phase of care, adherence was relatively low, including adherence to all staging recommendations (60%), adherence to timely surgery in those with early stage disease (68%), adherence to all treatments in those with locally advanced disease (37%) and adherence to surveillance in all those undergoing a major resection (51%). When timeliness is included, the situation appears worse, with only 20% of those with locally advanced disease receiving all adherent treatments and meeting timeliness benchmarks. Although the reasons for relatively poor adherence in each domain differ, the high proportion of non-adherence is concerning. This conclusion assumes that guideline adherent care represents high quality care, and that care providers believe adherent care is a priority. If these assumptions are true, then the delivery of rectal cancer care in Ontario needs to be improved.

Improvement in the adherence to recommended care may be achieved through how care is delivered. An important result from Chapter 6 was the large magnitude of effect and the consistency of associations between care provider factors and guideline adherence. Treatment by higher volume surgeons and/or at higher level cancer centres resulted in a significant increase in adherence in most domains. This was especially true for those with locally advanced cancer.

The improved adherence in these settings suggests that several quality improvement initiatives would be effective, including (i) centralization of care at regional cancer centres and (ii) ensuring care is provided by high volume surgeons. Centralization of surgical care at regional cancer centres has been mandated by Cancer Care Ontario for other disease sites, most notably for pancreatic cancer surgery. This mandate was driven by high mortality risks in low volume centres. (11). Mortality is a rare outcome following rectal cancer surgery, and thus CCO has been reluctant to mandate centralization. The results from this thesis provides evidence that this decision should be reconsidered.

An additional important predictor of adherence was later diagnosis year. Increasing adherence with advancing year may be related to a number of reasons. Those treated in later diagnosis years may have benefitted from increasing awareness and acceptance of clinical practice guidelines, compared with those in the early treatment periods. The evidence supporting most of the recommendations matured throughout the study period during which a number of well known trials and high quality systematic reviews/meta-analyses were published. The strengthening of evidence may have further encouraged adherence to clinical practice recommendations. The latter period's patients also may have benefitted from quality improvement initiatives by Cancer Care Ontario, most notably for the use of staging MRI and neoadjuvant therapy.

Reducing the time between publication of clinical practice guidelines and care provider acceptance would thus be effective in improving adherence across the province. There is increasing enthusiasm for total neoadjuvant therapy (i.e. neoadjuvant and adjuvant therapy before surgery) and "organ preservation" (i.e. omitting major surgical resection in select cases) for eligible patients with rectal cancer. Both options have already appeared on some well known

clinical practice guidelines (12), and it is certain they will appear on the next Canadian versions as well. In fact, many Canadian centres have already adopted total neoadjuvant therapy and non-operative management as the "standard of care" (including my own). Provincial health authorities must ensure that appropriate selection and use of these options are occurring by care providers within the province, through clinical practice guidelines. CCO has demonstrated a willingness to advocate for adherent care for some aspects of rectal cancer management and must continue to do so as treatment options evolve.

Next, this thesis identified that the majority of provinces regularly produce rectal cancer clinical practice guidelines. Presumably, health authorities believe that provincial (as opposed to national) guidelines are required based on demographics, resources or other differences between provinces. This thesis calls this assumption into question. Despite some variation in very specific circumstances, there was little major differences between the each province's recommendations. A national guideline, endorsed by each provincial health authority, would be preferable. Less resources and time would be required, there would be clarity on what the Canadian "standard of care" would be, and it would allow for representation from all provinces, not just those that currently produce guidelines. At the current time, there is no available guideline from 3 of the least populace provinces (New Brunswick, Prince Edward Island, Newfoundland and Labrador) or the territories (Nunavut, Northwest Territories, Yukon). The territories, in particular, represent a challenge in the delivery of health care due to the immensity of the area and sparseness of the population. As an example, the smallest territory (Yukon) has more than twice the land mass of the United Kingdom (480,000 km^2 vs. 244,000 km^2) but contains only 46,000 residents. The development of a detailed, common Canadian guideline through collaboration of all health authorities would be more efficient, more representative,

would continue to be relevant locally and would reduce some of the confusion from clinicians when trying to identify the most appropriate treatments for their patients.

This thesis has also demonstrates that developing a comprehensive, population-based resource for evaluating the delivery of cancer care and outcomes is feasible and useful. This resource allows for a detailed examination of predictors of outcomes, allows for understanding of differences in how care is delivered and can be updated regularly based on the available administrative data. There have been a few similar resources developed for other disease sites (13) or specific populations (14) within Ontario. These databases have been researcher led, and were developed with specific research objectives. Establishing population-based resources for all disease sites would allow for a fuller understanding of the cancer system within Ontario. There are likely common and specific challenges in the delivery of care within each cancer site. Researcher led studies restricts the scope of study to what is feasible and relies on the ongoing interest of the researcher, and on the researchers funding. Moving this work to the provincial health authorities would mitigate researcher related constraints.

Cancer Care Ontario should consider expanding its Surgical Oncology Quality Improvement program beyond the current focus on regional and institutional performance indicators and move to a comprehensive assessment of the delivery of rectal cancer care. The current quality improvement program identifies a limited number of outliers, which are defined as 2 standard deviations below average, or based on arbitrary benchmarks. Working groups established the indicators based on expert opinion, and data analysts at CCO provide quarterly summaries of each region and hospital's performance. Within each disease site, there are typically less than 5 indicators that are reported. Establishing comprehensive cohorts, as opposed to running simplified data analyses, would allow for a more in depth understanding of

the delivery of high quality cancer care, as well as allow for a more comprehensive understanding of the variability in the delivery of this care. Significant outliers could be identified, with specific quality improvement initiatives directly applied. It is clear from this thesis that there are significant opportunities for improving the delivery of rectal cancer care, and presumably other disease sites are faced with similar challenges.

Putting the Ontario results into a global context is challenging. Few studies have assessed overall adherence previously, as described in ***Chapter 4***. This makes it difficult to determine whether the findings from Ontario are consistent with those from other settings, when assessing the "big picture" of adherent rectal cancer care. Some studies provide insight into specific differences or similarities between the Ontario and international settings. There appears to be similar use of MRI in rectal cancer in other settings. In comparison to Ontario (68% in the curative cohort), Sweden (55%) (15), the United States (62%) (16), and Ireland (72%) (17) all report similar rates of preoperative MRI, perhaps implying similar challenges between different settings. Looking at neoadjuvant (preoperative) radiation demonstrates more variability. In Ontario, approximately 59% of patients who were eligible received adherent radiation. The proportion receiving radiation in other settings varied greatly. For example, low rates of radiation were found in the United States (49%) (18) with higher rates in France (59 – 85%) (19) and Spain (85%) (20). As there are differences in the organization of cancer system between these settings, it would have been advantageous to have more robust studies from international settings assessing overall guideline adherence. As reported in ***Chapter*** 4, the deficiency in available publications made determining which systems perform better and why is challenging. Some settings, such as the United Kingdom and Spain, have more centralized systems, while others such as the United States do not. Other important factors that may contribute to improved

adherence may have been proximity of cancer centre to patients residence, the incorporation of primary care into cancer care, the availability of diagnostic imaging, and capacity of the cancer system as a whole.

7.6 Future Research

This thesis has established the Ontario Rectal Cancer Cohort as a comprehensive and useful resource to evaluate the delivery of care and outcomes in those with rectal cancer. Based on the work contained within this thesis, I have obtained an $180,000 CAD operating research grant to further explore the delivery of rectal cancer care in Ontario.

Using these funds, the Ontario Rectal Cancer Cohort will be expanded to include those with a diagnosis up to 2024. An additional five years of data will be incorporated, which will further increase the sample size to allow for the assessment of uncommon outcomes or specific subgroups. In addition, new administrative databases such as "E-Path" have become available and the inclusion of laboratory results (including CEA) has occurred in the most contemporary groups of patients.

Including the last five years will also allow for the evaluation of the care delivered during the COVID-19 pandemic. The pandemic had a dramatic effect on screening for colorectal cancer in Ontario, access to diagnostic investigations and the ability to delivery timely and appropriate treatments. Thus, there has been significant delays in the diagnosis and treatment of those with cancer. The impact was not uniform, in that specific jurisdiction were more affected than others. Comparing the relative impact in different regions on outcomes provides a natural experiment to determine the impact of reduced screening, the risks of a delayed diagnosis and assessment of the appropriateness of current timeliness treatment benchmarks.

This period (2020 – 2024) also witnessed the most significant changes in rectal cancer treatments since the adoption of perioperative radiation. There has been substantial enthusiasm in Canada for Total Neoadjuvant Therapy and non-operative management based on increasing levels of evidence supporting these approaches. For example, at my local centre we now offer total neoadjuvant therapy to > 90% of individuals with locally advanced disease and selectively offer non-operative management in eligible patients with a complete clinical response, which occurs in 20 – 30% of patients. Prior to 2020, neither of these options were offered to rectal cancer patients.

In addition to updating the cohort, several specific research questions are being addressed with the additional funds. Including:

- **Guideline adherence and Survival:** An exploratory analysis of guideline adherence and survival was undertaken. Overall survival, including three year and five year, was determined for those who were adherent and non-adherent to each phase of care as well as to all recommendations ("Overall"). (Table 7 - 1). Survival was high in the early stage group, regardless of adherence status to each phase of care or overall adherence. In all groups, five year survival was >80%, with the highest survival found in those who were adherent to all aspects of care (93%). In those with locally advanced disease, there was a wider range of survival based on adherence status. Those who were adherent to all aspects of care had the highest five year survival (88%), while those who were non-adherent to any phase of care had worse survival (Range 58 – 69%). Interestingly, in both early stage disease and locally advanced disease those who were overall adherent had similar five year survivals (early stage disease 93%, locally advanced disease 88%).

Table 7-1 Overall Survival, by adherence for those with early stage and locally advanced disease

Early Stage Disease					
		3 Year Overall Survival		5 Year Overall Survival	
Adherent Staging (n, %) (a)					
No	923, 34.6%	90.8%	P = 0.16	84.3%	P = 0.53
Yes	1744, 65.5%	92.3%		85.1%	
Adherent Treatment (n, %) (b)					
No	929, 34.8%	92.4%	P = 0.40	84.5%	P = 0.84
Yes	1738, 65.2%	91.5%		84.9%	
Adherent Surveillance (n, %) (c)					
No	1438, 53.9%	88.9%	P <0.0001	80.0%	P <0.0001
Yes	1229, 46.1%	95.2%		90.5%	
Overall Adherence (n, %) (d)					
No	2097, 78.6%	90.6%	P <0.0001	82.8%	P <0.0001
Yes	570, 21.4%	96.3%		92.5%	
Locally Advanced Disease					
		3 Year Overall Survival		5 Year Overall Survival	
Adherent Staging (n, %) (a)					
No	1527, 22.8%	77.9%	P <0.0001	68.5%	P <0.0001
Yes	5158, 77.2%	84.1%		75.4%	
Adherent Treatment (n, %) (b)					
No	4059, 60.7%	78.9%	P <0.0001	68.8%	P <0.0001
Yes	2626, 39.3%	88.3%		81.5%	
Adherent Surveillance (n, %) (c)					
No	2951, 44.1%	69.3%	P <0.0001	58.3%	P <0.0001
Yes	3734, 55.9%	92.7%		85.3%	
Overall Adherence (n, %) (d)					
No	5150, 77.0%	79.0%	P <0.0001	69.3%	P <0.0001
Yes	1535, 23.0%	94.3%		88.3%	

(a) Underwent Local-Regional Staging, Assessment for Metastatic Disease and Colonic Assessment prior to first treatment date
(b) Early Stage Disease – Received Timely Surgery (<35 days from diagnosis); Locally Advanced Disease – Received Preoperative Radiation, Surgery, Postoperative Chemotherapy
(c) Received colonoscopy and assessment of metastatic disease (Chest, Abdomen, Pelvis) within 18 months of surgery
(d) Was adherent to staging, treatment and surveillance

A simple Cox Regression Analysis was completed to determine the associations between adherence to aspect of the guidelines and survival. Interestingly, adherence was not found to be associated with survival in the early stage group, but was for those with locally advanced disease. (Table 7 – 2) Further work will include addressing competing risks of death,

accounting for the impact of timely diagnosis and treatment, and acuity of symptoms and/or disease presentation.

Table 7-2 Univariable and Multivariable Survival Analyses of the association between adherence (Staging, Treatment, Surveillance and Overall) and Survival

Early Stage Disease				
	Univariable Analysis HR, 95% CI and Significance testing		Multivariable Analysis (a) HR, 95% CI and Significance testing	
Adherent Staging - No	1.23 (0.93, 1.64)	P = 0.15	1.24 (0.93, 1.66)	P = 0.13
Adherent Staging - Yes	Referent		Referent	
Adherent Treatment - No	0.88 (0.65, 1.18)	P = 0.39	0.88 (0.65, 1.20)	P = 0.42
Adherent Treatment - Yes	Referent		Referent	
Surveillance Adherent - No	1.51 (0.97, 2.34)	P = 0.066	1.19 (0.76, 1.87)	P = 0.44
Surveillance Adherent - Yes	Referent		Referent	
Overall Adherence (b) - No	2.16 (1.12, 4.18)	P = 0.022	1.82 (0.94, 3.56)	P = 0.077
Overall Adherence (b) - Yes	Referent		Referent	
Locally Advanced Disease				
	Univariable Analysis HR, 95% CI and Significance testing		Multivariable Analysis (a) HR, 95% CI and Significance testing	
Adherent Staging - No	1.45 (1.27, 1.65)	P <.0001	1.21 (1.06, 1.39)	P = 0.006
Adherent Staging - Yes	Referent		Referent	
Adherent Treatment - No	2.02 (1.76, 2.32)	P <.0001	1.42 (1.22, 1.65)	P <.0001
Adherent Treatment - Yes	Referent		Referent	
Surveillance Adherent - No	3.09 (2.56, 3.73)	P <.0001	2.60 (2.14, 3.16)	P <.0001
Surveillance Adherent - Yes	Referent		Referent	
Overall Adherence (b) - No	2.58 (1.95, 3.42)	P <.0001	2.08 (1.56, 2.78)	P <.0001
Overall Adherence (b) - Yes	Referent		Referent	

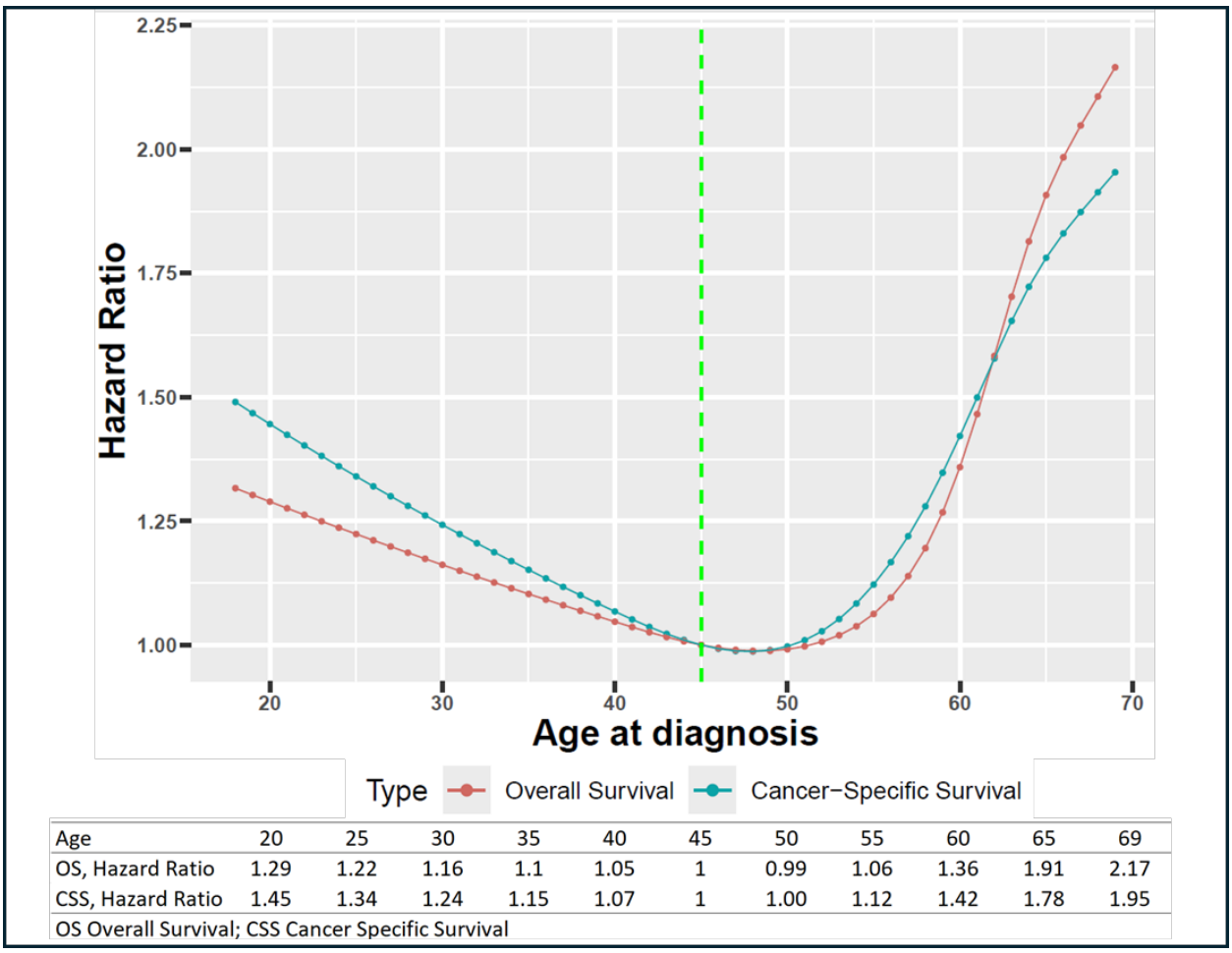
(a)Cox regression model adjusted for age group, sex, year of surgery, Cancer Centre Designation, Surgeon Volume, Income Quintile, Rurality, Co-morbidity
(b) Overall Adherence included adherence to all staging, treatment and surveillance recommendations

- **Management and Outcomes of Local Excision vs. Radical Resection for early stage rectal cancer**: Using the histopathology data, in combination with the linked administrative data, a comparison between outcomes in those who underwent a local excision and those who underwent radical resection for T1 disease is being completed.

Approximately 700 individuals within the OntaReCC had T1Nx disease identified on histopathology. Approximately half underwent a local excision and half underwent a radical resection. The overall survival was comparable between groups, and the classically described high risk factors for local excision failure (piecemeal excision and positive margin) did not predict failure of local excision. A manuscript has been prepared and this study was presented at both the Canadian Surgical Forum and the American Society of Colon and Rectal Surgeons Annual Meeting.

- **Rectal cancer in the very young (age < 40), a more aggressive cancer?:** Only a small proportion of individuals less than 40 were diagnosed with rectal cancer during the study period. This group tended to have more aggressive treatments, but survival in this group was modest compared to those in slightly older age groups. This finding led to reconsidering age as a continuous variable. Using non-linear methods, it was demonstrated the survival was best in those aged 45 - 50, after adjusting for important confounders. (Figure 7 - 1). This study is being completed to determine the implications of this finding. The initial results were presented at the American Society of Colon and Rectum Surgeons Annual Meeting.

Figure 7-1 Hazard Ratio of Overall Survival and Cancer Specific Survival by Age at Diagnosis



Age	20	25	30	35	40	45	50	55	60	65	69
OS, Hazard Ratio	1.29	1.22	1.16	1.1	1.05	1	0.99	1.06	1.36	1.91	2.17
CSS, Hazard Ratio	1.45	1.34	1.24	1.15	1.07	1	1.00	1.12	1.42	1.78	1.95

OS Overall Survival; CSS Cancer Specific Survival

- **Fragmentation of Care in those with rectal cancer, impact on timeliness and completeness of treatment in those with locally advanced disease:** Fragmented care is defined as receiving multimodal treatment at different institutions or hospitals. Those with locally advanced rectal cancer are at risk of fragmentation as they require radiation, chemotherapy and surgery. In Ontario, radiation delivery occurs in < 20 sites and chemotherapy often needs to be delivered at Level 1 – 3 cancer centres, while there are no restrictions on the location of surgical management. In those who received all three treatments, only 35% received these all at the same institution. This study will determine

the impact on fragmented care on timeliness of treatment, completeness of treatment and the impact on survival. If fragmentation results poor outcomes, a further argument for centralization of care can be made.

- **Variation in the delivery of rectal cancer care in Ontario:** The correlation between care provider and adherence to recommendation was explored in detail in this thesis. Care providers were demonstrated to be important mediators in how care is delivered. This study will determine the extent of unwarranted (or harmful) variation in Ontario at the regional and institutional levels. Small area analyses will be used to determine the degree of variation above and beyond that which would be expected due to chance alone. Identifying areas with high levels of harmful variation can allow for directed quality improvement initiatives as well as demonstrate what features places such an area at high risk of unwarranted variation.
- **Practice Patterns and Outcomes in those undergoing synchronous or metachronous resections for rectal cancer metastasis:** There is increasing adoption of surgical management of those with "resectable" metastatic rectal cancer to the liver or lungs. Although this practice is largely accepted, evaluation of who is being offered resection and where is warranted. Determining whether similar criteria for resection are being applied universally vs. selectively would allow for an assessment on how this care is being delivered in the province.
- **The predictors and impact of completing neoadjuvant and adjuvant therapy in locally advanced rectal cancer:** This thesis assesses neoadjuvant (radiation) and adjuvant (systemic chemotherapy) treatments in a general way. It includes an assessment of whether these therapies were attempted, but did not comprehensively assess the

completeness of each therapy, the predictors and impact on outcomes. Interruptions in both neoadjuvant and adjuvant therapy are common in those with rectal cancer. Future work will determine the predictors and impact. Interruptions in treatment and completeness of treatment are available in the OntaReCC and can be assessed.

- **Adoption of outcomes of Total Neoadjuvant Therapy (TNT) for locally advanced rectal cancer in Ontario:** Adoption of TNT in Ontario will be evaluated. Comparison between TNT options, and comparison between TNT and traditional treatments will be completed using real world data.

In addition to the future research as a direct extension of the thesis, several other projects are planned. I have obtained grants to establish an Appendiceal Cancer Cohort and a Colon Cancer Cohort. The objectives of establishing these cohorts are the same as the objectives of this thesis: To determine practice patterns and outcomes, as well as determine adherence to guideline recommended care. Although both appendiceal and colon cancer share similar histology and treatments as rectal cancer, there are interesting differences that are worth examining. For example, appendiceal cancer is typically diagnosed after appendectomy for what is typically a benign process (appendicitis), is a rare cancer, there is little level 1 evidence supporting the recommended treatments. The proposed research will allow for real world evaluation.

7.7 Thesis Conclusions

This thesis in Evidence Based Health Care advances the understanding of guideline adherent care in those with rectal cancer. I have established rectal cancer as a complex disease, requiring multidisciplinary care. The complexity of the disease necessitates the use of clinical practice guidelines, which are generally consistent in their recommendations across Canada.

Clinical practice guidelines are created to encourage health care providers to make the best decisions regarding a patient's care. These guidelines are widely available, easily accessible and created based on the best available evidence. A large proportion of rectal cancer patients in Ontario are not receiving basic investigations and treatments which are recommended, available and cost effective. Simply receiving all necessary diagnostic investigations was associated with a vastly increased likelihood of receiving the appropriate treatments.

Evaluating guideline adherent cancer care is an important part in assessing how cancer care is being delivered within a population. Innovations in rectal cancer treatments such as total neoadjuvant therapy and non-operative management are becoming adopted in a number of Canadian settings. New guidelines supporting these practices are expected. Ensuring appropriate patient selection and effective treatment regimens to ensure the safe delivery of rectal cancer care will be important for those managing these patients in Ontario. Assessing evolving changes in recommendations can be accomplished using resources such as the Ontario Rectal Cancer Cohort, which was developed specifically for this purpose.

The challenges in providing adherent care in those with rectal cancer in Ontario, which were identified in this thesis, supports the need to focus on the “Cancer Ground -shot”, in which resources need to be dedicated to improving the use of cost effective and proven interventions which are readily available at the present time.

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7.8 Chapter 7 References

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Chapter 8 Thesis Appendices

8.1 Appendix Chapter 3: Management of Rectal Cancer in Canada An evidence based comparison of clinical practice guidelines

Management of rectal cancer in Canada: an evidence-based comparison of clinical practice guidelines

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Background: Rectal cancer requires a multidisciplinary and multimodality treatment approach. Clinical practice guidelines (CPGs) provide a framework for delivering consistent, evidence-based health care. We compared provincial/territorial CPGs across Canada to identify areas of variability and evaluate their quality.

Methods: We retrieved CPGs from Canadian organizations responsible for cancer care oversight and evaluated their quality and developmental methodology using the AGREE-II instrument. Recommendations for diagnostic and staging investigations, treatment by stage, and post-treatment surveillance of stage I–III rectal cancers were abstracted and compared.

Results: We identified 7 sets of CPGs for analysis, varying in content, presentation, quality, and year last updated. Differences were noted in locoregional staging: 4 recommended magnetic resonance imaging over endorectal ultrasonography, 2 recommended either modality, and 3 specified scenarios for one over the other. Recommendations also varied for use of staging computed tomography of the chest versus chest radiography and for surgical management and indications for transanal excision. Recommendations for neoadjuvant therapy in stage II/III disease also differed: 3 guidelines recommended long-course chemoradiation over short-course radiation therapy alone, while 3 others recommended short-course radiation in specific clinical scenarios. Adjuvant chemotherapy for stage II/III disease was uniformly recommended, with variable protocols. The use of proctosigmoidoscopy and interval/duration of endoscopic post-treatment surveillance varied among guidelines.

Conclusion: Canadian CPGs vary in their recommendations for staging, treatment, and surveillance of rectal cancer. Some of these differences reflect areas with limited definitive evidence. Consistent guidelines with uniform implementation across provinces/territories may lead to more equitable care to patients.

Contexte : Le cancer rectal requiert une approche thérapeutique multidisciplinaire et multimodalité. Les guides de pratique clinique (GPC) procurent un cadre pour assurer la prestation de soins de santé constants reposant sur des données probantes. Nous avons comparé les GPC des provinces et des territoires canadiens pour identifier les secteurs où ils varient et pour en évaluer la qualité.

Méthodes : Nous avons obtenu les GPC des organisations canadiennes responsables des soins oncologiques et nous avons évalué leur qualité et la méthodologie de leur élaboration au moyen de l'outil AGREE II (Appraisal of Guidelines for Research & Evaluation). Nous avons extrait et comparé les recommandations en ce qui concerne les épreuves diagnostiques et la stadification, les traitements en fonction du stade et la surveillance post-thérapeutique du cancer rectal de stade I à III.

Résultats : Nous avons recensé 7 GPC aux fins de cette analyse; leur contenu, leur présentation, leur qualité et l'année de leur plus récente mise à jour variaient. Des différences ont été observées au plan de la stadification locorégionale : 4 recommandaient l'imagerie par résonnance magnétique plutôt que l'échographie endorectale, 2 recommandaient l'une ou l'autre et 3 précisaient des circonstances où utiliser l'une plutôt que l'autre. Les recommandations variaient aussi pour ce qui est de l'utilisation de la scintigraphie c. radiographie thoracique de stadification, de la prise en charge chirurgicale et des indications de l'excision transanale. Les recommandations variaient également en ce qui concerne le traitement néoadjuvant pour la maladie de stade II/III : 3 guides recommandaient un traitement par chimioradiothérapie à long terme plutôt qu'une brève radiothérapie seule, tandis que 3 autres recommandaient une radiothérapie brève dans certains cas particuliers. La chimiothérapie adjuvante pour la maladie de stade II/III était uniformément recommandée, mais les protocoles variaient. L'utilisation de la proctosigmoïdoscopie et l'intervalle/durée de la surveillance endoscopique post-thérapeutique variaient d'un guide à l'autre.

Conclusion : Les GPC canadiens varient quant à leurs recommandations pour la stadification, le traitement et la surveillance du cancer rectal. Certaines de ces différences témoignent du manque de données probantes concluantes dans certains secteurs. L'uniformisation des guides et de leur application entre les provinces et les territoires pourrait faciliter une prestation plus équitable des soins aux patients.

Colon and rectal cancers represent 15% of all newly diagnosed cancers in Canadian men, and 12% of all newly diagnosed cancers in Canadian women.[1] The detection, staging and management of rectal cancer has evolved dramatically over the last 30 years, with improved surgical techniques, involvement of multidisciplinary cancer disease site groups, and the utilization of a multimodal approach to treatment.[2–4] During this time, there has been an improvement of outcomes in locoregional control and overall survival.[5,6] However, with the volume and pace of evidence being generated, there remains some uncertainty and controversy regarding several elements of care, including the optimal neoadjuvant protocol, use of local excision and utility of adjuvant systemic therapy.[5–8] This leads to variability in decision-making and clinical practice as well as knowledge gaps among clinicians. Previous Canadian studies have highlighted such differences among surgeons managing rectal cancer across the country.[9,10]

Clinical practice guidelines (CPGs) are systematically developed statements that are meant to inform decision-making regarding specific clinical situations.[11,12] They have the ability to improve the quality and consistency of care provided by bridging the gap between clinicians' knowledge/practices and what is supported in the literature.[12,13] Ideally, CPGs should analyze and distil the best evidence to provide direction to health care providers. However, guidelines may contain flawed or inaccurate content, may be presented in a suboptimal fashion, or may be poorly generalizable to individual patients.[12,13] Other barriers to implementation include clinician factors such as lack of agreement with published guidelines or limited time and resources, or patient factors such as specific preferences and expectations.[14]

The Appraisal of Guidelines for Research & Evaluation II instrument (AGREE-II) is a standardized and validated tool used to evaluate the quality and methodology of CPGs.[15,16] It is considered by many to be the gold standard for guideline appraisal.[17,18]

Given the potential variation in practice patterns among Canadian surgeons, our objective was to examine Canadian rectal cancer CPGs to evaluate their quality, developmental methodology, presentation and interprovincial concordance.

Methods

We obtained CPGs from the websites and/or publications of the responsible organization within each province and territory.[19–31] These included the British Columbia Cancer Agency, Alberta Health Services, Saskatchewan Cancer Agency, Cancer Care Manitoba, Cancer Care Ontario, Institut national d'excellence en santé et en services sociaux and Groupe d'étude en oncologie du Québec, and Cancer Care Nova Scotia. The latest published guidelines from each organization were used for this study; these were separate from care pathways or care maps published by the same organizations. From these guidelines, 2 of us (Z.M.M. and D.Y.) independently extracted information regarding stage I, II and III (i.e., curable) rectal cancers. Accuracy of extracted information was verified by a third, independent assessor (S.V.P.).

Recommendations for diagnostic and staging work-up (locoregional staging, assessment for distant metastases), treatment by stage (neoadjuvant therapy, surgery, adjuvant therapy) and protocols for post-treatment surveillance (endoscopic evaluation, imaging, tumour marker assessment, clinical visits) were assessed.

Each English guideline was evaluated and scored independently by 2 reviewers (Z.M.M. and D.Y.) for quality using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument. The domains of evaluation included scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability, and editorial independence. In addition to these, there are 2 global rating items within the assessment that rate the overall quality of each guideline and whether they would be recommended for use; however, we chose not to make a recommendation for or against the use of each CPG. Scaled domain scores for each guideline were then calculated as per AGREE-II methodology; within each domain, a score from 1 to 7 was assigned by each reviewer. A score of 1 reflects either no information or poor reporting of an AGREE II item/concept. Conversely, a score of 7 indicates exceptional reporting of an AGREE II item/concept. Each pair of scores was summed, and the total was scaled as a percentage of the maximum possible score for that domain. A Spearman rank correlation coefficient was calculated to determine interrater agreement.

It should be noted that the AGREE-II process does not have a set minimum domain score to delineate the difference between a guideline that is considered to be of higher quality versus one considered to be of lower quality; such decisions are subjective and left to the user of the instrument.

Results

We obtained CPGs specific to rectal cancer management from 7 of the 13 Canadian provinces and territories (Table 1). Most were available as published documents, but the BC guidelines were published online only. Guidelines from New Brunswick, Newfoundland & Labrador, Prince Edward Island, Nunavut, Yukon, and the Northwest Territories were not available, despite our attempts to obtain them. The CPGs varied with respect to year of most recent update(s).

Guideline evaluation using AGREE-II

All English guidelines were rated across different domains using the AGREE-II instrument (Table 2 and Fig. 1). Guidelines from Manitoba, Ontario and Nova Scotia scored well; average domain scores were above 50%. Conversely, guidelines from Saskatchewan and British Columbia scored the lowest; their average domain scores were below 20%. The majority of differences were noted within the domains of applicability and rigour of development, as defined by the AGREE-II instrument. The Spearman rank correlation coefficient was 0.90, indicating a statistically significant agreement of domain scores between the 2 assessors.

Diagnosis and staging work-up

All 7 guidelines recommended measuring carcinoembryonic antigen (CEA) levels, complete colonoscopy (if possible), and computed tomographcy (CT) of the abdomen and pelvis as part of the initial staging work-up for rectal cancer. The primary difference was noted in the use of magnetic resonance imaging (MRI) versus endorectal ultrasound (ERUS) for local staging of tumours. Guidelines from British Columbia and Saskatchewan did not indicate a strong preference for either MRI or ERUS, whereas guidelines from Alberta, Ontario, Quebec and Nova Scotia recommended MRI (Table 3). Ontario and Manitoba guidelines provided specific scenarios for the use of MRI and ERUS in staging. In addition, while the majority of guidelines suggested CT to stage the chest, the BC guidelines recommended chest radiography over CT, and the Manitoba guidelines did not declare a preference (Table 3).

Table 1. Guideline availability and year of publication, by province/territory

Province/territory	Availability	Year(s) of publication
British Columbia	Yes	2012
Alberta	Yes	2013, 2014, 2017
Saskatchewan	Yes	2011, 2013
Manitoba	Yes	2014, 2015, 2018
Ontario	Yes	2013, 2014, 2016
Quebec	Yes	2016
Nova Scotia	Yes	2016
Newfoundland & Labrador	No	—
New Brunswick	No	—
Prince Edward Island	No	—
Nunavut	No	—
Northwest Territories	No	—
Yukon	No	—

Neoadjuvant recommendations by stage

Guidelines frrom British Columbia, Alberta, Manitoba, Ontario and Nova Scotia did not recommend neoadjuvant therapy for stage I rectal cancer (Table 4); however, guidelines from Saskatchewan and Quebec suggested neoadjuvant therapy in the setting of select T2N0 and low tumours to obtain better opportunities for sphincter preservation at the time of surgery. All guidelines recommended neoadjuvant therapy for stage II and III rectal cancers, but their recommendations differed for short-course radiotherapy versus long-course chemoradiotherapy as the protocol of choice (Table 4). Guidelines from Saskatchewan, Ontario and Nova Scotia recommended long-course neoadjuvant treatment, whereas the guideline from Manitoba recommended short-course. British Columbia recommended long-course for patients with fixed tumours, predicted positive circumferential margins, and distal rectal cancers versus short-course for nonfixed and middle/proximal rectal cancers. Alberta recommended long-course for patients "not amenable to resection." Overall, the neoadjuvant protocols themselves were fairly consistent (data not shown).

Surgery recommendations by stage

Surgical resection was recommended as the primary curative option for stage I rectal cancer in all of the guidelines. Transanal excision (TAE) in stage I disease was mentioned in most guidelines (British Columbia, Alberta, Quebec, Nova Scotia), whereas

Table 2. Guideline evaluation using AGREE-II domain scores

	Province, score					
AGREE II Domain	British Columbia	Alberta	Saskatchewan	Manitoba	Ontario	Nova Scotia
Scope & purpose	0%	86%	17%	100%	94%	50%
Stakeholder involvement	8%	11%	6%	61%	58%	33%
Rigour of development	0%	19%	1%	86%	50%	30%
Clarity of presentation	81%	53%	56%	94%	94%	92%
Applicability	0%	0%	0%	65%	52%	42%
Editorial independence	0%	88%	0%	100%	75%	67%
Average domain score	15%	43%	13%	84%	71%	52%

AGREE II = Appraisal of Guidelines for Research & Evaluation II instrument.

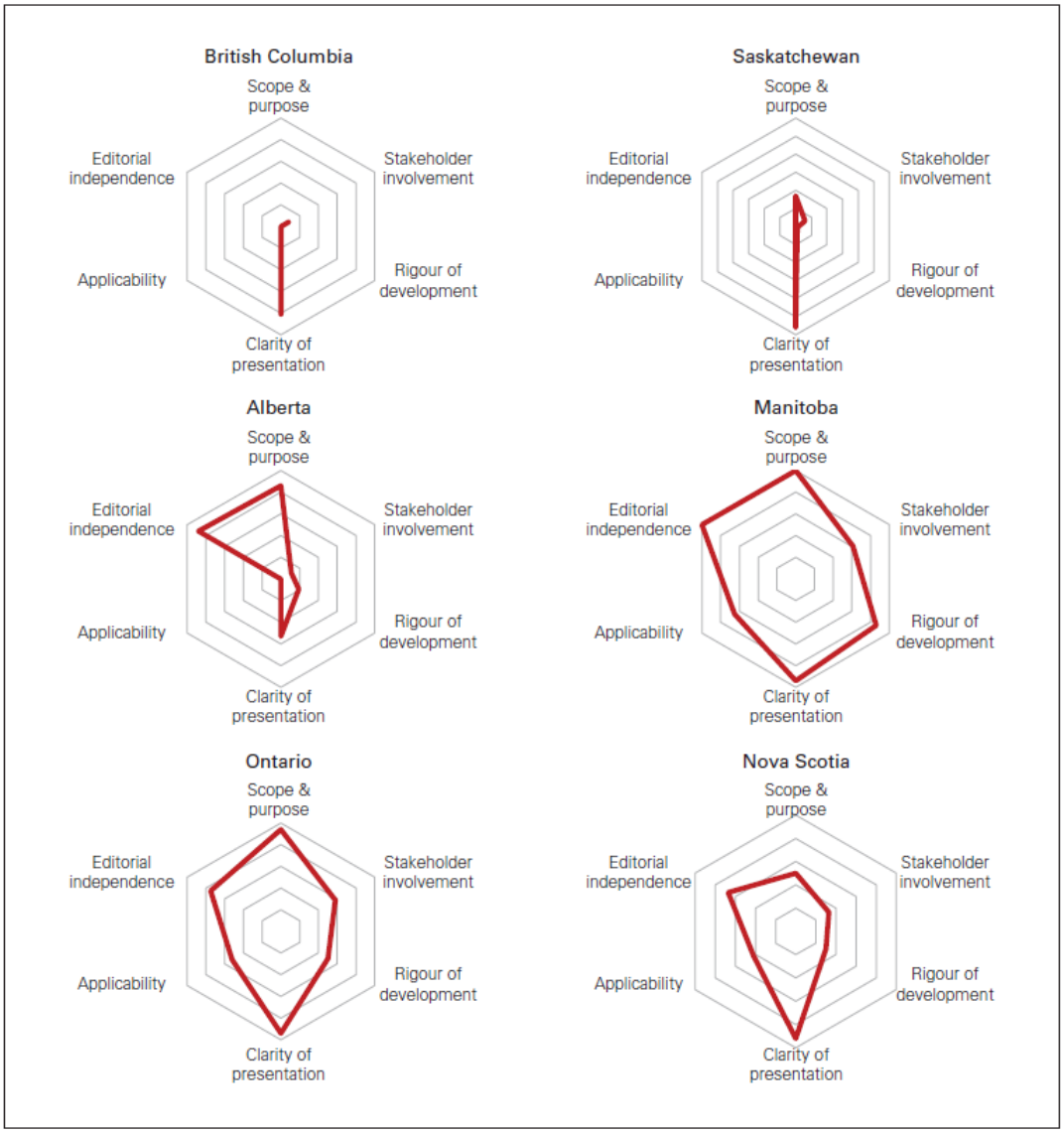

Fig. 1. Appraisal of Guidelines for Research & Evaluation II instrument (AGREE-II) domain scores of each provincial guideline.

Manitoba and Ontario guidelines did not comment specifically on TAE (Table 5). Specific considerations for TAE eligibility include node-negative cancers, absence of lymphovascular or perineural invasion, and tumour size < 3 cm. The guideline from Saskatchewan did not discuss surgical technique in any great detail.

