Evaluation of Clinical Practice over Time for Patients with Stage II and III Rectal Cancer: A Collaborative study of Newfoundland and Labrador and Ontario

by

Ian P. B. Short

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ABSTRACT

Background: In 1990, the National Institutes of Health released the first published guidelines for the treatment of rectal cancer, which recommended chemo-radiation therapy in the postoperative setting for patients with stage II and III of the disease. Since then, numerous studies have suggested the superiority of neoadjuvant chemo-radiation therapy in terms of local control, acute and long-term toxic effects, patient compliance, and sphincter preservation. As a result, the current standard of care for patients with stage II and III rectal cancer has become neoadjuvant chemo-radiation therapy followed by surgery with curative intent. The objective of this research is to evaluate the changes made to the clinical practice of rectal cancer over time by comparing the effects of neoadjuvant chemo-radiation therapy to standard therapy on patient survival and disease recurrence.

Methods: We examined the clinicopathological data for a sample of 757 confirmed cases of rectal adenocarcinoma collected from 1 of 3 cohorts: the Newfoundland Colorectal Cancer Registry from 1997 to 2003, the Ontario Familial Colorectal Cancer Registry from 1997 to 2000, and the single practice of a general surgeon working in Newfoundland and Labrador from 1993 – 2014. The primary outcome of our study was overall survival in patients with stage II and III of the disease, which was measured from the date of diagnosis to the date of death. We investigated the effect of neoadjuvant chemo-radiation therapy on overall survival for these patients.

Results: For patients with stage I-IV rectal cancer, age, anterior resection surgery, complete excision, grade, vascular and perineural invasion, and stage were independent predictors of overall survival ($p < 0.05$). For patients with stage II and III of the disease, age, anterior resection surgery, complete excision, grade, stage, and the presence of perineural invasion were independently associated with overall survival ($p < 0.05$). Again, no significant association between neoadjuvant therapy and patient survival was observed independent of these variables. The rate of neoadjuvant chemo-radiation therapy was significantly higher for stage II and III patients diagnosed after December 2003 (5% vs. 41%, $p < 0.001$). For this cohort, age, sex, stage, and vascular invasion were independent significant predictors of overall survival ($p < 0.05$). Again, neoadjuvant chemo-radiation therapy had no significant effect on survival. However, the relative risk for neoadjuvant chemo-radiation therapy was 0.428 ($p= 0.107$).

Conclusions: In the cohort with stage II and III rectal cancer diagnosed after 2003, the magnitude of the relative risk for neoadjuvant chemo-radiation suggested benefit, but it did not achieve statistical significance because of the inadequate power caused by the small study size.

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List of Abbreviations

AJCC	**American Joint Committee for Cancer**
APR	**Abdominal Perenial Resection**
AR	**Anterior Resection**
CINAHL	**Cumulative Index of Nursing and Allied Health Literature**
CRC	**Colorectal Cancer**
CRM	**Circumferential Resection Margin**
CRT	**Chemoradiation Therapy**
CT	**Computed Tomography**
ERUS	**Endorectal Ultrasound**
IUCC	**International Union for Cancer Control**
MeSH	**Medical Subject Heading**
MRI	**Magnetic Resonance Imaging**
NFCCR	**Newfoundland & Labrador Colorectal Cancer Registry**
OFCCR	**Ontario Familial Colorectal Cancer Registry**
TME	**Total Mesorectal Excision**
TNM	**Tumor Node Metastasis Standardized Staging System**

Chapter 1: INTRODUCTION

Colorectal Cancer (CRC) is one of the most prominent and deadly diseases in the western world today (Madlensky, 2004). During 2019, it was estimated that 26, 300 Canadians were diagnosed with CRC and that 9, 500 Canadians died from the disease (Canadian Cancer Society, 2020). Approximately 30% of all CRC cases can be attributed to patients with rectal cancer, who have been historically susceptible to developing locally recurrent disease following surgical intervention (Ucar, 2013; Kapiteijn, 2001; Van den broek, 2013). To account for this high rate of local recurrence, William Heald developed the principles of Total Mesorectal Excision (TME), which were subsequently incorporated into the standard surgical care for patients with locally advanced rectal cancer, stages II (T3-4, N0, M0) and III (any T, N1-2, M0). These principles, which involve a complete resection of the mesorectum and surrounding lymph nodes, have been shown to improve both local control and patient survival (Rodríguez-Luna, 2015).

Prior to the 1980s, surgery was often the sole treatment for stage II and III rectal cancer, which resulted in a 5-year patient survival rate of just 50% (Yorio, 2012; Fisher 1988). Since then, management has evolved to incorporate a multidisciplinary régime, which includes chemotherapy, radiation therapy, and definitive surgery (Krook, 1991). The efficacy of postoperative chemoradiation therapy (CRT) was first established from the results of three prospective randomized controlled trials, which were conducted by the Gastrointestinal Tumor Study Group, the Mayo/North Central Cancer Treatment group, and the National Surgical Adjuvant Breast and Bowel Project. These studies showed that patients, who were treated with postoperative CRT, benefited from improvements in

disease-free and overall survival in comparison to individuals treated with surgery alone. As a result, the 1990 U.S. National Institute of Health consensus conference on the treatment of CRC recommended post-operative CRT for the treatment of stage II and III rectal cancer (NIH consensus conference, 1990).

During the 1990s, studies demonstrated the superiority of preoperative, or "neoadjuvant", radiation therapy for patients with locally advanced rectal cancer in regards to local control (Frykholm, 1993; Swedish Rectal Cancer Trial, 1997). However, these trials began before the standardization of TME and therefore, the results may have been due to changes in surgical technique itself. In 2001, the Dutch Colorectal Cancer Group designed a prospective randomized trial with standardized surgical procedure to deal with this issue. Although their results showed that neoadjuvant radiotherapy significantly reduced the rates of local recurrence among patients, no improvement in patient survival was observed (Kapiteijn, 2001). In 2004, the German Rectal Cancer Study group published the results of their seminal paper that compared neoadjuvant and postoperative CRT. The results of the 5-year follow up favored neoadjuvant CRT in terms of local control, acute and long-term toxic effects, patient compliance, and sphincter preservation (Sauer, 2004). As a result, clinical practice began to favor a recommendation of neoadjuvant CRT followed by radical surgery for patients with stage II and III rectal cancer (de Campos-Lobato, 2011; Lim, 2008; Pahlman, 2009).

There is a need for ongoing research to examine the change in clinical practice following the recommendation of neoadjuvant CRT. Further studies that compare patient survival before and after this change in practice will benefit the prognosis and future management of patients with locally advanced rectal cancer.

1.1 Aim of the study

The objective of this study is to examine overall survival for patients, with stage II & III rectal cancer, inhabiting Newfoundland & Labrador and Ontario during the period of 1993 – 2014. The study will compare overall survival before and after the changes in clinical practice from postoperative to neoadjuvant CRT.

Specifically, the main objectives are:

1. To examine the rate of overall survival in stage II and III rectal cancer patients following the change in clinical practice from postoperative to neoadjuvant CRT;

2. To examine the rate of disease-free time to event in stage II and III rectal cancer patients following the change in clinical practice from postoperative to neoadjuvant CRT;

3. To examine the rate of local recurrence-free time to event in stage II and III rectal cancer patients following the change in clinical practice from postoperative to neoadjuvant CRT;

Chapter 2: LITERATURE REVIEW

This literature review summarizes the published research findings that have impacted the management of patients with stage II and III rectal cancer. A computerized literature search was conducted using The Cochrane Library, PubMed, and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases. The Cochrane Library was used to search for relevant meta-analysis and systematic reviews, finding several papers that provided an overview of the key findings pertinent to the research question. Next, PubMed and CINAHL were consulted for meta-analysis and reviews by specifying the publication type, and then for original research articles. Search strategies included key words “rectal cancer”, “colorectal cancer”, “rectal carcinoma”, “TNM staging”, “pathologic”, “preoperative”, “postoperative”, “abdominoperineal resection”, “anterior resection”, “total mesorectal excision”, “rectal cancer surgery”, “sphincter-saving surgery”, “stoma”, “multimodality therapy”, “recurrent”, “local recurrence”, “margin”, “spread”, “treatment”. Medical Subject Heading (MeSH) terms included “rectal neoplasms”, “chemoradiotherapy”, “radiotherapy”, “neoadjuvant therapy”, “recurrence”, and “mortality”, “survival”, “history”. The focus of this review was to familiarize the investigator with information pertaining to the management of rectal cancer. An expert in the field of colorectal surgery was consulted to attain knowledge of the therapies that are currently available to patients with locally advanced stages of the disease. This information was also used to ensure the selection of appropriate papers. This literature review is limited to only those articles published in English as of March 2020.

2.1 Background information

Rectal cancer, which accounts for approximately 30% of colorectal cancer (CRC) cases, is a leading cause of cancer mortality in the western world. Most individuals that are diagnosed with rectal cancer present with locally advanced disease, which are stages II and III. As a result, these patients are at an increased risk of local recurrence following surgery (Agarwal, 2013; Gunderson, 2010). Unfortunately, locally recurrent disease is frequently inoperable and patients who relapse often suffer a painful death (Nagtegaal, 2002). Consequently, a primary goal for rectal cancer treatment has become optimizing local control (Lin, 2013). In an attempt to improve local control and survival among patients with stage II and III rectal cancer, treatment has evolved to incorporate a multi-modal regime that includes chemotherapy, radiotherapy, and radical surgery.

In 1990, the U.S. National Institutes of Health released the first evidence-based guidelines for the treatment of patients with CRC. Based on the results of three randomized controlled trials, the standard care for patients with locally advanced disease became rectal surgery followed by postoperative CRT. However, this recommendation was premature and highly criticized (Pasetto, 2004). In 2004, Sauer et al. published one of the most influential articles to the field of rectal cancer treatment, suggesting neoadjuvant CRT to be more beneficial in terms of local control, acute and long-term toxic effects, patient compliance, and sphincter preservation. As a result, patients with stage II and III rectal cancer now undergo neoadjuvant CRT followed by radical surgery that incorporates the principles of TME. Although neoadjuvant CRT has improved the rates of local control in patients with locally advanced stages of the disease, it remains unclear whether an association exists between neoadjuvant therapy and improved patient survival.