For stage II and III disease, surgical recommendations were within the context of neoadjuvant protocols, and radical resection was recommended with a focus on total mesorectal excision (TME). The time between completion of neoadjuvant therapy and surgery was similar in all assessed guidelines (i.e., time from short-course to surgery 7–10 days; time from long-course to surgery 4–6 weeks or 6–10 weeks).

Table 3. Imaging modality recommendations for local and distant staging of tumours

Province	MRI v. ERUS	Abdominal staging	Chest staging
British Columbia	No preference	CT abdomen/pelvis	CXR preferred
Alberta	MRI preferred (especially if SC planned)	CT abdomen/pelvis	CT preferred
Saskatchewan	No preference	CT abdomen/pelvis	CT preferred
Manitoba	ERUS preferred (especially for small or low tumours) MRI for all stenotic tumours	CT abdomen/pelvis	CXR or CT
Ontario	MRI preferred ERUS for low tumours	CT abdomen/pelvis	CT preferred
Quebec	MRI preferred	CT abdomen/pelvis	CT preferred
Nova Scotia	MRI preferred	CT abdomen/pelvis	CT preferred

CT = computed tomography; CXR = chest radiography; ERUS = endorectal ultrasound; MRI = magnetic resonance imaging; SC = short-course radiotherapy only.

Table 4. Neoadjuvant therapy recommendations, by stage

Province	Stage I	Stage II & III
British Columbia	—	SC for non-fixed, upper 2/3 location LC for fixed or predicted +CRM
Alberta	—	SC for "amenable to resection" LC preferred for stage II/III, and if "not amenable to resection"
Saskatchewan	Chemoradiation for select T2N0 and low tumours	LC standard
Manitoba	—	SC preferred LC for down-staging, sphincter preservation
Ontario	—	LC Preferred
Quebec	For sphincter preservation	No specific preference but states that majority of clinicians use LC
Nova Scotia	—	LC preferred

CRM = circumferential radial margin; LC = long-course chemoradiotherapy; SC = short-course radiotherapy only.

Table 5. Surgical treatment recommendations, by stage

Province	Stage I	Stage II & III
British Columbia	TAE offered	For SC, surgery within 10 d For LC, surgery within 6–10 wk
Alberta	TAE offered	For SC, surgery within 1 wk For LC, surgery within 6–8 wk
Saskatchewan	No details	For SC, surgery within 7–10 d For LC, surgery within 6–8 wk
Manitoba	Highlights importance of TME technique	For SC, "immediate" surgery For LC, surgery within 6–8 wk
Ontario	Highlights importance of TME technique	For SC, surgery within 10 d For LC, surgery within 4–6 wk
Quebec	TAE offered	For SC, "immediate" surgery For LC, does not specify time to surgery
Nova Scotia	TAE offered	For SC, surgery within 10 d For LC, surgery within 6–10 wk

LC = long-course chemoradiotherapy; SC = short-course radiotherapy only; TAE = transanal excision; TME = total mesorectal excision.

Table 6. Adjuvant treatment recommendations, by stage

Province	Stage I	Stage II & III
British Columbia	Radiotherapy if LE	Capecitabine x 6 mo post-SC Capecitabine x 4 mo post-LC For stage III disease, mFOLFOX6 may be considered, especially if N+
Alberta	—	6 mo of adjuvant therapy recommended for stage II with "high-risk features" and all stage III (CAPOX/XELOX, mFOLFOX6, or capecitabine)*
Saskatchewan	—	Capecitabine, 5-FU, mFOLFOX, or CapeOX x 6 mo
Manitoba	If upstaged	Fluoropyrimidine-based therapy offered postoperatively
Ontario	If upstaged	No adjuvant therapy if upstaged to II/III Fluoropyrimidine-based therapy, post-op Oxaliplatin-based therapy, or capecitabine for high risk of systemic recurrence
Quebec	If upstaged	5FU/LV or FOLFOX for 8–12 cycles (FOLFOX preferred if upstaged)
Nova Scotia	—	5FU or capecitabine; FOLFOX if high risk of recurrence

LC = long-course chemoradiotherapy; LE = local excision; SC = short-course radiotherapy only.
*Extrapolated from colon cancer.

Adjuvant protocols by stage

Adjuvant systemic therapy was not recommended for stage I rectal cancer in any of the CPGs. Manitoba, Ontario and Quebec guidelines did discuss adjuvant therapy for stage I disease if there was pathological upstaging postresection (Table 6). The BC guideline recommended adjuvant radiotherapy if local excision was carried out.

For stage II and III disease, all guidelines recommended some form of adjuvant systemic therapy, although there was variability in recommendations among the guidelines (Table 6). Adjuvant radiotherapy was not routinely recommended in any CPG.

Post-treatment surveillance recommendations

Post-treatment surveillance for stage I disease was limited to routine screening colonoscopy in all provinces. For stage II/III disease, surveillance included routine clinical visits, CEA testing, abdomen/pelvic imaging and

Table 7. Post-treatment surveillance protocols for stage II/III disease

Province	History/physical	CEA	CT abdomen/pelvis	Colonoscopy
British Columbia	Every 3–6 mo for 3 yr Every 6 mo for 2 yr	At each visit	Annually for 3 yr	At 1 & 4 yr post-op Every 5 yr thereafter
Alberta	Not specified	Every 3 mo for 3 yr	Annually for 2 yr (± third year)	At 1 & 4 yr post-op Every 5 yr thereafter
Saskatchewan	Every 3–6 mo for 3 yr Every 6–12 mo for 2 yr Annually thereafter	Every 3–6 mo for 3 yr Every 6–12 mo for 2 yr	Annually for 3 yr	At 1 yr post-op If no polyps, every 3–5 yr thereafter Flexible proctosigmoidoscopy ever 6 mo for 5 yr*
Manitoba	Every 3 mo for 3 yr Every 6 mo for 2 yr	Every 3 mo for 3 yr	Annually for 3 yr	At 1 & 3 yr post-op Every 5 yr thereafter Flexible sigmoidoscopy every 6 mo for 3 yr post-op*
Ontario	Every 6 mo for 5 yr	At each visit	Annually for 3 yr	At 1 yr post-op Every 5 yr thereafter Rectosigmoidoscopy every 6 mo for 2–5 yr post-op*
Quebec	Every 3–6 mo for 3 yr Annually thereafter	At each visit	Annually for 3 yr	At 1 yr post-op If no polyps, every 3–5 yr thereafter
Nova Scotia	Every 3 mo for 3 yr Every 6 mo for 2 yr	At each visit	Annually for 3 yr	At 1 yr post-op No specific surveillance recommendation thereafter Rigid or flexible sigmoidoscopy at 6, 18, 24 and 36 mo post-op

CEA = carcinoembryonic antigen; CT = computed tomography.
*If no pelvic radiation.

colonoscopy. The various recommendations by province are shown in Table 7. While we noted minor differences across most of these domains among the guidelines, the main variation existed in evaluation of the colon and rectum. Only 4 of the guidelines (Saskatchewan, Manitoba, Ontario, Nova Scotia) explicitly advised clinicians to perform proctosigmoidoscopy postoperatively, in addition to colonoscopies, to assess anastomoses. The duration of endoscopic surveillance postoperatively also differed among guidelines.

Discussion

The management of rectal cancer is a complex and evolving area that relies on accurate diagnosis, staging and multidisciplinary treatment for optimal patient outcomes. Clinical practice guidelines play an important role in synthesizing the latest literature and subsequently disseminating evidence-based recommendations to clinicians. We present the assessment and comparison of Canadian provincial CPGs for the management of rectal cancer. Of the 13 provinces and territories, we obtained and analyzed 7 guidelines (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia); guidelines from the remaining provinces/territories were not readily available. We noted that available CPGs were not all current and had been updated at variable intervals. Using the validated AGREE-II instrument for guideline evaluation, we noted varying quality, developmental methodology and presentation among the CPGs. In addition, there was notable interprovincial variation in clinical recommendations. These differences were within the areas of imaging for locoregional staging, assessment for pulmonary metastases, neoadjuvant therapy protocols (short-course v. long-course), recommendations for transanal excision, adjuvant therapy indications and protocols, and post-treatment surveillance algorithms.

While recent work has shown significant variation in recommendations between North American, European, and Japanese rectal cancer guidelines, it focused on describing the differences without an actual appraisal of each CPG.[39] To our knowledge, our study is the first such evaluation of rectal cancer CPGs in Canada, and we provide an objective comparison as well as an appraisal of the recommendations within these guidelines. While we endeavour to highlight the differences between these CPGs as well as the scientific standards surrounding their development, the evaluation of the actual clinical content within them is outside of the scope of this study. Nonetheless, the strengths of our study lie in its comprehensive examination of national CPGs, thereby providing useful feedback for stakeholders involved in guideline development to consider as they update, improve and disseminate their recommendations.

From a pragmatic standpoint, an important question is whether there are differences in the care received by patients with rectal cancer. Previous Canadian studies have highlighted self-reported differences in practice patterns among rectal cancer surgeons through the use

of national and provincial surveys, suggesting that this may be the case.[9,10,32] These differences are attributed to factors such as level of training (i.e., subspecialty v. nonfellowship), participation in continuing professional development, length of time in practice, location of practice, and access to clinical resources (e.g., MRI, ERUS). Whether or not these self-reported differences in practice patterns translate to variability in patient-level outcomes is unclear at this time. It is possible that differences in CPGs may contribute at least in part to variations in clinical practice, but there are likely multiple causative factors.

Unlike variation among surgeons and clinicians, it is harder to discern specific factors contributing to the variation among CPGs. Certainly, the resources available to each provincial/territorial cancer agency as well as the volume and size of institutions within each province dictate the amount of time and expertise that can be devoted toward the development of CPGs.[12,13] As a result, we assume recommendations are made taking each province's respective health care context (i.e., health care funding, clinical volume, technology, number of specialists) into account.

Another consideration relates to the body of evidence on which CPGs are based. In the context of rectal cancer, this is best illustrated by recommendations for neoadjuvant therapy. Owing to the amount of ongoing research comparing and evaluating neoadjuvant chemoradiotherapy protocols (e.g., short-course, delayed short-course, long course), recommendations continue to evolve, and certainly there remains equipoise in this area.[5,7,33–35] This is reflected in the guidelines we examined, which differed in their endorsement of specific neoadjuvant protocols, as there is no definitive evidence yet for clinical practice.

When trying to reconcile the observed variations across Canada in clinical practice guidelines and self-reported practice patterns for rectal cancer, what ultimately matters most is whether these translate into worse outcomes for patients. If yes, then philosophically this highlights the notion of acceptable and unacceptable variations in clinical practice. When there is uncertainty in the literature about a particular intervention, then variations in recommendations and practice are expected and may be acceptable as long as the care is competent.[36] Conversely, if there is no equipoise, or if there is a lack of consistency due to modifiable provider and system factors, then we may consider differences in clinical guidelines and practice patterns to be unacceptable. From our study, the majority of variability in CPGs reflected areas with either limited or evolving evidence. Explaining the relationship between CPG variability and outcomes in patients with rectal cancer is beyond the scope of our investigation, and is also a complex relationship to disentangle.

Limitations

Our study is not without limitations; some of these relate to our use of the AGREE-II instrument for guideline evaluation. Despite being a validated and frequently used tool for guideline appraisal, the instrument does not provide a context for interpreting the scaled domain scores of a guideline.[16,37,38] Therefore, once domain scores have been determined, the evaluator must interpret these scores on their own when considering whether or not to recommend a guideline for use. While it stands to reason that higher domain scores suggest higher-quality guidelines, this lack of context introduces an element of subjectivity into the entire appraisal process. For this reason, we felt compelled to present only the scaled domain scores for each guideline rather than subjectively assess whether or not we would recommend them for use.

Conclusion

We found that rectal cancer CPGs in Canada vary in their presentation style, content, quality and recency. We know from previous studies that self-reported practice patterns within this area already vary among Canadian surgeons, and given the rapidly evolving evidence surrounding rectal cancer management, CPGs can serve to provide vetted and clear recommendations for clinicians to follow. Thus, there may be a role for uniform CPGs in the management of rectal cancer, and further research is necessary to determine if and how this might affect patient outcomes.

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Contributors: Z. Mir and S. Patel designed the study. Z. Mir, D. Yu and S. Patel acquired the data, which all authors analyzed. Z. Mir, D. Yu and S. Patel wrote the article, which all authors reviewed and approved for publication.

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8.2 Appendix Chapter 4

8.2.1 Appendix Chapter 4 – 1: EMBASE and MEDLINE Search Terms

Table 8-1 MEDLINE and EMBASE Search Terms for the Systematic Review and Meta-analysis of Predictors of Guideline Adherent Care

	Medline Search Terms		**Embase Search Terms**
1)	rectal cancer.mp. or exp Rectal Neoplasms/	1)	rectal cancer.mp. or exp rectum cancer/
2)	compliance.mp.	2)	compliance.mp.
3)	adherence.mp.	3)	adherence.mp.
4)	uptake.mp.	4)	uptake.mp.
5)	exp Health Services Accessibility/ or exp Health Equity/	5)	exp health equity/
6)	exp "Delivery of Health Care"/	6)	exp health care access/
7)	exp Healthcare Disparities/ or exp Health Status Disparities/	7)	exp health disparity/
8)	exp Urban Population/ or exp Socioeconomic Factors/ or exp Rural Population/ or exp Rural Health/	8)	exp health care disparity/
9)	barriers.mp.	9)	*health care delivery/
10)	race.mp. or exp Continental Population Groups/	10)	((barrier? or challeng* or obstac* or difficult*) and (facilitator? or enab* or opportunit*)).ti.
11)	exp Religion/ or religion.mp.	11)	((barrier? or challeng* or obstac* or difficult* or facilitator? or enab* or opportunit*) adj5 (care or healthcare or service?)).ti,ab.
12)	exp Ethnic Groups/ or ethnicity.mp.	12)	(accessib* or equity or equitable or disparit*).ti.
13)	((barrier? or challeng* or obstac* or difficult*) and (facilitator? or enab* or opportunit*)).ti.	13)	((access* or equity or equitable or disparit*) adj5 (care or healthcare or service?)).ti,ab.
14)	((barrier? or challeng* or obstac* or difficult* or facilitator? or enab* or opportunit*) adj5 (care or healthcare or service?)).ti,ab.	14)	exp rural area/ or exp rural population/ or rurality.mp. or exp rural health care/
		15)	exp geography/ or geography.mp.
		16)	exp race difference/ or race.mp. or exp race/
		17)	exp ethnic group/ or exp ethnicity/ or ethinicity.mp.
		18)	religion.mp. or exp religion/
		19)	*health care delivery/
15)	2 or 3 or 4	20)	2 or 3 or 4
16)	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	21)	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
17)	1 and 15 and 16	22)	1 and 20 and 21
Staging Investigation Specific Search Terms			
18)	exp Diagnostic Tests, Routine/	23)	exp diagnostic test/
19)	exp COLONOSCOPY/	24)	exp nuclear magnetic resonance imaging/

20)	exp Tomography, X-Ray Computed/ or exp Magnetic Resonance Imaging/	25)	exp computer assisted tomography/
21)	Ultrasound.mp.	26)	exp colonoscopy/
22)	transrectal ultrasound.mp.	27)	exp transrectal ultrasonography/ or exp ultrasound/
23)	exp Ultrasonography/	28)	CEA.mp. or exp carcinoembryonic antigen/
24)	18 or 19 or 20 or 21 or 22 or 23	29)	23 or 24 or 25 or 26 or 27 or 28
25)	17 and 24	30)	22 and 29
Treatment Specific Search Terms			
18)	exp Colorectal Surgery/	23)	exp rectum surgery/
19)	exp Radiotherapy/	24)	exp radiotherapy/
20)	exp Drug Therapy/	25)	exp chemotherapy/
21)	exp Antineoplastic Combined Chemotherapy Protocols/	26)	neoadjuvant therapy/
22)	exp Fluorouracil/	27)	exp adjuvant chemoradiotherapy/ or exp cancer adjuvant therapy/ or exp adjuvant/ or exp adjuvant radiotherapy/ or exp adjuvant therapy/ or exp adjuvant chemotherapy/
23)	exp Neoadjuvant Therapy/		
24)	exp Laparoscopy/ or exp Anastomosis, Surgical/ or low anterior resection.mp.		
25)	abdominoperineal resection.mp.		
26)	adjuvant.mp. or exp CHEMOTHERAPY, ADJUVANT/ or exp CHEMORADIOTHERAPY, ADJUVANT/ or exp RADIOTHERAPY, ADJUVANT/		
27)	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	28)	23 or 24 or 25 or 26 or 27
28)	17 and 27	29)	22 and 28
Surveillance Specific Search Terms			
18)	follow up.mp.	23)	surveillance.mp.
19)	cancer surveillance.mp.	24)	exp follow up/
20)	disease surveillance.mp.	25)	disease surveillance.mp. or exp disease surveillance/
		26)	cancer surveillance.mp.
21)	18 or 19 or 20	27)	23 or 24 or 25 or 26
22)	17 and 21	28)	22 and 27

8.2.2 Appendix Chapter 4 – 2: Characteristics of Studies Included in the Systematic Review and Meta-analysis

Table 8-2 Characteristics of Studies assessing at least one staging investigation (part 1)

Author	Year	Number of Patients	Included Patients	Setting	Diagnosis or Treatment Years
Staging Investigation Review					
Bergin	2020	433	All Colorectal Cancer patients > 40 years old	Australia (a)	2012 - 2014
Bao	2016	405	Adult admitted to hospital with Rectal Cancer	China (b)	2012
Cavalli-Bjorkman	2011	3899	Stage I - IV, Age < 75	Sweeden (a)	1995 - 2006
Charlton	2016	2300	Stage II/III, Older than 65	United States (a)	2005 - 2009
Comber	2012	581	All Patients with Rectal Cancer	Ireland (a)	2007
Esteva	2014	777	All Colorectal Cancer Patients	Spain (a)	2006 - 2008
Garfunkle	2020	2217	Adults Undergoing Rectal Resection	North America (a)	2016 - 2017
Helewa	2013	2086	All Colorectal Cancer Patients	Canada (a)	2004 - 2006
Jestin	2004	1841	All Patients with Rectal Cancer	Sweeden (a)	1995 - 2000
Levine	2012	288	All rectal cancer patients referred to the Clinic	United States (b)	2008 - 2009
Ma	2015	277	All Colorectal Cancer Patients	United States (b)	2008 - 2013
McGrath	2005	1900	All Colorectal Cancer Patients	Australia (a)	2000
Phelip	2004	683	All Patients with Rectal Cancer	France (a)	1995
Richardson	2016	130	All Patients with Rectal Cancer	United States (b)	up to 2014
Van Der Geest	2012	539	Stage I - III who underwent surgery	Netherlands (a)	2006 - 2008

(a) Multicentred (b) Single Centre (c) Randomized Controlled Trial

Table 8-3 Characteristics of Studies assessing at least one staging investigation (part 2)

Author	Year	Risk Factors Assessed/Intervention	Investigation or Treatment Assessed	Clinical Practice Guideline
Staging Investigation Review				
Bergin	2020	Remoteness, Socioeconomic Status, Health Insurance	Metastatic, Colonoscopy, CEA	Australia National Guideline
Bao	2016	Presence/Absence of Clinical Pathway	Local-Regional, Metastatic, CEA	National Health and Family Planning Commission
Cavalli-Bjorkman	2011	Education Level	Local-Regional, Metastatic, Colonoscopy	Referenced Guideline not explicitly stated
Charlton	2016	Type of Treating Hospital	Local-Regional, Metastatic, CEA	Referenced Guideline not explicitly stated
Comber	2012	Surgeon/Hospital Volume	Local-Regional, Metastatic	ACPGBI
Esteva	2014	Age	Local-Regional, Metastatic, Colonoscopy, CEA	Referenced Guideline not explicitly stated
Garfinkle	2020	Age, Gender, Ethnicity	"Overall Compliance"	ASCRS
Helewa	2013	Geographic Location	Colonoscopy	Previously Published/Manitoba Specific
Jestin	2004	Hospital Type	Metastatic	Swedish National Guideline
Levine	2012	Presence/Absence of Multidisciplinary Clinic	Local-Regional, Metastatic, CEA	NCCN
Ma	2015	Age, Gender, Ethnicity, Physician Specialty, Hospital Type	Metastatic	NCCN
McGrath	2005	Surgeon Volume	Local-Regional, Metastatic, Colonoscopy	NHMRC
Phelip	2004	Geographic District	Local-Regional, Metastatic, Colonoscopy, CEA	French National Guideline
Richardson	2016	Pre/Post implementation of Multidisciplinary Tumur Conference	Local-Regional, Metastatic, Colonoscopy, CEA	NCCN
Van Der Geest	2012	Gender, Hospital Volume, Hospital Type	Local-Regional	Netherlands National Guidelines

ACPGBI Association of Coloproctology of Great Britain and Ireland; ASCRS American Society of Colon and Rectum Surgeons; NCCN National Comprehensive Cancer Network;

Table 8-4 Characteristics of Studies assessing at least one treatment outcome (part 1)

Author	Year	Number of Patients	Included Patients	Setting	Diagnosis or Treatment Years
Treatment Review Papers					
Abraham	2006	73	Rectal Cancer	United States (b)	1999 - 2003
Abrams	2016	6752	Rectal Cancer	United States (a)	2004-2011
Adelson	2018	792	Rectal Cancer	Australia (a)	2000 - 2010
Bao	2016	405	Rectal (also including colon)	China (b)	2012
Baxter	2005	45627	Rectal Cancer	United States (a)	1976 - 2000
Beckman	2014	900	Rectal Cancer	Australia (a)	2003 - 2008
Chapman	2018	161	Rectal Cancer	United States (b)	2013 - 2015
Charlton	2013	201	Rectal Cancer	United States (a)	2003 - 2005
Cheung	2009	6059	Rectal Cancer	United States (a)	1991 - 2002
Comber	2012	581	Rectal Cancer	Ireland (a)	2007
Cree	2009	524	Rectal	Canada (a)	2004
Del Vecchio	2019	2231	Rectal Cancer	United States (a)	2005 - 2015
Eldin	2012	910	Rectal	Canada (a)	2002 - 2005
Elliot	2014	2610	Rectal	Sweden (a)	2000 - 2010
Fitzgerald	2012	22136	Rectal Cancer	United States (a)	1998-2007
Fleming	2014	184	Rectal (also including colon)	United States (a)	2006 - 2008
Guillerme	2014	240	Rectal	France (b)	2000 - 2008
Haas	2011	6083	Rectal	United States (a)	1992 - 2005
Hegi-Johnson	2007	542	Rectal Cancer	Australia (a)	1994-2001
Jorgenson	2014	498	Rectal	Australia (a)	2007 - 2008
Lee	2012	4961	Rectal Cancer	United States (a)	1988-2006
Lefresne	2017	1964	Rectal Cancer	Canada (a)	2004-2009
Levine	2012	288	Rectal	United States (b)	2008 - 2009

Lau	2021	17954	Rectal Cancer	United States (a)	2010 - 2015
Manchon-Walsh	2011	1831	Rectal Cancer	Spain (a)	2005-2007
McGory	2006	5388	Rectal Cancer	United States (a)	1994-2001
Midura	2017	23488	Rectal Cancer	United States (a)	2005-2010
Monson	2014	30994	Rectal Cancer	United States (a)	2006-2011
Morris	2004	52864	Rectal Cancer	United States (a)	1988-1999
Morris	2008	2716	Rectal Cancer (elderly)	United States (a)	1992-1999
Mou	2013	776	Rectal Cancer	Canada (a)	2004-2009
Murphy	2015	3016	Colorectal Cancer	United States (a)	1990-2005
Neugut	2002	1807	Rectal Cancer	United States (a)	1992-1996
Nielsen	2010	161	Colorectal Cancer (And others)	United States (a)	2003-2005
Olsson	2011	16713	Rectal Cancer	Sweden (a)	1995-2005
Quipourt	2011	2990	Colorectal Cancer	France (a)	2004-2007
Rayson	2012	494	Colorectal Cancer	Canada (a)	2001-2005
Richardson	2016	130	Rectal Cancer	United States (b)	2013-2014
Sarasqueta	2019	503	Rectal Cancer	Spain (a)	2010 - 2012
Schrag	2001	1411	Rectal Cancer	United States (a)	1992-1996
Schroen	2001	637	Rectal Cancer	United States (a)	1994-1996
Sinclair	2012	1263	Colorectal Cancer	United States (a)	2004-2006
Sineshaw	2016	68182	Rectal Cancer	United States (a)	2004-2012
Van Der Geest	2012	539	Rectal * (Also Included Colon separately)	Netherlands (a)	2006 - 2008
VanEenwyk	2002	388	Colorectal Cancer	United States (a)	1996-1997

Vernet	2018	3770	Rectal Cancer	Spain (a)	2005 - 2007 & 2010 - 2011
Wong	2021	436	Rectal Cancer	United States (a)	2005 - 2014
Xu	2017	14742	Rectal Cancer	United States (a)	2006-2011

(a) Multicentred (b) Single Centre

Table 8-5 Characteristics of Studies assessing at least one Treatment Outcome (part 2)

Author	Year	Risk Factors Assessed/Intervention	Investigation or Treatment Assessed	Clinical Practice Guideline
Treatment Review Papers				
Abraham	2006	Age, Race, Marital Status, Insurance, MDT	Composite (Chemo, Radiation)	NCI PDQ
Abrams	2016	Age, Sex, Race, Stage, Year Diagnosed	Surgery vs. Not	NCCN
Adelson	2018	Age, Sex, Remoteness, Rurality,	Systemic Chemotherapy	Australian National Guidelines
Bao	2016	Clinical Pathway	TME Surgery	Local
Baxter	2005	Age, Gender, Race	Radiation Therapy	NIH
Beckman	2014	Age, Sex, Rurality, SES, Co-morbidities	Radiation Therapy (Chemo assessed with CRC)	Australian National Guidelines
Chapman	2018	Age, Distance from Hospital, Insurance, Surgeon Experience	Composite	ASCRS
Charlton	2013	Age, Sex, Ethnicity, Comorbidities,	Preop (vs. postop) CRT	NCCN
Cheung	2009	Age, Sex, Ethnicity, Marital Status, Rurality, Comorbidity, SES	Systemic Chemotherapy Delays	NIH
Comber	2012	Surgeon, Hospital Volume	Radiation, Surgery, Systemic Chemotherapy	ACPGBI
Cree	2009	Sex, Age, Rurality (Stage)	Composite	NIH
Del Vecchio	2019	Age, Sex, Race, Comorbidity, Marital Status, Hospital Size	Neoadjuvant Chemoradiation, Systemic Chemotherapy	NCCN
Eldin	2012	Age, Sex, Geography, Co-Morbidity, Education, SES	Composite	NIH, Ontario
Elliot	2014	Age, Sex, Comorbidity, Hospital Volume	Radiation	ESMO, NCCN, EURECA
Fitzgerald	2012	Age, Sex, Race, Stage, Year Diagnosed	Radiation	NIH, European Consensus
Fleming	2014	Age	Radiation	ACS
Guillerme	2014	Age (< 75 vs. 75+), Comorbidity	Composite	Unclear
Haas	2011	Race, Insurance, SES	Radiation	NIH
Hegi-Johnson	2007	Age, Sex, SES, Surgeon Volume, Hospital Volume,	Radiation	Australian National Guidelines
Jorgenson	2014	Age, Sex, Comorbidity, Discussed at MDT,		
Lee	2012	Age, Sex, Race, SES, Stage	Radiation	NIH
Lefresne	2017	Rurality	Radiation	Unclear
Levine	2012	Multidisciplinary Clinic	Radiation	NCCN

Lau	2021	Age, Sex, Race, Insurance, Rurality, Education, SES, Hospital Type, Comorbidity	Chemoradiation/Radiation	NCCN
Manchon-Walsh	2011	Hospital Volume	Radiation, Surgery, Systemic Chemotherapy	Spanish Guidelines
McGory	2006	Age, Sex, Race, Comorbidity, Insurance, SES	Systemic Chemotherapy	NIH
Midura	2017	Age, Sex, Race, Insurance, SES, Education, Rurality, Comorbidity,	Radiation	NCCN, ASCRS
Monson	2014	Age, Sex, Rurality, Comorbidity, Hospital Type, Hospital Volume,	Radiation, Systemic Chemotherapy	NCCN
Morris	2004	Race (black vs. white)	Neoadjuvant, Surgery	NIH
Morris	2008	Race (black vs. white)	Radiation, Systemic Chemotherapy	Unclear
Mou	2013	Age, Sex, Remoteness	Radiation	Manitoba
Murphy	2015	Age, Race, Comorbidity, Insurance	Radiation	NIH
Neugut	2002	Age, Sex, Race, Comorbidity	Radiation	NCCN
Nielsen	2010	Race, Immigration Status	Radiation	NCCN
Olsson	2011	Age, Sex, Hospital Type, Region, Marital Status, Education, SES	Radiation	Sweden/Unclear
Quipourt	2011	Age, Comorbidity	Radiation	French
Rayson	2012	Age, Sex, SES, Rurality	Systemic Chemotherapy	NIH
Richardson	2016	Multidisciplinary Team	Radiation, Surgery, Systemic Chemotherapy	Multiple
Sarasqueta	2019	Age, Sex, SES, Education, Comorbidities,	Radiation	Unclear
Schrag	2001	Age, Sex, Comorbidity, Race, SES, Comorbidity	Radiation (alone and combined)	NIH
Schroen	2001	Age, Sex, Hospital Type, Hospital Size	Combined (Radiation, Surgery, Systemic Chemotherapy)	NIH
Sinclair	2012	Age, Sex, Race, SES, Marital Status, Co-morbidity, Hospital Size	Radiation, Systemic Chemotherapy	NCCN
Sineshaw	2016	Age, Race, Comorbidity, SES, Hospital Type, Hospital Volume, Insurance, Education	Chemoradiation	NCI Consensus Statement
Van Der Geest	2012	Age, Comorbidity, Hospital Volume	Radiation	Dutch Guidelines
VanEenwyk	2002	Age, Sex, Race, Rurality, SES, Insurance, Comorbidities, Hospital Type	Adjuvant Radiation and/or Chemotherapy (Composite)	NIH, NCI

Vernet	2018	Age, Sex	Radiation	NCCN
Wong	2021	Age, Sex, Race, SES, Insurance,	Chemoradiation	ACS coc
Xu	2017	Age, Sex, Race, Insurance, Comorbidity, Hospital type	Systemic Chemotherapy	NCCN

NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; NIH National Institute of Health; ACPGBI Association of Coloproctology of Great Britain and Ireland; ESMO European Society of Medical Oncology; EURECCA European Registration of Cancer Care; ACS coc American Cancer Society commission on cancer; ASCRS American Society of Colon and Rectum Surgeons; NCI National Cancer Institute;

Table 8-6 Study characteristics of studies assessing at least one surveillance adherence outcome (part 1)

Author	Year	Number of Patients	Included Patients	Setting	Diagnosis or Treatment Years
Surveillance Review Papers					
Brawarsky	2013	38000	Colorectal Cancer Patients ages 66 - 85 who underwent surgery	United States (a)	1993 - 2005
Carey	2017	604	Colorectal Cancer Patients < 12 months after surgery	Australia (a)	2010-2012
Cooper	2008	9426	Colorectal Cancer Patients age > 65	United States (a)	2000 - 2001
Le/Pisu	2014	60	Colorectal Cancer Patients, African American	United States (b)	2003 - 2007
Kosmider	2010	619	Colorectal Cancer Patients	Australia (a)	1988 - 2008
Kupfer	2018	241	Colorectal Cancer Patients	United States (a)	2010 - 2017
Rulyak	2004	1002	Colorectal Cancer Patients	United States (a)	1993 - 1999
Salloum	2012	2297	Colorectal Cancer Patients	United States (a)	2000 - 2008
Salz	2010	1423	Colorectal Cancer Patients	United States (a)	2003 - 2005
Sehdev	2017	2263	Colorectal Cancer Patients at the Veteran Affairs Hospital	United States (a)	2001 - 2009
Sisler	2012	250	Colorectal Cancer Stage II or III	Canada (a)	2004
Tan	2014	4960	Colorectal Cancer	Canada (a)	2003 - 2007
Urquhart	2012	731	Colorectal Cancer Stage II or III	Canada (a)	2001 - 2005
Vargas	2013	12381	Colorectal Cancer, > 65 years	United States (a)	2000 - 2009

Table 8-7 Study characteristics of studies assessing at least 1 surveillance outcome (part 2)

Author	Year	Risk Factors Assessed/Intervention	Investigation or Treatment Assessed	Clinical Practice Guideline
Surveillance Review Papers				
Brawarsky	2013	Ethnicity, Age, Sex, Stage, Cancer Type, Insurance, Setting Resources,	Colonoscopy, CEA, Clinic Visit, Composite Outcome	NCCN
Carey	2017	Additional Patient Education (intervention) vs. Standard Education (Control) (c)	Colonoscopy	Australia Colonoscopy Surveillance 2017
Cooper	2008	Age, Sex, Race, Cancer Type, Stage, Co-morbidity, State of Residence	Colonoscopy, CEA, Clinic Visit, Composite Outcome	ASCO, NCCN
Le/Pisu	2014	Sex, Age, Stage, Rurality	Composite Outcome	ASGE, ACS
Kosmider	2010	Age, Sex, Co-morbidities, Cancer Site, Cancer Stage	Clinic Visit	"Australian Guidelines"
Kupfer	2018	Age, Gender, Race, Stage	CEA, Colonoscopy, Metastatic Assessment, Composite	ASCRS, ASCO, NCCN
Rulyak	2004	Gender, Age, Race, Marital Status, SES, Cancer Location, Cancer Stage, Year of Diagnosis	Colonoscopy	NCCN
Salloum	2012	Age, Gender, Ethnicity, Cancer Stage, Geographic Location	Colonoscopy, Metastatic Assessment	NCCN, ASCO
Salz	2010	Age, Sex, Cancer Location, Cancer Stage, Co-morbidities, Race, Education, SES, Marital Status, Geographic Location,	Colonoscopy	ACS, US Multi-Society Task Force on Colorectal Cancer
Sehdev	2017	Age, Marital Status, Insurance, SES, Race, Stage of Disease, Year of Diagnosis, Co-morbidities, Geographic Region	Metastatic Assessment	ASCO, NCCN
Sisler	2012	Age, Sex, Geographic Region, SES, Cancer Location, Cancer Stage, Co-morbidities,	Colonoscopy, CEA, Metastatic Assessment	ASCO
Tan	2014	Age, Sex, Risk Category, Rurality, SES, Region	Colonoscopy, Metastatic Assessment	CCO, NCCN, ASCO
Urquhart	2012	Age, Sex, Co-morbidities, Cancer Site, Cancer Stage, SES,	Colonoscopy, Clinic Visits	ASCO
Vargas	2013	Age, Sex, Race, Cancer Type, Stage, Co-morbidity, Year of Diagnosis, Education, Income	Colonoscopy, CEA, Composite Outcome	ASCO, AGA, ASCRS, NCCN, ACS, ASGE

CEA Carcinoembryonic Antigen; SES Socioeconomic Status; NCCN National Comprehensive Cancer Network; ASCO American Society of Clinical Oncology; ASGE American Society of

Gastroenterology; ACS American Cancer Society; ASCRS American Society of Colon and Rectal Surgeons; AGA American Gastroenterologic Association

8.2.3 Appendix Chapter 4 – 3: Detailed Study Results for the Systematic Review and Meta-analysis of Predictors of Guideline Adherent Care

Table 8-8 Associations between age and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Age Group	Direction of Association, notes
	Local Regional Staging		
Esteva 2014	42% (< 65 yrs); 35.5% (65 - 80 yrs); 36% (> 80 yrs) P=0.55 *		No Association, Univariable Analysis
	Metastatic Disease Assessment		
Esteva 2014	83% (< 65) vs. 74% (65 - 80) vs. 62% (>80) (P = 0.02)*		Older less likely, Univariable Analysis
Ma 2015	61.9%(< 50) vs. 38.3% (>= 50) (P = 0.004)*		Older less likely, Univariable Analysis
	Colonoscopy		
Esteva 2014	86.7% (< 65) vs. 85.6% (65 - 80) vs. 87% (>80) (P = 0.98)*		No Association, Univariable Analysis
	CEA Testing		
Esteva 2014	88.4% (<65) vs. 88.7% (65 - 80) vs. 84.4% (> 80) (P = 0.36)*		No Association, Univariable Analysis
	Combined (Colonoscopy, Local Regional Staging, Metastatic Assessment)		
Garfunkle 2020	Median Age: Compliant 60 (IQR 51 - 69) vs. Non Compliant 63 (54 - 72)*		Compliant were younger, Univariable Analysis only

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-9 Association between age and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Age Group	Direction of Association, Notes
	Combined Multimodal Treatment (Radiation, Chemotherapy)		
Abraham 2006	Age 65+ OR 0.19 (95%CI 0.06 - 0.62)	Age < 65	Older less likely to receive
Cree 2009	Age < 65 OR 2.35 (95%CI 1.79 - 3.09); Age 65 - 74 OR 1.83 (95%CI 1.36 - 1.47)	Age 75+	Older less likely to receive
Eldin 2009	Age 70 - 74 OR 1.97 (95%CI 1.50 - 2.55); Age 75+ OR 2.23 (95%CI 1.89 - 2.64)	Age < 70	Older more likely to not receive guideline treatment
Guillerme 2014	Age 75+ OR 0.42 (95%CI 0.23 - 0.77)	Age < 75	Older less likely to receive
Schroen 2001	Age < 60 OR 9.52 (95%CI 4.26 - 21.29); Age 60 - 69 OR 4.02 (95%CI 1.90 - 8.50); Age 70 - 75 OR 4.23 (95%CI 1.87 - 9.56)	Age 76+	Older less likely to receive
VanEenwyk 2002	Age 65 - 74 OR 3.2 (95%CI 1.6 - 6.4); Age 75 - 84 OR 6.4 (95%CI 3.3 - 12.6); Age 85+ OR 59.8 (95%CI 15.3 - 234.2)	Age < 65	Older more likely to not receive adjuvant treatments
	Radiation		
Baxter 2005	Age 61 - 70 OR 3.03 (95%CI 2.76 - 3.33); Age <= 60 OR 4.95 (95%CI 4.48 - 5.46)	Age > 70	Older less likely to receive
Beckman 2014	Age 60 - 69 OR 0.93 (95%CI 0.78 - 1.12); Age 70 - 79 (95%CI 0.53 - 0.80)	Age 50 - 59	Older less likely to receive
Del Vecchio 2019	Age 18 - 54 OR 3.62 (95%CI 2.29 - 5.71); Age 55 - 64 OR 2.90 (95%CI 1.70 - 4.96); Age 65 - 74 OR 1.74 (95%CI 1.08 - 2.82)	Age 75+	Older less likely to receive
Elliot 2014	Age 65 - 79 OR 0.56 (95%CI 0.45 - 0.70); Age 80+ OR 0.05 (95%CI 0.04 - 0.07)	Age < 65	Older less likely to receive
Fitzgerald 2013	Age < 50 OR 1.68; Age 50 - 59 OR 1.47; Age 60 - 69 OR 1.20; Age 70 - 79 OR 1.10	Age > 80	Older less likely to receive
Fleming 2014	Per 5 year increase OR 0.90 (95%CI 0.841 - 0.974)		Older less likely to receive
Hegi-Johnson 2007	Age < 70 OR 2.96 (95%CI 1.75 - 5.03)	Age 70+	Older less likely to receive
Jorgensen 2014	Age 65 - 69 OR 0.59 (95%CI 0.30 - 1.18); Age 70 - 74 OR 0.55 (95%CI 0.27 - 1.12); Age 75 - 79 OR 0.44 (95%CI 0.21 - 0.93); Age 80 - 84 OR 0.19 (95%CI 0.07 - 0.47); Age 85+ OR 0.24 (95%CI 0.08 - 0.76)	Age < 65	Older less likely to receive
Lee 2012	Per 1 year increase OR 1.03 (95%CI 1.02 - 1.04)		Yes, younger LESS likely
Lau 2021	Age 50 - 65 OR 1 (95%CI 0.9 - 1.1); Age > 65 OR 1.5 (95%CI 1.3 - 1.7)	Age < 50	Older received more "non guideline" based care
Midura 2017	Per 1 year increase OR 0.97 (95%CI 0.96 - 097)		Older less likely to receive
Monson 2014	Per 10 year increase OR 0.73 (95%CI 0.70 - 0.75)		Older less likely to receive
Mou 2013	Age 60 - 69 OR 0.86 (95%CI 0.55 - 1.35); Age 70 - 79 OR 0.46 (95%CI 0.30 - 0.71); Age 80+ OR 0.11 (95%CI 0.07 - 0.19)	Age < 60	Older less likely to receive
Murphy 2015	Age 55 - 64 OR 0.93 (95%CI 0.84 - 1.04) Age 65 - 74 OR 0.87 (95%CI 0.78 - 0.98); Age 75 - 80 OR 0.59 (95%CI 0.47 - 0.74); Age 80+ OR 0.33 (95%CI 0.25 - 0.45)	Age < 55	Older less likely to receive
Neugot 2002	Age 70 - 74 OR 0.75 (95%CI 0.51 - 1.09); Age 75 - 79 OR 0.43 (95%CI 0.29 - 0.65); Age 80 - 84 OR	Age 65 - 69	Older less likely to receive

	0.29 (95%CI 0.18 - 0.47); Age 85+ OR 0.07 (95%CI 0.03 - 0.16)		
Neugot 2002	Age 70 - 74 OR 0.38 (95%CI 0.36 - 0.58); Age 75 - 79 OR 0.25 (95%CI 0.16 - 0.40); Age 80 - 84 OR 0.14 (95%CI 0.08 - 0.23); Age 85+ OR 0.04 (95%CI 0.02 - 0.11)	Age 65 - 69	Older less likely to receive
Olsson 2010	Per 1 year increase OR 0.96 (95%CI 0.95 - 0.96)		Older less likely to receive
Quipourt 2011	Age < 75 85.0%; Age 75 - 84 65.2%; Age 85+ 33.5% *		Older less likely to receive
Sarasqueta 2019	Age 65 - 80 OR 0.9 (95%CI 0.6 - 1.4); Age > 80 OR 0.5 (95%CI 0.3 - 0.8)	Age < 65	Older less likely to receive
Schrag 2001	Age 70 - 74 OR 0.70 (95%CI 0.51 - 0.96); Age 75 - 79 OR 0.40 (95%CI 0.29 - 0.57); Age 80 - 84 OR 0.22 (95%CI 0.15 - 0.31); Age 85+ OR 0.10 (0.06 - 0.16)	Age 65 - 69	Older less likely to receive
Sinclair 2012	Age < 45 OR 0.90 (95%CI 0.34 - 2.37); Age 45 - 54 OR 1.79 (95%CI 0.72 - 4.46)	Age 55 - 64	No Association
Sinclair 2012	Age 65 - 69 OR 2.20 (95%CI 1.13 - 4.28); Age 70 - 74 OR 1.55 (95%CI 0.80 - 2.99)	Age 75+	Older less likely to receive
Sineshaw 2016	Age 50 - 64 OR 0.86 (95%CI 0.82 - 0.91); Age 65 - 79 OR 0.69 (95%CI 0.65 - 0.74); Age 80+ OR 0.26 (95%CI 0.24 - 0.28)	Age 18 - 49	Older less likely to receive
Van Der Geest 2012	Age 60 - 74 OR 1.22 (95%CI 0.58 - 2.59); Age 75+ OR 0.52 (95%CI 0.25 - 1.10)	Age < 60	No Association
Vernet 2018	Age < 70 OR 4.45 (95%CI 3.43 - 5.76); Age 70 - 80 OR 3.13 (95%CI 2.38 - 4.11)	Age > 80	Older less likely to receive
Wong 2021	Per 10 year increase OR 0.72 (95%CI 0.52 - 1.00)		Older less likely to receive
	Surgery		
Abrams 2016	Age 50 - 65 OR 1.20 (95%CI 0.96 - 1.50)	< 50	No association
	Chemotherapy		
Adelson 2018	Age 60 - 69 OR 0.76 (95%CI 0.51 - 1.36); Age 70 - 79 OR 0.50 (95%CI 0.34 - 0.75); Age 80+ OR 0.19 (95%CI 0.12 - 0.32)	Age < 60	Older less likely to receive
Cheung 2009	Age 65 - 69 30%; Age 70 -74 34%; Age 75 - 79 24%; Age 80+ 12% *		Older less likely to receive
McGory 2016	Per 1 year increase OR 0.939 (95%CI 0.93 - 0.948) (Stage II)		Older less likely to receive
McGory 2016	Per 1 year increase OR 0.925 (95%CI 0.913 - 0.937) (Stage III)		Older less likely to receive
Monson 2014	Per 10 year increase OR 0.79 (95%CI 0.76 - 0.83)		Older less likely to receive
Rayson 2012	Per 1 year increase OR 0.9 (95%CI 0.9 - 0.9)		Older less likely to receive
Sinclair 2012	Age < 45 OR 1.90 (95%CI 0.49 - 7.46); Age 45 - 54 OR 0.96 (95%CI 0.36 - 2.59)	Age 55 - 64	No Association
Sinclair 2012	Age 65 - 69 OR 2.62 (95%CI 1.46 - 4.71); Age 70 - 74 OR 1.84 (95%CI 1.05 - 3.23)	Age 75+	Older less likely to receive
Xu 2017 Cancer	Age 51 - 60 OR 0.79 (95%CI 0.71 - 0.89); Age 61 - 70 OR 0.61 (95%CI 0.52 - 0.70); Age > 70 OR 0.33 (95%CI 0.28 - 0.41)	Age <= 50	Older less likely to receive
Del Vecchio 2019	Age 18 - 54 OR 1.38 (95%CI 0.90 - 2.12); Age 55 - 64 OR 2.87 (95%CI 1.80 - 4.57); Age 65 - 74 OR 1.10 (95%CI 0.70 - 1.73)	Age 75+	Older less likely to receive

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-10 Association between age and surveillance adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Age Group	Direction of Association, Notes
	Combined Surveillance		
Brawarsky 2013	Age 71 - 75 OR 0.9 (95%CI 0.8 - 0.95); Age 76 - 80 OR 0.65 (95%CI 0.6 - 0.7); Age 80 - 85 OR 0.5 (95%CI 0.45 - 0.7)	Age 66 to 70	Decreased adherence with increased age
Cooper 2008	Age 70 - 74 OR 0.77 (95%CI 0.67 - 0.88); Age 75 - 80 OR 0.71 (95%CI 0.62 - 08.1); Age 80 - 84 OR 0.39 (95%CI 0.33 - 0.45); Age 85+ OR 0.16 (95%CI 0.13 - 0.20)	Age 66-69	Decreased adherence with increased age
Kupfer 2018	Age > 65 OR 1.03 (95%CI 0.51 - 2.06)	Age 65 +	No Association with age
Le 2014	Age 40 - 64 63%; Age 65 - 74 29%; Age 75+ 58% *		No association with age
Vargus 2013	Age 66 - 69 OR 2.80 (95%CI 2.09 - 3.74); Age 70 - 74 OR 2.55 (95%CI 1.92 - 3.39); Age 75 - 79 OR 2.47 (95%CI 1.85 - 3.28); Age 80 - 84 OR 1.84 (95%CI 1.36 - 2.50)	Age 85+	Decreased adherence with increased age
Pisu 2014	Age 40 - 64 62.5%; Age 65 - 74 29%; Age 75+ 58% *		No Association with age
	Surveillance Colonoscopy		
Brawarsky 2013	Age 70 - 74 OR 0.84 (95%CI 0.79 - 0.90); Age 75 - 79 OR 0.61 (95%CI 0.57-0.65); Age 80+ OR 0.41 (95%CI 0.38-0.44)	Age 66 - 70	Decreased adherence with increased age
Carey 2017	Age < 50 OR 0.44 (95% CI 0.11-1.83); Age 50 - 59 OR 0.56 (95%CI 0.24-1.34); Age 60 - 69 OR 0.77 (95%CI 0.42-1.4); Age 80+ OR 2.0 (95% CI 1.05-3.98)	Age 70 - 79	**Increased adherence with increased age**
Cooper 2008	Age 66 - 70 82.7%; Age 71 - 75 81.3% vs. Age 76-80 76.4% vs. Age 81 - 85 68.9% vs Age 85+ 47.3%*		Decreased adherence with increased age
Kupfer	Age 65+ OR 0.84 (95%CI 0.46 - 1.52)	Age < 65	Decreased adherence with increased age
Le 2014	Age 40 - 64 62.5%; Age 65 - 75 29.4%; Age 75+ 57.9% *		No Association
Rulyak 2004	Age 50 - 59 OR 0.67 (95%CI 0.48-0.93); Age 60 - 69 OR 0.78 (95% CI 0.54-0.98); Age 70 - 79 OR 0.65 (95%CI 0.49-0.86) ; Age 80+ OR 0.32 (95% CI 0.22-0.45)	Age < 50	Decreased adherence with increased age
Salloum 2012	Age < 50 63%; Age 50 - 64 64.1%; Age 65 - 74 62.1%; Age 75+ 41.0% *		Decreased adherence with increased age
Salz 2010	Age < 65 OR 1.05 (95%CI Not Reported)	Age > 65	No Association
Sisler 2012	Age 70+ OR 0.37 (95%CI 0.18 - 0.79)	Age < 70	Decreased adherence with increased age
Urquhart 2012	OR 9.0 95% CI 2.7 - 29.9 (Age < 50); OR 5.6 95%CI 3.30 - 9.50 (Age 50 - 64); OR 2.7 95%CI 1.80 - 4.20 (Age 65 - 74)	Age > 75	Decreased adherence with increased age
Vargus 2013	84.9% (Age 66 - 69); 81.7% (Age 70 - 74);77.6% (Age 75 - 79); 68.0% (Age 80 - 84); 46.8% (Age 85+) *		Decreased adherence with increased age
	Surveillance CEA		

Brawarsky 2013	Age 71-75 OR 0.82 (95% CI 0.75-0.89), Age 76-80 OR 0.57 (95% CI 0.52-0.62), Age 81-85 OR 0.38 (95% CI 0.34-0.41)	Age 66-70	Decreased adherence with increased age
Cooper 2008	Age 66-69 56.3%, Age 70-74 51.9%, Age 75-79 50.8%, Age 80-84 38.9%, Age 85+ 26.5% *		Decreased adherence with increased age
Kupfer 2018	Age > 65 OR 0.73 (95%CI 0.43 - 1.22)	Age < 65	No association with age
Sisler 2012	Over 70 OR 0.37 (95% CI 0.18-0.78)	Age < 70	Decreased adherence with increased age
Vargas 2013	Age 66-69 36.6%, Age 70-74 34%, Age 75-79 30.2%, Age 80-84 22.1%, Over 85 14.4% *		Decreased adherence with increased age
	Surveillance Clinic		
Brawarsky 2013	Age 71-75 OR 1.13 (95% CI 1.05-1.21), Age 76-80 OR 1.09 (95% CI 1.02-1.18), Age 81-85 OR 1.09 (95% CI 1.00-1.18)	Age 66-70	**Increased adherence with increased age**
Cooper 2008	Age 66-69 92.4%, Age 70-74 93.3%, Age 75-79 93.7%, Age 80-84 82.2%, Age Over 85 87.6% *		**Increased adherence with increased age**
Urquhart 2012	Age Under 50 OR 2.20 (95% CI 1.00-4.70); Age 50-64 OR 2.30 (95% CI 1.40-3.70); Age 65-74 OR 1.70 (95% CI 1.10-2.80)	Age 75+	Decreased adherence with increased age
	Surveillance Metastatic Disease		
Kupfer 2018	Age > 65 OR 0.91 (95%CI 0.51 - 1.62)	Age < 65	No association with age on Multivariable analysis
Salloum 2012	Age <50 OR 1.31 (1.06-1.63) ,p<.01, Age 50-64 OR 1.25 (1.10 - 1.42), p<.01, Age 65-74 OR 1.11 (0.98-1.26)	Age 75+	Decreased adherence with increased age
Sehdev 2017	Age 40-64 OR 2.19 (95% CI 1.65-3.10), p<.01, Age 65-79 OR 1.89 (95% CI 1.36-2.61)	Age 80+	Decreased adherence with increased age
Sisler 2012	Age Over 70 OR 0.81 (95% CI 0.38-1.73), p<.05	Age 70+	Decreased adherence with increased age
Tan 2014	Age 50-64 OR 0.97 (95% CI 0.68-1.39), Age 65-74 OR 1.07 (95% CI 0.75-1.52), Over 75 OR 1.21 (95% CI 0.83-1.74)	Age < 50	No Association with Age
Vargus 2013	Age 66 - 69 OR 1.85 (95%CI 1.54 - 2.21); Age 70 - 74 OR 1.71 (95%CI 1.44 - 2.03); Age 75 - 79 OR 1.59 (95%CI 1.34 - 1.88); Age 80 - 84 OR 1.28 (95%CI 1.07 - 1.53)	Age 85+	Decreased adherence with increased age

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-11 Association between sex/gender and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Staging		
Garfunkle 2020	Males 36.8%; Females 39.1% (P = 0.27) *		No Association, Univariable
	Local Regional Staging		
Van der Geest 2012	Males OR 1.64 95%CI 1.05 - 2.55	Female	Males More Likely
	Metastatic Assessment		
Ma 2015	41.4% (Male) vs. 42.4% (Female) (P = 0.99)*		No Association, Univariable

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-12 Association between sex/gender and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
Combined Multimodality Treatment (Surgery, Chemotherapy and/or Radiation) (Unless otherwise specified)			
Cree 2009	Female OR 1.05 (95%CI 0.90 - 1.22)	Male	No Association
Del Vecchio 2019	Female OR 0.71 (95%CI 0.51 - 0.97)	Male	Females less likely to be adherent
Eldin 2009	Male 43.3%; Female 47.1%, P = 0.31 *		No Association, Univariable Analysis
Schroen 2001	Female OR 0.89 (95%CI 0.51 - 1.52)	Male	No Association
VanEenwyk	Female OR 1.6 (95%CI 1.0 - 2.5)* ^	Male	Females more likely to not have recommended treatment, Univariable analysis
Radiation			
Baxter	Female OR 0.81 (95%CI 0.75 - 0.88)	Male	Females less likely to be adherent
Beckman 2014	Male OR 0.95 (95%CI 0.81 - 1.11)	Female	No Association
Elliot 2014	Female OR 0.90 (95%CI 0.74 - 1.09)	Male	No Association
Fitzgerald 2013	Males OR 1.16, P < 0.0001 (CI not provided)	Female	Females less likely to be adherent
Hegi Johnson 2007	Male 38%; Female 30%, P = 0.07*		No Association
Jorgensen	Female OR 0.42 (95%CI 0.25 - 0.69)	Male	Females less likely to be adherent
Lee 2012	Female OR 0.86 (95%CI 0.69 - 1.07)	Male	No Association
Lau 2021	Male OR 0.99 (95%CI 0.96 - 1.03)	Female	No Association (*Note outcome was "non guideline" treatment)
Midura 2017	Male 69.4%; Female 64.6%, P < 0.001*		Females less likely to be adherent
Monson 2014	Female OR 0.90 (95%CI 0.85- 0.95)	Male	Females less likely to be adherent
Mou 2013	Female OR 0.89 (95%CI 0.63 - 1.25)	Male	No Association
Neugot 2002	Male OR 1.14 (95%CI 0.85 - 1.52) (STAGE II)	Female	No Association
Neugot 2002	Male OR 0.83 (95%CI 0.61 - 1.12) (STAGE III)	Female	No Association
Olsson 2011	Female OR 0.89 (95%CI 0.82 - 0.97)	Male	Females less likely to be adherent
Sarasqueta 2019	Male 60.7%; Female 61.8%, P = 0.85*		No Association, Univariable Analysis
Schrag 2001	Female OR 0.93 (95%CI 0.73 - 1.18)	Male	No Association
Sinclair 2012	Male OR 1.05 (95%CI 0.47 - 2.34) (Age < 65)	Female	No Association
Sinclair 2012	Male OR 0.95 (95%CI 0.53 - 1.72) (Age 65+)	Female	No Association
Vernet 2018	Male OR 1.28 (95%CI 1.07 - 1.52)	Female	Females less likely to be adherent
Wong 2021	Female OR 0.69 (95%CI 0.35 - 1.34)*	Male	No Association, Univariable Analysis
Surgery			

Abrams 2016	Male OR 1.20 (95%CI 0.96 - 1.50)	Female	No Association (*Note outcome was use of non-operative management)
	Chemotherapy		
Adelson 2018	Female OR 0.98 (95%CI 0.72 - 1.32)*	Male	No Association, Univariable Analysis
Beckman 2014	Male OR 1.09 (95%CI 1.01 - 1.18)	Female	Males more likely (combined with colon cancer)
Del Vecchio 2019	Female OR 1.50 (95%CI 1.12 - 2.02)	Male	**Females more likely to be adherent**
McGory 2016	Male OR 1.37 (95%CI 1.166 - 1.61) (Stage II only)	Female	Females less likely to be adherent
McGory 2016	Male OR 0.99 (95%CI 0.825 - 1.192)	Female	No association
Rayson 2012	Female OR 0.6 (95%CI 0.4 - 1.0)	Male	Females less likely to be adherent
Sinclair 2012	Male OR 0.94 (95%CI 0.75 - 1.67) (Age < 65)	Female	No Association
Sinclair 2012	Male OR 1.25 (95%CI 0.76 - 2.05) (Age 65+)	Female	No Association
Xu 2017	Female OR 1.11 (95%CI 1.01 - 1.22)	Male	**Females more likely to be adherent**

OR Odds Ratio, CI Confidence Interval, * univariable

Table 8-13 Association between gender/sex and surveillance adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined		
Brawarsky 2013	Males OR 0.77 (95%CI 0.73 - 0.81)	Female	Males less adherent
Cooper 2008	Female OR 1.19 (95%CI 1.09 - 1.30)	Male	Males less adherent
Kupfer 2018	Male OR 0.90 (95%CI 0.46 - 1.76)	Female	No association
Le 2014	42% (Male) vs 58% (Female), P = 0.46 *		No association, Univariable analysis
Vargus 2013	Male OR 1.14, (95%CI 1.00 - 1.29)	Female	**Males more adherent**
	Colonoscopy		
Brawarsky 2013	Male OR 0.83 (95%CI 0.80 - 0.87)	Female	Males less adherent
Carey 2017	Female OR 0.91 (95%CI 0.56-1.47)	Male	No Association
Cooper 2008	74.2% (Male) vs 73.2% (Female) P = 0.3*		No association, Univariable analysis
Kupfer 2018	Female OR 1.15 (95%CI 0.65 - 2.03)	Male	No Association
Le/Pisu 2014	Male 42%; Female 58% p=0.46*		No association, Univariable analysis
Rulyak 2004	Male OR 1.02 (95%CI 0.86-1.21)	Female	No association
Salz 2010	Male OR 0.87, P = 0.26	Female	No Association, CI not provided
Sisler 2012	Female OR 0.75 (95%CI 0.40-1.40) *	Male	No association, Univariable analysis
Urquhart 2012	Female OR 0.90 (95%CI 0.60-1.40)	Male	No Association
Vargus 2013	76.2% (Male) vs 74.5% (Female) *		No association, Univariable analysis
	CEA		
Brawarsky 2013	Male OR 0.86 (95%CI 0.81-0.91)	Female	Males less adherent
Cooper 2008	45.5% (Male) vs 47.7% (Female) P < 0.05 *		Males less adherent, Univariable analysis
Kupfer 2018	Female OR 1.02 (95%CI 0.62 - 1.67)	Male	No Association
Sisler 2012	Female OR 0.83 (95%CI 0.46 - 1.52)	Male	No Association
Vargus 2013	29.3% (Female) vs. 29.7% (Male) *		No association, Univariable analysis
	Clinic		
Brawarsky 2013	Male OR 0.71 (95%CI 0.67 - 0.75)	Female	Males less adherent
Cooper 2008	90.9% (Male) vs 93.5% (Female), P < 0.001 *		Males less adherent, Univariable analysis
Kosmider 2010	79.6% (Male) vs. 78.1% (Female) *		No association, Univariable analysis
Pisu 2014	Male 41.9% vs. Female 44.8%, P = 0.82 *		No association, Univariable analysis

OR Odds Ratio, CI Confidence Interval, * Univariable

Table 8-14 Association between ethnicity and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Staging		
Garfunkle 2020	37.2% Compliant (White) vs. 38.9% Compliant (non-white) (P = 0.44)		No Association
	Metastatic Assessment		
Ma 2015	42.5% (White) vs. 40% (Black) vs. 43.3% (Other) (P =0.92)*		No Association

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-15 Association between ethnicity and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Treatment		
Abraham 2006	44.2% Compliant (White) vs. 38.1% Compliant (Non-white), P = 0.79*		No Association
VanEenwyk 2002	Asian Pacific Islander OR 0.9 (95%CI 0.2 - 3.4) vs. Black OR 1.4 (95%CI 0.2 - 7.6) *	Non Asian Pacific Island/Non Black	No Association
	Radiation		
Baxter 2005	African American OR 0.77 (95%CI 0.65 - 0.92)	Non African American	African American less adherent
Del Vecchio 2019	African American OR 0.77 (95%CI 0.53 - 1.12); Other OR 0.84 (95%CI 0.60 - 1.18)	White	No Association
Fitzgerald 2013	White 51.8% vs. Black 51.9% vs. Other 54.8%, P = 0.09*		No Association
Haas 2011	Black OR 0.68 (95%CI 0.53 - 0.88); Hispanic 1.12 (95%CI 0.89 - 1.40)	White	Black less adherent
Lee 2012	White 42.9%; Black 44.1%; Hispanic 48.4%; Asian 48.7%, P = 0.003*		Increased in Hispanic and Asian
Lau 2021	Black OR 0.91 (95%CI 0.83 - 1.11); Hispanic OR 1.02 (95%CI 0.83 - 1.25); Other OR 0.91 (95%CI 0.62 - 1.25); Asian Pacific Islander OR 1.04 (95%CI 0.83 - 1.25)	White	No Association
Midura 2017	White 56%; Black 59%; Asian 59%; Other 54%, P = 0.003 *		Black, Asian more adherent
Monson 2014	White 74.1%; Black 74.2%; Hispanic 71.7%; Other 75.6%, P = 0.129*		No Association
Morris 2008	Black OR 0.93 (95%CI 0.78 - 1.03)	White	No Association
Morris 2004	Black OR 0.77 (95%CI 0.68 - 0.87)	White	Black less adherent
Murphy 2015	Black OR 0.98 (95%CI 0.89 - 1.07); Hispanic OR 0.98 (95%CI 0.87 - 1.11); Other OR 1.00 (95%CI 0.92 - 1.15)	White	No Association
Neugut 2002	Black OR 0.45 (95%CI 0.20 - 1.00); Hispanic OR 0.55 (95%CI 0.28 - 1.07); Other OR 0.58 (95%CI 0.16 - 2.09)	White	No Association
Nielsen 2010	Hispanic OR 0.67 (95%CI 0.22 - 2.04); Asian OR 1.05 (95%CI 0.52 - 5.79)	White	No Association
Schrag 2001	Black OR 0.88 (95%CI 0.48 - 1.59); Other OR 0.69 (95%CI 0.16 - 1.06)	White	No Association
Sinclair 2012 (Age < 65)	Hispanic OR 1.10 (95%CI 0.39 - 3.11); Non White Non Hispanic OR 0.73 (95%CI 0.24 - 2.20)	White	No Association
Sinclair 2012 (Age 65+)	Hispanic OR 0.93 (95%CI 0.35 - 2.46); Non Hispanic Non White OR 0.43 (95%CI 0.16 - 1.22)	White	No Association
Sineshaw 2016	Black OR 0.85 (95%CI 0.80 - 0.91); Hispanic OR 0.86 (95%CI 0.80 - 0.93); Other OR 0.88 (95%CI 0.83 - 0.93)	White	White more adherent
Wong 2021	White OR 1.92 (95%CI 0.87 - 4.24)	Black	No Association
Xu 2017	Black OR 0.89; Hispanic OR 1.11; Other OR 0.93 (CI not reported)	White	No Association
	Chemotherapy		
Del Vecchio 2019	African American OR 0.87 (95%CI 0.62 - 1.21); Other OR 1.10 (95%CI 0.82 - 1.47)	White	No Association

Haas 2011	Black OR 0.62 (95%CI 0.51 - 0.72); Hispanic OR 1.13 (95%CI 0.95 - 1.35)	White	Black less adherent
McGory 2016 (Stage II)	Black OR 0.814 (95%CI 0.54 - 1.22); Hispanic OR 1.03 (95%CI 0.78 - 1.37); Asian OR 0.95 (95%CI 0.66 - 1.36); Other OR 0.39 (95%CI 0.09 - 1.68)	White	No Association
McGory 2016 (Stage III)	Black OR 1.12 (95%CI 0.72 - 1.74); Hispanic OR 1.07 (95%CI 0.81 - 1.42); Asian OR 1.21 (95%CI 0.84 - 1.75); Other OR 0.46 (95%CI 0.13 - 1.62)	White	No Association
Monson 2014	Black OR 0.81 (95%CI 0.69 - 0.95); Hispanic OR 0.91 (95%CI 0.74 - 1.11); Other OR 0.95 (95%CI 0.78 - 1.16)	White	Black less adherent
Morris 2008	Black OR 0.83 (95%CI 0.67 - 0.98)	White	Black less adherent
Sinclair 2012 (Age < 65)	Hispanic OR 1.43 (95%CI 0.42 - 4.86); Non White Non Hispanic OR 1.36 (95%CI 0.39 - 4.80)	White	No Association
Sinclair 2012 (Age 65+)	Hispanic OR 1.08 (95%CI 0.35 - 3.33); Non Hispanic Non White OR 1.20 (95%CI 0.50 - 2.90)	White	No Association
Xu 2017	Black OR 0.89; Hispanic OR 0.93; Other OR 0.69 (CI not reported)*	White	No Association
	Surgery		
Abrams 2016	Other OR 1.40 (95%CI 1.11 - 1.76) (Receipt of Non operative management)	White	Other more likely not to undergo surgery
Morris 2004	Black OR 1.30 (95%CI 1.12 - 1.95) (Odds of No Operation)	White	Black more likely not to undergo surgery
Morris 2004	Black OR 1.42 (95%CI 1.23 - 1.65) (Permanent Colostomy)	White	Black more likely to have a permanent colostomy

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-16 Association between ethnicity and surveillance outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Surveillance		
Brawarsky 2013	Black 0.75 (0.67 - 0.83) vs. Hispanic 1.1, 0.96 - 1.21	White	Black less likely to be adherent
Cooper 2008	Black OR 0.57, (95% CI 0.47-0.70); Hispanic OR 1.10 (95% CI 0.85-1.42); Asian OR 0.93 (95% CI 0.64-1.35); Other OR 0.98 (95% CI 0.71-1.35)	White	Black less likely to be adherent
Kupfer 2018	White OR 2.57 (95%CI 0.80 - 8.20); Other OR 4.51 (95%CI 1.0 - 20.67)	Black	No Association
Vargas 2013	Black OR 1.40 (95%CI 0.94 - 2.07); White OR 1.31 (95%CI 0.94 - 1.82); Other OR 1.13 (95%CI 0.63 -2.03)	Hispanic	No Association
	Colonoscopy		
Brawarsky 2013	Black OR 0.76, (95% CI 0.69-0.83); Hispanic OR 1.02, (95% CI 0.92-1.14)	White	Black less likely to be adherent
Cooper 2008	74.6% (White); 65.% (Black); 72.9% (Hispanic); 61.8% (Asian); 68.7% (Other); p<.001 *		Associated with Race
Kupfer 2018	White OR 1.30 (95%CI 0.52 - 3.22); Other OR 1.45 (95%CI 0.38 - 5.61)	Black	No Association
Rulyak 2004	Black OR 0.70, (95% CI 0.43-1.13);Other OR 1.47 (95% CI 0.99-2.18)	White	No Association
Salz 2010	Black OR 0.91, p=0.48; Hispanic OR 0.87, p=0.54; Other OR 1.50, P = 0.05 (CI not reported)	White	No Association
Sanchez 2020	Black OR 0.70 (95%CI 0.56 - 0.88); Hispanic OR 0.87 (95%CI 0.56 - 1.12)	Non Hispanic White	Black less likely to be adherent
Vargas 2013	76.4% (White), 70.7% (Black), 63.1% (Hispanic), 68.7% (Other), p<.05 *		Associated with Race
	CEA		
Brawarsky 2013	Black OR 0.77, (95% CI 0.67-0.87); Hispanic OR 1.14 (95% CI 0.98-1.32)	White	Black less likely to be adherent
Cooper 2008	46.7% (White), 40.8% (Black), 55.2% (Hispanic), 50% (Asian), 48.9% (Other) * P< 0.01		Associated with Race
Kupfer 2018	White OR 1.11 (95%CI 0.51 - 2.42); Other OR 1.88 (95%CI 0.57 - 6.20)	Black	No Association
Vargas 2013	29.8% (White), 26.6% (Black), 27.4% (Hispanic), 30.6% (Other) *		No Association
	Clinic Visit		
Brawarsky 2013	Black OR 0.75 (95% CI 0.67-0.83), p<.05; Hispanic OR 1.08, (95% CI 0.96-1.21)	White	Black less likely to be adherent
Cooper 2008	92.5% (White), 89.1% (Black), 94.3% (Hispanic), 87.5% (Asian), 94.4 (Other), p=0.002 *		Associated with Race

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-17 Association between socioeconomic status and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Colonoscopy		
Bergin 2020	Mid OR 0.58 (95%CI 0.22 - 1.52); Most OR 0.61 (95%CI 0.22 - 1.67)	Least Disadvantaged	No Association
	Metastatic Assessment		
Bergin 2020	Mid OR 1.18 (95%CI 0.39 - 3.57); Most OR 0.91 (95%CI 0.33 - 2.54)	Least Disadvantaged	No Association

OR Odds Ratio, CI Confidence Interval

Table 8-18 Association between socioeconomic status and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Treatment		
Eldin 2009	Q1 50.3%; Q2 51.7%; Q3 57.9%; Q4 63.4% P, trend = 0.007 *Univariable		Increase SES associated with adherence
VanEenwyk 2002	Q2 - Q4 (combined) OR 0.7 (95%CI 0.4 - 1.3)	Q1	Highest SES associated with adherence
	Radiation		
Beckman 2014	Lowest (Q1) OR 1.38 (95%CI 1.05 - 1.81); Q2 OR 1.36 (95%CI 1.02 - 1.81); Q3 OR 1.59 (95%CI 1.21 - 2.09); Q4 OR 1.09 (95%CI 0.80 - 1.46)	Highest Quintile (Q5)	Lowest SES associated with non-adherence
Haas 2011	Highest OR 0.83 (95%CI 0.69 - 0.99); Mid OR 0.96 (95%CI 0.84 - 1.10)	Lowest Household Income	No Association
Hegi-Johnson 2007	Q5 (Highest) 27%; Q4 27%; Q3 41%; Q2 28%; Q1 38%, P = 0.10 *Univariable Analysis		No Association
Lee 2012	Lowest OR 1.53 (95%CI 1.32 - 1.78); Mid OR 1.36 (95%CI 1.23 - 1.50); Unknown OR 1.38 (0.89 - 2.14)	Highest	Lowest SES associated with non-adherence
Lau 2021	Lowest (Q1) OR 0.9 (97.5% CI 0.8 - 1.0); Q2 OR 0.95 (97.5% CI 0.8 - 1.1); Q3 OR 1 (97.5%CI 0.9 - 1.1)	Highest Household Income (Q4)	No Association
Midura 2017	Q1 (lowest) 68.6%; Q2 68.5%; Q3 67.5%; Q4 (Highest) 65.6% P > 0.05 *Univariable Analysis		No Association
Olsson 2011	Q1 (lowest) OR 0.76 (95%CI 0.67 - 0.86); Q2 OR 0.89 (95%CI 0.79 - 1.00); Q3 OR 0.91 (95%CI 0.82 - 1.02)	Q4 (Highest Income)	Lowest SES associated with non-adherence
Sarasqueta 2019	Q1 (most deprived) 61.7%; Q2 54.8%; Q3 61.8%; Q4 (least deprived) 65.5% P = 0.31 *Univariable Analysis		No Association
Schrag 2001	Q1 (lowest) OR 0.92 (95%CI 0.63 - 1.33); Q2 OR 0.74 (95%CI 0.51 - 1.06); Q3 OR 1.20 (95%CI 0.83 - 1.73)	Q4 (Highest)	No Association
Sinclair 2012 (< 65 years)	Highest OR 1.21 (95%CI 0.45 - 3.25); Mid OR 1.08 (95%CI 0.4 - 2.94)	Lowest Household Income	No Association
Sinclair 2012 (65+ years)	Highest OR 1.00 (95%CI 0.51 - 1.97); Mid OR 1.44 (95%CI 0.62 - 3.31)	Lowest Household Income	No Association
Sineshaw 2016	Q1 (Lowest) OR 1.04 (95%CI 0.97 - 1.12); Q2 OR 1.08 (95%CI 1.02 - 1.15); Q3 OR 1.05 (95%CI 1.00 - 1.10)	Q4 (highest)	No Association
Wong 2021	OR 1.05 (95%CI 0.92 - 1.19) *Univariable	Mean Income, Per Unit Increase	No Association
	Chemotherapy		
Cheung 2009 Strata 1 (received neoadjuvant therapy)	Low Income OR 1.55 (95%CI 0.35 - 6.88)	High Income	No association between income and delay of > 3 months to Chemotherapy
Cheung 2009 strata 2 (did not receive neoadjuvant therapy)	Low Income OR 1.16 (95%CI 0.84 - 1.59)	High Income	No association between income and delay of > 3 months to Chemotherapy
McGory 2016 (Stage II)	Poverty OR 0.992 (95%CI 0.986 - 0.998), P = 0.007	Those not impoverished	Non adherence associated with Poverty
McGory 2016 (Stage III)	Poverty OR 0.992 (95%CI 0.986 - 0.997)	Those not impoverished	Non adherence associated with Poverty

Sinclair 2012 (< 65 years)	Q4 (highest) OR 2.42 (95%CI 0.42 - 14.0); Q3 OR 0.91 (95%CI 0.24 - 3.51); Q2 OR 2.78 (95%CI 0.55 - 14.1)	Q1 (lowest income)	No Association
Sinclair 2012 (65+ years)	Q4 (highest) OR 0.93 (95%CI 0.44 - 1.93); Q3 OR 1.12 (95%CI 0.55 - 2.30); Q2 OR 0.66 (95%CI 0.34 - 1.31)	Q1 (lowest income)	No Association

OR Odds Ratio, CI Confidence Interval, Q Quintile or Quartile, *Univariable

Table 8-19 Association between socioeconomic status and surveillance adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Surveillance		
Brawarsky 2013	High OR 1.06 (95%CI 0.99 - 1.14) vs. Mid 1.03 (95%CI 0.97 - 1.09)	Low	No Association
	Colonoscopy		
Brawarsky 2013	High OR 1.08 (1.01 - 1.15); Mid OR 1.02 (0.96 - 1.08)	Low	High more adherent
Rulyak	High OR 1.29 (95%CI 1.03 - 1.61); Mid OR 1.06 (95%CI 0.87 - 1.29)	Low	High more adherent
Salz 2010	< $50k/year OR 0.74, P = 0.01 (CI not reported)	$50K +/year	High more adherent
Sisler 2012	High OR 3.86 (95%CI 1.98 - 7.56)	Low	High more adherent
Vargus 2013	Q1 71.3%; Q2 73.8%; Q3 76.7%; Q4 78.8%, P <0.02*Univariable		High more adherent
	CEA		
Sisler 2012	High OR 1.97 (95%CI 0.87 - 4.46)	Low	No Association
Vargus 2013	Q1 26.2%; Q2 27.2%; Q3 32%; Q4 32.2%, p<.02		High more adherent
	Clinic Visit		
Urquhart 2012	Q1 OR 0.90 (95%CI 0.50 - 1.70); Q2 OR 1.60 (95%CI 0.80 - 2.90); Q3 OR 1.40 (95%CI 0.80 - 2.60); Q4 OR 0.90 (95%CI 0.50 - 1.80)	Q0	No Association

Q Quintile or Quartile (1 – Lowest); OR odds ratio, CI confidence interval, CEA Carcinoembryonic Antigen,

Table 8-20 Association between geographic region and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Local Regional Staging		
Phelip 2004	No Difference Between Districts (9 assessed), P = "N.S." *Univariable		No Association
	Colonoscopy		
Helewa 2013	75% (Winnipeg) vs. 65% (Northern Manitoba) vs 74% (South Manitoba) vs 81.5% (Middle Manitoba) (P = 0.05)* Univariable		Associated with Geographic District
Philip 2004	40% - 88%. P < 0.01* (9 Districts Assessed) *Univariable		Associated with Geographic District
	Metastatic Assessment		
Phelip 2004	0.9% - 13.2%, P < 0.0001 (Chest Imaging); 13.4% to 69.2%, P < 0.001 (abdominal imaging) * Univariable		Associated with Geographic District
	CEA		
Philip 2004	50 - 81%, P < 0.001* Univariable Analysis		Associated with Geographic District

OR Odds Ratio, CI Confidence Interval, N.S. Not specified

Table 8-21 Association between geographic region and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Treatment		
Eldin 2012	5 Location in Alberta, Canada 46 - 62% adherent P = 0.23 * Univariable Analysis		Not associated

Table 8-22 Association between geographic region and surveillance adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Surveillance		
Cooper 2008	11 SEER locations, 33% - 44% adherent, P = 0.001 *Univariable		Associated
	Colonoscopy		
Cooper 2008	11 SEER location, 68 -79% adherent, P = 0.001 *Univariable		Associated
Helewa 2013	30% (Winnipeg) vs 25% (North Manitoba) vs 31.3% (South Manitoba) vs 26% (Middle Manitoba) P = 0.535 *Univariable		Not Associated
Salz 2010	Alabama OR 1.13; Los Angeles OR 0.97;, North Carolina OR 1.58 (CI not reported)	"managed care"	Associated
Sisler 2012	Winnipeg OR 0.64 (95%CI 0.33 - 1.25)	Rest of Manitoba	Not Associated
	CEA		
Cooper 2008	11 SEER locations, 37 - 50% adherent, P = 0.001 * Univariable		Associated
Sisler 2012	Winnipeg OR 0.4 (95%CI 0.22-0.73)	Rest of Manitoba	Associated
	Clinic Visit		
Cooper 2008	11 SEER location, 87 - 96% adherent, P = 0.001 *Univariable		Associated

OR Odds Ratio, CI Confidence Interval

Table 8-23 Association between rurality and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Metastatic Assessment		
Bergin 2020	Rural OR 0.90 (95%CI 0.41 - 1.99)	Urban	No association
	Colonoscopy		
Bergin 2020	Rural OR 0.96 (95%CI 0.46 - 1.98)	Urban	No association
	CEA		
Bergin 2020	Rural OR 0.71 (95%CI 0.35 - 1.43)	Urban	No association

OR Odds Ratio, CI Confidence Interval, CEA Carcinoembryonic Antigen,

Table 8-24 Association between rurality and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Treatment		
Cree 2009	Rural OR 1.05 (95%CI 0.91 - 1.22)	Urban	No Association
Van Eenwyk 2002	Rural OR 1.1 (95%CI 0.7 - 2.0) *Univariable Analysis	Urban	No Association
	Radiation		
Adelson 2018	Non-metropolitan OR 1.18 (95%CI 0.72 - 1.93) *Univariable Analysis	Metropolitan	No Association
Beckman 2014	Outer Urban OR 0.87 (95%CI 0.68 - 1.11); Rural OR 0.87 (95%CI 0.69 - 1.11); Remote OR 1.13 (95CI 0.85 - 1.51)	Inner Urban	No Association
Lefresne 2014	No Difference (Proportions not reported), P = 0.80 *Univariable Analysis Only		No Association
Midura 2017	Urban 55.3%; Suburban 58.1%; Rural 57.6% P < 0.001 *Univariable Analysis Only		Urban less likely to receive preoperative radiation
Monson 2014	Rural OR 1.36 (95%CI 1.14 - 1.63); Urban OR 1.18 (95%CI 1.14 - 1.63)	Metro	Metro less likely to receive preoperative radiation
Lau 2021	Rural OR 0.9 (95%CI 0.7 - 1.1); Urban OR 1.1 (95%CI 0.96 - 1.2) (Note, outcome was non-adherence)	Metro	No Association
	Chemotherapy		
Adelson 2018	Non-metropolitan OR 0.95 (95%CI 0.58 - 1.53) *Univariable Analysis	Metropolitan	No Association
Beckman 2014	Outer Urban OR 1.03 (95%CI 0.91 - 1.17); Rural OR 0.87 (95%CI 0.77 - 1.00); Remote OR 0.86 (95CI 0.70 - 1.05)	Inner Urban	No Association
Cheung 2009 (a)	Non-Urban OR 2.44 (95%CI 0.48 - 12.33) (note outcome was non-adherent delay to chemotherapy)	Urban	No Association
Cheung 2009 (b)	Non-Urban OR 0.78 (95%CI 0.51 - 1.20)	Urban	No Association
Lefresne 2014	Rural 57%, Small Urban 56%, Large Urban 57%, P = 0.89, *Univariable Analysis only		No Association
Rayson 2012	Urban OR 2.2 (95%CI 1.4 - 3.4) (note outcome was receipt of adherent chemotherapy within 12 weeks)	Rural	Urban associated with higher odds of received adherent chemotherapy within 12 weeks

a) Received preop chemorads; b) did not receive preop chemorads

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-25 Association between rurality and surveillance adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Combined Surveillance		
Le/Pisu 2014	Urban 46.1% Compliant vs. Rural 55.9%, P = 0.45 Compliant *Univariable Analysis Only		No Association
	Colonoscopy		
Carey 2017	Urban OR 0.65 (95%CICI 0.4-1.05) p = 0.08	Rural	No Association