2.2 Definition, diagnosis, & staging of rectal Cancer

Previous studies have reported differences in the treatment of CRC due to surgeon-specific variables (McMullen, 2005; Hool, 1998; Hyman, 2007). For example, there has been considerable debate between surgeons regarding the definition of the rectum, its length, and the site of transition from rectum to sigmoid colon (Kenig, 2013). A study by McMullen et al. reported disagreement between surgeons who were asked to define the proximal and distal boundaries of the rectum. While 30% of respondents defined the upper boundary of the rectum in terms of distance from the anal verge, 66% used some other anatomic landmark to define this boundary. Similarly, 76% of respondents defined the distal boundary in terms of an anatomic landmark and another 23% described the distal boundary as anything below their definition of the upper boundary (McMullen et al, 2005). In 2010, Chuah et al. surveyed all general surgeons in Atlantic Canada to determine their preferences for screening and neoadjuvant assessment of rectal cancer. Their results also showed variability in the surgeon's definition of the rectum. Out of 82 respondents, 31% defined the rectum as at or below the peritoneal reflection, while another 27% defined it in terms of the coalescence of the tenia. Interestingly, 26% considered the rectum to be 15 cm within the anal verge and another 16% described it as the region below the sacral promontory. Furthermore, some respondents chose multiple answers to define the rectum (Chuah, 2010). The definition of the rectum is important for differentiating rectal cancers from cancers of the sigmoid colon. At present, many authors agree that rectal cancer can be defined as a tumor with its lower edge within 15cm of the anal verge (Ucar, 2013; Glimelius, 2013).

Most diagnoses of rectal cancer are made during colonoscopy after the patient presents to clinic with anemia, change in bowel habit, or blood in the stool. In addition, the cancer must be confirmed pathologically, as strictures and inflammatory diseases are benign conditions that may present similarly (Trakarnsanga, 2012). Following pathological diagnosis, the most common tests ordered are Computed Tomography (CT) scans of the chest, abdomen, and pelvis. CT imaging is useful for determining metastatic spread of the disease to lung, liver, pelvic, and periaortic lymph nodes, though it cannot accurately assess tumor penetration or nodal involvement (Trakarnsanga, 2012). The staging of rectal cancer is clinically important for deciding whether multi-modal therapy is necessary (Schrag, 2013). Staging refers to the size and extent of the primary tumor (T stage), the nodal involvement (N stage), and the spread of the disease (M stage). In an effort to organize patients into prognostic groups, the Tumor Node Metastasis standardized staging system (TNM) was collaboratively developed by the International Union for Cancer Control (IUCC) and the American Joint Committee for Cancer (AJCC). At present, the TNM is the most used staging system globally (Obrocea, 2011). Table 1 describes the TNM of CRC.

Adequate clinical staging begins with a digital rectal exam in order to determine the location and mobility of the lesion, the latter relating to the tumors penetration of the rectal wall. Most often, rigid sigmoidoscopy is used to better determine the distance of the primary tumor, which is measured from the anal verge (Trakarnsanga, 2012). For determining T and N staging, endorectal ultrasound (ERUS) and pelvic magnetic resonance imaging (MRI) represent the gold standard of care. MRI can be used to describe in detail the level, localization, shape, and extramural growth of bulky rectal

tumors, whereas ERUS is used to describe small, superficial tumors (Trakarnsanga, 2012). Once the tumor is surgically excised, it is sent to a lab for more accurate, pathological staging. In addition, lymphadenectomy is performed during surgery and the removed lymph nodes are used to determine the level of nodal involvement (Sauer, 2004; Kapiteijn, 2001; Roh, 2009). The IUCC and the AJCC have recommended the examination of at least 12 lymph nodes in order to ensure adequate cancer staging.

Tumor

- T1: Submucosa
- T2: Muscularis propria
- T3: Subserosa, perirectal tissues
- T4a: Visceral peritoneum
- T4b: Other organs or structures

Lymph Node

- N1a: One regional lymph node involved
- N1b: Two to three regional lymph nodes involved
- N1c: Satellites without regional lymph nodes
- N2a: Four to six regional lymph nodes involved
- N2b: Seven or more regional lymph nodes involved

Metastasis

- M1a: Metastasis to one organ
- M1b: Metastases to more than one organ or peritoneum
- y: Prefix indicates staging taking place during/following multimodal therapy
- c: Prefix indicates clinical staging
- p: Prefix indicates pathological staging

Figure 1: Tumor Node Metastasis standardized staging system (TNM) of rectal cancer

Adapted from Macgregor, Maughan, and Sharma, (2012) Pathological grading of regression following neoadjuvant chemoradiation therapy: the clinical need is now.

2.3 Patient Candidacy for treatment

Before multidisciplinary therapy is recommended, the nature and extent of the rectal tumor must be clearly established. Radical surgery comprised of either AR or APR is an appropriate treatment option for patients with stage I rectal cancer. With that said, a subgroup of T1 tumors may be managed by conservative local excision. Candicacy for this procedure is usually reserved for moderately- or well- differentiated T1 tumors, without lymphovascular invasion. In addition, the size of the tumor should be less than 3 cm in diameter and occupying no more than one-third of the circumference of the rectal lumen. In contrast, local excision for stage II tumors is controversial, as radical surgery has been associated with a lower local recurrence rates for this stage of disease (NCCN, 2012). For patients with stage II and III rectal cancer (T3–T4 and/or positive lymph nodes), neoadjuvant CRT followed by radical surgery is recommended. There are several contraindications to performing surgery for the treatment of locally advanced rectal cancer. For example, patient comorbidity may preclude surgery regardless of the potential to obtain a curative resection. Other factors that contraindicate radical surgery are described by Bouchard and Efron (2010), which include circumferential involvement of the pelvic sidewall, bilateral ureteric obstruction, tumor encasement of the iliac vessels, proximal sacral invasion extending to the sacral promontory, and the extension of tumor through the greater sciatic notch. For stage IV cancers, the presence of unresectable extrapelvic disease is considered a contraindication for rectal surgery. Furthermore, patients who are individually assessed by the surgeon to be a poor surgical candidate should not receive multi-modal therapy.

2.4 Historical Advances in Rectal Surgery

Surgery for rectal cancer began in the 18th century. In 1739, Jean Faget of France attempted the first rectal excision when he accidently discovered a perforated rectal tumor in a patient while draining an ischio-rectal abscess. Unfortunately, the surgery resulted in an "uncontrollable sacral anus", and the patient did not survive (Graney, 1980). In 1826, Jacques LisFranc was credited with the first successful rectal surgery. Without the use of anesthesia or hemostasis, the patient was asked to bear down while the rectum was turned inside out and resected via perineum. At this time, patient outcomes following surgery were poor due to complications, which included sepsis, hemorrhage, and recurrent disease (Gilbertsen, 1964). In 1874, Theodor Kocher introduced the idea of removing the rectum through the sacrum followed by an end-to-end anastomosis of the colon and anus. However, perineal and sacral approaches to surgery were eventually deemed inadequate due to small surgical fields with no possibility of radical resection and the construction of a sacral anus that caused difficulties to the patient.

In 1879, Carl Gussenbauer performed the first abdominal resection of a proximal rectal tumor (Goligher, 1984). This procedure was made possible due to developments in the surgical principles of asepsis and both spinal and gas anesthesia. The French surgeon, Henri Hartmann, became a strong advocate of abdominal resection because of the minimal blood loss associated with the operation. As a result, the surgery was named the Hartmann procedure, and it is still performed in both emergency and palliative care (Lange, 2009).

In 1908, William Ernest Miles developed Abdominal Perenial Resection (APR), which involves an en bloc removal of tumors occupying the lower one-third of the rectum

and their associated lymph nodes. This radical surgery resulted in an abdominal stoma, which was more controllable than the sacral anus produced from earlier procedures. Furthermore, the recurrence and mortality rate of APR was reported to be 29.5% and 10%, respectively (Miles, 1923). Despite improvements in these outcomes, APR causes permanent colostomy and urogenital dysfunction, which has been shown to impair patient quality of life (Sprangers 1995; Kasparek, 2012).

In 1910, Donald Balfour developed Anterior Resection (AR). This surgery is performed through an abdominal approach and incorporates an end-to-end anastomosis, leaving the rectal sphincter intact. Initially, this procedure was thought to be insufficiently radical (Mayo, 1916). Specifically, critics argued that AR would not fully remove the blood supply, lymph nodes and/or adjacent structures of the tumor and as a result, the cancer could be given a chance to spread. However, Cuthbert Dukes suggested that the downward and lateral spread of rectal cancer was unlikely to occur, as most lymph nodes are either parallel or proximal to the level of the tumor (Dukes, 1930). As a result, surgeons aimed to perform less radical surgery, while preserving the function of the anal sphincter. In 1948, Claude Dixon established the safety of sphincter-preserving surgery, when he reported a mortality and 5-year survival rate of 2.6% and 64%, respectively (Dixon, 1948). As a result, AR became the standard of care for tumors occupying the middle and upper third of the rectum.

Unfortunately, AR is less likely to be performed for tumors that inhabit the distal 5-cm of the rectum. During the 1970s, Alan Parks established low AR of the rectum to account for these low-lying tumors. This procedure creates an anastomosis between the colon and anus, allowing for low-lying tumors to be removed while avoiding colostomy

(Parks, 1972). At present, the risk of anastomotic leakage within irradiated fields remains high, which requires surgeons to construct diverting ileostomies in most patients (Peeters, 2005). Still, low colo-anal anastomoses often results in higher rates of stool frequency, urgency, and incontinence. As a result, surgeons have produced methods of pouch reconstruction, such as the J-pouch and coloplasty (Galler, 2010).

In addition, sphincter preservation is possible due to the revision of distal margins in rectal surgery. Initially, surgeons believed that a 5-cm margin between the resection and the distal edge of the tumor was necessary to achieve adequate local control (Goligher, 1951). However, studies have reported that distal margins smaller than 2-cm do not affect local control or survival for rectal cancer patients (Pollett, 1983, Williams, 1983). Furthermore, it has been shown that intramural submucosal spread rarely extends past 1 cm distally in patients with rectal cancer (kwok, 1996, Andreola, 1997). As a result, the National Comprehensive Cancer Network recommends a distal margin of > 1cm for patients with low-lying lesions (Nelson, 2001).

In 1982, William Heald established the principles of TME, which involves an en bloc resection of the tumor and the mesorectum to the level of the levator muscles. These principles were based on the assumption that rectal tumors spread laterally to the mesorectum. Heald noted that both organs were derived from the same tissue and as a result, he incorporated sharp dissection of embryologically defined planes into his surgical technique. In addition, Heald stressed the importance of a “holy plane” in rectal surgery, which he thought should result in the removal of the malignancy, but also the preservation of autonomic neural function (Heald, 1982). Hojo and Moriya are credited with developing the surgical techniques required to preserve the innervation of urogenital

organs (Hojo, 1991; Moriya, 1995). The American surgeon, Warren Enker, combined these techniques with the principles with TME in order to increase the rate of sphincter preserving surgery (Enker, 1992; Havenga, 2002). However, nerve damage due to rectal surgery still remains a major issue (Guren, 2005).