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-26 Association between education and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Metastatic Assessment		
Cavalli-Bjorkman 2011	50% (Low) vs. 59.8% (middle) vs. 58.3% (highly educated) (p < 0.001)* Univariable Only		Associated with Mid/Highly educated
	Local Regional Staging		
Cavalli-Bjorkman 2011	50% (Low Education); 60% (Mid Education); 58% (Highly Educated) P < 0.001 *Univariable Only		Associated with Mid/Highly educated
	Colonoscopy		
Cavalli-Bjorkman 2011	45.6% (Low) vs. 48.2% (Middle) vs. 50% (Highly Educated) (p = 0.657)*Univariable Analysis		No Association

Table 8-27 Association between education and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Radiation		
Midura 2017	Q1 (Highest) 56.3%; Q2 55.9%; Q3 55.7%; Q4 (Lowest) 55.8%), P = 0.25 *Univariable analysis only (Median Neighborhood Education)		No association
Olsson 2011	Further OR 1.04 (95%CI 0.94 - 1.15); University OR 0.92 (95%CI 0.81 - 1.06)	Compulsory	No association
Sineshaw 2011	Q2 OR 0.97 (95%CI 0.92 - 1.02); Q3 OR 0.88 (95%CI 0.83 - 0.93); Q4 (lowest) 0.82 (95%CI 0.77 - 0.88)	Q1 (highest)	Adherence associated with higher education (based on median neighborhood education)
Lau 2021	Q2 OR 1 (95%CI 0.9 - 1.1); Q3 OR 1 (95%CI 0.95 - 1.2); Q4 OR 1.1 (95%CI 0.9 - 1.2)	Q1 (highest)	No association
Sarasqueta 2019	No formal 62%; Primary 60.5%; Secondary 65.1%; University 55.6%, P = 0.78 * Univariable		No Association

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-28 Association between education and surveillance adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Overall Surveillance		
Pisu/Le 2014 Vargus 2013	Multiple assessments *Univariable, P>0.74		No Association
	Colonoscopy Surveillance		
Carey 2017	Secondary School OR 1.6 (95%CI 0.8-3.12); Did not complete secondary school OR 1.03 (95%CI 0.6-1.77)	University Education	No Association
Salz 2010	High School or Greater OR 1.22 (no CI provided), p=.07	Less than High School	No Association
Vargus 2013	Q1 (Lowest)71.2% vs Q2 74.6% vs Q3 76.5% vs Q4 (highest) 78.2%, p<.02		Adherence associated with higher education
	CEA Surveillance		
Vargus 2013	Q1 (lowest) 27.2% vs Q2 28.1% vs Q3 30.7% vs Q4 (highest) 31.6%, p<.02 *Univariable		Adherence associated with higher education

Table 8-29 Association between multidisciplinary care and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Colonoscopy		
Richardson 2016	95% (pre-MDT) vs. 100% (1 year post MDT) vs. 96% (2 year post MDT) (P = 0.3)*Univariable Analysis		Not associated with introduction of MDT
	Local Regional Disease		
Richardson 2016	26% (Prior to Introduction); 80% (2013); 81% (2014) (P < 0.0001)*Univariable Analysis		Associated with introduction of Multidisciplinary Tumor Conference
Levine 2012	88% (Multidisciplinary Clinic); 37.7% (Non Multidisciplinary Clinic) (P < 0;0001)*Univariable Analysis		Associated with Multidisciplinary Clinic
	Metastatic Disease Staging		
Levine 2012 (abdominal)	97.5% (Multidisciplinary Clinic) vs. 83.1% (Non Multidisciplinary Clinic) (P = 0.03)* Univariable Analysis		Associated with assessment at multidisciplinary clinic
Levine 2012 (chest)	95% (Multidisciplinary Clinic) vs. 37.1% (Non Multidisciplinary Clinic) (P < 0.0001)*Univariable Analysis		Associated with assessment at multidisciplinary clinic
Bao 2016	97% (Present) vs. 94% (Absent); (P = 0.293)*Univariable Analysis		Not associated with a clinical pathway
Richardson 2016	40% (Pre-MDT) vs. 63% (1 year post MDT) vs. 79% (2 year post MDT) (P = 0.01)*Univariable Analysis		Associated with introduction of Multidisciplinary Tumor Conference
	CEA Staging		
Bao 2016	97% (Present) vs. 96% (Absent) (P = 0.55)*Univariable		Not associated with a clinical pathway

MDT Multidisciplinary Tumor Board, OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-30 Association between multidisciplinary care and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Overall Treatment		
Abraham 2006	Presented at MDT OR 3.62 (95%CI 1.18 - 11.17)	Not Presented	Associated with presentation at MDT
	Radiation		
Jorgensen 2014	Presented at MDT OR 3.12 (95%CI 1.78 - 4.57)	Not Presented	Associated with presentation at MDT
Levine 2012	83% (multidisciplinary clinic) vs. 20% (non-multidisciplinary clinic) P < 0.001 *Univariable Analysis		Associated with multidisciplinary care clinic
Richardson 2016	83% (Pre-MDT) vs. 98% (1 year post MDT) vs. 96% (2 year post MDT), P = 0.02 *Univariable Analysis		Associated with presentation at MDT
Sarasqueta 2019	Presented at MDT 61.6% vs. Not Presented 57.9%, P =0.48 *Univariable Analysis		Not associated with presentation at MDT
	Chemotherapy		
Richardson 2016	84% (Pre-MDT) vs. 82% (1 year post MDT) vs. 71% (2 year post MDT), P = 0.43 *Univariable Analysis		No associated with presentation at MDT
	Surgery		
Richardson 2016 (appropriate APR)	50% (Pre-MDT) vs. 71% (1 year post MDT) vs. 78% (2 year post MDT), P = 0.19 *Univariable Analysis		No associated with presentation at MDT
Richardson 2016 (appropriate local excision)	22% (Pre-MDT) vs. 29% (1 year post MDT) vs. 75% (2 year post MDT), P = 0.16 *Univariable Analysis		No associated with presentation at MDT

Note, Surveillance Adherence outcomes were not assessed.
OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-31 Association between comorbidity and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Overall Treatment		
Eldin 2012	Score 0 58.3%; Score 1+ 35.4%, P < 0.001 *Univariable Analysis		Less adherence with higher comorbidity score
Guillerme 2014	Comorbidity Score 2+ OR 0.344 (95%CI 0.16 - 0.73)	Score 0 - 1	Less adherence with higher comorbidity score
	Radiation		
Beckman 2014	One OR 1.01 (95%CI 0.83 - 1.24); Multiple/Severe OR 1.13 (95%CI 0.85 - 1.50)	No Comorbidity	No Association
Del Vecchio 2019	Charlson 1+ OR 0.70 (95%CI 0.49 - 1.00)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Elliot 2014	Charlson Comorbidity 1 OR 0.55 (95%CI 0.40 - 0.76); Charlson Comorbidity 2+ OR 0.29 (95%CI 0.21 - 0.39)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Jorgensen 2014	Charlson Comorbidity 1 OR 0.93 (95%CI 0.40 - 2.14); Charlson Comorbidity 2 OR 0.75 (95%CI 0.24 - 2.31); Charlson Comorbidity 3+ OR 0.24 (95%CI 0.05 - 1.21)	Charlson Comorbidity 0	No Association
Lau 2021	Odds of Nonadherence Charlson Deyo 1 OR 1.1 (0.97 - 1.2); Charlson Deyo 2 OR 1.1 (95%CI 0.96 - 1.3); Charlson Deyo 3+ OR 1.5 (95%CI 1.2 - 1.9)	Charlson Deyo 0	Less adherence with higher comorbidity score
Midura 2017	Charlson Deyo 0 57.7%; Charlson Deyo 1 50.3%; Charlson Deyo 2+ 44.4%, P < 0.0001 *Univariable Analysis		Less adherence with higher comorbidity score
Monson 2014	CCS 1 OR 0.86 (95%CI 0.80 - 0.92); CCS 2+ OR 0.69 (95%CI 0.61 - 0.77)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Murphy 2015	CCS 1 OR 0.96 (95%CI 0.87 - 1.06); CCS 2+ OR 0.92 (95%CI 0.75 - 1.13)	Charlson Comorbidity 0	No Association
Neugot 2002 (Stage II)	Charlson Deyo 1 OR 1.03 (95%CI 0.68 - 1.54); Charlson Deyo 2+ OR 0.83 (95%CI 0.58 - 1.19)	Charlson Deyo 0	No Association
Neugot 2002 (Stage III)	Charlson Deyo 1 OR 1.08 (95%CI 0.71 - 1.64); Charlson Deyo 2+ OR 0.68 (95%CI 0.46 - 0.99)	Charlson Deyo 0	Less adherence with higher comorbidity score
Quipourt 2011	CCS 2+ OR 0.37 (95%CI 0.19 - 0.71)	CCS 0 - 1	Less adherence with higher comorbidity score
Sarasqueta 2019	Charlson Index 1 OR 0.9 (95%CI 0.6 - 1.4); Charlson Index 2+ OR 0.9 (95%CI 0.5 - 1.7)	Charlson Index 0	No Association
Schrag 2001	CCS 1 OR 0.79 (95%CI 0.60 - 1.03); CCS 2+ OR 0.70 (95%CI 0.51 - 0.96)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Sinclair 2012 (age <65)	CCS 1 OR 0.70 (95%CI 0.25 - 1.91); CCS 2+ OR 0.79 (95%CI 0.22 - 2.80)	Charlson Comorbidity 0	No Association
Sinclair 2012 (age 65+)	CCS 1 OR 0.72 (95%CI 0.38 - 1.37); CCS 2+ OR 0.70 (95%CI 0.36 - 1.34)	Charlson Comorbidity 0	No Association
Sineshaw 2016	CCS 1 OR 0.96 (95%CI 0.92 - 1.00); CCS 2+ OR 0.69 (95%CI 0.64 - 0.74)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Van der Geest 2012	CCS 1 OR 0.64 (95%CI 0.35 - 1.15); CCS 2+ OR 0.31 (0.16 - 0.60)	CCS 0	Less adherence with higher comorbidity score
	Chemotherapy		
Beckman 2014	One OR 0.95 (95%CI 0.86 - 1.06); Multiple/Severe OR 0.78 (95%CI 0.65 - 0.94)	None	Less adherence with multiple/severe comorbidity

Cheung 2009 (Preoperative oncology assessment))	Charlson Comorbidity 1 OR 0.71 (95%CI 0.04 - 11.49); Comorbidity 2 OR 0.56 (95%CI 0.01 - 3.88); Comorbidity 3+ OR 0.35 (95%CI 0.01 - 9.99)	Charlson Comorbidity 0	No Association
Cheung 2009 (No preoperative oncology assessment)	Charlson Comorbidity 1 OR 1.21 (95%CI 0.69 - 2.11); Comorbidity 2 OR 1.16 (95%CI 0.38 - 3.53); Comorbidity 3+ OR 1.06 (95%CI 0.21 - 5.37)	Charlson Comorbidity 0	No Association
Del Vecchio 2019	Charlson 1+ OR 0.69 (95%CI 0.49 - 0.97)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
McGory 2016 (Stage II)	Charlson Comorbidity 1 OR 0.827 (95%CI 0.678-1.009); Comorbidity 2 OR 0.615 (95%CI 0.439 - 0.862); Comorbidity 3+ OR 0.344 (95%CI 0.211 - 0.562)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
McGory 2016 (Stage III)	Charlson Comorbidity 1 OR 0.698 (95%CI 0.574 - 0.844); Comorbidity 2 OR 0.457 (95%CI 0.319 - 0.655); Comorbidity 3+ OR 0.387 (95%CI 0.239 - 0.627)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Monson 2014 (Received CRT))	CCS 1 OR 0.90 (95%CI 0.80 - 1.01); CCS 2+ OR 0.77 (95%CI 0.60 - 0.99)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Monson 2014 (Did not receive CRT)	CCS 1 OR 1.04 (95%CI 0.90 - 1.20); CCS 2+ OR 0.72 (95%CI 0.57 - 0.91)	Charlson Comorbidity 0	Less adherence with higher comorbidity score
Sinclair 2012 (age <65)	CCS 1 OR 1.38 (95%CI 0.40 - 4.77); CCS 2+ OR 1.09 (95%CI 0.25 - 4.81)	Charlson Comorbidity 0	No Association
Sinclair 2012 (age 65+)	CCS 1 OR 0.90 (95%CI 0.51 - 1.59); CCS 2+ OR 0.68 (95%CI 0.38 - 1.19)	Charlson Comorbidity 0	No Association
Xu 2017	Charlson Deyo 1 OR 0.85 (95%CI 0.75 - 0.96); Charlson Deyo 2+ OR 0.77 (95%CI 0.60 - 0.99)	Charlson Deyo 0	Less adherence with higher comorbidity score

CCS Charlson Comorbidity Score; OR Odds ratio, CI Confidence Interval, CRT chemoradiation, *Univariable

Table 8-32 Association between comorbidity and surveillance adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Overall Surveillance		
Cooper 2008	CCS 1 OR 0.9 (95%CI 0.8 - 1.03); CCS 2 OR 0.9 (95%CI 0.8 - 1.0); CCS 3+ OR 0.75 (95%CI 0.7 - 0.9)	CCS 0	Less adherence with higher comorbidity Score
Vargas 2013	CCS 1 OR 0.96 (95%CI 0.83 - 1.12); CCS 2 OR 0.76 (95%CI 0.60 - 0.96); CCS 3+ OR 0.75 (95%CI 0.55 - 1.01)	CCS 0	Less adherence with higher comorbidity Score
	Colonoscopy Surveillance		
Cooper 2008	CCS 0 75.4% vs CCS 1 74.3% vs CCS 2 71.3% vs CCS 3+ 69.1% p<.001 * Univariable Analysis Only		Less adherence with higher comorbidity Score
Salz 2010	Mild OR 0.92, p=.56, Moderate OR 0.69 p<.05, Severe OR 0.44 p<.01 (CI not provided)	No Comorbidities	Less adherence with higher comorbidity Score
Sisler 2012	High Comorbidity OR 0.39 (95%CI 0.18-0.83)	Low Comorbidity	Less adherence with higher comorbidity Score
Urquhart 2012	CCS 1 OR 0.90 (95%CI 0.60-1.50); CCS 2+ OR0.60 (95%CI 0.40-0.90)	CCS 0	Less adherence with higher comorbidity Score
Vargas 2013	CCS 0 76.9 % vs CCS 1 75.5% vs CCS 2 69.1% vs CCS 3+ 63.8% p<.02 *Univariable Analysis		Less adherence with higher comorbidity Score
	Metastatic Surveillance		
Salloum 2012	Charlson - Deyo (per 1 point increase) OR 1.10 (95%CI 1.07 - 1.14)		More Adherence with Higher Comorbidity Score
Sehdev 2017	"Catastrophic" 1.08 (95%CI 0.71-1.64); Moderate Disability OR 1.30 (95%CI 0.92-1.84); Medical Assistance OR 1.14 (95%CI 0.85-1.55)	No Disability	No Association
Sisler 2012	High Comorbidity OR 0.80 (95%CI 0.43 - 1.48)	Low Comorbidity	No Association
Vargus 2013	CCS 1 OR 1.12 (95%CI 1.00 - 1.27); CCS 2 OR 1.18 (95%CI 0.98 - 1.41); CCS 3+ OR 1.01 (95%CI 0.82 - 1.25)	CCS 0	No Association
	CEA Surveillance		
Cooper 2008	CCS 0 48.9% vs CCS 1 45.6% vs CCS 2 46.3% vs CCS 3+ 32.7% p<.001 *Univariable Analysis		Less adherence with higher comorbidity score
Sisler	High Comorbidity OR 0.91 (95%CI 0.50 - 1.65)	Low Comorbidity	No Association
Vargus 2013	CCS 0 31% vs CCS 1 28.4% vs CCS2 25.9% vs CCS3+ 24.6%, p<.02 * Univariable Analysis		Less adherence with higher comorbidity Score
	Clinic Surveillance		
Cooper 2008	CCS 0 90.2% vs CCS 1 95 4.5% vs CCS 2 93.3% vs CCS 3+ 93.6%, p<.001 *Univariable Analysis Only		Less adherence with higher comorbidity score
Kosmider 2010	Univariable Analysis Only *No association		No Association with Diabetes Status

CCS Charlson Comorbidity Score, OR Odds Ratio, CI Confidence Interval
Note, Comorbidity and staging adherence outcomes were not assessed.

Table 8-33 Association between physician volume and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Local Regional Disease		
Comber 2012	OR 1.10 (95% CI 1.05 - 1.18) (per additional case)	N/A	Higher Volume associated with increased adherence
McGrath 2005	10.4 % (Low Volume); 20.4% (High Volume, >6 cases/3 months) (P = 0.003)*Univariable Analysis Only		Higher Volume associated with increased adherence
	Metastatic Disease Staging		
Comber 2012 (Chest)	OR 0.94 95%CI 0.91 - 0.98 (per additional case)	N/A	Higher Volume associated with reduced adherence
Comber 2012 (Abdomen)	OR 0.92, 95%CI 0.87 - 0.97 (per additional case)		Higher Volume associated with reduced adherence
McGrath 2005	52.7% (High Volume, 6 cases/3 months) vs. 45.2% (Low Volume), P = 0.003 * Univariable Analysis Only		Higher Volume associated with increased adherence

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-34 Association between physician volume and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Radiation		
Comber 2012	OR 1.04 (95%CI 1.01 - 1.07) (per additional case)		Higher Volume associated with increased adherence
Hegi-Johnson	High Volume (20+ cases/year) OR 1.95 (95%CI 1.17 - 3.24)	Low Volume (<20 cases/year)	Higher Volume associated with increased adherence
	Chemotherapy		
Comber 2012	OR 1.00 (95%CI 0.96 - 1.03) (per additional case)		No Association with surgeon volume
	Surgery		
Comber 2012 (complete TME)	OR 1.07 (95%CI 1.01 - 1.13) (per additional case)		Higher Volume associated with higher quality surgery

(a received neoadjuvant therapy; (b) did not receive neoadjuvant therapy

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-35 Association between Hospital Volume or Hospital Type and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Metastatic Assessment		
Hospital Volume			
Comber 2012 (Chest)	OR 1.01 95%CI 0.96 - 1.07 (per additional case)		No Association with Volume
Comber 2012 (Abdomen)	OR 1.01; 95%CI 0.96 - 1.07 (per additional case)		No Association with Volume
Hospital Type			
Charlton 2016 (Abdomen)	NCI OR 1.28 (95%CI 0.91 - 1.79)	Non NCI Hospital	No Association with Hospital Type
Charlton 2016 (Chest)	NCI OR 1.80 (95%CI 1.10 - 2.93)	Non NCI Hospital	No Association with Hospital Type
Charlton 2016 (Abdomen)	Residency Program Present OR 1.00 (95% CI 0.81 - 1.23)	No Residency Program	No Association with Hospital Type
Charlton 2016 (Chest)	Residency Program Present OR 1.20 (95% CI 0.93 - 1.55)	No Residency Program	No Association with Hospital Type
Charlton 2016 (Abdomen)	Major Hospital OR 1.07 (95%CI 0.84 - 1.37)	No Affiliation	No Association with Hospital Type
Charlton 2016 (Chest)	Major OR 1.72 (95%CI 1.24 - 2.40)	No Affiliation	No Association with Hospital Type
Ma 2015	Academic OR 3.71 (95%CI 1.85 - 7.61)	Community Hospital	Adherence associated with Academic Hospital
Jestin 2004	34% (University Hospital) vs. 54% (General District) vs. 61% (District)* Univariable, significant testing not reported		
	Local Regional Staging		
Hospital Volume			
Comber 2012	OR 1.06 (1.03 - 1.08) (per additional case)		Higher Volume associated with increased adherence
Van der Geest 2012	Low (<40 cases/year) OR 1.65 (95% CI 0.39 - 7.05); Mid (40 - 80 cases/year) OR 3.12 (95%CI 1.91 - 5.09)	High (>80 cases/year)	No association with Volume
Hospital Type			
Van der Geest 2012	Academic OR 1.13 (95% CI 0.25 - 5.15); Training Program Only OR 0.58 (95% CI 0.23 - 1.45)	Non Academic/No Training Program	No Association with Hospital Type
Charlton 2016	NCI Hospital) OR 3.51 (95% CI 2.6 - 4.73)	Non NCI Hospital	Increased adherence with NCI hospital
Charlton 2016	Residency Program OR 1.75 (95%CI 1.44 - 2.14)	No Residency Program	Increased adherence with residency program
Charlton 2016	Medical School Affiliation OR 2.19 (95% CI 1.75 - 2.74)	No Medical School Affiliation	Increased Adherence with Medical School Affiliation
	Colonoscopy		
Hospital Volume			
Van der Geest 2012	Low (< 40/year) OR 0.80 (95%CI 0.42 - 1.51); Mid (40 - 80/year) OR 1.27 (95%CI 0.84 - 1.92)	High (>80 cases/year)	No Association with volume

	CEA		
Hospital Type			
Charlton 2016	NCI OR 1.90 (95%CI 1.39 - 2.61)	Non NCI Hospital	Adherence associated with NCI Hospital
Charlton 2016	Residency Program OR 1.38 (95% CI 1.15 - 1.66)	No Residency Program	Adherence associated with residency program hospital
Charlton 2016	Major OR 1.34 (95%CI 1.08 - 1.67)	Non-Affiliated	Adherence associated with Major Affiliation

NCI National Cancer Institute, OR Odds Ratio, CI Confidence Interval, *univariable

Table 8-36 Association between hospital volume or type and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Overall		
Hospital Type			
Schroen 2001	ACofS Approved OR 1.66 (95%CI 0.82 - 3.35)	Non ACofS Approved	No Association
Schroen 2001	Major Teaching Hospital OR 2.35 (95%CI 0.92 - 5.99); Minor Teaching Hospital OR 2.60 (95%CI 1.17 - 5.80)	Non Teaching Hospital	Adherence Associated with Teaching Hospital
Schroen 2001	Small (1 - 100 beds) OR 0.78 (95%CI 0.25 - 2.40); Mid (101 - 299 beds) OR 1.32 (95%CI 0.66 - 2.64) Non AcofS Approved OR 1.1 (95%CI 0.7 - 1.8)	Large (300+ beds)	No Association with hospital size
Van Eenwyk 2002	*Univariable Only, Outcome was NON-ADHERENCE	ACofS Approved	No Association
Hospital Volume			
Manchon Walsh 2011	Low Volume (<12 cases/year) 13.3%; Mid (12 - 30 cases/year) 23%; High Volume (>30 cases per year) 30% *Univariable P < 0.05)		Higher Adherence with Higher Volume Hospital
	Radiation		
Hospital Volume			
Comber 2012	OR 0.99 (95%CI 0.96 - 1.02) (per additional case/year)		No Association
Eliott 2014	High Volume (>40 cases/year) OR 1.06 (95%CI 0.65 - 1.72)	Low Volume (< 40 cases/year)	No Association
Manchon Walsh 2011	Low Volume (<12 cases/year) 21%; Mid (12 - 30 cases/year) 31%; High Volume (>30 cases per year) 44% *Univariable P < 0.05)		Higher Adherence with Higher Volume
Midura 2017	OR 1.00 (95%CI 1.00 - 1.01) (per additional case/year)		Higher adherence with higher volume
Monson 2014	High (31+) OR 1.46 (95%CI 1.34 - 1.59); Mid (11 - 30) OR 1.30 (95%CI 1.21 - 1.39)	Low (< 11/year)	Higher adherence with higher volume
Sineshaw 2014	Mid OR 0.83 (95%CI 0.79 - 0.87); Low OR 0.71 (95%CI 0.66 - 0.76)	High	Higher adherence associated with higher volume
Van Der Geest 2012	Low (< 40 per year) OR 3.45 (95%CI 1.26 - 9.44); Mid (40 - 80 per year) OR 2.50 (95%CI 1.50 - 4.18)	High	Lower volume associated with increased adherence
Hospital Type			
Hegi Johnson	Teaching Hospital 36%; Non Teaching 27%; Private 30%, * Univariable, P = 0.5		No Association
Del Vecchio 2019	Large (500+ beds) OR 2.06 (95%CI 1.35 - 3.13)	Small (< 500)	Adherence associated with larger hospital type
Midura 2017	Community Cancer Centre 13.2%; Comprehensive Cancer Centre 48%; Academic Medical Centre 39% *Univariable, P < 0.001		Associated with hospital type
Monson 2014	Comprehensive OR 0.95 (95%CI 0.85 - 1.06); Community OR 0.95 (95%CI 0.90 - 1.01)	Academic	No Association
Olsson 2011	District OR 0.88 (95%CI 0.79 - 0.97); GDH OR 0.89 (95%CI 0.82 - 0.98)	University Hospital	Associated with hospital type
Sinclair 2012	Small or Medium OR 0.94 (95%CI 0.58 - 1.52)	Large	No Association
Sineshaw 2014	Community OR 0.98 (95%CI 0.92 - 1.06); Comprehensive OR 1.00 (95%CI 0.95 - 1.05); NCI OR 1.21 (95%CI 1.13 - 1.29)	Teaching/Research Hospital	Associated with hospital type

Lau 2021	Community OR 1.2 (95%CI 1 - 1.4); Comprehensive OR 1 (95%CI 0.9 - 1.1); Integrated OR 0.9 (95%CI 0.8 - 1.0)	Academic	Associated with hospital type
	Chemotherapy		
Hospital Volume			
Comber 2012	OR 1.01 (95%CI 0.98 - 1.01) (per additional case/year)		No Association
Manchon Walsh 2011	Low Volume (<12 cases/year) 81%; Mid (12 - 30 cases/year) 84%; High Volume (>30 cases per year) 87% *Univariable P < 0.05)		Higher Adherence with Higher Volume
Monson 2014	High (31+ per year) OR 0.76 (95%CI 0.64 - 0.92); Mid (11 - 30/year) OR 0.82 (95%CI 0.71 - 0.94)	Low (<11/year)	Lower Volume associated with higher adherence
Xu 2017	High OR 1.29 (95%CI 1.01 - 1.66); Mid OR 1.23 (95%CI 1.01 - 1.49)	Low	Higher Adherence with Higher Volume
Hospital Type			
Del Vecchio 2019	Large (500+ beds) OR 1.34 (95%CI 0.98 - 1.84)	Small (< 500)	No Association
Monson 2014	Comprehensive OR 1.18 (95%CI 1.03 - 1.36); Community OR 1.09 (95%CI 0.87 - 1.36)	Academic	No Association
Sinclair	Small or Medium OR 0.73 (95%CI 0.43 - 1.23)	Large	No Association
Xu 2017	Community OR 1.59 (95%CI 1.15 - 2.11); Comprehensive OR 2.35 (95%CI 0.45 - 9.45)	Academic	Associated with Some hospital types
	Surgery		
Hospital Volume			
Comber 2012	OR 1.06 (95%CI 1.00 - 1.12) (per additional case/year)		Higher quality surgery associated with higher volume

Note, Hospital type/volume and surveillance adherence were not assessed in any studies
OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-37 Association between marital status and treatment/surveillance adherence outcomes (staging adherence was not assessed)

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Age Group	Direction of Association, notes
	Marital Status		
Overall Treatment			
Abraham 2006	Married OR 5.25 (95%CI 1.61 - 17.14)	Unmarried	Married associated with increased adherence
Radiation			
Olsson 2011	Widowed OR 0.75 (95%CI 0.67 - 0.83); Divorced OR 0.84 (95%CI 0.74 - 0.94); Unmarried OR 0.67 (95%CI 0.59 - 0.76)	Married	Associated with marital status
Sinclair 2012 (Age 65+)	Married OR 1.15 (95%CI 0.63 - 2.09)	Unmarried	No association
Sinclair 2012 (Age < 65)	Married OR 0.64 (95%CI 0.29 - 1.38)	Unmarried	No association
Del Vecchio 2019	Single OR 0.85 (95%CI 0.55 - 1.32); Separated/Divorced OR 0.90 (95%CI 0.55 - 1.48); Widowed OR 0.66 (95%CI 0.41 - 1.04)	Married	No Association
Chemotherapy			
Cheung 2009 (Neoadjuvant - Yes)	Unmarried OR 2.01 (95%CI 0.55 - 7.88) *Outcome was nonadherence	Married	No association
Cheung 2009 (Neoadjuvant - No)	Unmarried OR 1.09 (95%CI 0.84 - 1.42) *Outcome was non-adherence	Married	No association
Sinclair (age 65+)	Married OR 1.03 (95%CI 0.39 - 2.73)	Unmarried	No association
Sinclair (age < 65)	Married OR 1.39 (95%CI 0.85 - 2.27)	Unmarried	No association
Del Vecchio 2019	Single OR 1.24 (95%CI 0.84 - 1.82); Separated/Divorced OR 0.82 (95%CI 0.54 - 1.26); Widowed OR 1.49 (95%CI 0.89 - 2.49)	Married	No association
Overall Surveillance			
Tan 2012	Married OR (95%CI 0.41 - 1.72)	Unmarried	No association
Metastatic Surveillance			
Sehdev 2017	Married OR 0.92 (95%CI 0.71-1.19)	Unmarried	No association
Surveillance Colonoscopy			
Carey 2017	Married OR 1.01 (CI 0.58 - 1.76)	Unmarried	No association
Rulyak 2004	Married OR 1.27 (CI 1.05-1.53)	Unmarried	Married associated with increased adherence
Salz 2010	Married OR 1.20, p=.09 (no CI given)	Unmarried	No association

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-38 Association between health insurance status and staging/treatment adherence outcomes (note surveillance outcomes not assessed)

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association, notes
Staging CEA			
Bergin 2020	Public OR 0.45 (95%CI 0.20 - 1.00)	Private	Public insurance associated with lower adherence
Colonoscopy Staging			
Bergin 2020	Public OR 0.49 (95%CI 0.21 - 1.14)	Private	Public insurance associated with lower adherence
Overall Treatment			
Abraham 2006	Non-VA insurance 77.8%; VA insurance only 75.7%, P = 1.0 *Univariable Analysis only		No association
Chapman 2018	Private Insurance 56.5%; No Private Insurance 54.3%, P = 0.51, *Univariable Only		No association
Radiation			
Haas 2011	State Eligible Insurance OR 0.85 (95%CI 0.73 - 0.99)	No Eligible	State Eligible Insurance associated with lower adherence
Hegi - Johnson 2007	Private 30%; Public 35%, P = 0.5 *Univariable Only		No association
Murphy 2015	Private 27%; Medicaid 36%; Medicare 22%; None 24%; Unknown 7%; P < 0.05, *Univariable Analysis		Insurance type associated with adherence
Sineshaw 2016	Uninsured OR 0.93 (95%CI 0.86 - 1.01); Medicaid OR 0.90 (95%CI 0.83 - 0.97); Medicare OR 0.85 (95%CI 0.81 - 0.90); Other OR 0.44 (95%CI 0.39 - 0.49)	Private	Insurance type associated with adherence
Lau 2021	Uninsured OR 1 (95%CI 0.8 - 1.2); Medicaid OR 1 (95%CI 0.9 - 1.2); Medicare OR 1.2 (95%CI 1.1 - 1.4); Other Government OR 1.3 (95%CI 0.9 - 1.8) *Outcome is Non-adherence	Private	Insurance type associated with adherence
Wong 2021	Private OR 2.70 (95%CI 1.33 - 5.47)	Uninsured/Public	Private insurance associated with increased adherence
Xu 2017	Medicaid OR 1.05; Medicare OR 1.05; Other Government OR 1.06; Uninsured OR 0.47 *No CI provided)	Private	Uninsured associated with non adherence
Chemotherapy			
McGory 2016	Private OR 0.84 (95%CI 0.67 - 1.05); Medicaid OR 0.13 (95%CI 0.40 - 0.94)	Medicare	Insurance type associated with adherence
Monson 2014 (Neoadjuvant - Yes)	Uninsured OR 0.83 (95%CI 0.69 - 1.00); Medicaid OR 0.82 (95%CI 0.70 - 0.97); Medicare OR 0.79 (95%CI 0.70 - 0.89); Other OR 0.69 (95%CI 0.46 - 1.03)	Private	Insurance type associated with adherence
Monson 2014 (Neoadjuvant - No)	Uninsured OR 0.72 (95%CI 0.53 - 0.97); Medicaid OR 0.83 (95%CI 0.64 - 1.08); Medicare OR 0.83 (95%CI 0.71 - 0.96); Other OR 0.81 (95%CI 0.46 - 1.42)	Private	Some Insurance types associated with adherence
Xu 2017	Medicaid OR 0.64; Medicare OR 0.78; Other Government OR 0.41; Uninsured OR 0.94 *No CI provided)	Private	Other Insurance Type associated with non adherence

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-39 Association between physician specialty and staging/surveillance adherence outcomes (note treatment adherence not assessed)

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association, notes
	Metastatic Staging		
Ma 2015	Gastroenterologist OR 0.40 (95%CI 0.21 - 0.77)	All Other	Gastroenterologist associated with non-adherence
	Metastatic Surveillance		
Sehdev 2017	Specialist OR 1.11 (95%CI 0.99 - 1.25)	Primary Care	No association
Sisler 2012	Oncologist contact OR 4.74 (95%CI 2.28 - 9.88)	no contact	Specialty Contact associated with adherence
Vargas 2013	Oncologist following 61.5% vs. Not following 8.8% *Univariable Analysis Only		Specialty associated with adherence
	Colonoscopy Surveillance		
Carey 2017	No Specialist Following OR 0.35 (95%CI 0.14-0.91)	Specialist Following	Specialty associated with adherence
Salz 2010	Primary Care OR 1.44, p<.01, Oncologist OR 1.23, p=.17 *CI not reported	Not seen by Primary care of Oncologist	Specialty associated with adherence
Sisler 2012	Surgeon Contact OR 6.90 (95%CI 2.44 - 19.54); Oncologist Contact OR 1.89 (95%CI 0.84 - 4.24)	No Contact	Specialist Contact associated with adherence
Vargas 2013	Oncology Following 86%; Not Following 70%, P = 0.02 *Univariable Only		Specialty associated with adherence
	CEA Surveillance		
Sisler 2012	Oncologist contact OR 3.18 (95%CI 1.4 - 6.99); High Primary Care Contact OR 2.71 (95%CI 1.32 - 5.58)	No contact or low contact	Contact associated with adherence
Vargas 2013	Oncology Following 70.5%; Not Following 11%, P < 0.02 *Univariable		Specialty associated with adherence

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-40 Association between physician volume and staging adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Local Regional Disease		
Comber 2012	OR 1.10 (95% CI 1.05 - 1.18) (per additional case)	N/A	Higher Volume associated with increased adherence
McGrath 2005	10.4 % (Low Volume); 20.4% (High Volume, >6 cases/3 months) (P = 0.003)*Univariable Analysis Only		Higher Volume associated with increased adherence
	Metastatic Disease Staging		
Comber 2012 (Chest)	OR 0.94 95%CI 0.91 - 0.98 (per additional case)	N/A	Higher Volume associated with reduced adherence
Comber 2012 (Abdomen)	OR 0.92, 95%CI 0.87 - 0.97 (per additional case)		Higher Volume associated with reduced adherence
McGrath 2005	52.7% (High Volume, 6 cases/3 months) vs. 45.2% (Low Volume), P = 0.003 * Univariable Analysis Only		Higher Volume associated with increased adherence

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-41 Association between physician volume and treatment adherence outcomes

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association
	Radiation		
Comber 2012	OR 1.04 (95%CI 1.01 - 1.07) (per additional case)		Higher Volume associated with increased adherence
Hegi-Johnson	High Volume (20+ cases/year) OR 1.95 (95%CI 1.17 - 3.24)	Low Volume (<20 cases/year)	Higher Volume associated with increased adherence
	Chemotherapy		
Comber 2012	OR 1.00 (95%CI 0.96 - 1.03) (per additional case)		No Association with surgeon volume
	Surgery		
Comber 2012 (complete TME)	OR 1.07 (95%CI 1.01 - 1.13) (per additional case)		Higher Volume associated with higher quality surgery

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-42 Association between employment status and surveillance adherence outcomes (note staging and treatment not assessed)

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association, notes
	Employment		
	Colonoscopy Surveillance		
Carey 2017	Employed OR 0.58 (95%CI 0.3 - 1.12)	Unemployed	No association

OR Odds Ratio, CI Confidence Interval, *Univariable

Table 8-43 Association between immigration status and adherence outcomes (only overall treatment adherence assessed)

Author	Multivariable Analysis, OR, 95%CI (*Unless otherwise Specified)	Ref Group	Direction of Association, notes
	Immigration Status		
Overall Treatment			
Nielsen 2010	Foreign Born OR 0.35 (95%CI 0.12 - 0.99)	Not Foreign Born	Adherence associated with immigration

OR Odds Ratio, CI Confidence Interval, *Univariable

8.2.4 Appendix Chapter 4 – 4: Forest Plots of the Meta-analyses of Predictors of Guideline Adherent Care

Figure 8-1: The Association between age (per year increase) and receipt of guideline adherent radiation

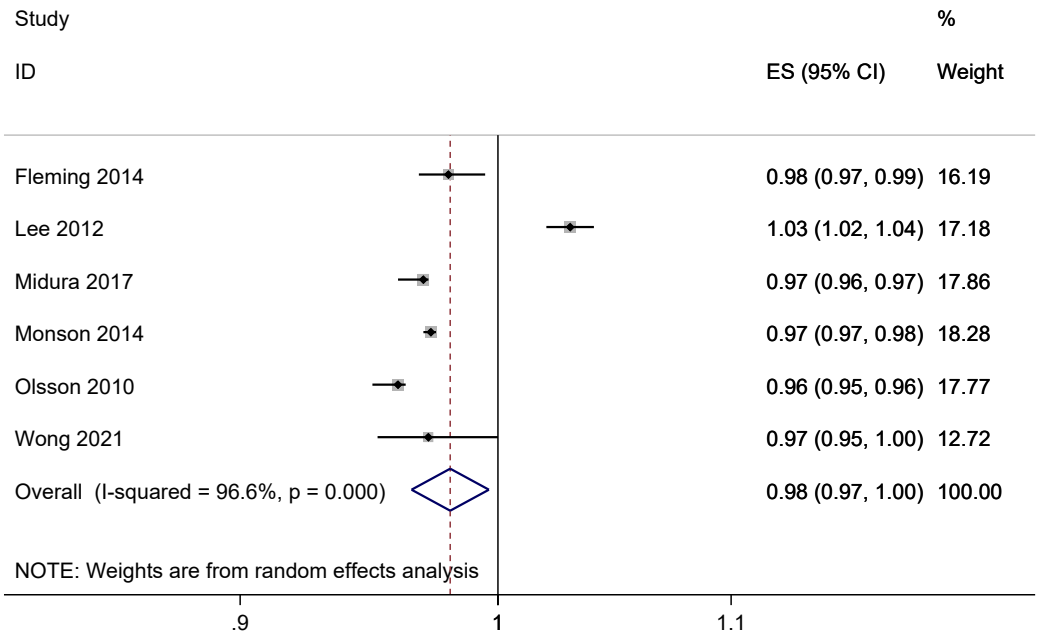


Figure 8-2 The Association between age (per year increase) and receipt of guideline adherent radiation, excluding study be Lee et al.

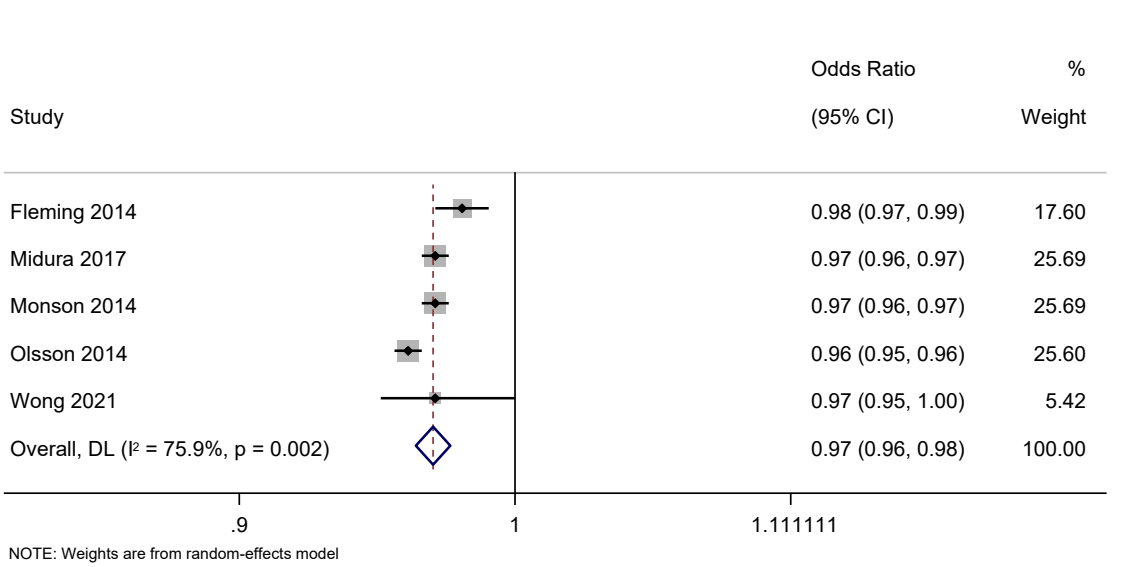


Figure 8-3: The association between age (per one year increase) and receipt of adherent chemotherapy

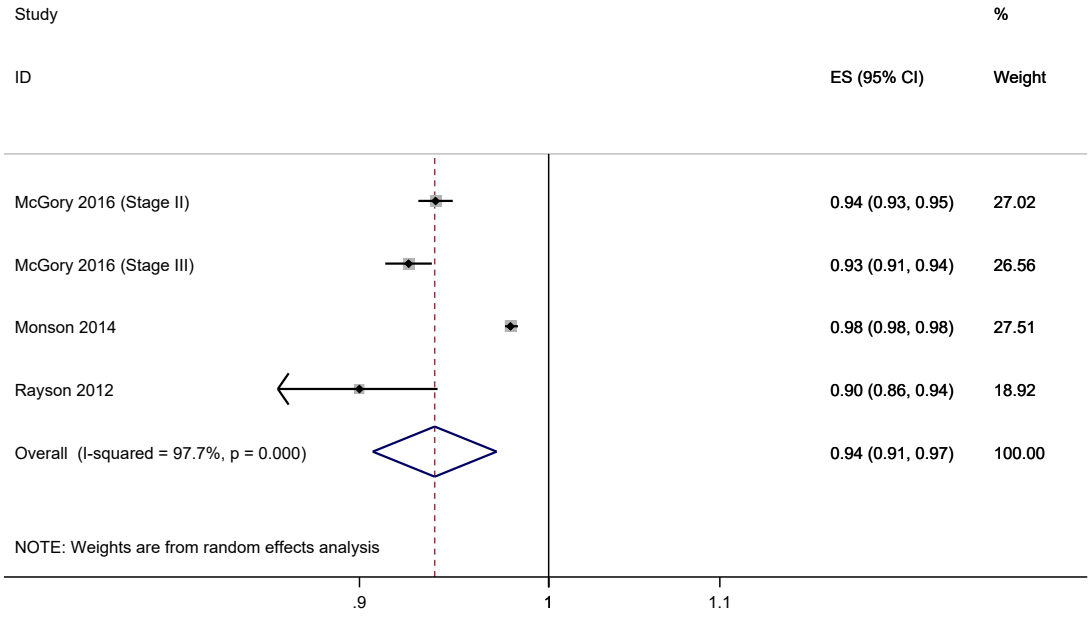


Figure 8-4 The association between age (per one year increase) and receipt of adherent chemotherapy, excluding the study by Monson et al.

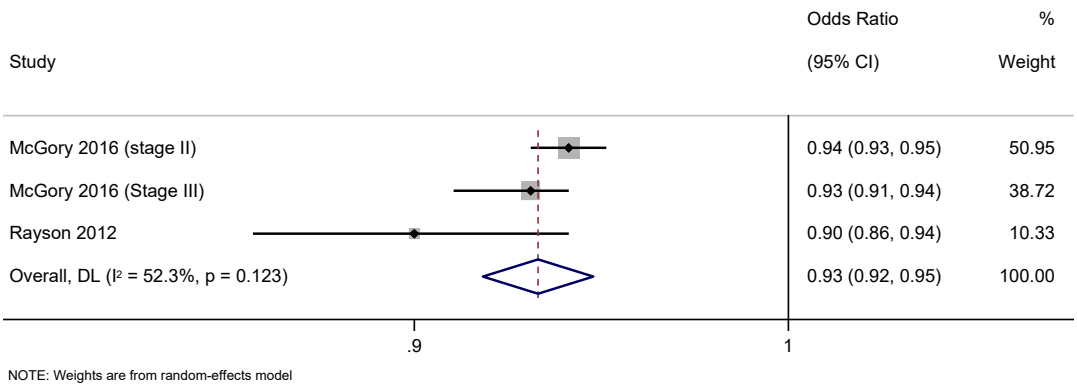


Figure 8-5: The association between sex/gender (male as referent) and overall treatment adherence

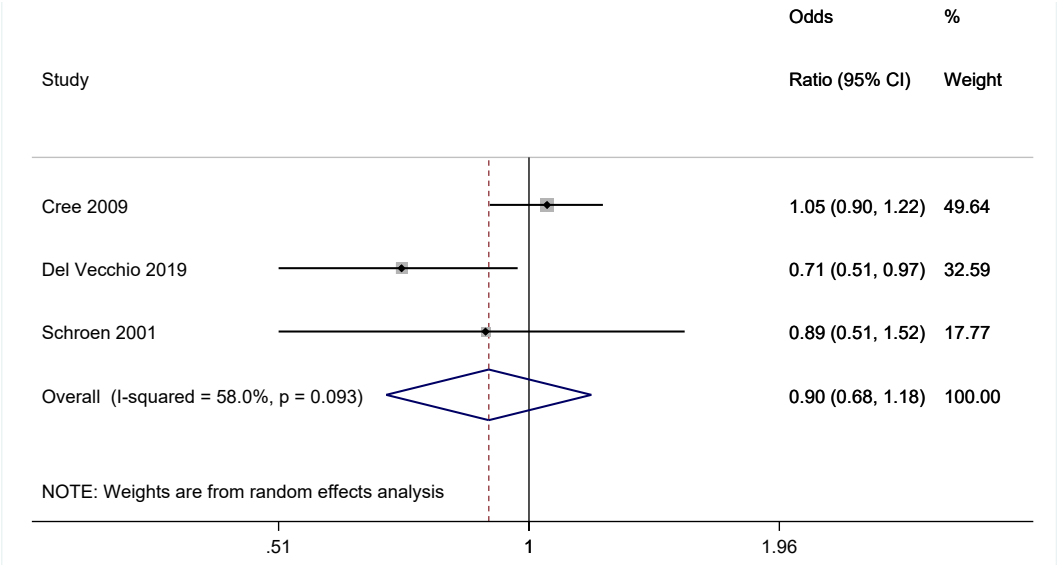


Figure 8-6: The association between Sex/Gender (male as referent) and receipt of guideline adherent radiation

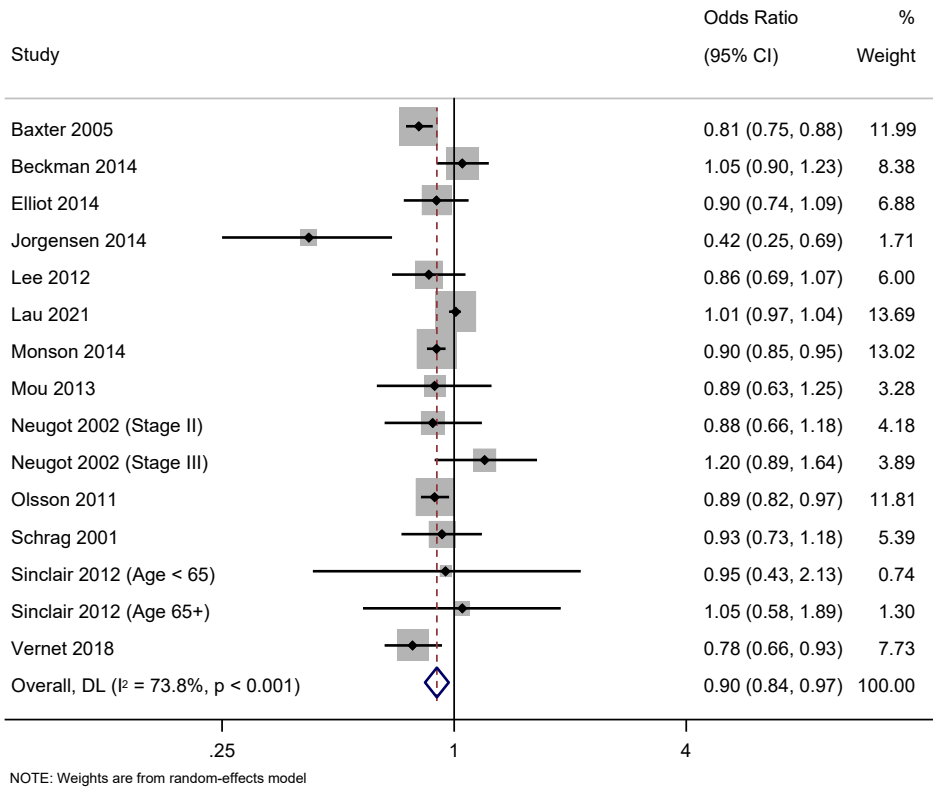


Figure 8-7: The association between Sex/Gender (male as referent) and receipt of guideline adherent chemotherapy

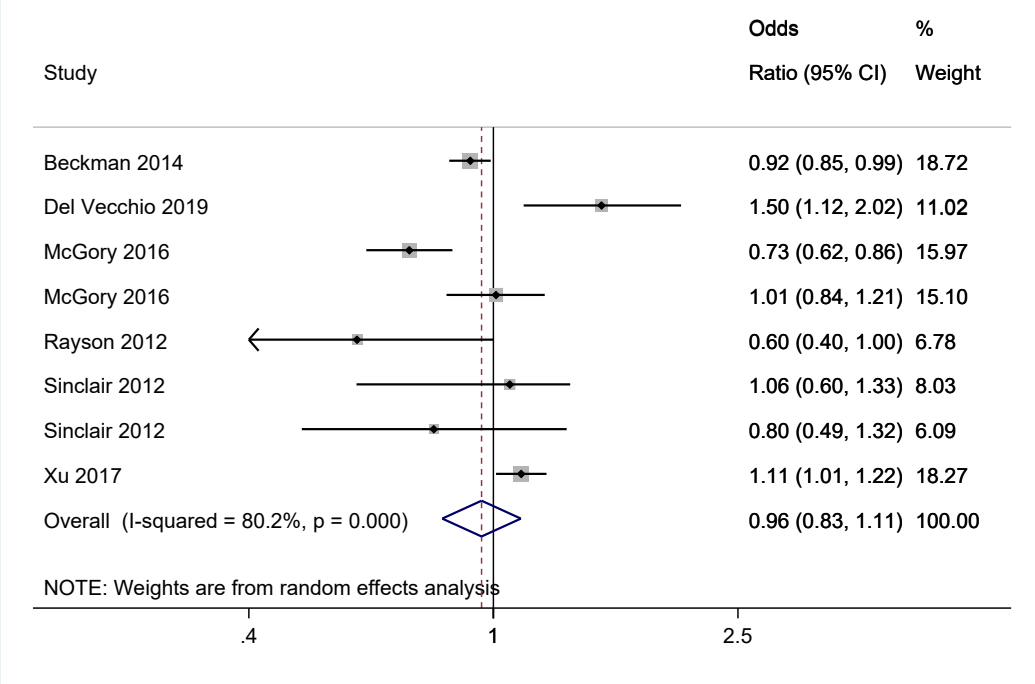


Figure 8-8 The association between Sex/Gender (male as referent) and receipt of guideline adherent chemotherapy, excluding the highest and lowest effect estimate outliers

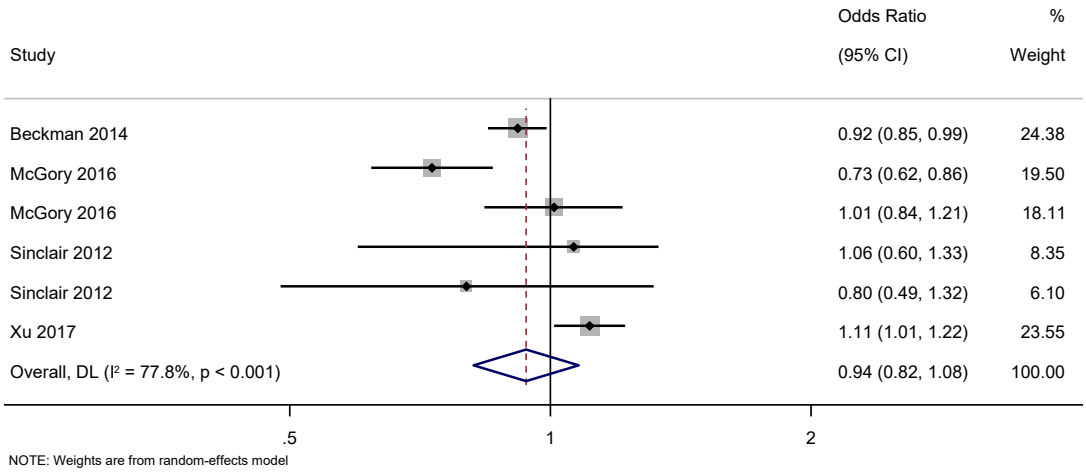


Figure 8-9: The association between Sex/Gender (male as referent) and Guideline adherent overall surveillance

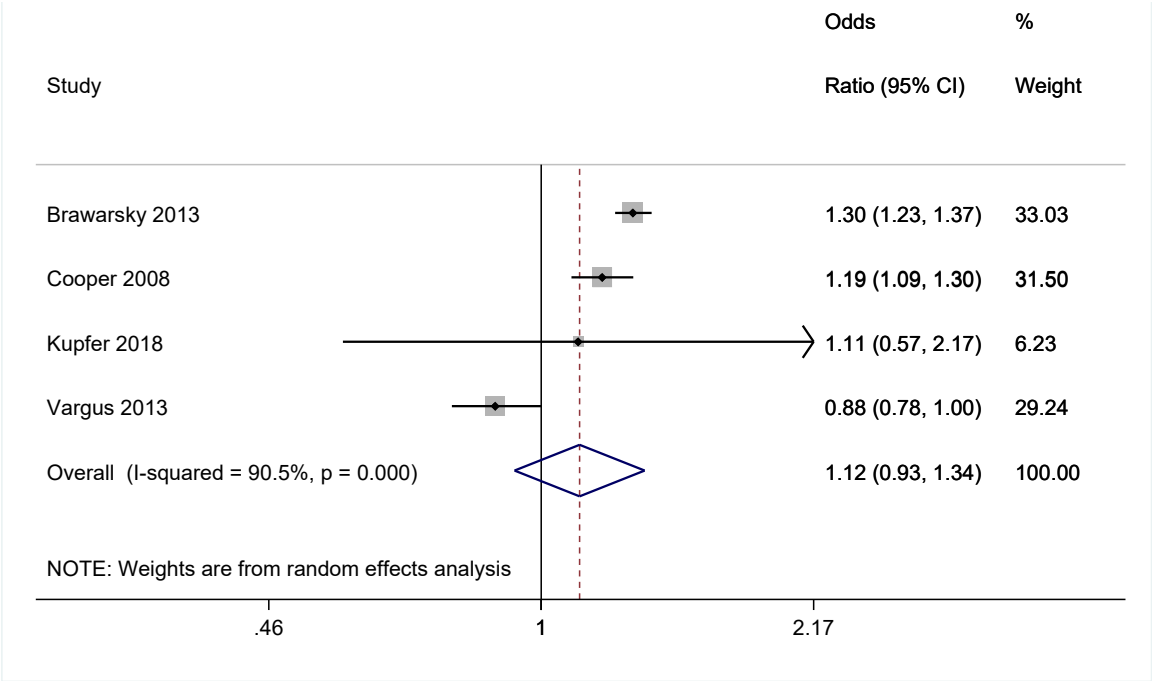


Figure 8-10 The association between Sex/Gender (male as referent) and Guideline adherent overall surveillance, excluding the study by Vargas et al.

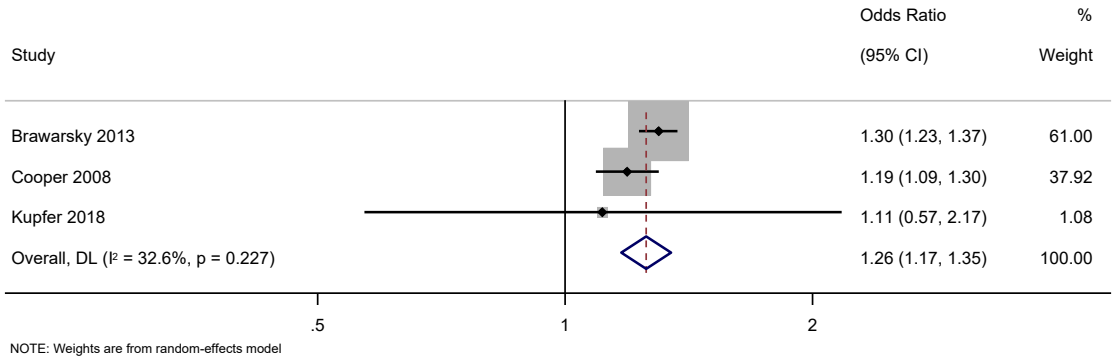


Figure 8-11: The association between Sex/Gender (male as referent) and receipt of Guideline adherent Surveillance Colonoscopy

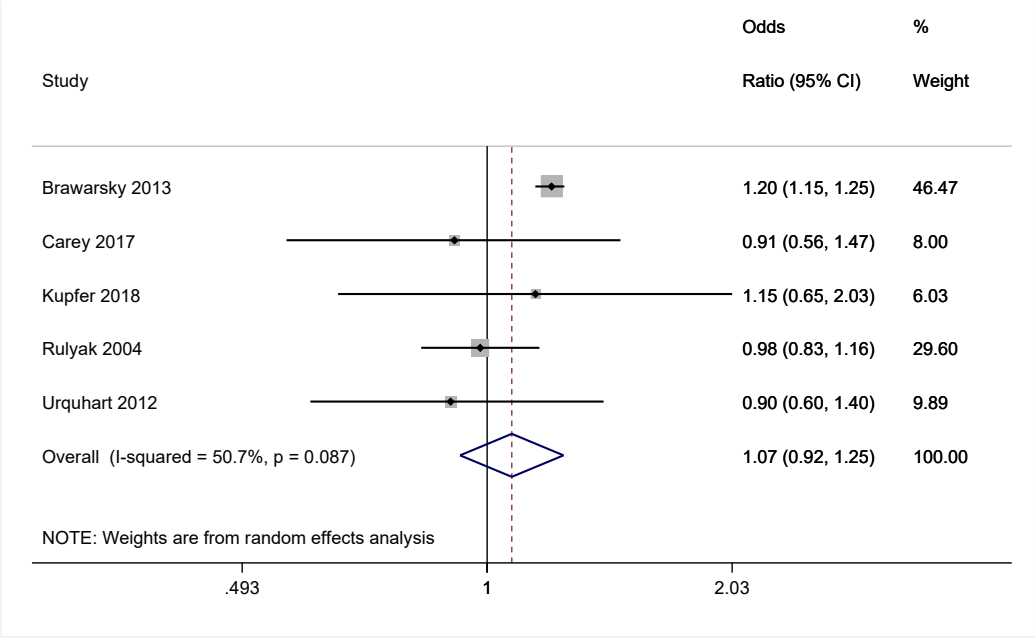


Figure 8-12: The association between Sex/Gender (male as referent) and Guideline adherent surveillance CEA

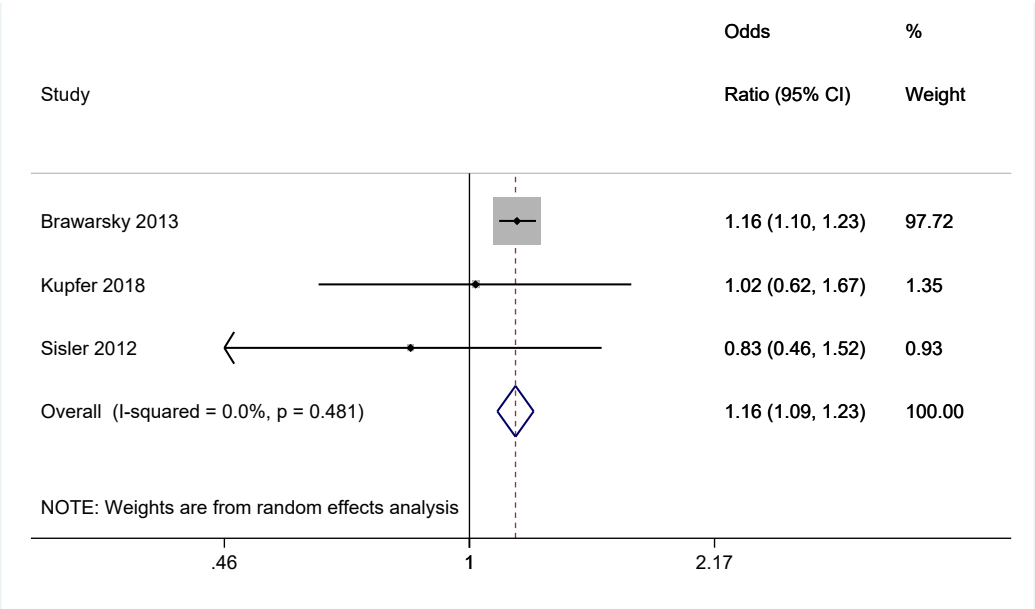


Figure 8-13: The association between Ethnicity (Black vs. White [referent]) and receipt of adherent radiation

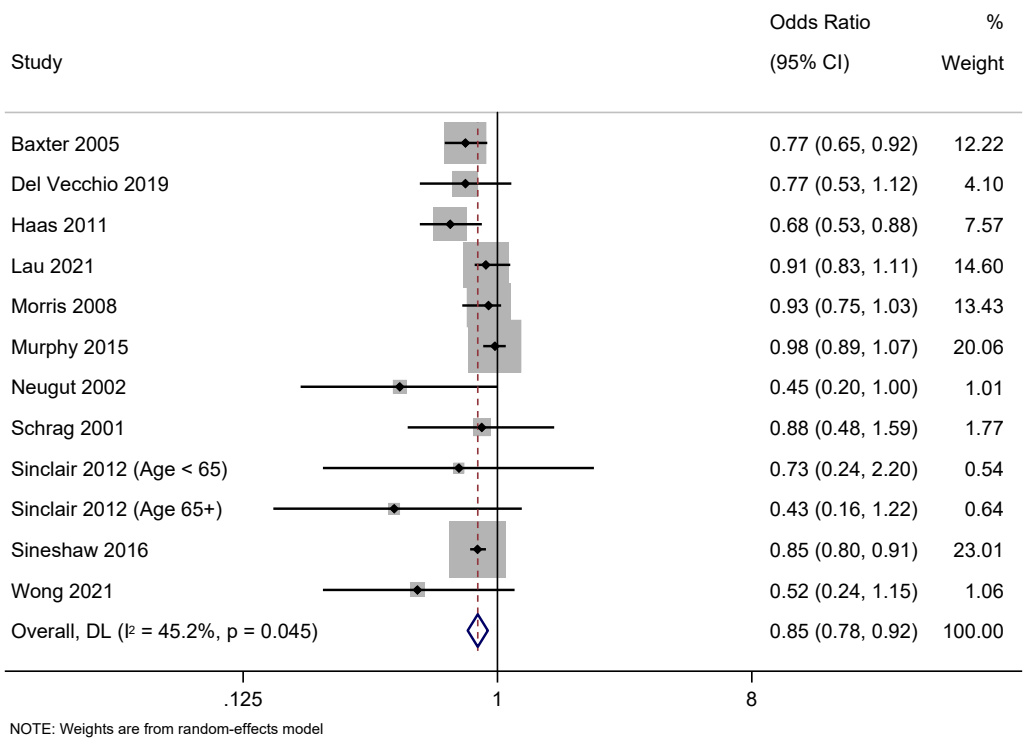


Figure 8-14: Ethnicity (Hispanic vs. White [ref]) and adherent Radiation

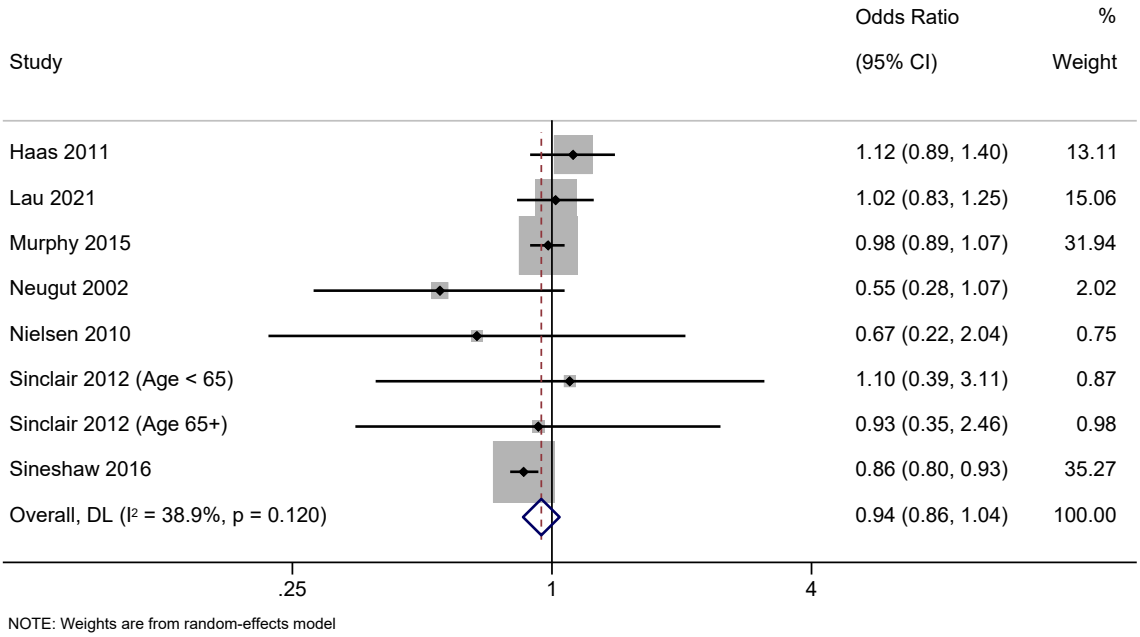


Figure 8-15: Ethnicity (Black vs. White [ref]) and adherent Chemotherapy

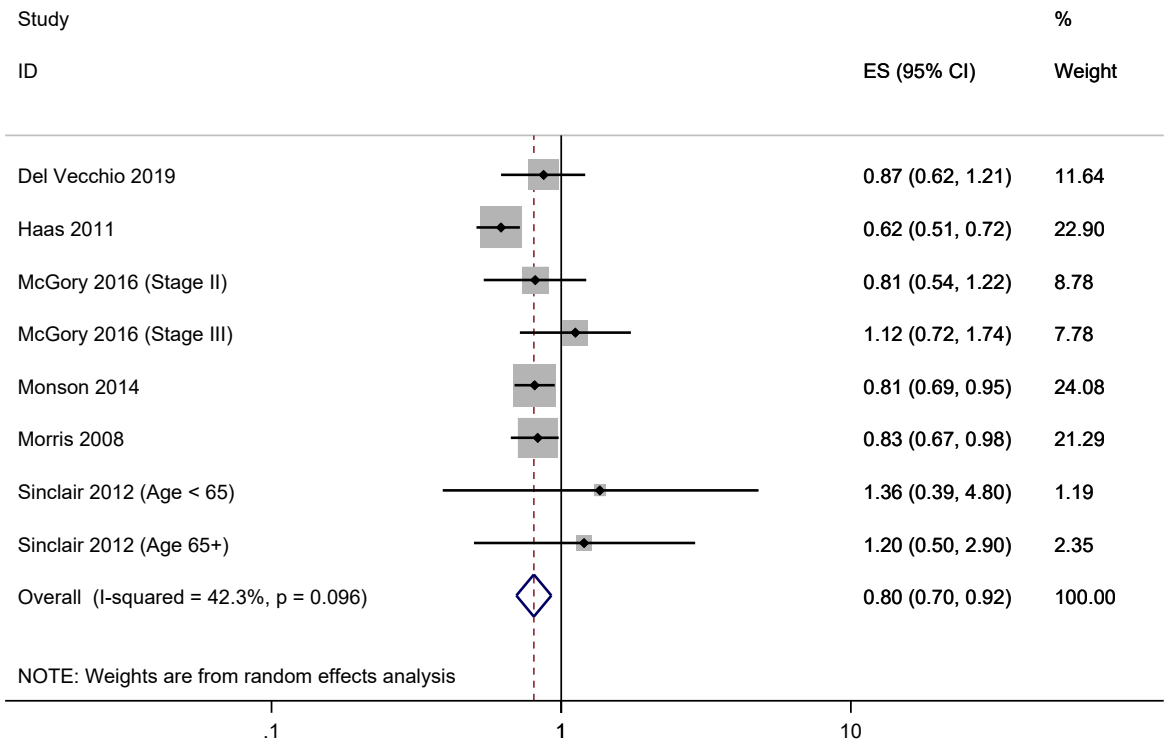


Figure 8-16: Ethnicity (Hispanic vs. White [ref]) and adherent Chemotherapy

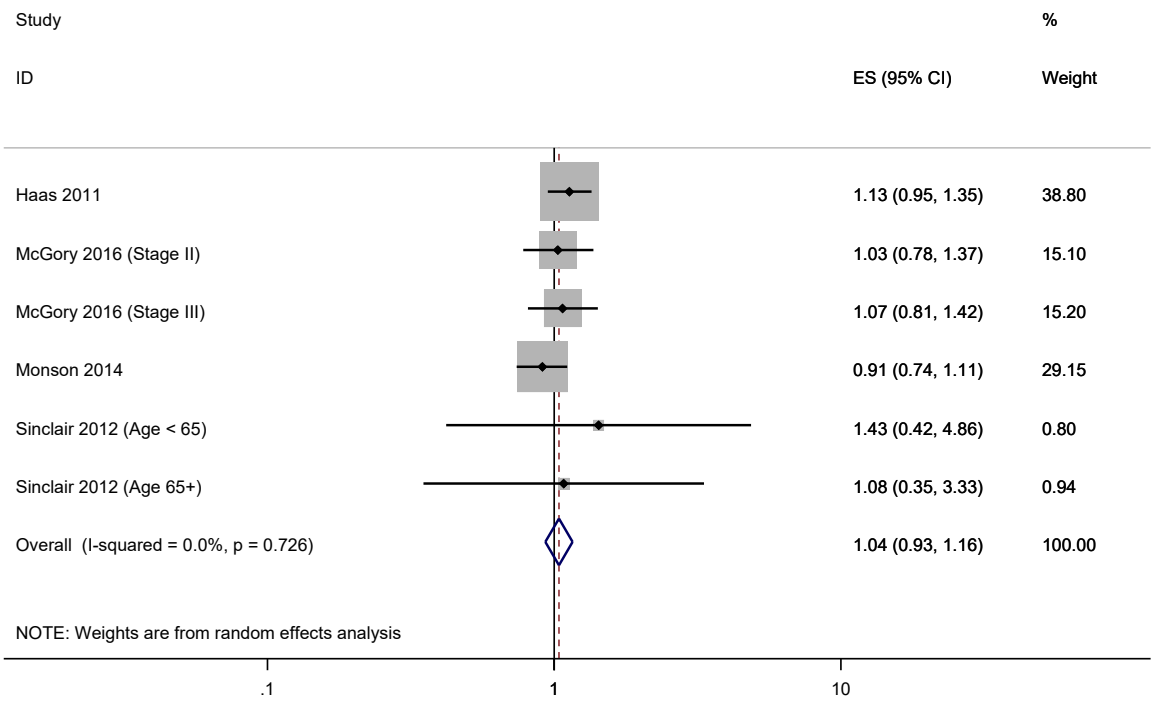


Figure 8-17: Ethnicity (Black vs. White [ref]) and adherent overall surveillance

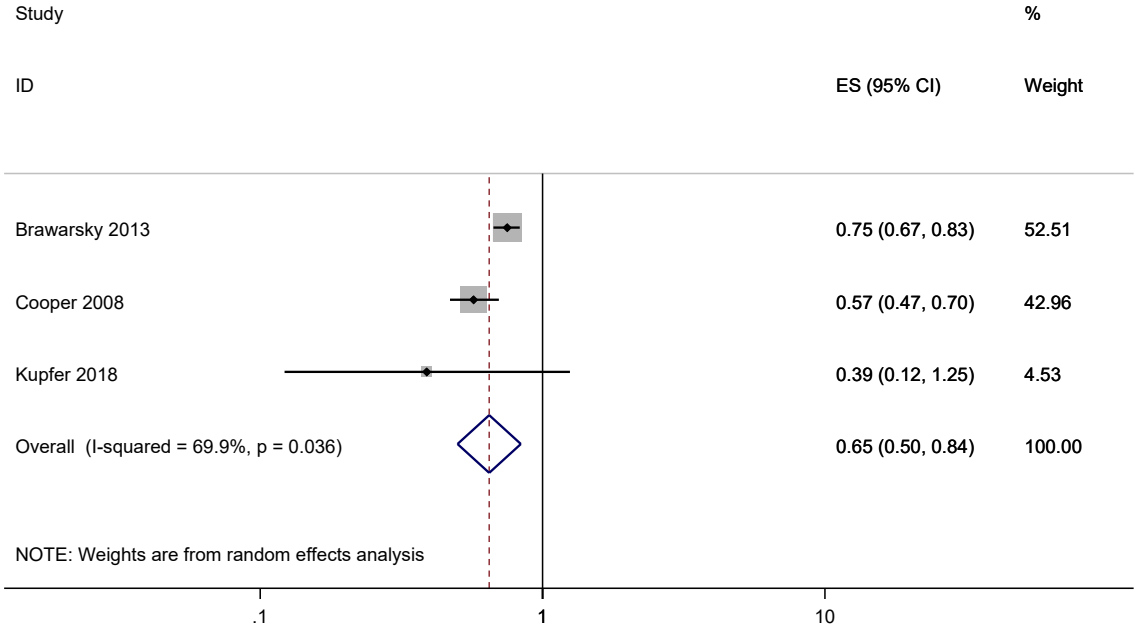


Figure 8-18: Ethnicity (Hispanic vs. White [ref]) and adherent overall surveillance

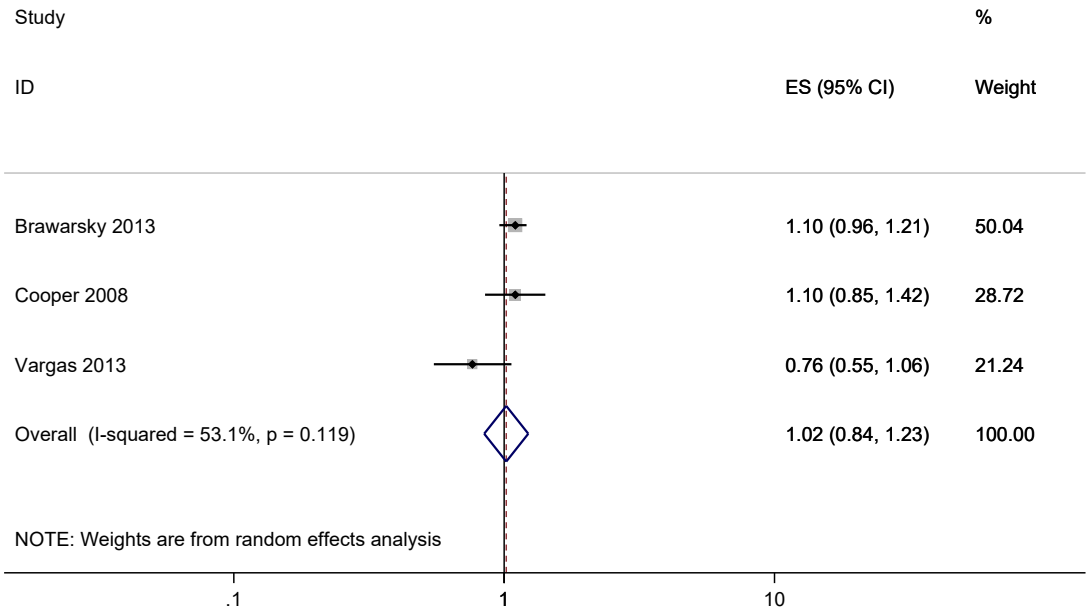


Figure 8-19: Ethnicity (Black vs. White [ref]) and adherent surveillance Colonoscopy

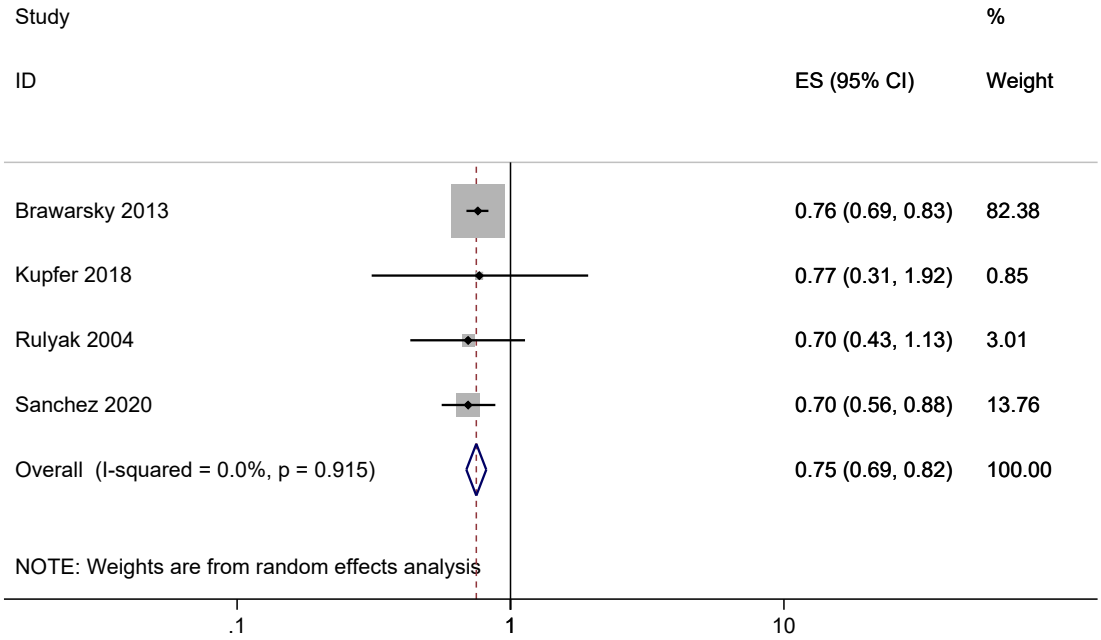


Figure 8-20: Ethnicity (Hispanic vs. White [ref]) and adherent surveillance colonoscopy