With the success of neoadjuvant CRT, emphasis has been placed on preserving the function of the anal sphincter for patients undergoing rectal surgery (Inoue, 2010). It has been hypothesized that neoadjuvant CRT may result in less invasive surgery and therefore higher rates of sphincter preservation for patients with locally advanced rectal cancer (Marks, 2013).

2.5 Adjuvant therapy

2.51 Radiation therapy

Adjuvant therapy for rectal cancer was implemented into clinical practice during the 1980s (Popek, 2011). Prior to this, surgery was often the sole treatment for patients, with a survival rate of just 50% (Yorio, 2012; Fisher, 1988; Julien, 2010). The addition of radiotherapy, whether administered pre- or postoperatively, has improved the rates of local recurrence.

In 1988, a study by the European Organization for Research and Treatment of Cancer found that the addition of neoadjuvant radiation therapy improved both the 5-year survival and local recurrence rates of patients with rectal cancer (Gérard, 1988). Similarly, the Swedish Rectal Cancer Trial, which compared short-course radiation

therapy and surgery with surgery alone found a significant improvement in both local recurrence and survival for patients at a median follow up of 13 years. At present, this study remains the only randomized trial to have shown a survival benefit for patients with locally advanced rectal cancer due to neoadjuvant therapy (Folkesson, 2005). However, this experiment began before the introduction of TME, which made it uncertain whether the survival benefit was due to radiation therapy or improvements in surgical technique. To account for this, the Dutch Rectal Cancer Study Group designed an experiment to compare patients treated with radiotherapy and TME verses those who received TME alone. Although their results suggested that neoadjuvant radiotherapy decreased the rate of local recurrence, no significant benefit to overall survival was observed (Kapiteijn, 2001). While short course radiotherapy has been shown to induce pathological response in some patients, significant tumor down staging is rarely achieved with radiation therapy alone.

2.52 Concurrent chemotherapy

The rationale for giving chemotherapy concurrently with radiotherapy is to potentiate local radiotherapy sensitization and as a result, induce tumor down staging. Initially, chemotherapeutic agents were introduced as an adjunct to radiotherapy in the postoperative setting. Three prospective randomized clinical trials established the effectiveness of postoperative chemotherapy in the treatment of rectal cancer. In 1985, the Gastrointestinal Tumor Study Group first showed that the combination of chemotherapy

and radiotherapy was superior to that of radiotherapy alone. Combination therapy resulted in less local recurrence and an increased time to recurrence for patients with locally advanced rectal cancer (Gastrointestinal Tumor Study Group, 1985). In 1991, the North Central Cancer Treatment Group also evaluated the effects of combining radiotherapy with chemotherapy. In comparison to post-operative radiotherapy alone, combination treatment was shown to significantly improve patient survival (Krook et al, 1991). Furthermore, findings from the National Surgical Adjuvant Breast and Bowel Project reported that adjuvant CRT reduced local recurrence, but did not affect overall survival for patients (Fisher, 1988). The results of these trials prompted the 1990 U.S. National institute of Health consensus conference to recommend postoperative CRT as the standard care for patients with stage II and III rectal cancer (NIH, 1990). However, this recommendation was premature and highly criticized. For example, the study by the Gastrointestinal Tumor Study Group was underpowered and the Krook et al. trial failed to significantly reduce the rate of local recurrence (Pasetto, 2004). The lack of evidence for postoperative CRT encouraged investigators to examine other treatment modalities.

More recently, studies have demonstrated the superiority of neoadjuvant CRT. In 1994, the German Rectal Cancer Study Group initiated a randomized controlled trial to compare the long-term efficacy of both neoadjuvant and postoperative CRT. The results of the 11-year follow-up showed that neoadjuvant CRT improved local control, and resulted in less short- and long-term toxic effects than those who received post-operative CRT. Furthermore, neoadjuvant CRT benefited patient compliance and doubled the rate of sphincter preservation (Sauer, 2004). The results of this trial had a major influence on clinical practice, which now favors neoadjuvant CRT as the standard care for patients

with stage II and III rectal cancer. In 2009, Roh et al. reported a higher disease-free survival rate and a non-significant trend toward improved overall survival for patients who received neoadjuvant CRT (Roh, 2009). Subsequently, a study by Park et al. found that neoadjuvant CRT improved sphincter preservation and decreased the risk of surgical complication. However, this study found no difference in survival or local recurrence between patients who received neoadjuvant and post-operative CRT (Park, 2011). Furthermore, a recent study by Lee et al. showed neoadjuvant CRT to be superior to postoperative CRT in terms of tumor down-staging and sphincter preservation (Lee, 2013). At present, most studies suggest that neoadjuvant CRT has a greater benefit to local control, toxicity, patient compliance, and sphincter preservation. However, no difference in patient survival has been consistently demonstrated.

2.6 Recurrent disease

The probability of a patient with recurrent rectal cancer surviving five years is less than 7%, with a mean life expectancy of just 7 months (McCarthy, 2012). As a result, a main goal of treatment is preventing both local and distant recurrence of rectal cancers following definitive surgery. Local recurrences refer to any tumor that recurs in the true pelvis, which includes the neorectum, mesentery, pelvic viscera, pelvic sidewall structures, and bone (Yeo, 2013). According to the IUCC, the term local recurrence can only be applied if a complete resection is achieved, leaving no macroscopic evidence of

tumor locally (Heriot, 2006). Cancer cells that are neither destroyed by CRT nor removed from surgery may act as seed cells for local recurrence (Peng, 2013).

The Memorial Sloan Kettering group describes a classification system of local recurrence based on their anatomical region of the pelvis. For example, axial recurrences were subdivided into anastomotic, residual mesorectum, or perirectal soft tissue of the pelvis and perineum. The term anterior describes recurrences of the genitourinary tract, while posterior involves the sacrum, presacral fascia or sacral root sheaths. Lastly, lateral recurrences involve the muscles and soft tissue of the pelvic sidewall, lymph nodes, major iliac vessels, sacral nerve plexis, and lateral bony pelvis (Guillem, 2008). The Dutch TME trial group used a similar classification of local recurrence, but separated anastomotic and perineum recurrences (Kusters, 2010).

A diagnosis of local recurrence is usually made by either one of the following major criteria: (1) histological confirmation, (2) palpable or evident disease with subsequent clinical progress, (3) evidence of bone destruction, or (4) positron emission tomography examination, and one of the following minor criteria: (1) gradual enlargement of mass with repeated CT or MRI scans, (2) invasion of nearby tissues, (3) a rise in the levels of tumor markers, and (4) findings made with endoscopic ultra sound, CT, or MRI (Enriquez-Navascues, 2011). The majority of local recurrences occur within 2 - 3 years following definitive surgery and approximately 33% of which can be resected (Palmer, 2007; Bakx, 2008). In the 1980s, Heald and Ryall introduced TME, based on the premise that primary rectal tumors have a tendency to spread laterally to the mesorectum (Heald, 1982; Heald 1986). The mesorectum is a fatty connective tissue layer that surrounds the rectum and contains blood vessels, lymphatics, and lymph nodes (Parfitt,

2007). As they predicted, removal of the mesorectal tissue successfully reduced the 5-year rate of local recurrence from 30 - 40% to < 10 % (Glimelius, 2013,Wibe 2003; MacFarlane, 1993; Enker, 1995).

Approximately 20-30% of patients with rectal cancer have a distant recurrence following surgery, with the most common sites being the liver and lungs (Arredondo, 2015). To date, neoadjuvant therapy has added little benefit in terms of managing metastatic disease (Ding, 2012). However, adjuvant therapy has been incorporated into practice in order to better prevent distant recurrences. Following neoadjuvant therapy and surgery, the patient often receives adjuvant therapy, which consists of chemotherapy for 4 – 6 months. Similar to the role of neoadjuvant therapy in reducing local failures, this postoperative treatment is given systemically to prevent distally recurrent disease (Berardi, 2014). This recommendation is made largely based on the results of a 2004 meta-analysis by Gunderson et al., which demonstrated a 20% survival benefit for patients receiving postoperative chemotherapy in comparison to those receiving postoperative radiation therapy (Gunderson, 2004). Still, some investigators do not agree with this practice, as most locally advanced rectal cancers are node negative following neoadjuvant therapy (Park, 2014). Although the presence of metastatic disease dramatically reduces the chance of survival, the number of distant recurrences treated with curative intent is increasing (Ding, 2012; Tjandra, 2007). Repeat surgical resection may be possible for certain patients, whereas others may avail of two-stage hepatectomy, portal vein embolism, radiofrequency ablation, or neoadjuvant systemic chemotherapy.

2.7 Prognostic factors

2.71 Surgical margins

The choice of surgical technique is largely dependent on the potential for achieving a curative or "R0" resection, which refers to the complete excision of the tumor, leaving no residual disease. Obtaining an R0 resection dramatically reduces the rate of disease recurrence and is an important determinant of patient survival (Martling, 2004; Hahnloser, 2003). In order to achieve a R0 resection, both the distal and the circumferential surgical margins must be uninvolved by tumor.

Approximately 10% of rectal cancer cases exhibit intramural extension below the level of the tumor, which describes the need for adequate distal margins in rectal surgery (Mezhir, 2012; Shimada, 2011). The distal margin refers to the amount of clearance allowed between the distal edge of the tumor and the resection. Given that intramural tumor extension rarely exceeds 1 cm distally, a margin of ≥1 cm is generally recommended for patients undergoing AR (Shirouzu, 2009; Guillem, 2007). Moreover, distal margins that exceed 1 cm tend to have no added benefit in terms of disease-free survival (Pahlman, 2013; Moore, 2003). Occasionally, this recommendation is violated for patients who have received neoadjuvant CRT (Silberfein, 2010; Nash, 2010). In this case, neoadjuvant therapy may cause regression of microscopic disease, allowing for smaller margins in patients who would otherwise need permanent colostomy (Bujko, 2012). The distal margin is measured in vivo or by pinning the specimen to a board immediately following surgery (Shirouzu, 2009).

The Circumferential Resection Margin (CRM), also known as the radial margin, is arguably the most important risk factor for local recurrence after radical surgery (Wibe, 2012; Nagtegaal, 2002). CRM refers to the shortest distance between the edge of the tumor and the mesorectal fascia (Monson, 2013). A CRM that is within 1 mm of the primary tumor is considered to be a positive margin and this result is associated with an increased risk of both local and distant recurrence, and worsened survival (Kennelly, 2013, Nagtegaal, 2008). In 1986, Quirke et al. first observed that 85% of patients with a positive CRM developed local recurrence, compared with only 3% of those who had uninvolved margins (Quirke, 1986). Similarly, the results of a large Dutch trial found that patients with a positive CRM had a local recurrence rate of 22%, in comparison to 4% of patients with negative margins (Peeters, 2007). Achieving a clear CRM with the removal of the rectal tumor should largely eliminate the risk of local recurrence (Taylor, 2013).