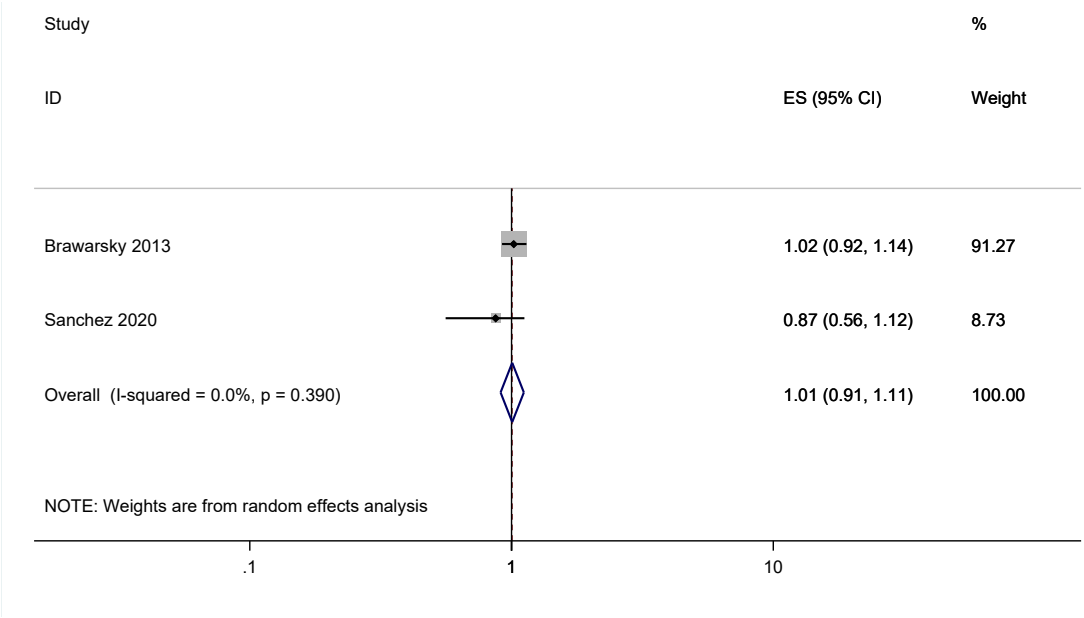


Figure 8-21: Ethnicity (Black vs. white [ref]) and adherent surveillance CEA

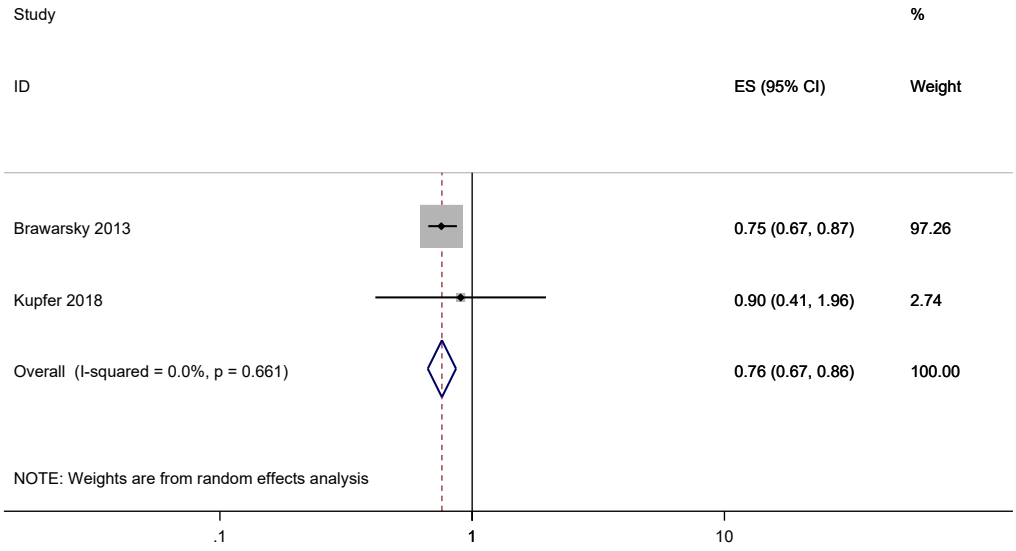


Figure 8-22: Socioeconomic Status (Low vs. high [ref]) and adherent radiation

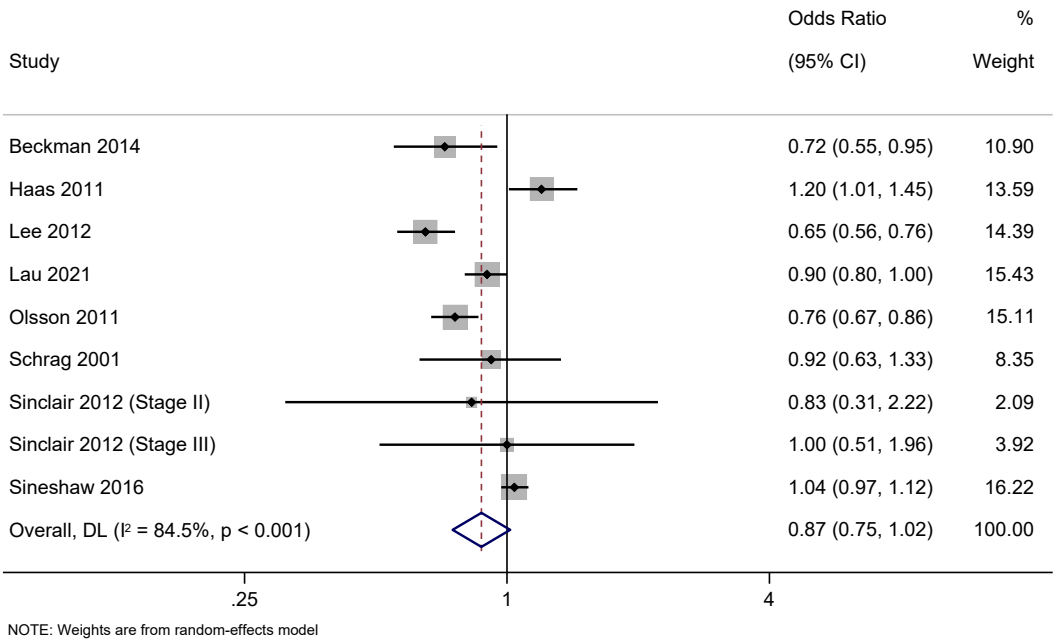


Figure 8-23 Socioeconomic Status (Low vs. high [ref]) and adherent radiation, excluding the outlying study

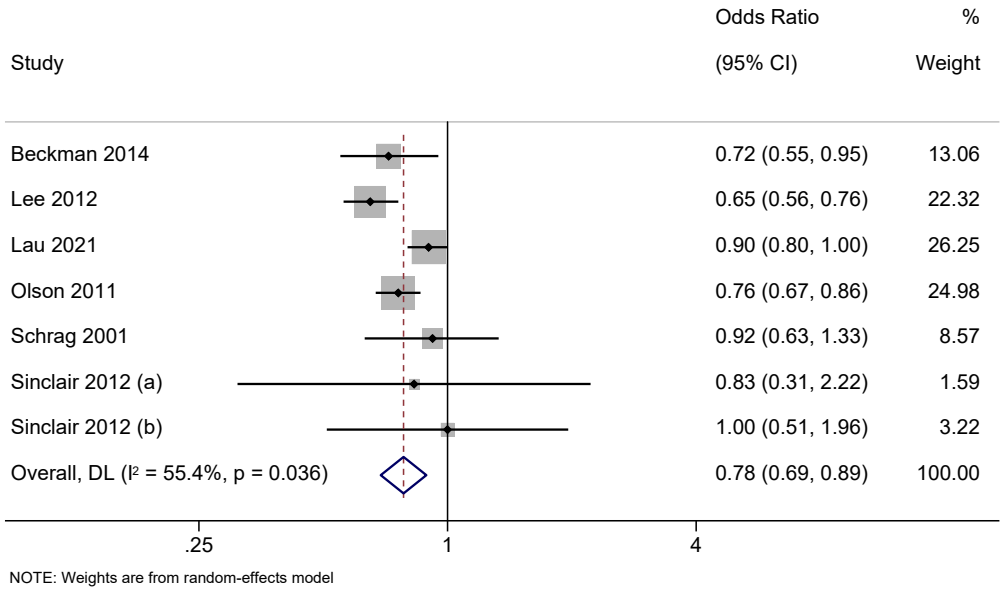


Figure 8-24: Socioeconomic Status (low vs. high [ref]) and adherent surveillance colonoscopy

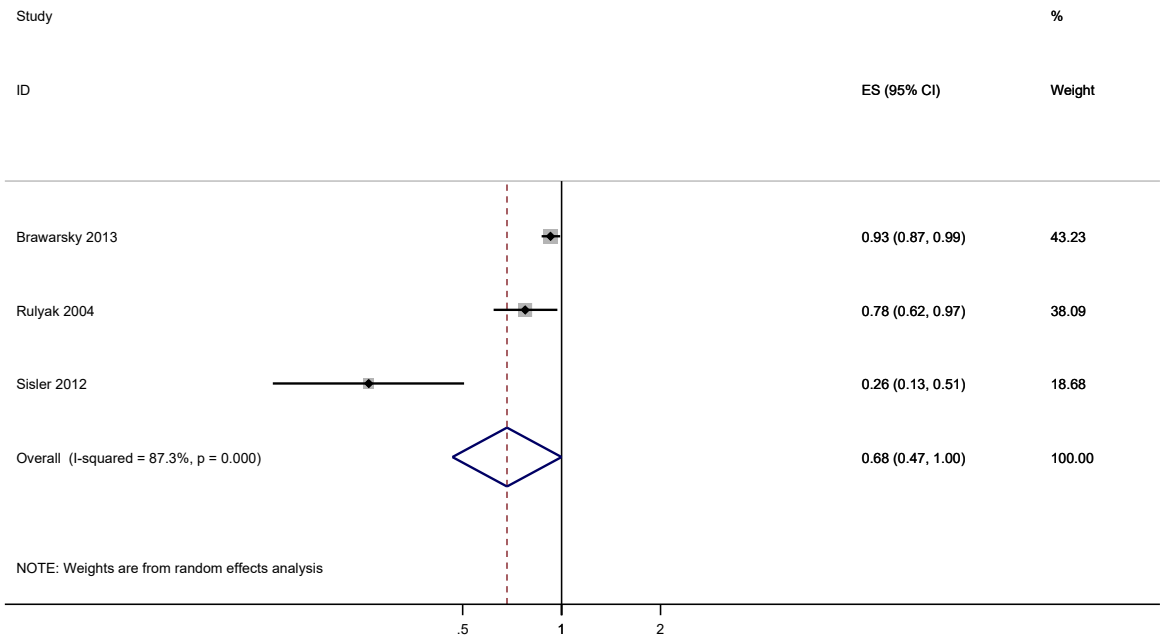


Figure 8-25 Socioeconomic Status (low vs. high [ref]) and adherent surveillance colonoscopy, excluding the outlying study

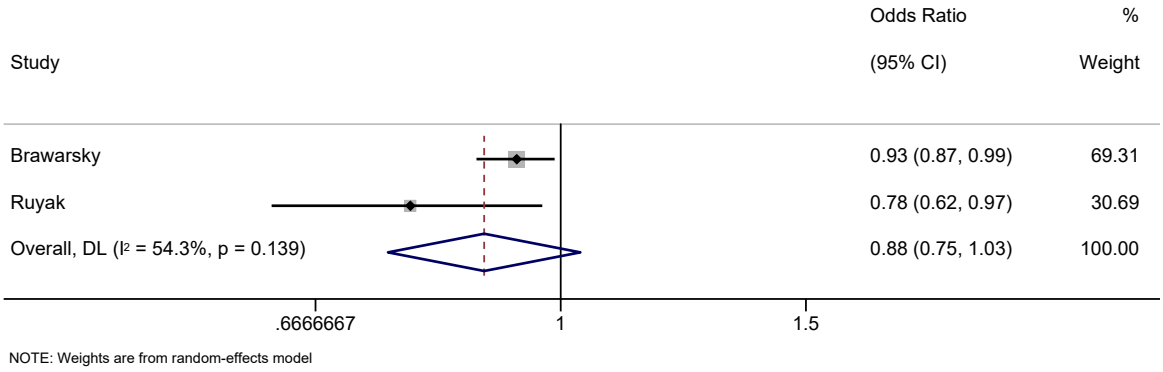


Figure 8-26: Education (Low vs. High [ref]) and adherent Radiation

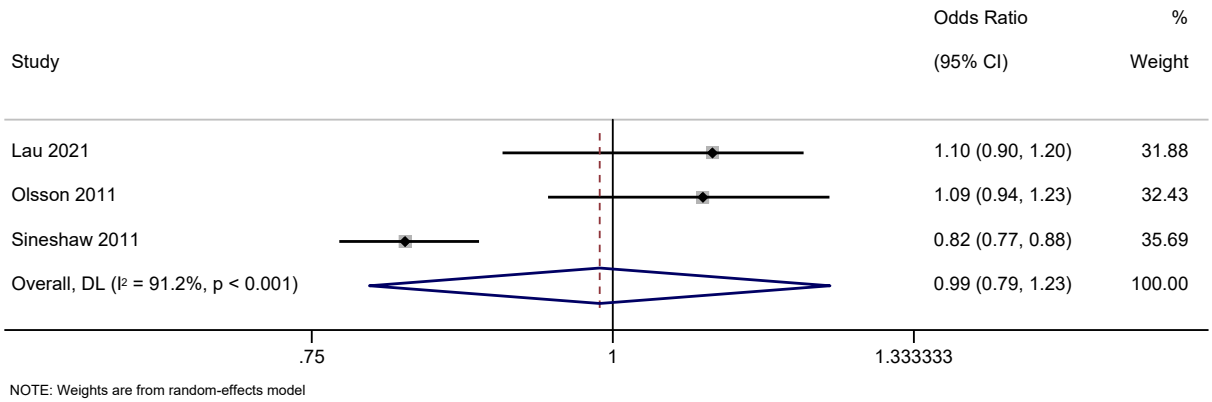


Figure 8-27 Education (Low vs. High [ref]) and adherent Radiation, excluding the outlying study

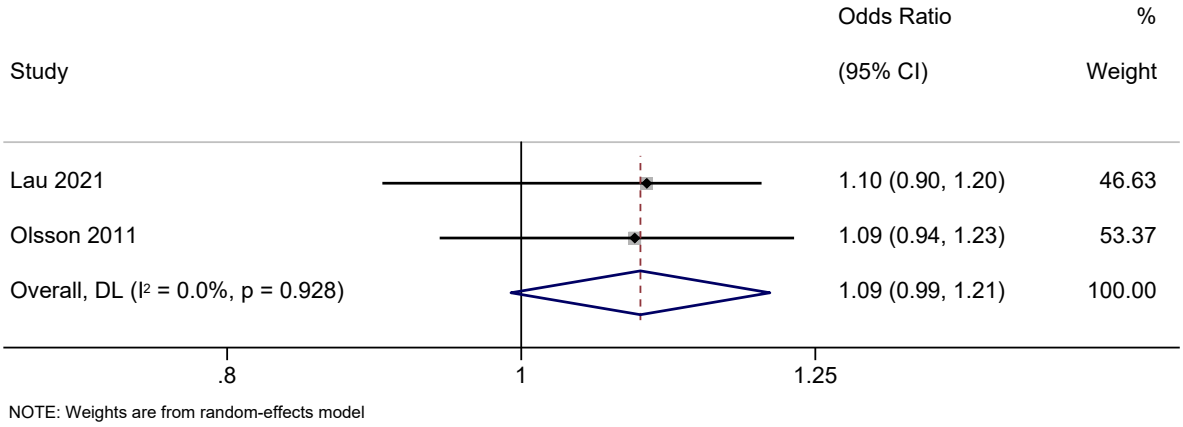


Figure 8-28: Comorbidity Score (Charlson Comorbidity Score 1 vs. Score 0 [ref]) and adherent Radiation

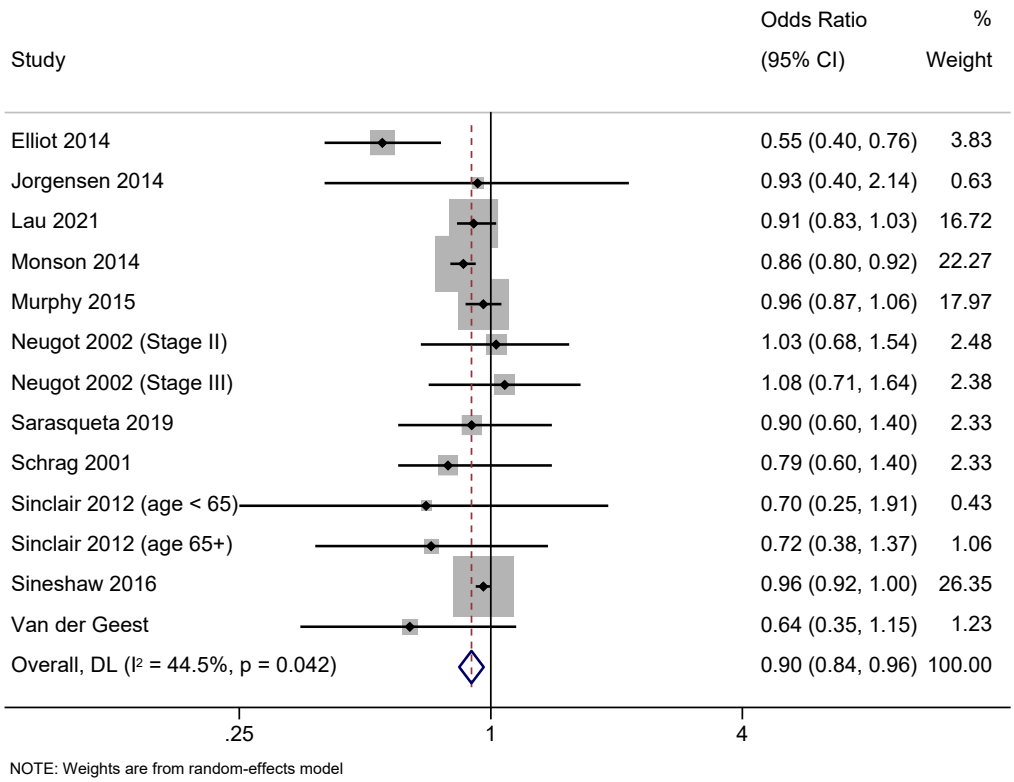


Figure 8-29: Comorbidity Score (Charlson Comorbidity Score 2+ vs. Score 0 [ref]) and adherent Radiation

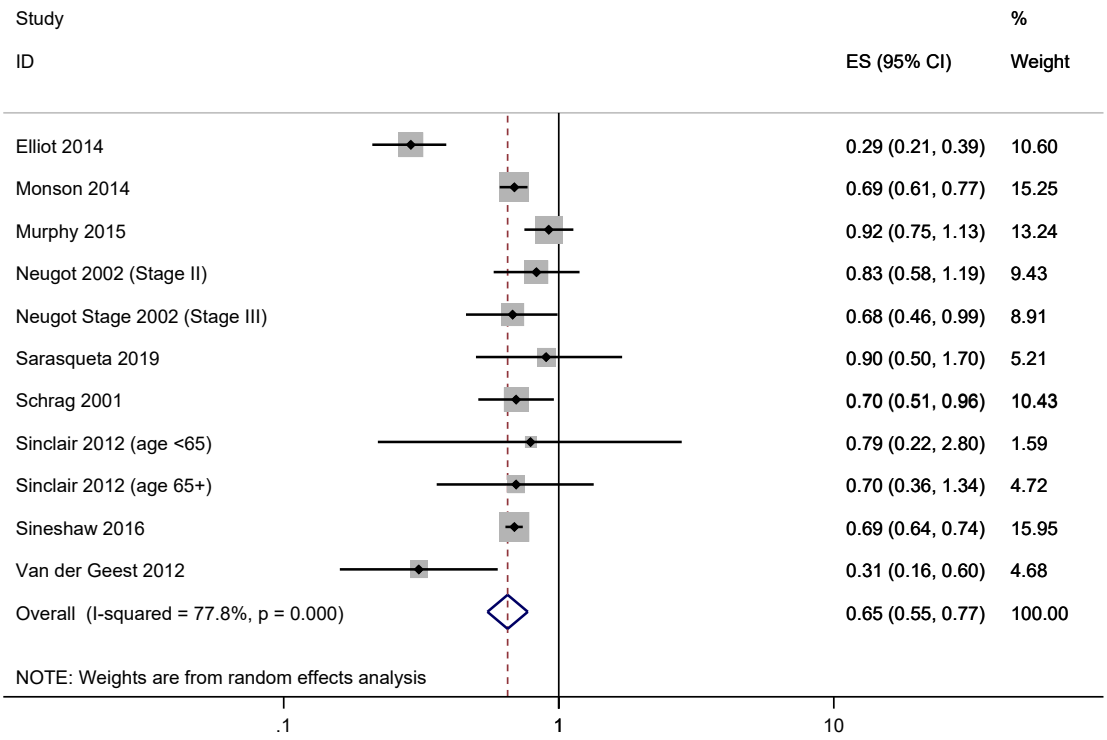


Figure 8-30 Comorbidity Score (Charlson Comorbidity Score 2+ vs. Score 0 [ref]) and adherent Radiation, excluding the two outlying studies

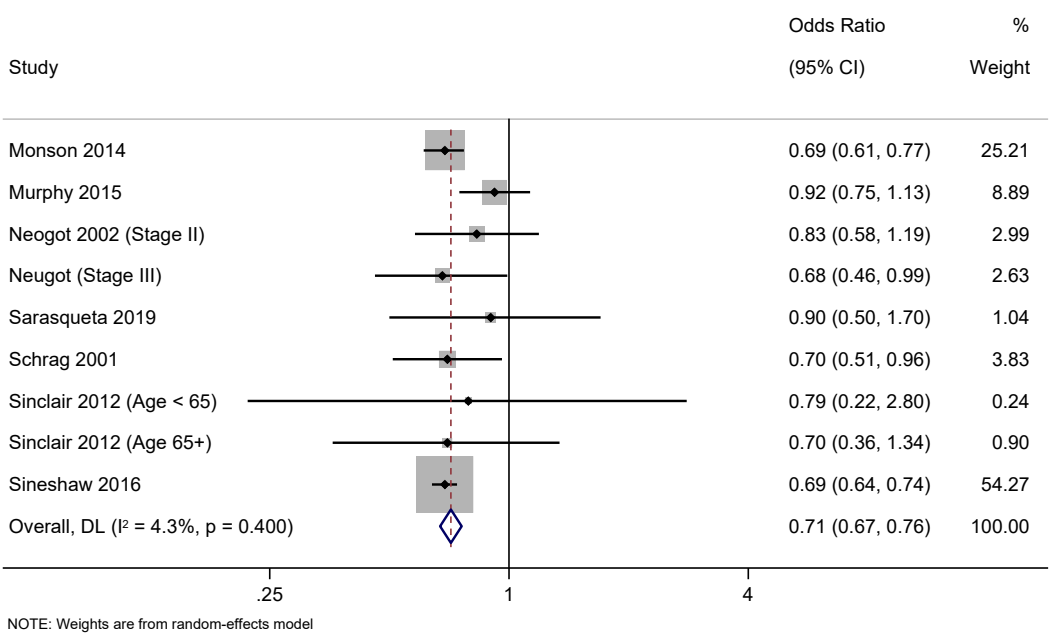


Figure 8-31: Comorbidity Score (Charlson Comorbidity Score 1 vs. Score 0 [ref]) and adherent Chemotherapy

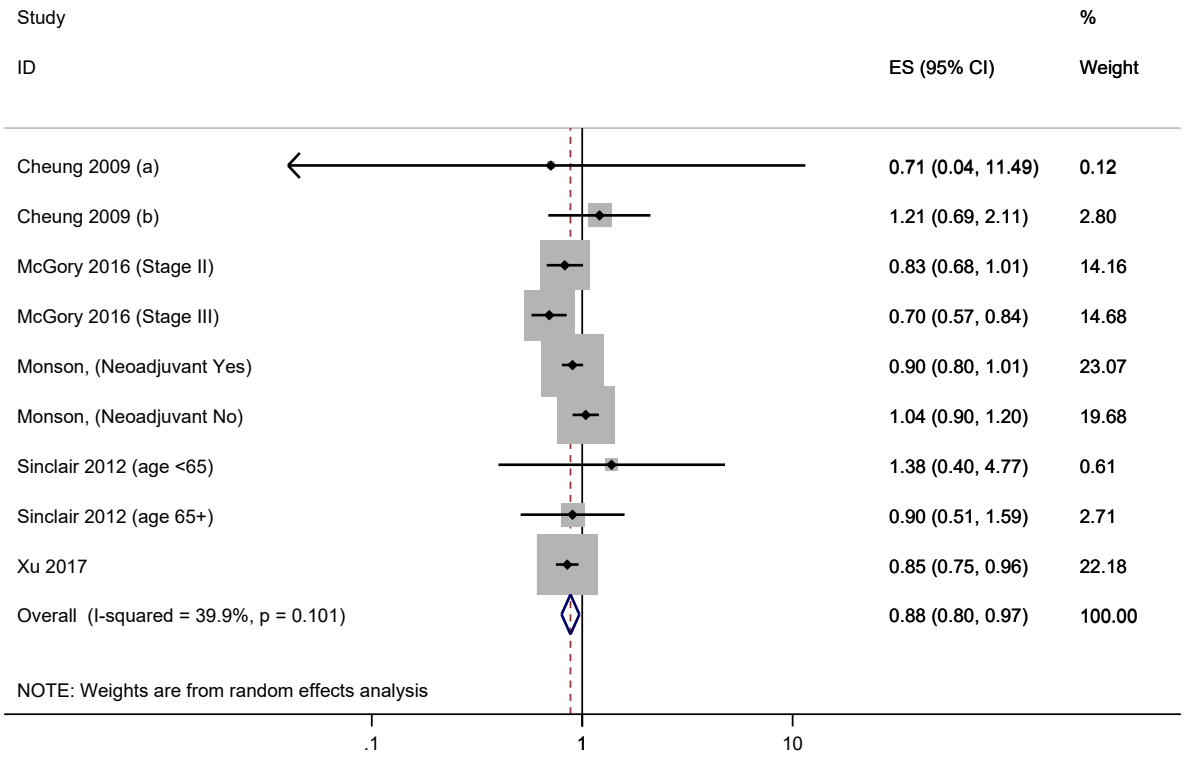


Figure 8-32: Comorbidity Score (Charlson Comorbidity Score 2+ vs. Score 0 [ref]) and adherent chemotherapy

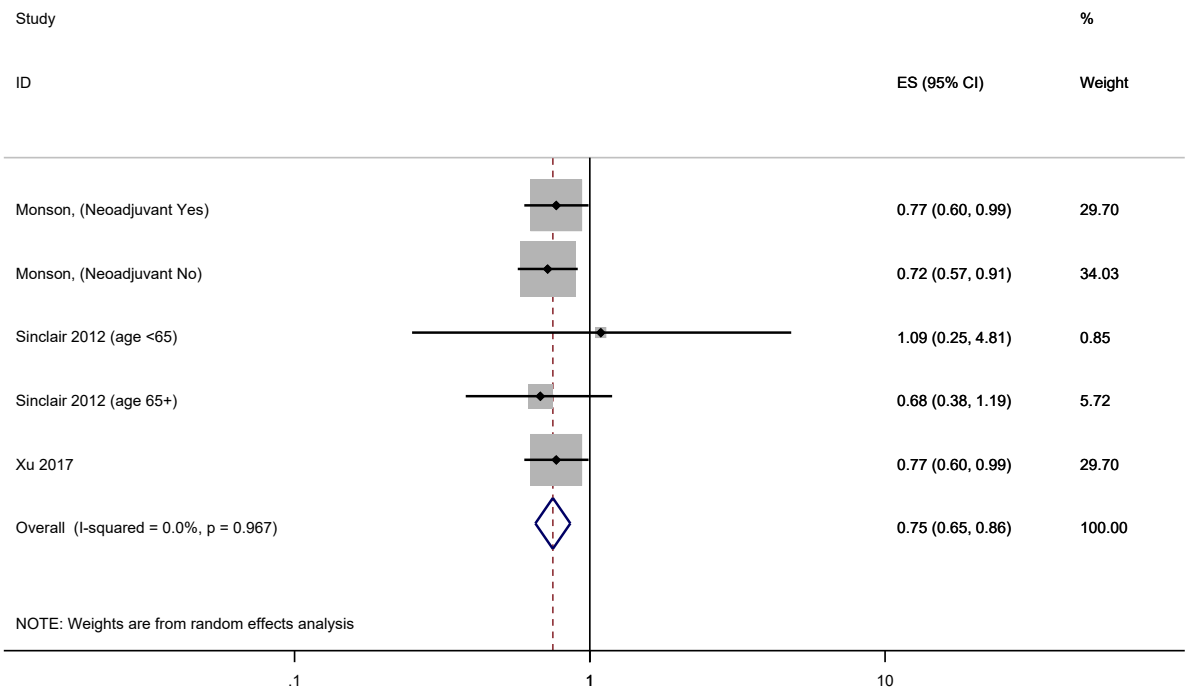


Table 8-44:Comorbidity Score (Charlson Comorbidity Score 3+ vs. Score 0 [ref]) and adherent chemotherapy

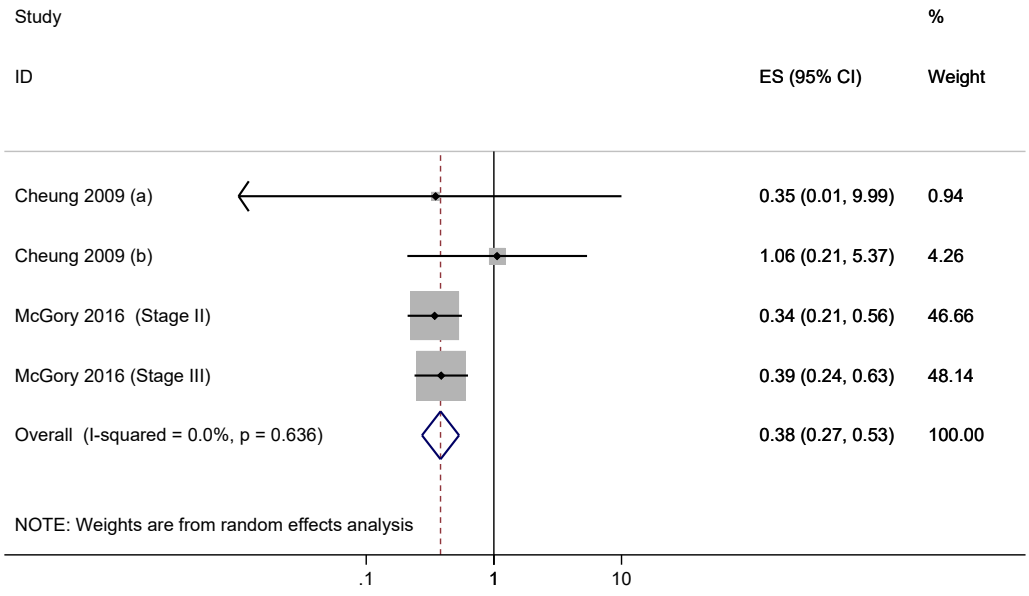


Figure 8-33: Marital Status (unmarried vs. married [ref]) and adherent Radiation

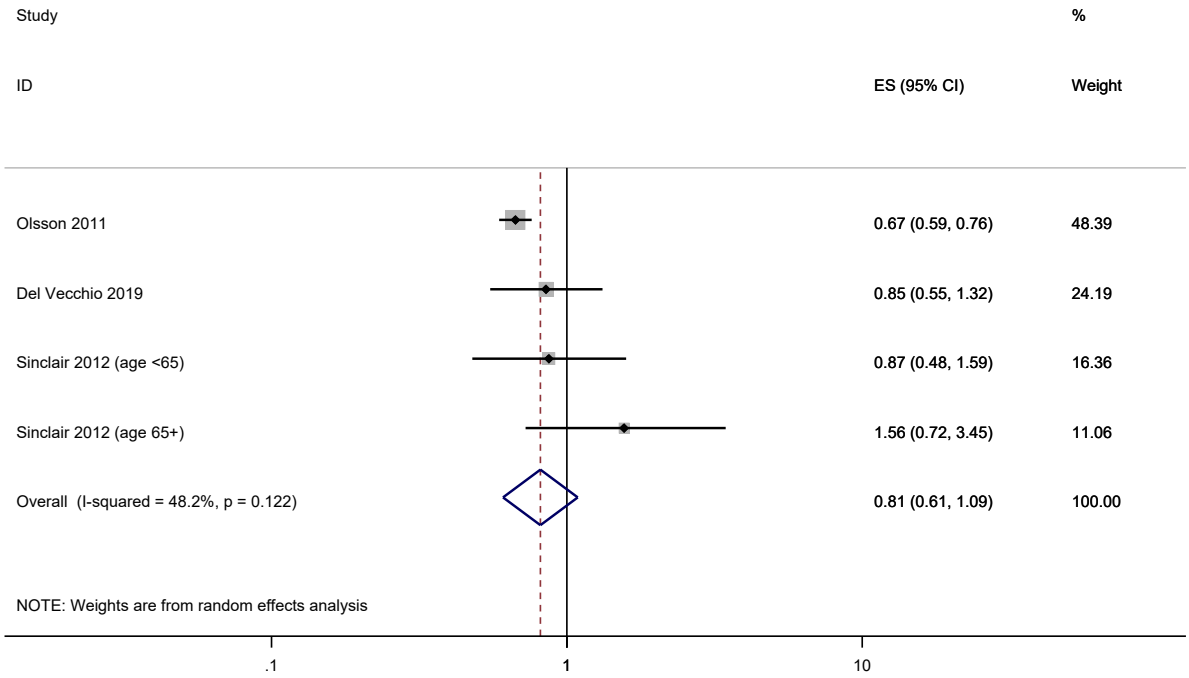


Figure 8-34: Marital Status (unmarried vs. married [ref]) and adherent Chemotherapy

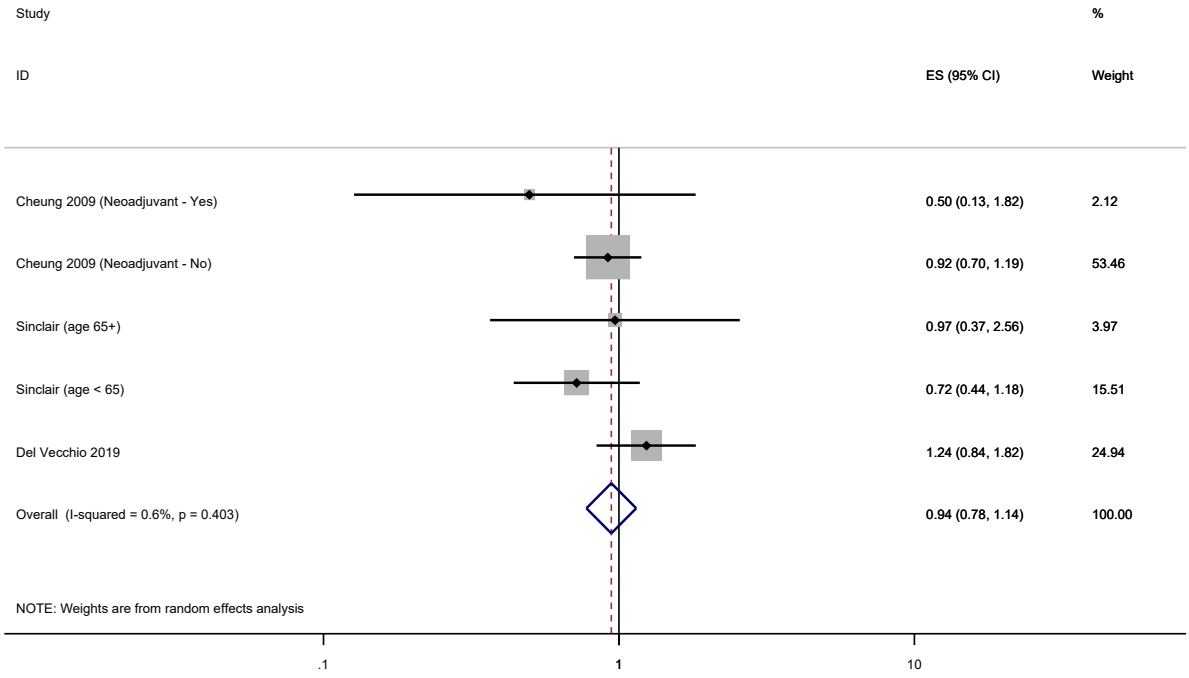
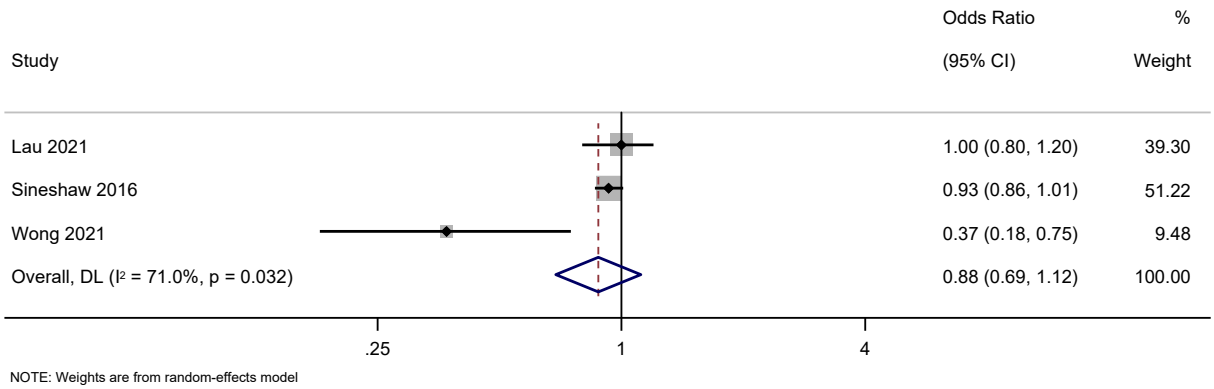


Figure 8-35: Insurance Status (No insurance vs. Private insurance [ref]) and adherent radiation



8.3 Appendix Chapter 5

8.3.1 Appendix Chapter 5 – 1: Screen shot of the histopathology access database

Figure 8-36: Screen shot histopathology access database - 1

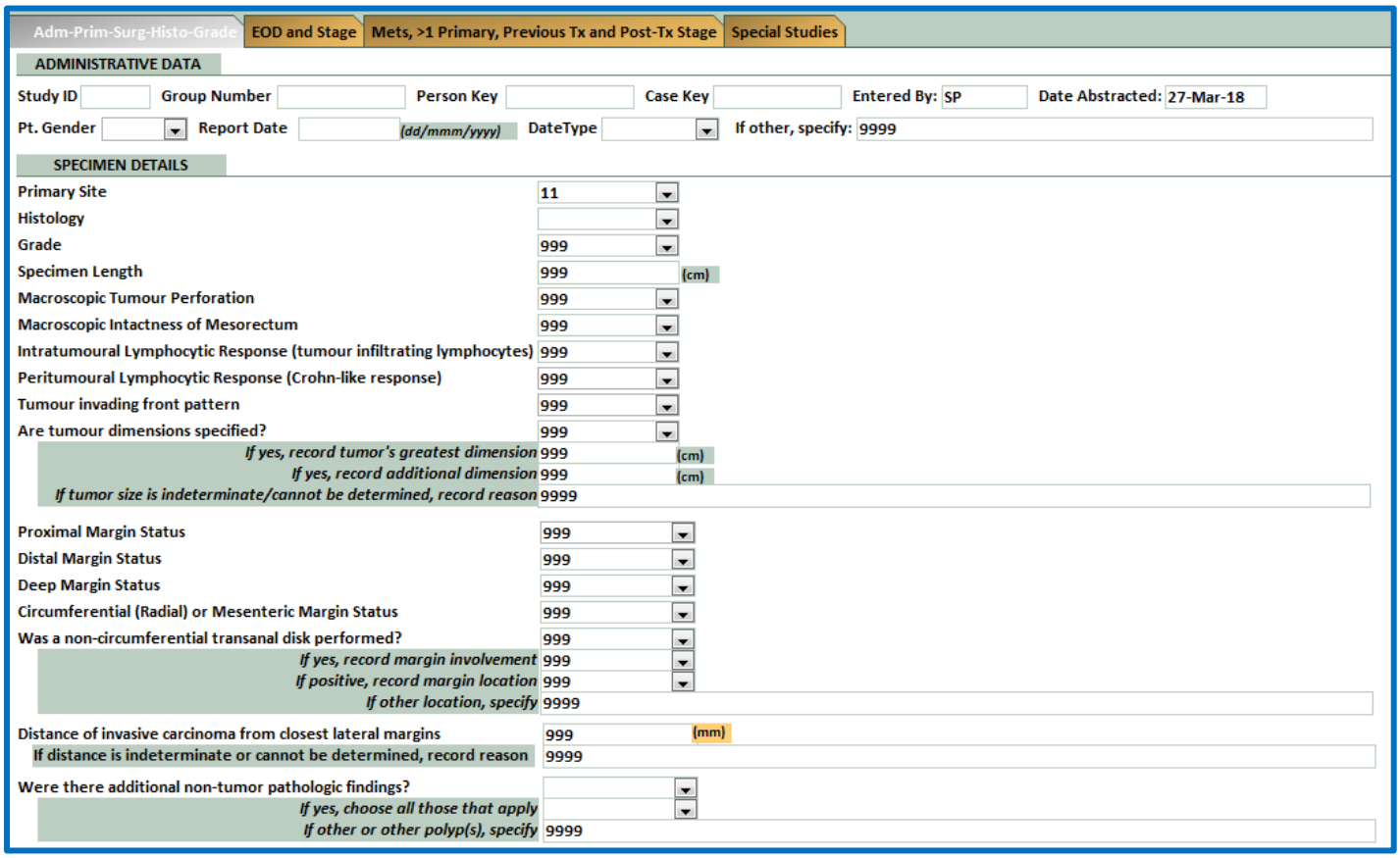


Figure 8-37: Screen shot histopathology access database - 2

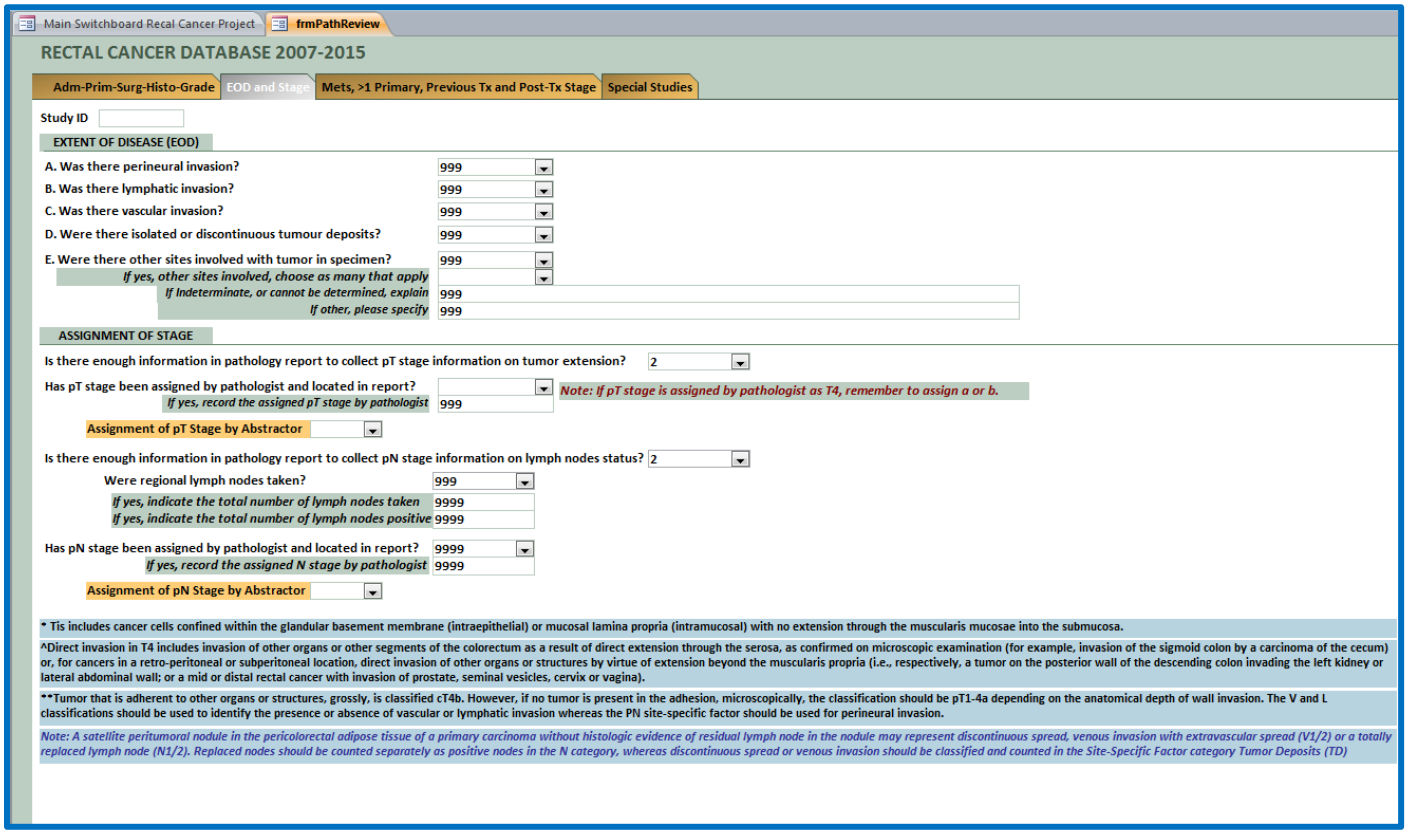


Figure 8-38: Screen shot histopathology access database - 3

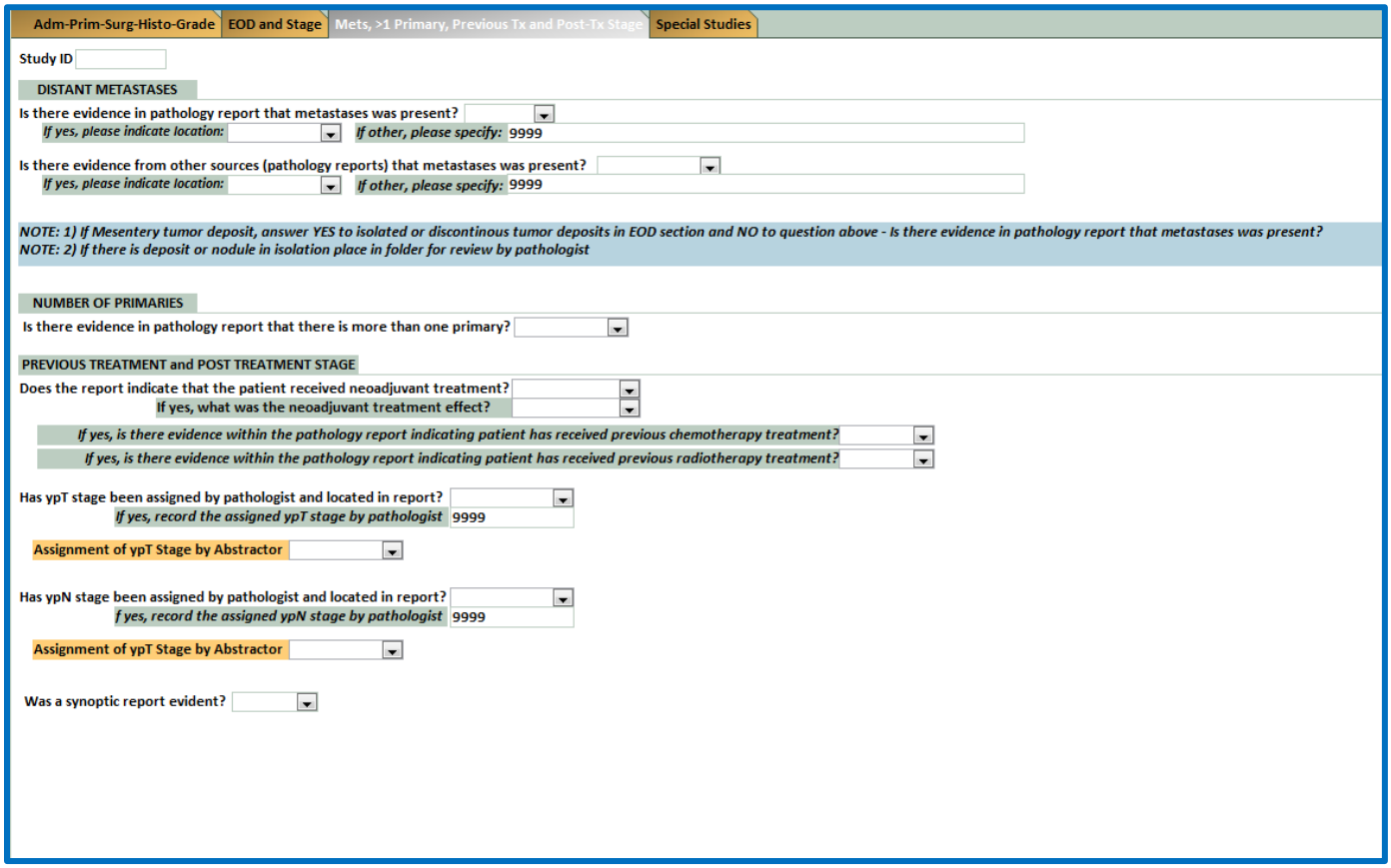
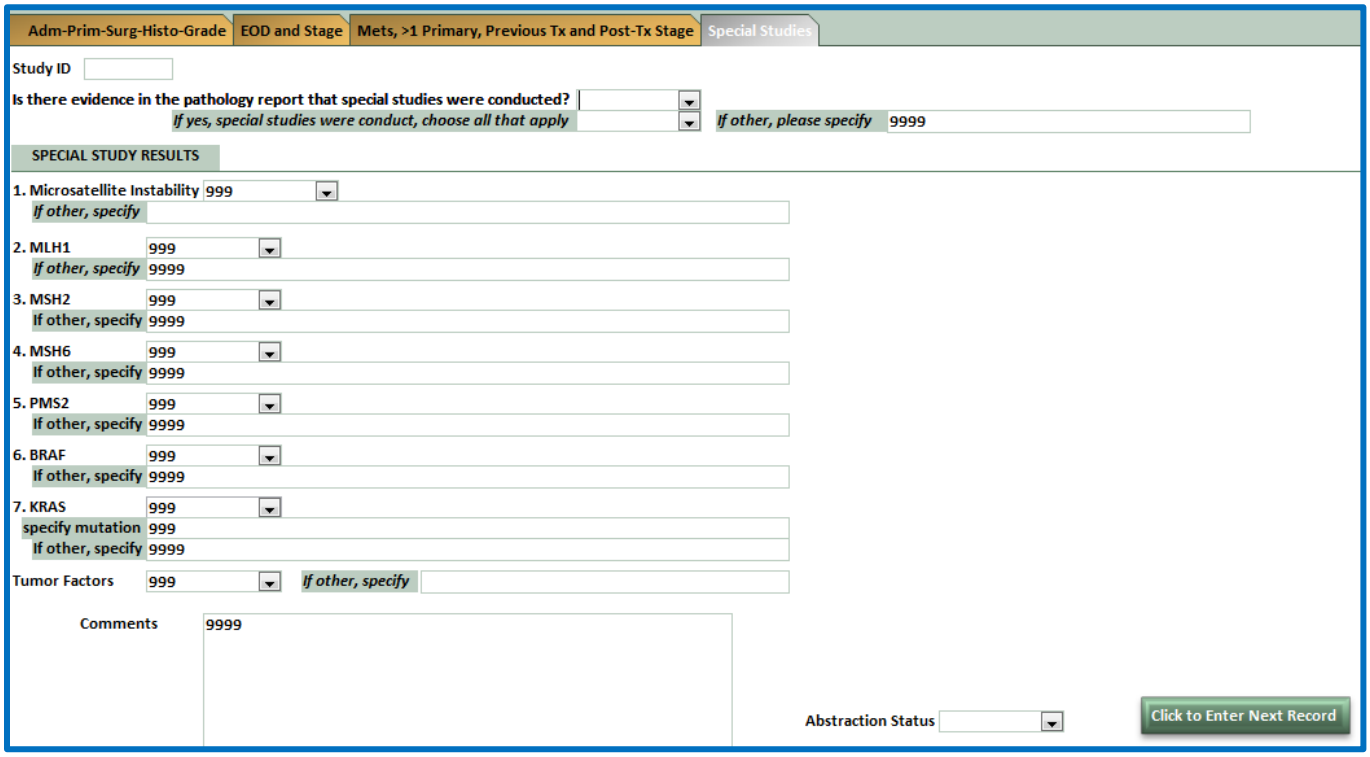


Figure 8-39: Screen shot histopathology access database - 4



8.3.2 Appendix Chapter 5 – 2: Histopathology data dictionary

Definition of Rectal Cancer

Rectal cancer is defined as adenocarcinoma of the rectum. The rectum is defined as existing between the sacral promontory and the dentate line and is divided into lower rectum (0 – 5 cm from the dentate line), middle rectum (5 – 10 cm from the dentate line) or proximal (10 – 15 cm from the dentate line). Rectal cancer location can also be defined based on its location in Comparison to the peritoneal reflection (entirely below, entirely above or straddling).

Diagnosis and Staging

A diagnosis of rectal cancer requires histopathologic confirmation of adenocarcinoma on a biopsy within the rectum. Staging investigations for rectal cancer determine the clinical (or pretreatment) stage and guide treatment. Complete staging requires local-regional staging, assessment for distant metastasis, evaluation for synchronous colorectal cancers and evaluation of tumor marker.

Local-regional staging can be completed using either Endorectal Ultrasound (ERUS) or Magnetic Resonance Imaging (MRI) of the Rectum. Local-regional staging should include Tumor (T) stage and Nodal (N) stage. Staging to assess for distant metastasis should include Computed Tomography (CT) of the abdomen and pelvis and either i) CT of the Chest or ii) Chest Xray. Positron Emission Tomography (PET) should not be used routinely.

Evaluation for synchronous colorectal cancers should be done with colonoscopy prior to treatment. If this is not possible due to bowel obstruction, then either CT Colonography prior to treatment or colonoscopy within 6 months of completions of treatment should be completed. Baseline Carcinoembryonic Antigen (CEA) should be drawn prior to treatment initiation. Adherence to staging will be defined as the presence of an MRI of the rectum; CT Abdomen and Pelvis; i) CT Chest or ii) CXR; Colonoscopy and CEA prior to the initiation of treatment. If colonoscopy is not preformed prior to treatment, adherence will still be considered if it is completed within 6 months of surgery.

Note: the above information taken from Dr. Patel's proposal "Identification and impact of barriers to rectal cancer treatment in the province of Ontario: a population study".

Time period of the study: 2007-2015

The information collected on these patients is for the period of January 1, 2007 to December 31, 2015 documenting the information in the surgical pathology report. For the purpose of this study specifically the pathology reports were requested to include 6 months prior to January 1, 2007 to eliminate anyone diagnosed earlier than the study dates and 6 months post December 31, 2015 to capture any other detail.

Inclusion Criteria

- Patient diagnosed with rectal cancer between January 1, 2007 and December 31, 2015
- Patient was diagnosed with rectal cancer in Ontario and a resident of Ontario
- Patient was diagnosed with a potentially curable rectal cancer i.e. stage I – III
- Patient diagnosed with Adenocarcinoma, with morphology codes beginning with 814_
- No age restriction
- Diagnosed with sigmoid-rectal cancer

Answering "no" to any of the above questions, this patient is not eligible for this study. Details of exclusion are to be documented.

Exclusion Criteria

- Diagnosed before January 1, 2007 and/or after December 31, 2015
- Patient was diagnosed outside of Ontario
- Patient was diagnosed with an incurable rectal cancer
- Patient not diagnosed with Adenocarcinoma
- Diagnosed with colon or anal cancer

Outcomes of the study

- Appropriate staging to be collected on all cases
- Did they receiving neoadjuvant treatment (where indicated)
- Did they receiving appropriate surgery and what was the quality of the surgery
- Time delay monitoring from diagnosis to treatment

General Rules

For the purpose of this study:

- A default value of "11" in the Primary Site = Rectum
- A default value of "999" = unstated, information not in pathology report
- A default value of "9999" = NA – not applicable

Admin-Prim-Surg-Histo-Grade:

Administrative Data

Study ID: Auto populated

Group Number: Copy and paste from tracking sheet

Person Key: Copy and paste from tracking sheet

Case Key: Copy and paste from tracking sheet

Entered By: Auto populated to SP

Date Abstracted: Auto populated

Pt. Gender:

- male
- female
- transgender
- unstated- information not in the path report

Report Date: DD/MMM/YYYY

- Hierarchy of date information collected: as laid out below…

Date Type:

- Specimen Collected (procedure) Date
- Specimen Received Date

- Other Date - If other, specify

Specimen Details:

Primary Site: default to rectum (11)

1. Cecum
2. Appendix
3. Ascending colon
4. Hepatic flexure of colon
5. Transverse colon
6. Splenic flexure of colon
7. Descending colon
8. Sigmoid colon
9. Colon, NOS
10. Rectosigmoid
11. Rectum

Note: If there is **no residual adenocarcinoma**, indicating a previous Sx or neoadjuvant treatment with complete response…include these cases and answer everything that you are able to including all margins negative.
Note: Rectum – 12 cm long; upper third covered by peritoneum; no peritoneum on lower third which is also called the rectal ampulla. About 10 cm of the rectum lies below the lower edge of the peritoneum (below the peritoneal reflection), outside the peritoneal cavity

Histology:

Note: Highest code rules apply

Grade:

- Gx - Grade cannot be assessed
- Low Grade – well differentiated to moderately differentiated
- High Grade – poorly differentiated to undifferentiated
- Unstated – Grade of differentiation not stated, information not in path report

Note: select highest grade if offered a range of grades

Specimen Length: in (cm)

Macroscopic Tumor Perforation:

- Present
- Not present (not identified)
- Indeterminate
- Unstated, information not in report

Macroscopic Intactness of Mesorectum: anchors the rectum to the body walls

- Complete
- Near complete

- Incomplete
- Indeterminate
- Unstated, information not in report
- NA – not applicable

Note: This is important information to collect, use the microscopic and/or the macroscopic descriptions

Intratumoral Lymphocytic Response (tumor infiltrating lymphocytes):

TILS – lymphocytes collected from the tumor site, the presence of TILS is associated with better outcome – they kill tumor cells.

- None
- Mild to moderate (0-2 per high-power field [x400]
- Marked (3 or more per high-power field)
- Present but not graded
- Unstated, information not in pathology report

Note 1): mild to moderate can also be stated as: not brisk or not significant
Note 2): marked can also be stated as: brisk, severe or significant

Peritumoral Lymphocytic Response (Crohn-like response): also called host response, inflammatory response, Crohn's-like, lymphoid reaction or lymphocytic infiltrate

- None
- Mild to moderate
- Marked
- Present but not graded
- Unstated, information not in pathology report

Note 1): mild to moderate can also be stated as: not brisk or not significant
Note 2): marked can also be stated as: brisk, severe or significant
Note 3): Crohn-like response does **not** = Crohn's disease

Tumor invading front pattern: tumor margin behaviour - referring to tumor border

- Infiltrative
- Pushing
- Irregular, not pushing
- Unstated, information not in pathology report

Note: pushing also described as relatively circumscribed, rounded, budding

Are Tumor dimensions specified?

- Yes
- No

If yes, record tumor's greatest dimension (cm)
If yes, record additional dimension (cm)

If tumor size is indeterminate/cannot be determined, record reason

Note: consider microscopic then macroscopic dimensions, just collect the greatest dimension…others not necessary

Note: collect dimensions to one (1) decimal point

Proximal Margin Status:

- Positive
- Negative
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

Note: also described as luminal margin

Distal Margin Status:

- Positive
- Negative
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

Note: also described luminal margin

Deep Margin Status:

- Positive
- Negative
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

Circumferential (Radial) or Mesenteric Margin Status:

- Positive
- Negative
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

Note: also described as soft tissue margin, mesenteric margin

Was a non-circumferential transanal disk performed? Also known as mucosal resection, TAMIS, TEMS, circumferential margin

- Yes
- No
- Uncertain (equivocal, etc.)
- Indeterminate

- Unstated, information not in pathology report
- NA – not applicable

If yes, record margin involvement
- Positive
- Negative
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

If positive, record margin location
- Deep
- mucosal
- Other, specify
- Unstated, information not in pathology report
- NA – not applicable

If other location, specify

Distance of invasive carcinoma from closest lateral margin: (mm)

If distance is indeterminate/cannot be determined, record reason

Note: Lateral margin also described as circumferential (radial) margin

Note: If the margin is positive enter zero (0.0) mm as distance from closest margin

Were there additional non-tumor pathologic findings?

If yes, chose all those that apply
- Adenoma (s)
- Chronic ulcerative proctocolitis
- Crohn disease
- Dysplasia arising in inflammatory bowel disease
- Other polyps, specify types
- Indeterminate
- Other, specify
- Unstated, information not in pathology report
- NA, not applicable

Note: only collect these findings as stated in the dropdown list

Extent of Disease (EOD) and Stage:

A. Was there perineural invasion?
- Yes
- No
- Uncertain (equivocal, etc.)

- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

B. Was there lymphatic invasion? Small lymphatic channels/vessels invaded by tumor

- Yes
- No
- Uncertain (equivocal, etc.)
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

Note: may be captured as a combined "lymph-vascular" or "lymphovascular" invasion, if the combined words are stated you must select yes or no for both lymphatic and vascular

C. Was there vascular invasion? Small vascular channels/vessels invaded by tumor

- Yes
- No
- Uncertain (equivocal, etc.)
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

Note: may be captured as a combined "lymph-vascular" or "lymphovascular" invasion, if the combined words are stated you must select yes or no for both lymphatic and vascular

D. Were there isolated or discontinuous deposits? Referring specifically to discontinuous extramural extension (a deposit not a lymph node)

- Yes
- No
- Uncertain (equivocal, etc.)
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

Note: isolated or discontinuous deposits affect the pN stage (located in the subserosa, mesentery, or non-peritoneal pericolic or perirectal/mesorectal tissues)
Note: isolated or discontinuous deposit reports should be reviewed with the PI

E. Were there other sites involved with tumor in specimen?

- Yes
- No

- Uncertain (equivocal, etc.)
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

If yes, other sites involved, choose as many that apply

1. Cecum
2. Appendix
3. Ascending colon
4. Hepatic flexure of colon
5. Transverse colon
6. Splenic flexure of colon
7. Descending colon
8. Sigmoid colon
9. Colon, NOS
10. Rectosigmoid
11. Small intestine, NOS (terminal ileum, ileocecal valve)
12. Indeterminate (cannot be determined) explain
13. Other, specify
14. Unstated, information not in pathology report
15. NA – not applicable

If indeterminate/cannot be determined, record reason

If other, please specify

Assignment of Stage:

Is there enough information in pathology report to collect stage information on tumor extension? :

- Yes
- No
- Unstated, information not in pathology report

Note: question includes stage elements not listed here i.e.: muscularis propria

Has pT stage been assigned by pathologist and located in report?

- Yes
- No
- Unstated, information not in pathology report

If yes, record the assigned T stage by pathologist

Note: If pT stage is assigned by pathologist as T4, remember to assign a or b

Assignment of pT Stage:

1. pTx - Primary tumor cannot be assessed
2. pT0 – No evidence of primary tumor

3. pTis – Carcinoma in-situ, intramucosal [involvement of lamina propria* with no extension through muscularis mucosa]
4. pT1 – Tumor invades submucosa [through the muscularis mucosa but not into the muscularis propria]
5. pT2 - Tumor invades muscularis propria
6. pT3 – Tumor invades through the muscularis propria into the pericolorectal tissues
7. pT4 – Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
8. pT4a – Tumor invades through the visceral peritoneum ** (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
9. pT4b – Tumor directly invades or adheres to other organs or structures ^,**
10. Note – Pathologist has assigned stage-abstractor agrees with assigned stage

Is there enough information in pathology report to collect stage information on lymph node status? For abstractor collect nodal status

- Yes
- No

If yes, complete the following: Were regional lymph nodes taken?

- Yes
- No
- Uncertain (equivocal, etc.)
- Indeterminate
- Unstated, information not in pathology report
- NA – not applicable

If yes, indicate the total number of lymph nodes taken:
If yes, indicate the total number of lymph nodes positive:

Note: Regional Lymph nodes - perirectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, pre-sacral, internal iliac, sacral promontory (Gerota's), superior hemorrhoidal, inferior hemorrhoidal

Has pN stage been assigned by the pathologist and located in the report?

- Yes
- No

If yes, record the assigned N stage by pathologist

Note: record verbatim

Assignment of pN stage by Abstractor:

1. pNx – Regional nodes cannot be assessed (e.g., previously removed for another reason or No lymph node dissection recorded)
2. pN0 – No regional lymph node metastasis
3. pN1 – One to three regional lymph nodes positive (tumor in lymph nodes measuring ~0.2mm), or any number of deposits are present and all identifiable lymph nodes are negative
4. pN1a – One (1) regional lymph node is positive
5. pN1b - Two (2) or three (3) regional lymph node are positive
6. pN1c – No regional lymph nodes are positive but there are tumor deposit(s) in the subserosa, mesentery, or non-peritoneal pericolic or perirectal/mesorectal tissues
7. pN2 - Four (4) or more regional lymph node are positive
8. pN2a - Four (4) to six (6) regional lymph node are positive
9. pN2b - Seven (7) or more regional lymph node are positive
10. Note – Pathologist has assigned stage-abstractor agrees with assigned stage

Note: If there is a deposit or nodule in isolation, place in folder for review by pathologist

* Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.
^ direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retro-peritoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix or vagina).
** Tumor that is adherent to other organs or structures, grossly, is classified T4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.
Note: A satellite Peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2) or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD)

Mets, >1 Primary & Previous Treatment and Post-Tx stage Distant Metastases:

Is there evidence in the pathology report that metastases were present?

- Yes
- No

If yes, please indicate location:

- Parietal peritoneum
- Mesentery – See Note
- Liver
- Omentum
- Lung

- Both liver and lung
- Other, please specify
- Unstated, information not in pathology report
- NA – not applicable

If other, please specify:

Is there evidence from other sources (pathology reports) that metastases were present?

- Yes
- No

If yes, please indicate location:

- Parietal peritoneum
- Mesentery – See Note
- Liver
- Omentum
- Lung
- Both liver and lung
- Other, please specify
- Unstated, information not in pathology report
- NA – not applicable

If other, please specify:

Note: 1) If mesentery tumor deposit, answer YES to isolated or discontinuous tumor deposits in EOD section and NO to questions about – Is there evidence in pathology report that metastases were present?
Note: 2) If there is deposit or nodule in isolation place in folder for review by pathologist

Number of Primaries:

Is there evidence in pathology report that there is more than one primary?

- Yes
- No

Previous Treatment and Post-Tx Stage:

Does the report indicate that the patient received neoadjuvant treatment?

- Yes
- No

` If yes, what was the neoadjuvant Treatment effect?

- Down-staging
- Complete pathologic response
- Indeterminate
- Other, specify
- Unstated, information not in path report

- NA, not applicable

If yes, is there evidence within the pathology report indicating patient has received previous chemotherapy treatment?

- Yes in Clinical Hx
- Yes in body of Path report
- Yes in both Clinical Hx and Path report
- No
- Unstated, information not in pathology report

If yes, is there evidence within the pathology report indicating patient has received previous radiotherapy treatment?

- Yes in Clinical Hx
- Yes in body of Path report
- Yes in both Clinical Hx and Path report
- No
- Unstated, information not in pathology report

Has ypT stage been assigned by pathologist and located in report?

- Yes
- No

If yes, record the assigned ypT stage by pathologist

Note: record verbatim

Assignment of ypT Stage:

1. ypTx - Primary tumor cannot be assessed
2. ypT0 – No evidence of primary tumor
3. ypTis – Carcinoma in-situ, intramucosal [involvement of lamina propria* with no extension through muscularis mucosa]
4. ypT1 – Tumor invades submucosa [through the muscularis mucosa but not into the muscularis propria]
5. ypT2 - Tumor invades muscularis propria
6. ypT3 – Tumor invades through the muscularis propria into the pericolorectal tissues
7. ypT4 – Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
8. ypT4a – Tumor invades through the visceral peritoneum ** (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
9. ypT4b – Tumor directly invades or adheres to other organs or structures ^,**
10. Note – Pathologist has assigned stage-abstractor agrees with assigned stage

Has ypN stage been assigned by pathologist and located in report?

- Yes
- No

If yes, record the assigned ypN stage by pathologist

Note: record verbatim

Assignment of ypN stage by Abstractor:

1. ypNx – Regional nodes cannot be assessed (e.g., previously removed for another reason or No lymph node dissection recorded)
2. ypN0 – No regional lymph node metastasis
3. ypN1 – One to three regional lymph nodes positive (tumor in lymph nodes measuring ~0.2mm), or any number of deposits are present and all identifiable lymph nodes are negative
4. ypN1a – One (1) regional lymph node is positive
5. ypN1b - Two (2) or three (3) regional lymph node are positive
6. ypN1c – No regional lymph nodes are positive but there are tumor deposit(s) in the subserosa, mesentery, or non-peritoneal pericolic or perirectal/mesorectal tissues
7. ypN2 - Four (4) or more regional lymph node are positive
8. ypN2a - Four (4) to six (6) regional lymph node are positive
9. ypN2b - Seven (7) or more regional lymph node are positive
10. Note – Pathologist has assigned stage-abstractor agrees with assigned stage

Note: If there is a deposit or nodule in isolation, place in folder for review by pathologist

Was a synoptic report evident?

- Yes
- No
- Synoptic Features present

Special Studies

Is there evidence in pathology report that special studies were conducted?

- Yes
- No

If yes, special studies were conducted, choose all that apply

1. Microsatellite instability
2. MLH 1
3. MSH 2
4. MSH 6
5. PMS 2
6. BRAF V600 mutation
7. KRAS mutation

8. Other, specify
9. Unstated, information not in pathology report
10. NA – not applicable

If other, please specify

Special Study Results:

1. Microsatellite Instability

- Stable
- Low
- High
- Other, specify
- Unstated, information not in pathology report
- NA – not applicable

If other, specify

2. MLH1

- Intact nuclear positivity, tumor cells
- Loss of nuclear positivity, tumor cells
- Pending
- Indeterminate
- Other, specify
- Unstated, information not in pathology report
- NA – not applicable

If other, specify

3. MSH2

- Intact nuclear positivity, tumor cells
- Loss of nuclear positivity, tumor cells
- Pending
- Indeterminate
- Other, specify
- Unstated, information not in pathology report
- NA – not applicable

If other, specify

4. MSH6

- Intact nuclear positivity, tumor cells
- Loss of nuclear positivity, tumor cells
- Pending
- Indeterminate
- Other, specify

- Unstated, information not in pathology report
- NA – not applicable

  If other, specify

5. **PMS2**
   - Intact nuclear positivity, tumor cells
   - Loss of nuclear positivity, tumor cells
   - Pending
   - Indeterminate
   - Other, specify
   - Unstated, information not in pathology report
   - NA – not applicable

     If other, specify
6. **BRAF V600 mutation**
   - Yes, mutant BRAF detected
   - No, mutant BRAF not detected (wild type BRAF allele)
   - Pending
   - Indeterminate
   - Other, specify
   - Unstated, information not in pathology report
   - NA – not applicable

     If other, specify
7. **KRAS mutation**
   - Yes, mutant KRAS detected (specify mutation)
   - No, mutant KRAS not detected (wild type KRAS allele)
   - Pending
   - Indeterminate
   - Other, specify
   - Unstated, information not in pathology report
   - NA – not applicable

     If other, specify

Note: a term indicating "suggestive" will indicate a positive/yes response to these items

Tumor Factors:

- Degree of differentiation
- Absence of mismatch pairs
- Indeterminate
- Other, specify
- Unstated, information not in pathology report

- NA – not applicable

If other, specify

Note: tumor factors: mismatch pairs = a reflection of hereditary concerns

Comments: Make comments on abstraction in the comments text box including items such as multiple primaries in the rectum, multiple primaries in other sections of the colon, post-review with PI decision and mesorectal completeness.

Abstraction of Pathology Report Complete: Check box if the abstraction is complete, needs review with PI or post review with PI…then click the "Click to Enter Next Record" tab to advance to next record

AJCC Prognostic Stage Groups

When T is…	And N is…	And M is…	Then then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

Surgical Procedure Types for Rectal Cancer – Resections

Figure 8-40: Low Anterior Resection

Low anterior resection

A low anterior resection removes the sigmoid colon and part of the rectum. The surgeon then joins the remaining colon to the remaining rectum (called the rectal stump). The procedure used to join them is called anastomosis.

Low anterior resection is used to remove tumours in the middle or upper part of the rectum.

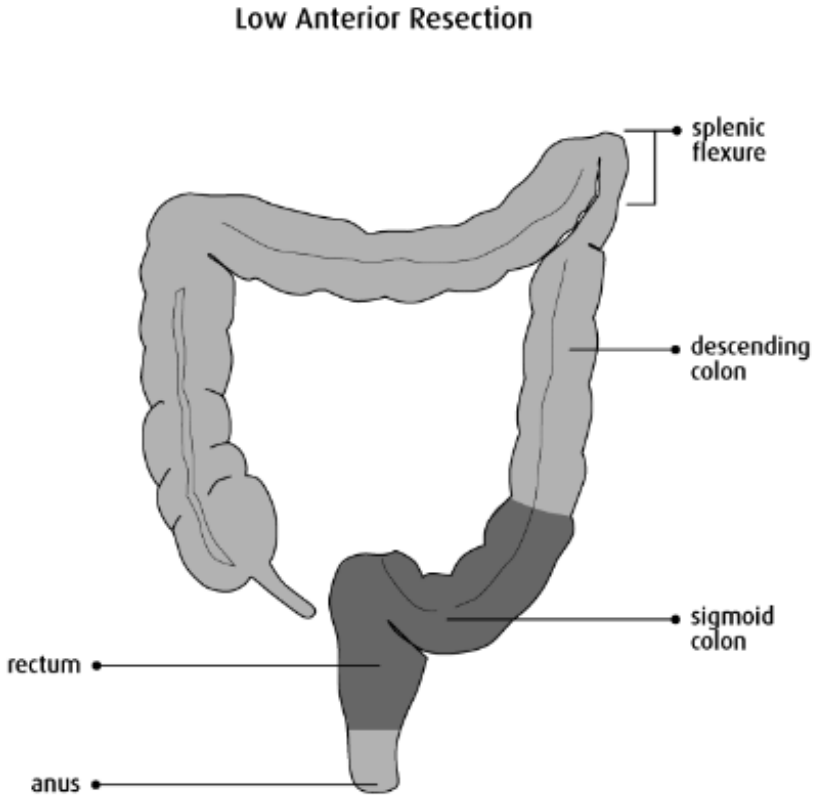


Figure 8-41: Proctocolectomy with colo-anal anastomosis

Proctocolectomy with coloanal anastomosis

Proctocolectomy (also called proctectomy) removes all of the rectum and part of the sigmoid colon. Coloanal anastomosis is a procedure the surgeon does to join the remaining colon to the anus.

This surgery is used to remove tumours in the lower part of the rectum. It is not used very often because many surgeons prefer to use a low anterior resection or abdominoperineal resection to remove rectal tumours.

Proctocolectomy with Coloanal Anastomosis

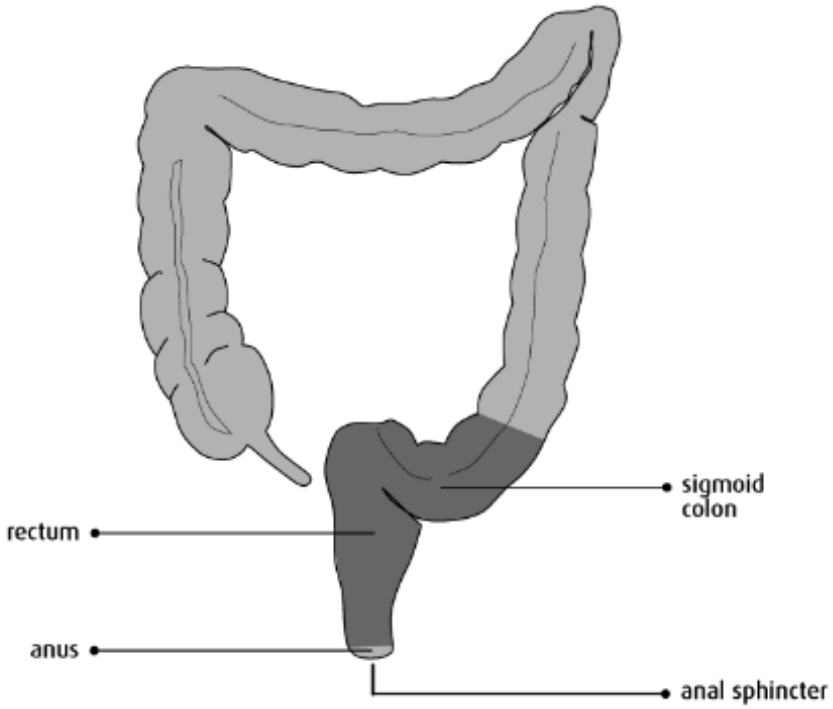


Figure 8-42: Abdominoperineal Resection

Abdominoperineal resection

An abdominoperineal resection removes the rectum, anus, anal sphincter and muscles around the anus. The surgeon makes one incision, or cut, in the abdomen and another one in the perineum (the area between the anus and vulva in women or between the anus and scrotum in men). A permanent colostomy is needed because the anal sphincter is removed.

An abdominoperineal resection is used to remove tumours that are close to the anus or have grown into muscles around the anus.

Abdominoperineal Resection

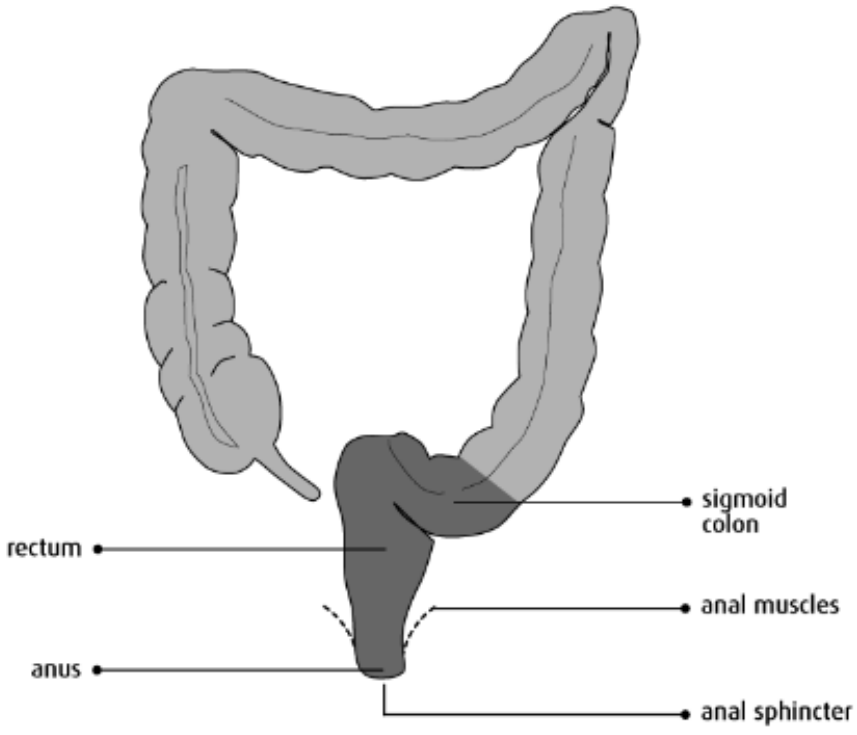
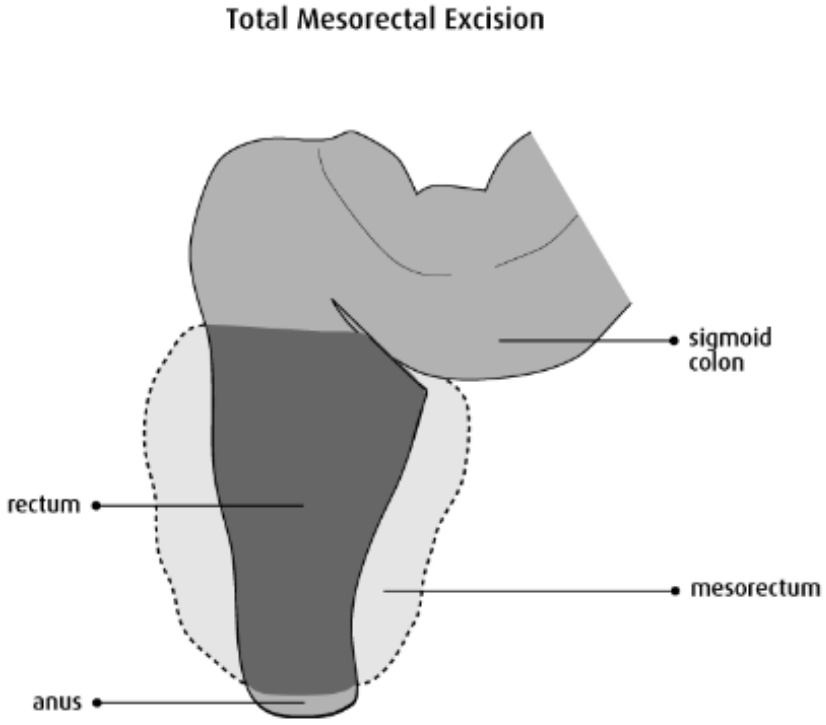


Figure 8-43: Lymph node dissection

Lymph node dissection

Lymph node dissection, or lymphadenectomy, is surgery to remove lymph nodes. It is always done during a bowel resection. At least 12 lymph nodes near the tumour are removed. They are examined to find out if cancer has spread to them.