2.72 Presence of lymphovascular and perineural invasion

Nodal involvement has been shown to accurately predict local recurrence (Kim, 2009). Historically, local recurrence rates were as high as 20 – 40%, likely because of failure to remove positive lymph nodes in the mesorectum and pelvic sidewall during surgery (Simunovic, 2008). Halsted et al. was among the first to suggest that tumor cells spread from the primary tumor to regional lymph nodes and as a result, radical surgery would decrease the rate of local recurrence (Halsted, 1894). Similarly, William Ernest Miles stressed the importance of removing the regional lymphatics during surgery following his post-mortem examinations of patients that revealed recurrence in the lymph nodes surrounding the left common iliac artery. The results of a study conducted by

Miholic et al. suggested nodal involvement to be a stage-independent risk factor for local recurrence (Miholic, 1991). Similarly, Elferink et al, found that patients with positive lymph nodes were more likely to develop locoregional recurrence in comparison to those without positive lymph nodes (Elferink, 2012).

In addition, vascular invasion is a stage-independent risk factor for local recurrence (Bhangu, 2013). Vascular invasion refers to the presence of malignant cells within the blood vessels of the rectum and is associated with locally advanced tumors (Smith, 2008). In 1938, Brown and Warren were credited with identifying vascular invasion as a risk factor for local recurrence. Their post-mortem study of 170 patients with rectal cancer revealed visceral metastases in 71% of those cases positive for vascular invasion. More recently, several other studies have suggested that patients, who have extramural venous invasion, are more likely than patients without venous invasion to develop locally recurrent rectal cancer (Megaurditchian, 2005; Dresen, 2009).

Perineural invasion occurs when the tumor invades and spreads via the nervous system. Although there is no agreed upon definition of perineural invasion, Batsakis et al. coined a broad and widely used description of perineural invasion in 1985, stating it as "invasion of the cancer in, around, and through the nerves" (Batsakis, 1985). Historically, perineural invasion has been an important prognostic factor in head and neck, prostate, pancreas, colon, and skin cancers. More recently, it has been established as a predictor for adverse outcomes in patients with locally advanced rectal cancer, who are receiving neoadjuvant therapy. Still, the rate of identification is below 31%, as it is an underreported measure. Perineural invasion has been shown to negatively impact disease-

free survival, local-recurrence free survival and overall survival (Kim, 2009; Dhadda, 2014; Chablani, 2015).

2.73 Histological grade of tumor

Tumor grading refers to the assessment of cellular appearance within cancerous tissue and it is another important prognostic factor in the treatment of CRC. According to categorization from the World Health Organization, the primary consideration for tumor grading is gland formation. As a result, signet ring, small cell, and undifferentiated carcinoma types are all classified as poorly differentiated (Hav, 2015). For adenocarcinomas of the rectum, this tumor grading is largely subjective, leading to inter-observer variability. In addition, numerous grading schemes with different criteria exist in the literature, further complicating this prognostic factor. With that said, grading remains a stage independent prognostic factor in the non-neoadjuvant setting. However, results from randomized controlled trials question its predictive ability of overall survival (Rullier, 2010; Sprenger, 2010). Most grading schemes separate tumors into 1 of 4 groups: well differentiated, moderately differentiated, poorly differentiated, and undifferentiated. In terms of risk stratification, a high tumor grade, signifying poor differentiation, indicates an aggressive form of the disease and a worsened chance of survival (Compton, 2002).

2.8 Mortality

During the past 30 years, survival rates of patients with locally advanced rectal cancer have significantly improved due to advancements in surgical technique and adjuvant therapy (Inoue, 2010). Prior to the introduction of adjuvant therapies, the 5-year overall survival rate was approximately 50% (Yorio, 2012; Julien, 2010). At present, 5-year overall survival for locally advanced rectal cancer is approaching 71% (ASCO, 2020; American Cancer Society, 2020). Although neoadjuvant therapy has successfully lowered the rate of local recurrence for patients with locally advanced rectal cancer, historically, it is thought to have no significant effect on patient survival (Kapiteijn, 2001, Sauer, 2004). The Swedish rectal cancer study, which began in 1997, was the first trial to suggest an improvement in overall survival due to neoadjuvant therapy. At this time, this result was largely attributed to non-standardized surgery, which did not include the principles of TME. To account for this, the Dutch Colorectal Cancer Study Group published a paper in 2001, which standardized surgical intervention between patients. The result of their trial showed no difference in the 5-year overall survival rate between groups that received either surgery alone or surgery with neoadjuvant short-course radiation (Kapiteijn, 2001). Similarly, the German Rectal Cancer Study Group's 2004 seminal paper reported no significant difference in 5-year overall survival between neoadjuvant and postoperative CRT groups (Sauer, 2004). In 2007, Cambray i Amenos et al. achieved the same result, as no difference in overall survival could be observed between groups receiving neoadjuvant and postoperative therapies (Cambray i Amenos, 2007).

In 2009, Sebag-Montefore et al. compared the effects of neoadjuvant radiation therapy verses post-operative CRT in terms of overall survival. Again, no significant association was found between neoadjuvant therapy and overall survival (Sebag-Montefore, 2009). However, a study by Roh et al. was published during that same year, suggesting a non-significant trend in overall survival for patients who had received neoadjuvant therapy. In 2012, Kang et al. demonstrated an association between neoadjuvant therapy and improved overall survival, specifically for patients with stage III rectal cancer (Kang, 2012). More recently, Tural et al. published a study that found no association between neoadjuvant therapy and overall survival (Tural, 2013).

Some investigators have begun to retrospectively analyze data collected from cohorts of patients over the past two decades in order to determine how the change in CRT practice has affected patient survival. In 2014, Wiegering et al. compared overall survival between patients receiving treatment over the past two decades. They found that patients, who were treated after 2002, had a significantly improved 5-year survival rate in comparison to patients in the earlier cohort (Wiegering,. 2014). However, a similar study by Zengel et al. showed no difference in overall survival between patients treated before and after 2004 (Zengel, 2015). Interestingly, Law et al. published a study this year comparing two cohorts of patients with locally advanced rectal cancer receiving surgery between either 1993 – 2001 or 2002 – 2011. The investigators observed a lower recurrence rate and a higher survival rate in the more recent cohort, which incorporated neoadjuvant therapy and laparoscopic surgery (Law, 2016). At present, it remains unclear whether an association between neoadjuvant CRT and overall survival exists.

Summary of Literature Review

At present, an extensive amount of research exists regarding the treatment of locally advanced rectal cancer. Routine management remains a multidisciplinary effort, consisting of diagnosis, staging, adjuvant therapy, and surgical resection. Historically, the main burden of rectal cancer was a high risk of locally recurrent disease. However, neoadjuvant therapy has reduced the rate of local failure to < 10%, while adding no benefit to managing distant recurrences. As a result, metastatic disease now presents the next challenge to improving patient survival. At present, it remains unclear whether neoadjuvant CRT benefits overall survival in comparison to therapy administered postoperatively. Specifically, only one randomized controlled trial to date has suggested neoadjuvant therapy results in improved survival. However, this result is largely attributed to the effects of unstandardized surgery. More recently, retrospective cohort studies have suggested that neoadjuvant therapy may offer a survival benefit (Roh, 2009; Kang, 2012; Wiegering, 2014; Law, 2016). Still, other studies refute these findings (Sebag-Montefore , 2009; Cambray, 2007; Tural, 2013; Park, 2011; Sauer, 2012; Schiffman, 2013; Zengel, 2015).

Chapter 2: METHOD

3.1 Study Approval

Approval to conduct this study was granted by the Health Research Ethics Board of the Faculty of Medicine, Memorial University of Newfoundland (Appendix A) in September 2013.

3.2 Ascertainment

In the province of Newfoundland & Labrador, retrolective chart audits were conducted on all incident cases of rectal cancer diagnosed between January 4th, 1999, and December 15th, 2003 in patients aged 20 – 74 years. The Newfoundland & Labrador Colorectal Cancer Registry (NFCCR) is a population-based registry that has collected information on all patients diagnosed with CRC, aged 20 – 74 years old. Each patient was given an International Classification of Diseases code to indicate colon (153) or rectal (154) cancer by the Newfoundland Cancer Treatment and Research Centre. In addition, a hospital based staff pathologist reviewed each pathology report to confirm a correct diagnosis of adenocarcinoma or its subtypes: mucinous or signet ring cell carcinoma. Information letters were sent via mail to the attending physicians of all patients with a diagnosis of rectal cancer (154). This letter described the study and provided contact information for those who were interested in participating. The next of kin was identified by contacting family physicians and nursing clinics in the circumstances that the patient was either deceased or alive with a preference for next of kin (proxy) contact. Each next

of kin was contacted using the original method as the patient themselves and was asked to consent to a review of the affected family member's medical charts (proxy consent). Consent was given by the patient or next of kin to abstract information from the patients' medical records regarding the diagnosis, treatment, and prognostic variables related to their cancer care. Recruitment occurred at a later date in the NFCCR cohort in comparison to other cohorts and as a result, proxy consent was used throughout given many of the patients has already passed.

Similarly, chart reviews were performed for patients enrolled in the Ontario Familial Colorectal Cancer Registry (OFCCR). The OFCCR is a National Cancer Institute consortium that promotes the genetic and epidemilological study of CRC. Furthermore, this registry is 1 of 6 international sites that contribute to the Cooperative Familial Registry for Colorectal Studies (Wirtzfeld, 2009). Since 1997, the OFCCR has collected family history information, epidemiological data, blood samples, and tumour tissue from a population-based sample of patients (probands) with CRC and their families (Cotterchio, 2000). The population-based Ontario Cancer Registry was used to identify all cases of rectal cancer that were diagnosed between July 3, 1997, and June 23, 2000, among residents of Ontario aged 18– 74 years. Patients were recruited into the OFCCR based on their familial risk of developing CRC. All patients that have high or moderate risk are selected to participate in the OFCCR, and an additional 25% of the sample is randomly selected from patients at low risk of developing CRC. Consent was given in order to extract information from the patients' medical records regarding their diagnosis and treatment. Proxy consent was not sought for the Ontario sample.