Total mesorectal excision (TME) is a type of lymph node dissection that removes the mesorectum, which is fat around the rectum that contains lymph nodes and blood vessels. TME is usually done during a low anterior resection or abdominoperineal resection to remove a tumour in the rectum. This surgery allows the surgeon to remove lymph nodes as well as a margin of tissue around the tumour (called the surgical margin).



Find out more about lymph node dissection.

8.3.3 Appendix Chapter 5 – 3: Ontario Health – Cancer Care Ontario Research Agreement

Ontario Health
Cancer Care Ontario

RESEARCH AGREEMENT

17-021B Barriers to standard of care treatment for rectal cancer patients
in Ontario, Canada and the effect on cancer outcomes: A population based study

THIS RESEARCH AGREEMENT ("Agreement") made as of the 17th day of November, 2020 (the "Effective Date") by and between Ontario Health ("OH"), Queen's University at Kingston and Sunil Patel (the "Investigator" and collectively, with the Institution, the "Researcher")

BACKGROUND

A. OH is an agency under the Ministry of Health, Government of Ontario with a mandate to oversee health care delivery across the province in accordance with the objects set out in the Connecting Care Act, 2019.

B. Pursuant to a transfer order made by the Minister of Health under subsection 40(1) of the Connecting Care Act, 2019, effective December 2, 2019, Cancer Care Ontario ("CCO"), along with its assets, liabilities, rights and obligations, including personal health information ("PHI"), was transferred to OH.

C. Prior to December 2, 2019, CCO collected PHI as a prescribed entity ("PE") under section 45 of the Personal Health Information Protection Act, 2004 ("PHIPA") and section 18 of Ontario Regulation 329/04 made under PHIPA (the "Regulation"). CCO is also a prescribed person ("PP") under section 39(1)(c) of PHIPA and subsection 13(1) of the Regulation in respect of the Ontario Cancer Screening Registry ("Registry"). Further, as a PP and PE, CCO could collect PHI without the consent of the individual to whom the information relates if, among other matters, the Information and Privacy Commissioner of Ontario (the "IPC") approves its privacy practices and procedures every three years.

D. OH was added as a PP and a PE pursuant to Ontario Regulation 377/19 dated December 2, 2019 and therefore has the legal authority to collect, use and disclose PHI as a PP and PE under the Personal Health Information Protection Act, 2004 ("PHIPA"). The IPC most recently approved OH's privacy practices and procedures as a PP and PE on October 30, 2020 which confirm that OH continues to have in place practices and procedures to protect the privacy of individuals whose PHI it receives and to maintain the confidentiality of that information in accordance with PHIPA..

E. Both as a PE and a PP , OH is permitted under, respectively, subsections 18(4) and 13(5) of the Regulation, to disclose PHI as if it were a health information custodian for the purpose of research, subject to OH's compliance with section 44 of PHIPA.

F. The Researcher wishes to conduct research that requires information including PHI that OH has collected as a PE and/or a PP, more particularly Barriers to standard of care treatment for rectal cancer patients in Ontario, Canada and the effect on cancer outcomes: A population based study

and OH is prepared to disclose such information to the Researcher under the terms and conditions set out in this Agreement.

G. OH and the Researcher are entering into this Agreement in accordance with section 44(5) of PHIPA, and to ensure that the collection, use, protection, disclosure, return or disposal of PHI for the purposes of the Research complies with PHIPA.

NOW THEREFORE, FOR VALUE RECEIVED, the sufficiency of which is hereby acknowledged by each of OH and the Researcher, OH and the Researcher covenant and agree as follows.

Definitions

1. In this Agreement:

(a) "**Agent**" has the same meaning as "agent" in PHIPA;

(b) "**Application**" means the Researcher's *Application for Disclosure of Information for Research Purposes* (which will include the Approved Research Plan), which constitutes the application required under section 44(1)(a)(i) of PHIPA;

(c) "**Approved Research Plan**" means the Research Plan as approved by the REB, and any other documents approved by the REB in connection with the Approved Research Plan;

(d) "**OH Data**" means collectively the information including but not limited to PHI set out in the Approved Research Plan and disclosed by OH to the Researcher under this Agreement;

(e) "**Data Disclosure Team**" means the applicable work unit at OH, the contact information for which is in Schedule "C" to this Agreement;

(f) "**De-identify**" means to remove any information that identifies an individual or which it is reasonably foreseeable in the circumstances could be utilized, either alone or with other information to identify an individual and "De-identification" has a corresponding meaning.

(g) "**Derivative Data**" means any information created by or on behalf of the Researcher from OH Data disclosed to the Researcher, including but not limited to PHI.

(h) "**IPC**" means the Office of the Information and Privacy Commissioner of Ontario;

(i) "**PHI**" means information that is "personal health information" under PHIPA that OH has collected as a Prescribed Entity or Prescribed Person;

(j) "**Projected Date**" means the date approved by the REB as part of the Application, on which the Researcher anticipates that OH Data will no longer be required for the Research;

(k) "**Research**" means the study, evaluation and/or research described in the Application;

(l) "**Research Plan**" means the written description of the Research containing the information required under section 44(1)(2) of PHIPA submitted by the Researcher to OH;

(m) "**Research Team**" means collectively, the individuals or organizations (each a "Research Team Member") engaged by the Institution and/or Investigator to carry out or assist in carrying out the Research and described in the Approved Research Plan, and who for the purposes of this Agreement are Agents of the Institution or the Investigator as agreed to between the Research Team Member and the Institution and/or the Investigator;

(n) "**REB**" means a research ethics board, as more particularly described in Section 15 of the Regulation;

(o) "**Secure Disposal**", "**Securely Dispose**" and any other variations of same means the destruction of OH Data in a manner that ensures that the reconstruction of the records is not reasonably foreseeable in the circumstances and that is in accordance with any guidance on the secure destruction of personal information and/or PHI by the IPC.

Limiting Collection, Use and Disclosure of PHI

2. The Researcher has submitted an Application and Research Plan and a copy of the decision of an REB approving the Research Plan.

3. OH and the Researcher acknowledge and agree that:

(a) the terms of the Application, attached hereto as Schedule "A", are incorporated by reference into this Agreement;

(b) the PHI that has been identified in the Approved Research Plan and is being disclosed by OH to the Researcher pursuant to this Agreement is necessary for the Research and that De-identified information and/or aggregate information will not serve the Research purpose;

(c) OH is only disclosing and the Researcher will only collect PHI that is identified in the Approved Research Plan;

(d) the Researcher will not collect or use more OH Data than is reasonably necessary to meet the Research purpose; and

(e) OH Data will be delivered or otherwise made available to the Researcher in a secure manner in accordance with *Secure Transfer of Personal Health Information Policy, Standard and Procedures*, and as more particularly set out in the Application.

Obligations of Researcher

4. **Compliance**. The Researcher shall:

(a) comply with the provisions of the Application and the conditions, if any, specified by the REB in respect of the Approved Research Plan;

(b) without limiting the generality of the preceding clause, only use OH Data for the purposes set out in the Approved Research Plan and not for any other purpose;

(c) maintain a log of any data the Researcher creates using OH Data and provide such log to OH upon request; and

(d) immediately notify OH if an REB approves amendments to the Approved Research Plan.

5. **Protection of PHI**. The Researcher shall:

(a) take steps that are reasonable in the circumstances to ensure that OH Data is protected against theft, loss and unauthorized access, collection, use (including copying, modification and disposal) and disclosure, including at a minimum, the security measures set out in the Approved Research Plan, if any, and in this Agreement;

(b) not copy or otherwise transfer OH Data onto any mobile device, including without limitation any storage mobile device, unless encrypted in accordance with guidance from the IPC from time to time;

(c) not download or otherwise copy, link or combine OH Data with other information except in accordance with the Approved Research Plan;

(d) not take any steps to re-identify any De-identified OH Data (including attempting to decrypt information that is encrypted, attempting to identify an individual based on unencrypted information and attempting to identify an individual based on prior knowledge);

(e) only De-identify OH Data by means that comply with accepted practices and/or standards including any practices or standards established by the IPC, and without limitation, relating to small cell counts; and

(f) not make contact with or attempt to contact, directly or indirectly, individuals to whom the OH Data relates except with the prior express written authorization of OH so as to ensure compliance with the consent requirement in section 44(6)(e) of PHIPA.

6. **Research Team**. The Researcher shall:

(a) not permit any Research Team Member access to OH Data except to the extent such access is required for the Research;

(b) ensure that every Research Team Member who will have access to OH Data has executed the Acknowledgement and Undertaking in Schedule "B" to this Agreement prior to being given access to OH Data; and

(c) provide OH with information relating to each person on the Research Team at OH's request.

7. **Restrictions on Disclosure of PHI**. The Researcher shall:

(a) not disclose any OH Data except as required by a law of Ontario or a law of Canada applicable in Ontario, or permitted under the regulations made under PHIPA;

(b) notwithstanding the preceding, not disclose PHI pursuant to a legal requirement without giving OH sufficient notice to permit it to seek a protective order or other remedy to prevent or limit the disclosure; and

(c) not publish any OH Data or Derivative Data in a form that could reasonably enable a person to ascertain the identity of the individuals to whom the data relates.

8. **Reporting.** The Researcher shall immediately upon discovery;

(a) report any variation from the Approved Research Plan to the REB; and

(b) notify the Data Disclosure Team of any breach of this Agreement, including without limitation, any breach of privacy or security that could reasonably impact OH Data, or any breach of section 44(6) of PHIPA (Compliance by researcher).

9. **Breach Management.** The Researcher shall:

(a) in addition to giving the notice required by section 8 above, immediately take measures to contain the breach, including terminating the access of Research Team Members to OH Data and/or recovering and/or quarantining OH Data where appropriate; and

(b) provide reasonable information to OH regarding the breach to permit OH to evaluate whether any changes to this Agreement and/or its policies and processes regarding research with OH Data warrant review or change.

10. **Acknowledgement, Publication**. The Researcher shall:

(a) include in any materials created through the use of OH Data an acknowledgment in the following form: "Parts of this material are based on data and information provided by Ontario Health (through its business division, Cancer Care Ontario) however the analysis, conclusions, opinions and statements expressed herein are those of the author(s) and not necessarily those of Ontario Health";

(b) provide the Data Disclosure Team, (i) in confidence, with a copy of any abstract, report, or publication regarding the Research findings a minimum of thirty (30) business days prior to submission for publication, and remove any OH Data identified by OH (if so requested by OH); (ii) in confidence, with a copy of any abstract, report, publication or presentation a minimum of thirty (30) business days prior to the publication or delivery date; and (iii) with a citation and the applicable manuscript for the publication within three (3) months of publication or acceptance of publication; and

(c) provide OH with any draft media release pertaining to the Research at least three (3) business days prior to its release and not issue any such media releases without OH's written agreement.

11. **Destruction of OH Data.** The Researcher shall:

(a) securely Dispose of OH Data that the Researcher is holding on or before the destruction date specified in the Application; and

(b) provide the Data Disclosure Team with a signed certificate of destruction, in a form satisfactory to OH, within ten (10) days of the destruction.

Use of OH Data for Research by Students

12. Any Application for a research project to be conducted by a student, including in connection with a thesis or dissertation, must be submitted by the student's supervisor.

13. For such a research project, the supervisor will be considered the Investigator and the student a Research Team Member for the purposes of this Agreement.

14. For clarity, where research using OH Data is to be conducted by a student, the student's supervisor will be required to execute a Research Agreement in the form of this Agreement and the student will be required to execute an Acknowledgement and Undertaking in the form of Schedule "B" to this Agreement.

OH Data Processing

15. Where the Researcher provides data to OH for data processing and like services in accordance with the Approved Research Plan (collectively, "Data Processing"), OH shall only use the data for the Data Processing and will securely destroy the data once OH's obligations under this Agreement have been fulfilled .

16. OH is the limited Agent of the Researcher with respect to the handling of the data provided to OH for Data Processing, and will use reasonable safeguards to protect data being used for Data Processing against theft, loss and unauthorized collection, use, disclosure and destruction

Non-Compliance

17. Failure by the Researcher or any Research Team Member to comply with this Agreement, any documents executed under this Agreement, or any applicable policy or procedure of OH is cause for OH to take any or all of the following actions, among others: (i) terminating this Agreement on notice; (ii) reporting the non-compliance to one or more REB; (iii) reporting the non-compliance to academic institutions and/or professional bodies with which the Researcher and/or the student is affiliated; and (iv) reporting the non-compliance to the IPC or equivalent data protection authority and/or law enforcement and/or affected individuals.

Disclaimer, Limitation of OH Liability

18. OH Data is provided to the Researcher "as is". OH does not warrant the quality, accuracy or completeness of OH Data and disclaims any liability whatsoever or howsoever caused that the Researcher or any other party may incur resulting from the collection, use, reliance upon, or disclosure of OH Data.

19. The Institution *[Institution <or, if Institution is not a part > Investigator]* shall indemnify and hold harmless OH and its directors, officers, employees, professional staff and other representatives and agents against any losses, damages, and third party claims, demands, suits, actions, cause of actions, judgments or other proceedings of any kind related to or arising out of any non-compliance by the Institution, Investigator or Research Team Members with this Agreement or the use of OH Data.

Intellectual Property

20. Ownership of intellectual property existing as of the Effective Date is not affected by this Agreement, and no party to this Agreement will have any claims to or rights in any pre-existing intellectual property of another party, except as may be otherwise expressly provided in a separate written agreement between two or more of the parties.

Term and Termination

21. This Agreement will come into effect on the Effective Date and terminate on the date on which the Research is completed and the Researcher no longer has access to OH Data for the purposes of the Research, unless earlier terminated in accordance with its terms.

22. This Agreement may be terminated by any of OH, the Institution and/or the Researcher:

(a) without cause on at least two (2) month's prior written notice;

(b) immediately on written notice in the event of a breach of this Agreement by another party to the Agreement;

(c) immediately on written notice if OH ceases to be a Prescribed Entity or a Prescribed Person or is otherwise no longer authorized to disclose PHI for the purpose of research.

23. This Agreement may be immediately terminated by OH where an REB has approved amendments to the Approved Research Plan that would have caused OH, in its sole discretion, to decline to enter into this Agreement had they been a part of the Approved Research Plan originally submitted to OH.

24. On termination of this Agreement:

(a) OH will cease disclosing OH Data to the Researcher and the Researcher will cease collecting OH Data from OH; and

(b) OH will determine and give the Researcher notice regarding whether (i) some or all of any OH Data previously disclosed to the Researcher may continue to be used to complete the Research; and/or (ii) any OH Data previously disclosed to the Researcher must be Securely Destroyed.

General

25. **Amendment**. Any additions or modifications to this Agreement must be made in writing and signed by OH and the Researcher.

26. **Governing Law**. This Agreement will be governed by, construed and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable in Ontario (other than any conflict of law rules that would result in the choice of laws of another jurisdiction).

27. **Entire Agreement**. This Agreement constitutes the entire agreement between the Parties relating to the subject matter of this Agreement and supersedes all prior agreements, understandings, negotiations and discussions, whether oral or written, among the Parties with respect thereto.

28. **Waiver**. No waiver by a party to this Agreement of any breach of any of the provisions of this Agreement by any other party to the Agreement will take effect or be binding unless in writing and signed by the waiving party. Unless otherwise provided therein, such a waiver will not limit or affect the tights of the waiving party with respect to any other breach.

29. **Assignment.** This Agreement is not be assignable by either the Institution or Investigator without the prior written consent of OH. This Agreement will enure to the benefit of and be binding upon each party to the Agreement and its successors and permitted assigns.

30. **Notice.** Any notice required or permitted to be given under this Agreement will be in writing and delivered by the means and to the addresses listed in Schedule "C" to this Agreement.

31. **Survival.** All provisions of this Agreement which, by their nature, ought reasonably to survive the termination or expiry of this Agreement shall survive any such termination or expiry, including without limitation the terms and conditions relating to: the collection and use of OH Data; the return or destruction of OH Data; disclosure of OH Data and Derivative Data; publication; and indemnification of OH by the Institution.

32. **Relationship of the Parties**. Nothing in this Agreement will be construed so as to imply, constitute or create a partnership, employment, joint venture or agency relationship between the parties to this Agreement and nothing in this Agreement or arising from the terms of this Agreement shall be construed to confer on any party any right, authority or power to act for, or to assume, create or undertake any obligation or responsibility on behalf of any other of them.

33. **Counterparts.** This Agreement may be executed in counterparts and when each party to the Agreement has executed an identical counterpart and delivered a copy thereof to each other party (by personal delivery or facsimile transmission), then all the counterparts taken together will be deemed to constitute a single identical agreement dated as of the Effective Date.

[Signing page follows.]

IN WITNESS WHEREOF each of OH, the Institution and the Investigator has executed this Agreement as of the Effective Date.

ONTARIO HEALTH

March 19, 2021

Signature: Interim Chief Privacy Officer

Sylvie Gaskin

Name (print)

Signature: Interim Executive Lead,
Clinical Institutes and Quality Programs

Elaine Meertens

Name (print)

March 17, 2021

Signature: Director, Finance – Planning, Budget

Sandra Hua

Name (print)

INSTITUTION

Signature

Jim Banting

Name (print)

Assistant Vice-Principal (Partnerships & Innovations)

Title (print)

INVESTIGATOR

Signature

Sunil Patel

Name (print)

8.3.4 Appendix Chapter 5 – 4: Research Ethics Approval

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

HSREB Delegated Amendment to Ethics Clearance

June 01, 2021

Dr. Sunil Patel
Department of Surgery
Queen's University

TRAQ #: 6019418
Department Code: SURG-369-16
Study Title: "SURG-369-16 Barriers to standard of care treatment for rectal cancer patients in Ontario, Canada and the effect on cancer outcomes: A population based study"
Review Type: Delegated
Date Ethics Clearance Issued: June 01, 2021

Dear Dr. Patel:

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the amendment event form and is granting ethics clearance for the changes listed below:

Document Name	Comments	Version Date
Protocol	Updated Study Protocol Barriers to standard of care treatment for colorectal cancer patients in Ontario, Canada and the effect on outcomes: A population based study?	2021/05/26

Regards,

Albert F. Clark.

Albert F Clark, PhD
Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the international Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Product Regulations; Part 3 of the Medical Devices Regulations, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#: 00004184, IRB#: 00001173. HSREB members involved in the research project do not participate in the review, discussion or decision.

8.3.5 Appendix Chapter 5 – 5: Ontario Cancer Registry "Best Stage" vs. Ontario Cancer Registry Tumor, Nodal and Metastatic Stage

	Ontario Cancer Registry "Best Stage"				
	Early stage (N = 4,353)	**Locally advanced stage (N = 8,172)**	**Stage IV (N = 2,577)**	**Missing Stage (N = 3,529)**	**Total (N = 18,631)**
OCR Tumor Stage					
Tis	79 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	79 (0.4%)
T1	2,467 (87.7%)	196 (7.0%)	115 (4.1%)	34 (1.2%)	2812 (15.1%)
T2	1,557 (70.0%)	598 (26.9%)	65 (2.9%)	6 (0.3%)	2,226 (12.0%)
T3	0 (0.0%)	5,356 (84.8%)	932 (14.8%)	27 (0.4%)	6,315 (33.9%)
T4	0 (0.0%)	1,125 (67.6%)	522 (31.4%)	17 (1.0%)	1,664 (8.9%)
Missing	250 (4.5%)	897 (16.2%)	939 (17.0%)	3,435 (62.2%)	5,521 (29.6%)
OCR Nodal Stage					
N0	4,096 (54.3%)	2,618 (34.7%)	502 (6.7%)	328 (4.4%)	7,544 (40.5%)
N1-2	< 6 (<0.1%)	4,690 (78.3%)	1,285 (21.5%)	6 - 11 (< 0.2%)	5,985 (32.1%)
Missing	260 - 265 (5.1 - 5.2%)	864 (16.9%)	790 (15.5%)	3,189 - 3,194 (62.5 - 62.6%)	5,102 (27.4%)
OCR Metastatic Stage					
M0	4,102 (34.3%)	7,308 (61.1%)	0 (0.0%)	543 (4.5%)	11,953 (64.2%)
M1	< 6 (< 0.2%)	0 (0.0%)	2,325 -2,330) (99.9 – 100%)	0 (0.0%)	2230 (12.5%)
Missing	245 - 250 (5.6 - 5.7%)	864 (19.9%)	246 - 251 (5.6 - 5.7%)	2,986 (68.7%)	4,348 (23.3%)

"Best Stage"	**TNM Stage Derivation**				
	Early Stage	**Locally Advanced**	**Metastatic (Stage IV)**	**Missing**	**Total**
Early Stage	4095	1	1	256	**4353**
Locally Advanced	19	7289	0	864	**8172**
Metastatic (Stage IV)	0	0	2329	248	**2577**
Missing	0	6	0	3523	**3529**
Total	4114	7296	2330	4891	**18631**

8.4 Appendix Chapter 6

8.4.1 Appendix Chapter 6 – 1: Adherence to Recommended Care by Predictor

Table 8-45: Adherence vs. Non-adherent to staging colonic assessment, by predictor

Characteristic	Adherent (N = 14,363)	Non-Adherent (N = 4,268)	X^2 Test or ANOVA
Mean Age, year (STD)	64.6 (13.0)	68.6 (14.4)	P< 0.0001
Age Group			
18-39	435 (75.7%)	140 (24.3%)	P<0.0001
40-49	1,265 (81.6%)	285 (18.4%)	
50-59	3,363 (82.3%)	721 (17.7%)	
60-69	4,038 (80.0%)	1,012 (20.0%)	
70 - 79	3,275 (76.9%)	985 (23.1%)	
80+	1,987 (63.8%)	1,125 (36.2%)	
Sex			
Female	5,385 (75.8%)	1,717 (24.2%)	P = 0.001
Male	8,978 (77.9%)	2,551 (22.1%)	
Diagnosis Year			
2009-2013	6,305 (76.8%)	1,905 (23.2%)	P = 0.003
2014-2016	3,960 (78.7%)	1,071 (21.3%)	
2017-2019	4,098 (76.0%)	1,292 (24.0%)	
Income Quintile			
1 (lowest)	2,815 (72.9%)	1,046 (27.1%)	P<0.0001
2 - 4	8,749 (77.6%)	2,519 (22.4%)	
5 (highest)	2,799 (79.9%)	703 (20.1%)	
Geographical Location			
Rural	2,593 (77.4%)	756 (22.6%)	P = 0.61
Urban	11,770 (77.0%)	3,512 (23.0%)	
Charlson Co-morbidity Score			
Low (< 3)	8,949 (80.2%)	2,213 (19.8%)	P < 0.0001
Mid (3)	1,812 (79.1%)	478 (20.9%)	
High (> 3)	3,602 (69.6%)	1,577 (30.4%)	

Table 8-46 Adherence vs. Non-adherence for Chest and Abdominal Staging for the entire cohort, by predictor

	Chest Imaging			Abdominal Imaging		
Characteristic	**Adherent (N = 15,884)**	**Non-Adherent (N = 2,747)**	**X^2 Test or ANOVA**	**Adherent (N = 16,538)**	**Non-Adherent (N = 2,093)**	**X^2 Test or ANOVA**
Mean Age, year (STD)	65.9 (13.2)	62.9 (14.4)	P <.0001	65.7 (13.3)	63.8 (14.3)	P <.0001
Age Group						
18-39	428 (74.4%)	147 (25.6%)	P <.0001	481 (83.7%)	94 (16.3%)	P <.0001
40-49	1,285 (82.9%)	265 (17.1%)		1,376 (88.8%)	174 (11.2%)	
50-59	3,348 (82.0%)	736 (18.0%)		3,530 (86.4%)	554 (13.6%)	
60-69	4,330 (85.7%)	720 (14.3%)		4,486 (88.8%)	564 (11.2%)	
70 - 79	3,785 (88.8%)	475 (11.2%)		3,888 (91.3%)	372 (8.7%)	
80+	2,708 (87.0%)	404 (13.0%)		2,777 (89.2%)	335 (10.8%)	
Sex						
Female	5,941 (83.7%)	1,161 (16.3%)	P <.0001	6,222 (87.6%)	880 (12.4%)	P<.0001
Male	9,943 (86.2%)	1,586 (13.8%)		10,316 (89.5%)	1,213 (10.5%)	
Diagnosis Year						
2009-2013	6,941 (84.5%)	1,269 (15.5%)	P = 0.002	7,235 (88.1%)	975 (11.9%)	P = 0.02
2014-2016	4,270 (84.9%)	761 (15.1%)		4,470 (88.8%)	561 (11.2%)	
2017-2019	4,673 (86.7%)	717 (13.3%)		4,833 (89.7%)	557 (10.3%)	
Income Quintile						
1 (lowest)	3,336 (86.4%)	525 (13.6%)	P = 0.06	3,449 (89.3%)	412 (10.7%)	P = 0.45
2 - 4	9,585 (85.1%)	1,683 (14.9%)		9,982 (88.6%)	1,286 (11.4%)	
5 (highest)	2,963 (84.6%)	539 (15.4%)		3,107 (88.7%)	395 (11.3%)	
Geographical Location						
Rural	2,949 (88.1%)	400 (11.9%)	<.0001	3,000 (89.6%)	349 (10.4%)	P = 0.10
Urban	12,935 (84.6%)	2,347 (15.4%)		13,538 (88.6%)	1,744 (11.4%)	
Charlson Co-morbidity Score						
Low (< 3)	9,017 (80.8%)	2,145 (19.2%)	P <.0001	9,545 (85.5%)	1,617 (14.5%)	P <.0001
Mid (3)	2,015 (88.0%)	275 (12.0%)		2,071 (90.4%)	219 (9.6%)	
High (> 3)	4,852 (93.7%)	327 (6.3%)		4,922 (95.0%)	257 (5.0%)	

Table 8-47 Adherence vs. Non-adherence for Local Regional Staging adherence for the entire cohort, by predictor

Characteristic	Adherent (N = 14,363)	Non-Adherent (N = 4,268)	X^2 Test or ANOVA
Mean Age, year (STD)	64.7 (13.0)	66.9 (14.2)	P <.0001
Age Group			
18-39	383 (66.6%)	192 (33.4%)	P <.0001
40-49	1,093 (70.5%)	457 (29.5%)	
50-59	2,711 (66.4%)	1,373 (33.6%)	
60-69	3,459 (68.5%)	1,591 (31.5%)	
70 - 79	2,856 (67.0%)	1,404 (33.0%)	
80+	1,693 (54.4%)	1,419 (45.6%)	
Sex			
Female	4,617 (65.0%)	2,485 (35.0%)	P = 0.32
Male	7,578 (65.7%)	3,951 (34.3%)	
Diagnosis Year			
2009-2013	4,885 (59.5%)	3,325 (40.5%)	P <.0001
2014-2016	3,477 (69.1%)	1,554 (30.9%)	
2017-2019	3,833 (71.1%)	1,557 (28.9%)	
Income Quintile			
1 (lowest)	2,466 (63.9%)	1,395 (36.1%)	P = 0.048
2 - 4	7,402 (65.7%)	3,866 (34.3%)	
5 (highest)	2,327 (66.4%)	1,175 (33.6%)	
Geographical Location			
Rural	2,206 (65.9%)	1,143 (34.1%)	P = 0.58
Urban	9,989 (65.4%)	5,293 (34.6%)	
Charlson Co-morbidity Score			
Low (< 3)	7,238 (64.8%)	3,924 (35.2%)	P = 0.042
Mid (3)	1,545 (67.5%)	745 (32.5%)	
High (> 3)	3,412 (65.9%)	1,767 (34.1%)	

Table 8-48 Adherence vs. non-adherent surgery in those with early stage disease, by predictor

Characteristic	Timely Surgery			Significance Testing (χ^2, ANOVA)
	Not Adherent (N=1,177, 31.1%)	Adherent (N=2,608, 68.1%)	Total (N=3,785)	
Surgery Type				
Local Excision	248 (22.2%)	870 (77.8%)	1118 (29.5%)	P < .0001
Major Resection	929 (34.8%)	1738 (65.2%)	2667 (70.5%)	
Mean Age, year (STD)	66.0 (12.5)	65.5 (12.9)	65.7 (12.8)	P = 0.28
Age Group				
18-39	27 (30.3%)	62 (69.7%)	89 (2.4%)	P = 0.71
40-49	84 (29.7%)	199 (70.3%)	283 (7.5%)	
50-59	247 (29.6%)	588 (70.4%)	835 (22.1%)	
60-69	329 (31.2%)	724 (68.8%)	1053 (27.8%)	
70-79	319 (33.0%)	647 (67.0%)	966 (25.5%)	
80+	171 (30.6%)	388 (69.4%)	559 (14.8%)	
Sex				
Female	474 (30.9%)	1061 (69.1%)	1535 (40.6%)	P = 0.81
Male	703 (31.2%)	1547 (68.8%)	2250 (59.4%)	
Year of Surgery				
2010-2013	392 (24.6%)	1203 (75.4%)	1595 (42.1%)	P <.0001
2014-2016	410 (32.4%)	855 (67.6%)	1265 (33.4%)	
2017-2019	375 (40.5%)	550 (59.5%)	925 (24.4%)	
Cancer Centre Designation				
Regional	631 (35.9%)	1126 (64.1%)	1757 (46.4%)	P <.0001
Affiliate	408 (30.7%)	923 (69.3%)	1331 (35.2%)	
Satellite/Non-Designated	138 (19.8%)	559 (80.2%)	697 (18.4%)	
Surgeon Volume (cases/year)				
Missing	422 (28.0%)	1086 (72.0%)	1508 (39.8%)	P <.0001
Low (<3.5)	226 (26.2%)	635 (73.8%)	861 (22.7%)	
Mid (3.5 - 14.5)	218 (30.7%)	493 (69.3%)	711 (18.8%)	
High (>14.5)	311 (44.1%)	394 (55.9%)	705 (18.6%)	
Income Quintile				
1 (lowest)	216 (30.0%)	505 (70.0%)	721 (19.0%)	P = 0.72
2 – 4 (mid)	715 (31.5%)	1553 (68.5%)	2268 (59.9%)	
5 (highest)	246 (30.9%)	550 (69.1%)	796 (21.0%)	
Geographical Location				
Rural	218 (31.4%)	476 (68.6%)	694 (18.3%)	P = 0.84
Urban	959 (31.0%)	2132 (69.0%)	3091 (81.7%)	
Charlson Co-morbidity Score				
Low (< 3)	823 (31.0%)	1831 (69.0%)	2654 (70.1%)	P = 0.011
Mid (3)	172 (27.6%)	452 (72.4%)	624 (16.5%)	
High (> 3)	182 (35.9%)	325 (64.1%)	507 (13.4%)	

Table 8-49 Adherence vs. Non-adherence to major surgery for those with locally advanced disease.

Characteristic	Non Adherent (a) (N=370, 5.2%)	Adherent (N=6685, 94.8%)	Total (N=7055)	Significance Testing (χ^2, ANOVA)
Mean Age, year (STD)	70.4 (13.6)	64.8 (12.7)	65.1 (12.8)	P<.0001
Age Group				
18-39	9 (4.4%)	196 (95.6%)	205 (2.9%)	P<.0001
40-49	19 (3.2%)	569 (96.8%)	588 (8.3%)	
50-59	50 (3.3%)	1477 (96.7%)	1527 (21.6%)	
60-69	80 (3.9%)	1984 (96.1%)	2064 (29.3%)	
70-79	92 (5.6%)	1555 (94.4%)	1647 (23.3%)	
80+	120 (11.7%)	904 (88.3%)	1024 (14.5%)	
Sex				
Female	119 (4.6%)	2444 (95.4%)	2563 (36.3%)	P = 0.087
Male	251 (5.6%)	4241 (94.4%)	4492 (63.7%)	
Year of Surgery				
2010-2013	97 (3.4%)	2729 (96.6%)	2826 (40.1%)	P<.0001
2014-2016	102 (4.6%)	2101 (95.4%)	2203 (31.2%)	
2017-2019	171 (8.4%)	1855 (91.6%)	2026 (28.7%)	
Cancer Centre Designation				
Regional	120 (3.2%)	3634 (96.8%)	3754 (53.2%)	P<.0001
Affiliate	139 (5.9%)	2203 (94.1%)	2342 (33.2%)	
Satellite/Non-Designated	111 (11.6%)	848 (88.4%)	959 (13.6%)	
Income Quintile				
1 (lowest)	89 (6.1%)	1376 (93.9%)	1465 (20.8%)	P = 0.17
2 - 4	223 (5.2%)	4078 (94.8%)	4301 (61.0%)	
5 (highest)	58 (4.5%)	1231 (95.5%)	1289 (18.3%)	
Geographical Location				
Rural	67 (4.9%)	1287 (95.1%)	1354 (19.2%)	P = 0.59
Urban	303 (5.3%)	5398 (94.7%)	5701 (80.8%)	
Charlson Co-morbidity Score				
Low (< 3)	245 (6.7%)	3410 (93.3%)	3655 (51.8%)	P<.0001
Mid (3)	63 (6.7%)	875 (93.3%)	938 (13.3%)	
High (> 3)	62 (2.5%)	2400 (97.5%)	2462 (34.9%)	

(a) Non adherent = local excision

Table 8-50 Adherence vs. non adherence to preoperative radiation in those with locally advanced disease, by predictor.

Characteristic	Adherent Radiation			Significant Testing (χ^2, ANOVA)
	No (N=2,905, 41.2%)	Yes (N=4,150, 58.8%)	Total (N=7,055)	
Mean Age, year (STD)	67.8 (13.2)	63.2 (12.2)	65.1 (12.8)	P<.0001
Age Group				
18-39	71 (34.6%)	134 (65.4%)	205 (2.9%)	P<.0001
40-49	194 (33.0%)	394 (67.0%)	588 (8.3%)	
50-59	512 (33.5%)	1015 (66.5%)	1527 (21.6%)	
60-69	770 (37.3%)	1294 (62.7%)	2064 (29.3%)	
70-79	712 (43.2%)	935 (56.8%)	1647 (23.3%)	
80+	646 (63.1%)	378 (36.9%)	1024 (14.5%)	
Sex				
Female	1065 (41.6%)	1498 (58.4%)	2563 (36.3%)	P = 0.63
Male	1840 (41.0%)	2652 (59.0%)	4492 (63.7%)	
Year of Surgery				
2010-2013	1247 (44.1%)	1579 (55.9%)	2826 (40.1%)	P =0.0001
2014-2016	877 (39.8%)	1326 (60.2%)	2203 (31.2%)	
2017-2019	781 (38.5%)	1245 (61.5%)	2026 (28.7%)	
Cancer Centre Designation				
Regional	1311 (34.9%)	2443 (65.1%)	3754 (53.2%)	P<.0001
Affiliate	1057 (45.1%)	1285 (54.9%)	2342 (33.2%)	
Satellite/Non-Designated	537 (56.0%)	422 (44.0%)	959 (13.6%)	
Surgeon Volume (cases/year)				
Missing	604 (80.9%)	143 (19.1%)	747 (10.6%)	P<.0001
Low (<3.5)	1057 (48.4%)	1128 (51.6%)	2185 (31.0%)	
Mid (3.5 - 14.5)	742 (35.6%)	1340 (64.4%)	2082 (29.5%)	
High (>14.5)	502 (24.6%)	1539 (75.4%)	2041 (28.9%)	
Income Quintile				
1 (lowest)	598 (40.8%)	867 (59.2%)	1465 (20.8%)	P = 0.95
2 - 4	1776 (41.3%)	2525 (58.7%)	4301 (61.0%)	
5 (highest)	531 (41.2%)	758 (58.8%)	1289 (18.3%)	
Geographical Location				
Rural	571 (42.2%)	783 (57.8%)	1354 (19.2%)	P = 0.41
Urban	2334 (40.9%)	3367 (59.1%)	5701 (80.8%)	
Charlson Co-morbidity Score				
Low (< 3)	1511 (41.3%)	2144 (58.7%)	3655 (51.8%)	P = 0.38
Mid (3)	402 (42.9%)	536 (57.1%)	938 (13.3%)	
High (> 3)	992 (40.3%)	1470 (59.7%)	2462 (34.9%)	

Table 8-51 Adherence vs. non-adherence to postoperative chemotherapy in those with locally advanced disease, by predictor

Characteristic	Postoperative Chemotherapy			Significant Testing (χ^2, ANOVA)
	No (N=2987, 42.3%)	Yes (N=4068, 57.7%)	Total (N=7,055)	
Mean Age, year (STD)	70.6 (12.5)	61.1 (11.4)	65.1 (12.8)	<.0001
Age Group				
18-39	41 (20.0%)	164 (80.0%)	205 (2.9%)	<.0001
40-49	131 (22.3%)	457 (77.7%)	588 (8.3%)	
50-59	420 (27.5%)	1107 (72.5%)	1527 (21.6%)	
60-69	695 (33.7%)	1369 (66.3%)	2064 (29.3%)	
70-79	857 (52.0%)	790 (48.0%)	1647 (23.3%)	
80+	843 (82.3%)	181 (17.7%)	1024 (14.5%)	
Sex				
Female	1140 (44.5%)	1423 (55.5%)	2563 (36.3%)	0.006
Male	1847 (41.1%)	2645 (58.9%)	4492 (63.7%)	
Year of Surgery				
2010-2013	1400 (49.5%)	1426 (50.5%)	2826 (40.1%)	<.0001
2014-2016	828 (37.6%)	1375 (62.4%)	2203 (31.2%)	
2017-2019	759 (37.5%)	1267 (62.5%)	2026 (28.7%)	
Cancer Centre Designation				
Regional	1429 (38.1%)	2325 (61.9%)	3754 (53.2%)	<.0001
Affiliate	1128 (48.2%)	1214 (51.8%)	2342 (33.2%)	
Satellite/Non-Designated	430 (44.8%)	529 (55.2%)	959 (13.6%)	
Surgeon Volume (cases/year)				
Missing	358 (47.9%)	389 (52.1%)	747 (10.6%)	<.0001
Low (<3.5)	1025 (46.9%)	1160 (53.1%)	2185 (31.0%)	
Mid (3.5 - 14.5)	878 (42.2%)	1204 (57.8%)	2082 (29.5%)	
High (>14.5)	726 (35.6%)	1315 (64.4%)	2041 (28.9%)	
Income Quintile				
1 (lowest)	701 (47.8%)	764 (52.2%)	1465 (20.8%)	<.0001
2 - 4	1811 (42.1%)	2490 (57.9%)	4301 (61.0%)	
5 (highest)	475 (36.9%)	814 (63.1%)	1289 (18.3%)	
Geographical Location				
Rural	494 (36.5%)	860 (63.5%)	1354 (19.2%)	<.0001
Urban	2493 (43.7%)	3208 (56.3%)	5701 (80.8%)	
Charlson Co-morbidity Score				
Low (< 3)	1506 (41.2%)	2149 (58.8%)	3655 (51.8%)	<.0001
Mid (3)	482 (51.4%)	456 (48.6%)	938 (13.3%)	
High (> 3)	999 (40.6%)	1463 (59.4%)	2462 (34.9%)	

(a) per 10-year increase