In addition, data from a third cohort of patients with rectal cancer was obtained from the health records of a surgeon's single practice in Newfoundland & Labrador. A retrospective chart review was conducted on all of this surgeon's patients diagnosed between January 1st, 1992, and April 16th, 2014, aged 22 - 97 years. Information regarding patient mortality and date of death obtained from the surgeon's files was cross-referenced with the patient's records abstracted from the H. Bliss Murphy Cancer Center. If there was a discrepancy in mortality between the two patient records, then information from the H. Bliss Murphy Center was preferentially included. In terms of recurrent disease, every case of local recurrence was reviewed by the surgeon of the single practice to improve validity. If cases of distant recurrence varied between the two patient records, then the files of those participants were again reviewed by the surgeon. Any patient of the single practice cohort that was also a patient in the NFCCR was excluded from the single practice cohort to prevent duplicate cases. Cases were also excluded from the single practice cohort if the patient was identified as receiving palliative management, if a local excision was performed prior to radical surgery, or if the patient had no operation completed. Consent was given for the investigators of this study to review the charts of each patient and information was collected by two medical students, using the same abstraction form as mentioned previously.

3.3 Data Collection

This was a retrolective cohort study of patients with rectal cancer, who received treatment before the beginning of our study. Subsequently, the existing charts of these

patients were retrospectively reviewed and data obtained from each patient's file was recorded in our dataset. This patient information was updated prospectively at appropriate follow up visits. Trained Health Record Technicians and Research Nurses reviewed and abstracted each patient's medical records. The standardized abstraction form (Appendix B) included information on patient demographics, diagnosis (symptoms, location of diagnosis, site of cancer and date of diagnosis), surgical intervention (date, type of surgery, operative findings, hospital/surgeon), pathology (stage, number of lymph nodes, tumor differentiation/cell type, microscopic margins confirmed by pathologist, perineural/lymphovascular invasion), adjuvant treatment (start date, type of chemotherapy), follow-up (first documented loco-regional and/or distant recurrence and treatment for recurrence), time to last follow up, and/or death and cause of death. In addition, approximately 50% of the charts were randomly selected and reviewed by two physician researchers to ensure the data entered in the dataset was correct.

3.4 Statistical Analysis

Patients were separated into 1 of 3 cohorts: the NFCCR from 1999 – 2003, the OFCCR from 1997 - 2000, and the single practice of a colorectal surgeon working in Newfoundland and Labrador from 1993 - 2014. The primary outcome of our study was overall survival, which was measured from date of diagnosis to the date of death or the date of last follow-up, if death had not yet been documented. A secondary outcome of this study was local recurrence-free time to event, which was measured from date of diagnosis to the diagnosis of a recurrence, localized to the true pelvis, or to the date of last follow-

up. Another secondary outcome was disease-free time to event, which was measured from date of diagnosis to the date of recurrence outside of the true pelvis, or to the date of last follow-up.

- Descriptive statistics were performed to determine if there were significant differences between the three cohorts at baseline. Categorical variables were analyzed and presented as n (%) using chi square (χ^2) analysis to ascertain possible confounding factors. The only continuous variable analyzed was age, which was compared between the cohorts by using the one-way analysis of variance (ANOVA) test. In addition, the three main study outcomes:
    - Overall survival,
    - local recurrence-free time to event,
    - and disease-free time to event,

  were compared among cohorts using the log-rank test and presented using Kaplan-Meier survival curves. Univariate analysis was performed to determine the prognostic effect of each predictor on overall survival, local recurrence-free time to event and disease-free time to event. Multivariate cox regression models were performed on overall survival, local recurrence-free time to event and disease-free time to event to evaluate the effect of neoadjuvant therapy independent of potential confounding variables.

Chapter 4: RESULTS

4.1 Description of study sample

From 1993 to 2014, a total of 757 patients with rectal cancer were recruited from the NFCCR, the OFCCR, and the single practice of a colorectal surgeon in Newfoundland. Of these, 27.5% (208) of participants came from the NFCCR, 36.5% (276) came from the OFCCR, and another 36.1% (273) came from the records of the colorectal surgeon's single practice. Given that this is a non-randomized trial, the SPSS 23 computer program was used to investigate potential differences at baseline between each of the three cohorts. Pearson chi-square tests were performed to investigate patient factors, such as gender, cell type, neoadjuvant therapy, surgery type, staging, surgical margins, tumor grade, and presence of invasion. For the continuous variable, age, a non-parametric Kruskal-Wallis test was performed to assess differences between the three cohorts.

Table 1 shows the baseline differences between the NFCCR, the OFCCR, and the patients of the surgeon's single practice. As depicted in the table, no statistically significant difference exists between the three cohorts in terms of age, rates of APR, rates of locally advanced and advanced cancers, and the rate of poorly differentiated disease. In contrast, there was a significant difference in regards to male gender between the three cohorts, with the OFCCR having fewer males than both the NFCCR and the single practice (60% vs. 69% vs. 70%, respectively; p-value = 0.018). In addition, there was a baseline difference between the numbers of rectal adenocarcinomas between the three cohorts, with the patients of the single practice having a significantly lower rate of

adenocarcinomas (81% vs. 89% vs. 87%, single practice vs. NFCCR & OFCCR, respectively). As hypothesized, there are an increased proportion of patients treated with neoadjuvant therapy in the single practice cohort, as this is the only group with patients diagnosed after 2004 (27% vs. 4% vs. 8%; single practice vs. NFCCR vs. OFCCR, respectively). This result reflects the widespread acceptance of neoadjuvant therapy as standard practice following the publication of Sauer's seminal paper. Similarly, there is a higher rate of AR in the surgeon's single practice cohort than either registry's data (68% vs. 54% vs. 47%; Single practice vs. NFCCR vs. OFCCR, respectively).

The only baseline difference in terms of staging can be seen among stage I disease in the OFCCR cohort. The OFCCR has an increased rate of localized cancers in comparison to the NFCCR and the OFCCR, respectively (33% vs. 18% vs. 25%). This effect can be partly explained by the absence of proxy consent in the recruitment of OFCCR's participants, resulting in a higher proportion of earlier staged cancers. In addition, there was a significantly lower rate of completely excised tumors for patients in the single practice cohort (85% vs. 90% vs. 93%; Single practice vs. NFCCR vs. OFCCR, respectively). In terms of tumor grade, the single practice cohort had a significantly higher percentage of well-differentiated cancers than both the NFCCR and the OFCCR, respectively (16% vs. 10% vs. 10%). Similarly, the single practice had a lower proportion of moderately differentiated cancers (56% vs. 78% vs. 74%; single practice vs. NFCCR vs. OFCCR, respectively). The presence of vascular, lymphatic, and perineural invasion was statistically different between the three cohorts. The NFCCR had a significantly higher rate of vascular invasion than both the OFCCR and the single practice (33% vs. 11% vs. 17%, respectively). Similarly, the NFCCR had an increased proportion of

lymphatic invasion (34% vs. 12% vs. 23%; NFCCR vs. OFCCR vs. single practice, respectively) and perineural invasion (27% vs. 4% vs. 14%; NFCCR vs. OFCCR vs. single practice, respectively) compared to the OFCCR and the single practice cohorts.

Table 1: Baseline clinical & pathological characteristics of cohorts

	Total	NFCCR	OFCCR	Single practice	P - value
n	757	208	276	273	
Age; median (SD)	61 (10)	61 (9)	61 (10)	62 (12)	NS
Male gender; n (%)	501 (66)	144 (69)	165 (60)	192 (70)	0.018
Cell-type; n (%)					
Adenoncarcinoma, NOS; n (%)	646 (85)	185 (89)	240 (87)	221 (81)	0.041
Neo-adjuvant therapy; n (%)	103 (14)	9 (4)	21 (8)	73 (27)	< 0.001
Type of surgery performed; n (%)					
Anterior resection; n (%)	428 (57)	112 (54)	130 (47)	186 (68)	< 0.001
Abdominoperineal resection; n (%)	211 (28)	69 (33)	79 (29)	63 (23)	NS
Pathological staging (pTNM); n (%)					
Stage 1; n (%)	194 (26)	37 (18)	90 (33)	67 (25)	0.001
Stage 2; n (%)	213 (28)	68 (33)	74 (27)	71 (26)	NS
Stage 3; n (%)	275 (36)	80 (39)	89 (32)	106 (39)	NS
Stage 4; n (%)	62 (8)	23 (11)	21 (8)	18 (7)	NS
Tumor entirely resected; n (%)	676 (89)	188 (90)	256 (93)	232 (85)	0.002
Grade of primary tumor					
Well differentiated; n (%)	93 (12)	21 (10)	27 (10)	45 (16)	0.01
Moderately differentiated ; n (%)	519 (69)	163 (78)	204 (74)	152 (56)	< 0.001
Poorly differentiated; n (%)	80 (11)	21 (10)	27 (10)	32 (12)	NS
Presence of invasion; n (%)					
Vascular invasion; n (%)	145 (19)	69 (33)	29 (11)	47 (17)	< 0.001
Lymphatic invasion; n (%)	169 (22)	71 (34)	34 (12)	64 (23)	< 0.001
Perineural invasion; n (%)	106 (14)	57 (27)	10 (4)	39 (14)	< 0.001

4.2 Outcome measurements by patient cohort

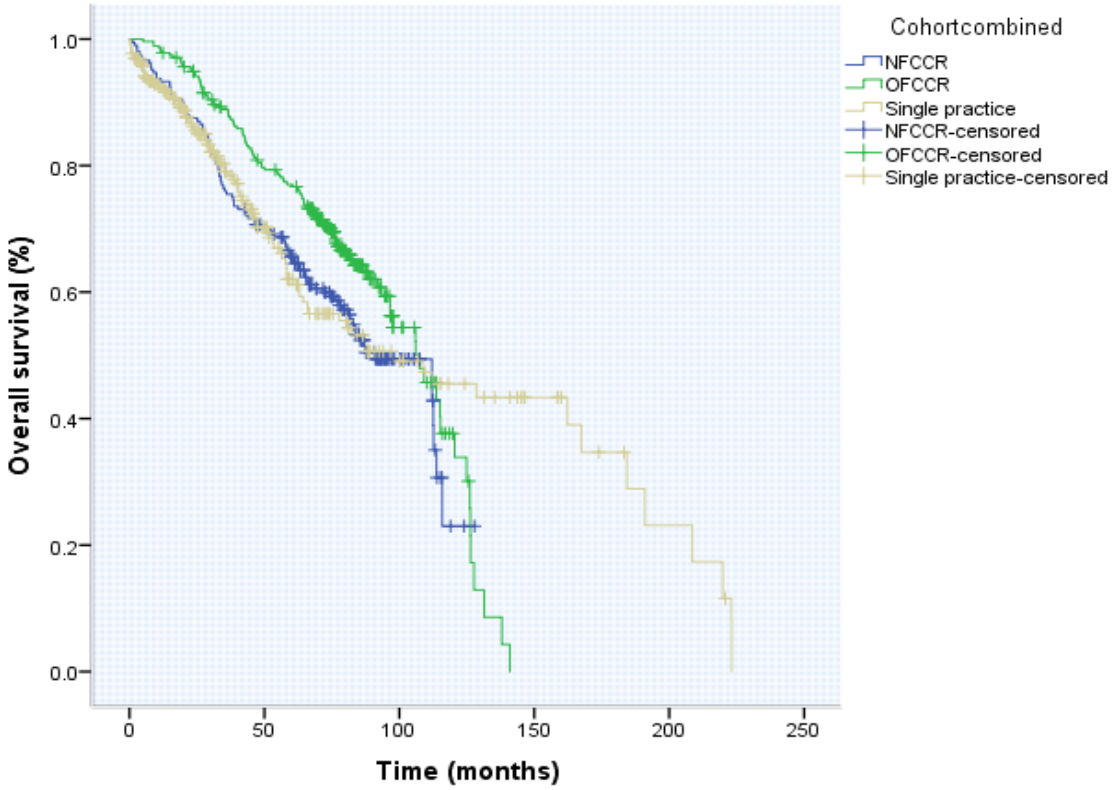
Table 2 shows the overall survival among the three cohorts recorded at 2, 4, 6, 8, and 10-years of follow up. The three cohorts of patients were compared in order to determine if there was a statistical difference in the average time between cancer diagnosis and the date of all-cause mortality. There was no significant difference in survival rate between any of the three cohorts ((log rank (mantel-cox) = 3.992; p-value = 0.136). The median survival for the NFCCR, the OFCCR, and the single practice was 90.7 months, 107.6 months, and 97.3 months respectively, with all three confidence intervals overlapping.

Table 2: Overall survival at follow-up by patient cohort

Cohort	N	N of events	Survival (% alive at follow-up)					Median suvival (months)	95% CI
			2 years	4 years	6 years	8 years	10 years		
NFCCR	208	100	87.5	70.7	60	49.4	23	90.74	(72.594, 108.886)
OFCCR	274	110	94.5	80.5	70.6	59.3	37.6	107.605	(94.210, 121.001)
Single practice	262	89	85.5	70.2	56.6	50.6	45.5	97.315	(59.534, 135.096)

Figure 2 shows these same survival rates in graphical representation. As depicted by the graph, the survival curves of the 3 cohorts overlap, suggesting that there is no

statistical difference in the time between cancer diagnosis and all-cause mortality for any group of patients.



Log rank (Mantel-Cox) = 3.992; df=2; p = 0.136

Figure 2: Kaplan-Meier curves of overall survival by patient cohort for patients of all stages

Table 3 shows the local recurrence-free time to event for each cohort at 2, 4, 6, 8, and 10 years of follow up. Each cohort was compared in order to determine if there was a statistical difference between the average local recurrence-free time to event, measured from date of diagnosis to date of local recurrence, or if not applicable, the date of last

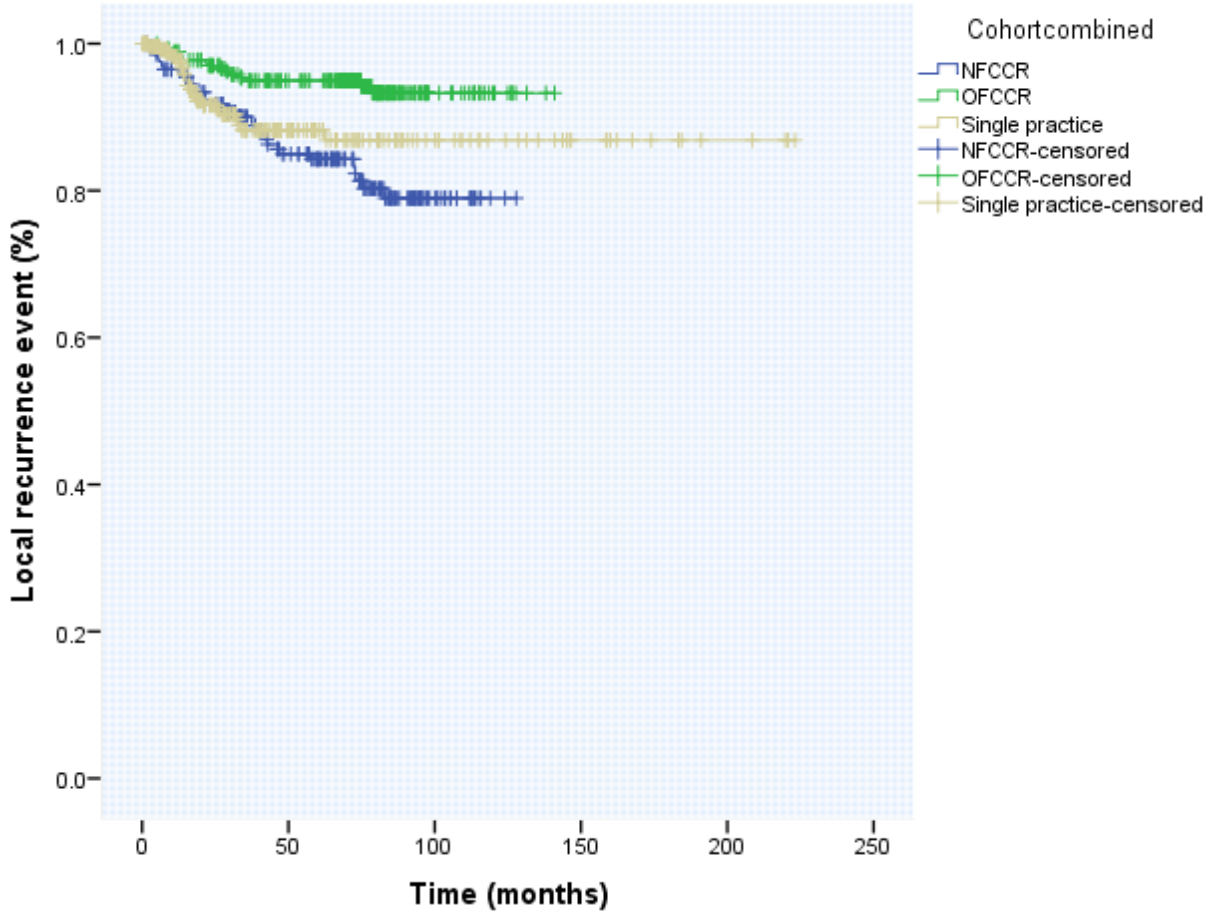
follow-up. Patients of the OFCCR experienced a significantly improved local recurrence-free time to event in comparison to both the NFCCR and the single practice cohort (log rank (mantel-cox) = 15.783; p-value < 0.001). Given that the time to event rate never reached 50% over 10 years for either cohort, median time to event estimates were not calculated. From the table, one can tell that the time to local recurrence event was significantly improved for patients of the OFCCR, as 93.3% of patients were without local recurrence at 10 years in comparison to 79% and 86.9% of the patients in the OFCCR and NFCCR, respectively.

Table 3: Time to local recurrence by cohort for patients of all stages

Cohort	N	N of events	Time to event (% with no event at follow-up)				
			2 years	4 years	6 years	8 years	10 years
NFCCR	205	33	92.3	85	84.3	79	79
OFCCR	274	15	97	95	95	93.3	93.3
Single practice	260	23	91.6	88.2	86.9	86.9	86.9

Figure 3 shows the Kaplan-Meier curve of local recurrence-free time to event for the NFCCR, the OFCCR, and the single practice cohorts. As shown by the graph, the local recurrence-free time to event for patients in the OFCCR cohort is significantly better than both the NFCCR and the single practice. Given that the OFCCR did not incorporate proxy consent into the recruitment of participants, the improved local recurrence-free

time to event may be partially explained by not recruiting these patients with more advanced stages of disease and worse prognosis. As a result, an increased proportion of patients with stage I cancer is observed in this cohort.



Log (Mantel-Cox) = 15.783; df = 2; p < 0.001

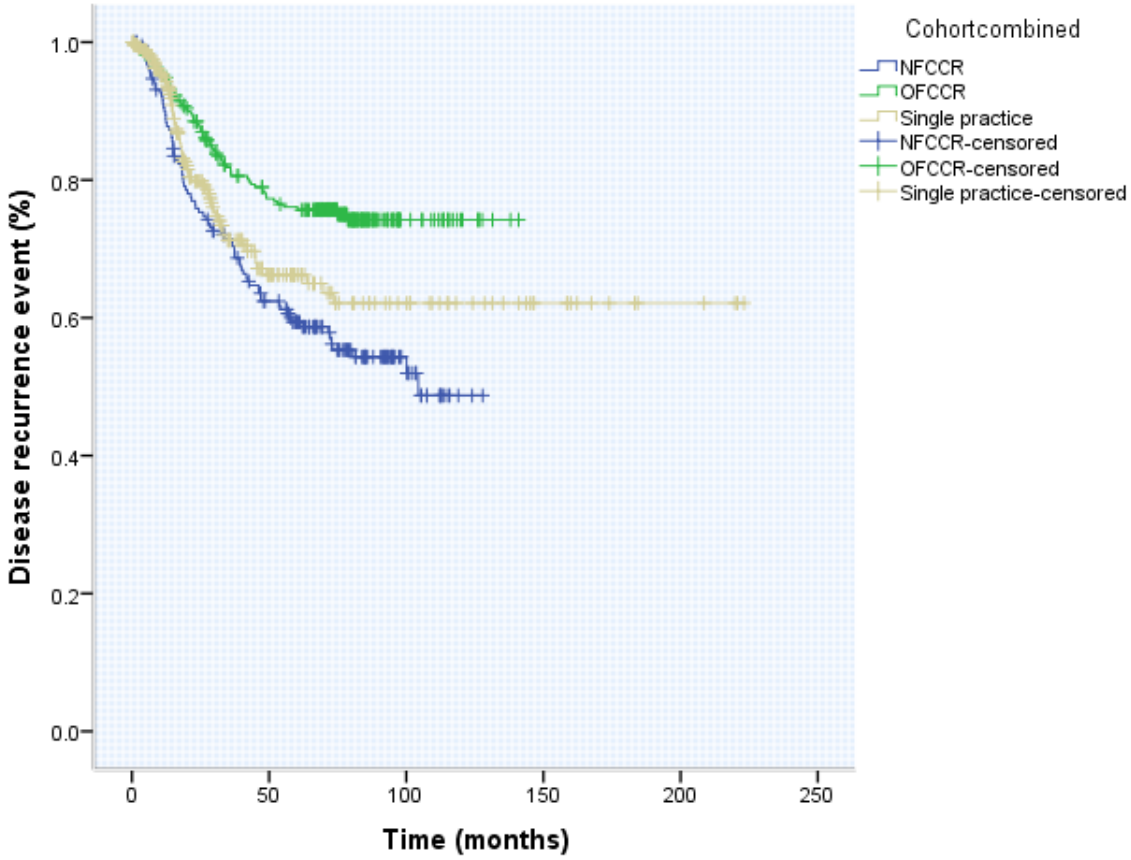
Figure 3: Kaplan-Meier curves of local recurrence-free time to event by patient cohort for patients of all stages

Table 4 shows the disease-free time to event for each of the three cohorts at 2, 4, 6, 8, and 10 years of follow up. Each cohort was compared in order to determine if there was a statistical difference between average disease-free time to event, measured from the date of primary cancer diagnosis to the date of disease recurrence, whether it be local or distant spread. If the patient did not experience either local or distant disease recurrence, then the date of last follow-up was used instead. Patients of the OFCCR experienced a significantly improved disease-free time to event in comparison to both the NFCCR and the single practice cohorts (log rank (mantel-cox) = 19.357; p-value < 0.001). Given that the disease-free recurrence curves for the OFCCR and single practice cohorts did not reach 50%, median time to event estimates were not calculated. At 10 years, the proportion of patients without recurrent disease for the NFCCR, OFCCR, and the single practice was 48.6%, 74.2%, and 62.1%, respectively.

Table 4: Disease-free time to event by cohort for patients of all stages

Cohort	N	N of events	Time to event (% with no event at follow-up)				
			2 years	4 years	6 years	8 years	10 years
NFCCR	192	82	75.9	62.3	57.8	54.2	48.6
OFCCR	274	65	88.1	78.1	75.6	74.2	74.2
Single practice	257	63	79.8	67.1	63.6	62.1	62.1

Figure 4 shows the disease-free recurrence curves for the NFCCR, the OFCCR, and the single practice cohorts. As depicted by the figure, the OFCCR time to event estimates are significantly improved, as the curve does not overlap that of any other cohort. Again, this can likely be explained by the absence of proxy consent during the recruitment phase of patients in the OFCCR cohort.



Log (Mantel-Cox) = 19.161; df = 2; p < 0.001

Figure 4: Kaplan-Meier curves of disease-free time to event by patient cohort for patients of all stages

4.3 Univariate predictors of survival and of recurrence

Table 5 shows the results of the univariate analysis of overall survival for the patients of the three cohorts. Age at diagnosis was found to be a significant predictor of overall survival. For each year of age, the risk of patient mortality increases by 2.6% (1.014 – 1.038; $p < 0.001$). In addition, a significant association was found between sex and overall survival, as male patients had a 36% higher chance of death than their female counterparts (1.057 – 1.748; $p = 0.015$). No significant association was found between neoadjuvant therapy and overall survival. Similarly, cell type had no effect on overall survival. AR surgery was associated with a 38% risk reduction in mortality (0.497 – 0.784; $p < 0.001$). Other significant predictors of overall survival include complete excision, tumor grade, vascular, lymphatic, and perineural invasion. As expected, later stages of cancer were associated with an increased risk of all-cause mortality, as patients with stage IV cancers were 9.5 times more likely to experience mortality in comparison to patients with stage I disease (6.371 – 14.289; $p < 0.001$). In terms of cohort, patients of the OFCCR had a 24% reduced risk of all-cause mortality in comparison to the NFCCR (0.579 – 0.996; $p = 0.046$). Again, this may be attributed to the fact that the OFCCR did not perform proxy consent when recruiting their sample.

Table 5: Results for univariate analysis of overall survival for patients of all stages

		n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)		744 (100)	1.026	1.014 - 1.038	< 0.001
Male Sex		493(66)	1.36	1.057 - 1.748	0.015
Adenocarcinoma, NOS		637 (86)	0.755	0.555 -1.027	NS
Neoadjuvant therapy		103 (14)	1.097	0.777 - 1.549	NS
Anterior resection		428 (58)	0.624	0.497 - 0.784	< 0.001
Tumor completely excised		669 (90)	0.343	0.245 - 0.480	< 0.001
Grade of tumor, poorly differentiated		80 (11)	2.124	1.538 - 2.934	< 0.001
Vascular invasion		145 (19)	2.025	1.572 - 2.608	< 0.001
Lymphatic invasion		169 (23)	1.748	1.368 - 2.235	< 0.001
Perineural invasion		106 (14)	2.314	1.754 - 3.053	< 0.001
Stage					
	I	194 (26)	1		
	II	213 (29)	1.857	1.282 - 2.689	0.001
	III	275 (37)	2.538	1.803 - 3.573	< 0.001
	IV	62 (8)	9.541	6.371 - 14.289	< 0.001
Cohort					
	NFCCR	208 (28)	1		
	OFCCR	274 (37)	0.759	0.579 - 0.996	0.046
	Single practice	262 (35)	0.867	0.641 - 1.172	NS

Table 6 shows the results of the univariate analysis of local-recurrence free time to event for patients of the three cohorts. The adenocarcinoma cell type was found to be a significant predictor of local recurrence. Specifically, the presence of this pathology was associated with a 49% reduced risk of developing local recurrence (0.289 – 0.882; p = 0.016). No significant association was found between neoadjuvant CRT and the development of local recurrence. Complete excision of the tumor was associated with a 52% risk reduction of local recurrence (0.237 – 0.965; p = 0.039). As shown in table 6, predictors of poor prognosis included poorly differentiated grade, and the presence of vascular, lymphatic, and perineural invasion. In regards to stage of the disease, stage II

and III rectal cancers were found to multiply the risk of local recurrence by 2.3 times (1.043 – 4.974; p = 0.039) and 3.5 times (1.685 – 7.215; p = 0.001), respectively. Lastly, cohort was found to have a significant effect on the risk of local recurrence. Specifically, patients of the OFCCR cohort were found to have a 24% risk reduction in developing locally recurrent disease.

Table 6: Results for univariate analysis of local recurrence-free time to event for patients of all stages

	n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)	744 (100)	1.006	0.983 - 1.030	NS
Male Sex	489 (66)	1.019	0.626 - 1.658	NS
Adenocarcinoma, NOS	633 (85)	0.505	0.289 - 0.882	0.016
Neoadjuvant therapy	103 (14)	0.927	0.444 - 1.936	NS
Anterior resection	426 (57)	0.677	0.425 - 1.078	NS
Tumor completely excised	666 (90)	0.478	0.237 - 0.965	0.039
Grade of tumor, poorly differentiated	80 (11)	3.068	1.753 - 5.368	< 0.001
Vascular invasion	143 (19)	2.685	1.649 - 4.371	< 0.001
Lymphatic invasion	167 (22)	2.276	1.404 - 3.689	0.001
Perineural invasion	105 (14)	1.946	1.100 - 3.444	0.022
Stage				
I	193 (26)	1		
II	212 (28)	2.278	1.043 - 4.974	0.039
III	273 (37)	3.487	1.685 - 7.215	0.001
IV	61 (8)	1.968	0.531 - 7.297	NS
Cohort				
NFCCR	205 (28)	1		
OFCCR	274 (37)	0.309	0.168 - 0.568	< 0.001
Single practice	260 (35)	0.754	0.442 - 1.287	NS

Table 7 shows the results of the univariate analysis of local-recurrence free time to event for patients of the three cohorts. Male sex was found to increase the risk of disease recurrence by 46% (1.078 – 1.969; $p = 0.014$). AR surgery and complete excision were associated with a 28% (0.547 – 0.940; $p = 0.016$) and and 39% (0.387 – 0.956; $p = 0.031$) risk reduction of disease recurrence, respectively. Similar to local recurrence-free time to event, poorly differentiated cancers and the presence of vascular, lymphatic, and perineural invasion were all significantly associated with increased risk of disease recurrence. In regards to stage of the disease, patients with stage II disease were 1.9 times (1.170 – 2.943; $p = 0.009$) more likely to develop local recurrence, patients with stage III disease were 3.7 times more likely to develop local recurrence, and those with stage IV disease were 5.2 times more likely to develop local recurrence than stage I patients, respectively. Again, the OFCCR cohort was associated with a 51% reduced risk of developing disease recurrence (0.353 – 0.677; $p < 0.001$).

Table 7: Results for univariate analysis of disease-free time to event for patients of all stages

		n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)		744 (100)	0.995	0.982 - 1.008	NS
Male Sex		478 (64)	1.457	1.078 - 1.969	0.014
Adenocarcinoma, NOS		622 (84)	0.746	0.514 - 1.082	NS
Neoadjuvant therapy		102 (14)	1.214	0.820 - 1.797	NS
Anterior resection		419 (56)	0.717	0.547 - 0.940	0.016
Tumor completely excised		654 (88)	0.608	0.387 - 0.956	0.031
Grade of tumor, poorly differentiated		78 (10)	1.883	1.284 - 2.761	0.001
Vascular invasion		137 (18)	2.03	1.505 - 2.739	< 0.001
Lymphatic invasion		161 (22)	1.986	1.487 - 2.652	< 0.001
Perineural invasion		100 (13)	2.678	1.951 - 3.675	< 0.001
Stage					
	I	190 (26)	1		
	II	208 (28)	1.856	1.170 - 2.943	0.009
	III	269 (36)	3.696	2.441 - 5.595	< 0.001
	IV	56 (8)	5.226	2.907 - 9.395	< 0.001
Cohort					
	NFCCR	192 (26)	1		
	OFCCR	274 (37)	0.489	0.353 - 0.677	< 0.001
	Single practice	257 (35)	0.778	0.560 - 1.082	NS

4.4 Multivariate models of survival and disease recurrence

Subsequently, a multivariate model was constructed to determine the effect of neoadjuvant therapy on overall survival for patients of all stages across the three cohorts. As depicted in table 8, age, complete excision, poorly-differentiated grade, vascular and perineural invasion, stage, and AR were all shown to be significant independent predictors of overall survival. Neoadjuvant CRT was removed from the model, suggesting no significant effect on patient survival for this sample when controlled for other variables. Of note, complete excision and AR surgery were associated with a 52% (0.327 – 0.695; $p < 0.001$) and 41% (0.468 – 0.748; $p < 0.001$) risk reduction,

respectively. In contrast, poorly differentiated cancers, vascular invasion, perineural invasion, and stage were all associated with poor survival. When controlled for all other variables, there was no difference in mortality among the three cohorts for the complete sample of patients.

Table 8: Results of multivariate analysis of overall survival for patients with rectal cancer of all stages

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age	.032	.006	28.768	1	.000	1.033	1.021	1.045
Complete excision	-.741	.192	14.854	1	.000	.476	.327	.695
Poorly differentiated	.471	.171	7.590	1	.006	1.602	1.146	2.240
Vascular invasion	.349	.148	5.566	1	.018	1.417	1.061	1.894
Perineural invasion	.475	.160	8.807	1	.003	1.608	1.175	2.200
Stage 1			92.212	3	.000			
Stage 2	.548	.192	8.137	1	.004	1.729	1.187	2.520
Stage 3	.819	.182	20.319	1	.000	2.268	1.589	3.238
Stage 4	1.995	.218	83.642	1	.000	7.354	4.795	11.278
Anterior resection	-.524	.120	19.225	1	.000	.592	.468	.748

Table 9 shows the results of a multivariate analysis used to assess the impact of neoadjuvant CRT on local recurrence for patients among the three cohorts. As depicted in the table, the adenocarcinoma cell type and AR surgery were associated with a 46%

(0.297 – 0.986; p = 0.045) and a 43% (0.348 – 0.923; p = 0.023) risk reduction, respectively. Poor tumor grade was associated with a 2.1 fold increase (1.176 – 3.848; p = 0.013) in the relative risk of local recurrence compared to less aggressive disease. In terms of stage, stage III patients were 2.9 times (1.387 – 6.073; p = 0.005) more likely to develop local recurrence. When compared to the NFCCR, the OFCCR was associated with a 69% reduced risk of developing local recurrence independent of controlled variables.

Table 9: Results of multivariate analysis of local recurrence-free time to event for patients with rectal cancer of all stages

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
adenocarcinoma, NOS	-.614	.306	4.028	1	.045	.541	.297	.986
Anterior resection	-.568	.249	5.202	1	.023	.567	.348	.923
Poorly differentiated	.755	.302	6.236	1	.013	2.128	1.176	3.848
Stage 1			10.110	3	.018			
Stage 2	.493	.409	1.456	1	.228	1.638	.735	3.650
Stage 3	1.065	.377	7.997	1	.005	2.902	1.387	6.073
Stage 4	.419	.674	.386	1	.535	1.520	.405	5.700
NFCCR			14.454	2	.001			
OFCCR	-1.187	.315	14.150	1	.000	.305	.164	.566
Single practice	-.232	.286	.659	1	.417	.793	.453	1.388

4.4.3 Multivariate model of disease recurrence-free time to event

Table 10 shows the results of a multivariate analysis used to assess the impact of neoadjuvant CRT on disease recurrence for patients among the three cohorts. The results

of this analysis suggest neoadjuvant CRT to have no significant association with disease recurrence for the total sample of patients. With that said, male patients were 41% (1.009 – 1.978; p = 0.044) more likely to suffer a disease recurrence in comparison to females. In addition, the presence of perineural invasion increased the risk of disease recurrence by 2.1 fold (1.486 – 3.029; p < 0.001). In regards to staging, progressive disease was more likely to result in disease recurrence following surgery. For example, stage III and IV patients were 3.27 times (2.054 – 5.214; p < 0.001) and 4.72 times (2.490 – 8.955; p < 0.001) more likely to develop either a local or distant recurrence.

Table 10: Results of multivariate analysis of disease-free time to event for patients with rectal cancer of all stages

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Perineural invasion	.752	.182	17.137	1	.000	2.122	1.486	3.029
Stage 1			39.916	3	.000			
Stage 2	.441	.265	2.768	1	.096	1.555	.924	2.615
Stage 3	1.186	.238	24.886	1	.000	3.273	2.054	5.214
Stage 4	1.552	.327	22.591	1	.000	4.722	2.490	8.955
Sex	.345	.172	4.048	1	.044	1.413	1.009	1.978

4.5 Analysis by stage of disease

Table 11 shows the 5-year overall survival estimates for patients based on stage of the disease. The estimates of 5-year survival between the NFCCR, the OFCCR, and the

single practice are similar when stratified by stage. The 5-year survival worsens progressively with each advancing stage of disease. With that said, a survival benefit seems to be present for earlier-staged disease in the OFCCR cohort, specifically for stage II disease (86.5% vs. 67.2% vs. 62.2%; OFCCR vs. NFCCR vs. single practice).

Table 11: Overall survival by cohort and stage

Cohort	5-year survival (% alive at follow-up)			
	Stage 1	Stage 2	Stage 3	Stage 4
NFCCR	89	67.2	67.3	17.4
OFCCR	93.8	86.5	64.8	25.3
Single practice	87.1	62.2	52.3	15.6

Table 12 shows the 5-year local recurrence-free time to event estimates for patients based on stage of disease. As shown in the table, the rate of local recurrence is fairly low among each cohort and stage of disease. The NFCCR appears to have a lower local recurrence free time to event rate for patients with stage I rectal cancer (86.4% vs 98.9% vs 96.3%; NFCCR vs. OFCCR vs. single practice). Similarly, the OFCCR appears to have a higher rate of local recurrence-free time to event for patients with stage III disease (95.3% vs. 78.4% vs. 79.4%; OFCCR vs. NFCCR vs. Single practice).

Table 12: Local-recurrence-free time to event by cohort and stage

Cohort	5-year LRF time to event (% without local recurrence at follow up)			
	Stage 1	Stage 2	Stage 3	Stage 4
NFCCR	86.4	88.6	78.4	95.5
OFCCR	98.9	90.3	95.3	94.7
Single practice	96.3	92.4	79.4	92.3

Table 13 shows the 5-year disease-free time to event estimates for patients based on stage of disease. As shown in the table, the rate of disease recurrence is fairly low among each cohort for earlier stages of disease, specifically stages I and II. The OFCCR appears to have a higher disease free time to event rate for patients for all stages of the disease in comparison to the NFCCR and OFCCR. In contrast, the NFCCR had lower rates of disease-free time to event for stage II disease (63.7% vs 80.6% vs. 76%; NFCCR vs. OFCCR vs. Single practice) and stage IV disease (37.3% vs. 54.6% vs. 49.7%; NFCCR vs. OFCCR vs. Single practice).

Table 13: Disease-free time to event by cohort and stage

Cohort	5-year Disease-free time to event (% without disease recurrence at follow up)			
	Stage 1	Stage 2	Stage 3	Stage 4
NFCCR	79.9	63.7	50.3	37.3
OFCCR	89.4	80.6	62.2	54.6
Single practice	82	76	50.2	49.7

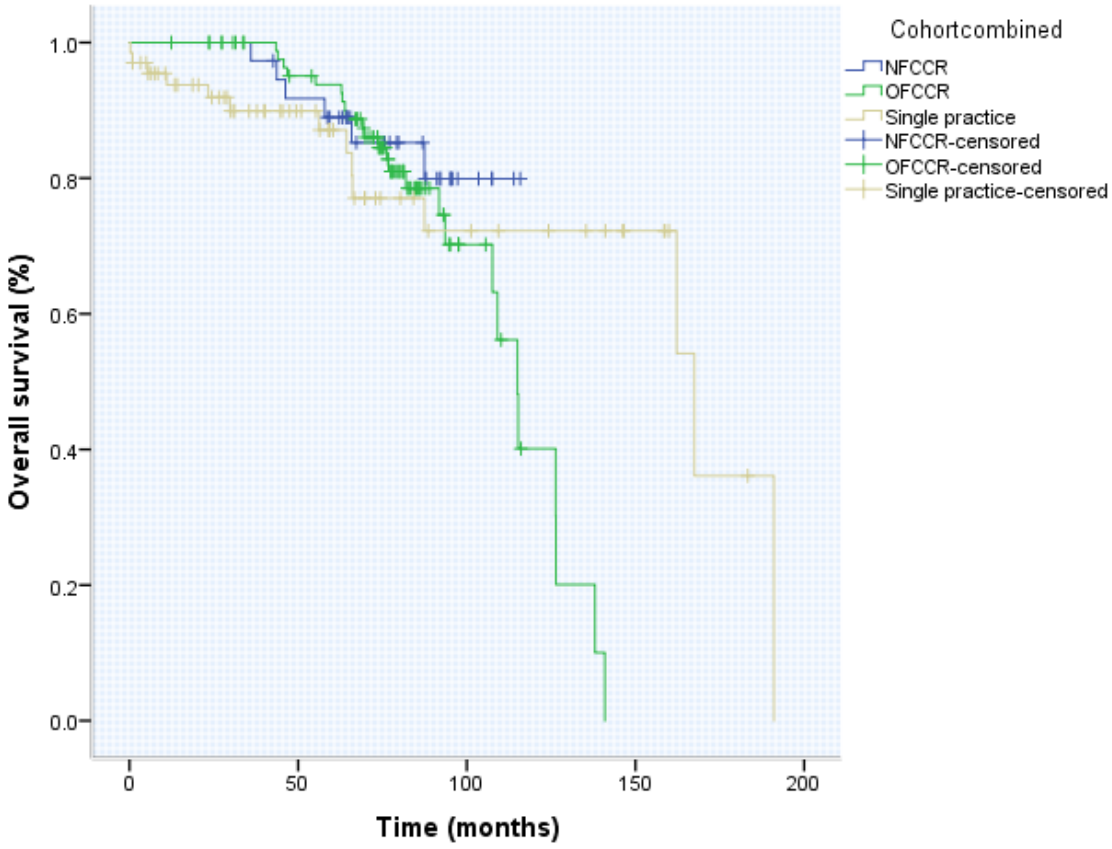
4.5.1 Analysis of outcomes for stage I patients

Table 14 shows the results of overall survival for stage I patients among each cohort. There was a larger number of stage I patients in the OFCCR cohort (n = 90) in comparison to both the NFCCR (n = 37) and the single practice (n = 67). During the 10-year period, the NFCCR, OFCCR, and single practice had 6, 25, and 14 deaths, respectively. Given that < 50% of the patients of the NFCCR cohort were alive at the 10-year follow up, a median survival estimate could not be calculated for this cohort. The median survival estimates for the OFCCR and single practice cohorts were 115.0 months and 167.5 months, respectively. With that said, overall survival between the NFCCR, the OFCCR, and the single practice cohorts were not statistically different for stage I patients (log rank (mantel-cox) = 2.502; p = 0.286).

Table 14: Overall survival by cohort for patients with stage I rectal cancer

Cohort	N	N of events	Time to event (% alive at follow-up)					Median time to event (months)	95% CI
			2 years	4 years	6 years	8 years	10 years		
NFCCR	37	6	100	91.7	79.9	79.9	79.9	N/A	N/A
OFCCR	90	25	100	95.1	86	70.2	40.1	115.036	(106.181, 123.890)
Single practice	67	14	91.9	89.9	77	72.2	72.2	167.474	(87.142, 247.806)

Figure 5 shows the corresponding Kaplan-Meier survival curves for the overall survival analysis of stage I patients by cohort. There is significant overlap between the curves of each cohort and therefore, there is no statistically significant difference in patient survival for stage I patients between cohorts.



Log rank (Mantel-Cox) = 2.502; df = 2; p = 0.286

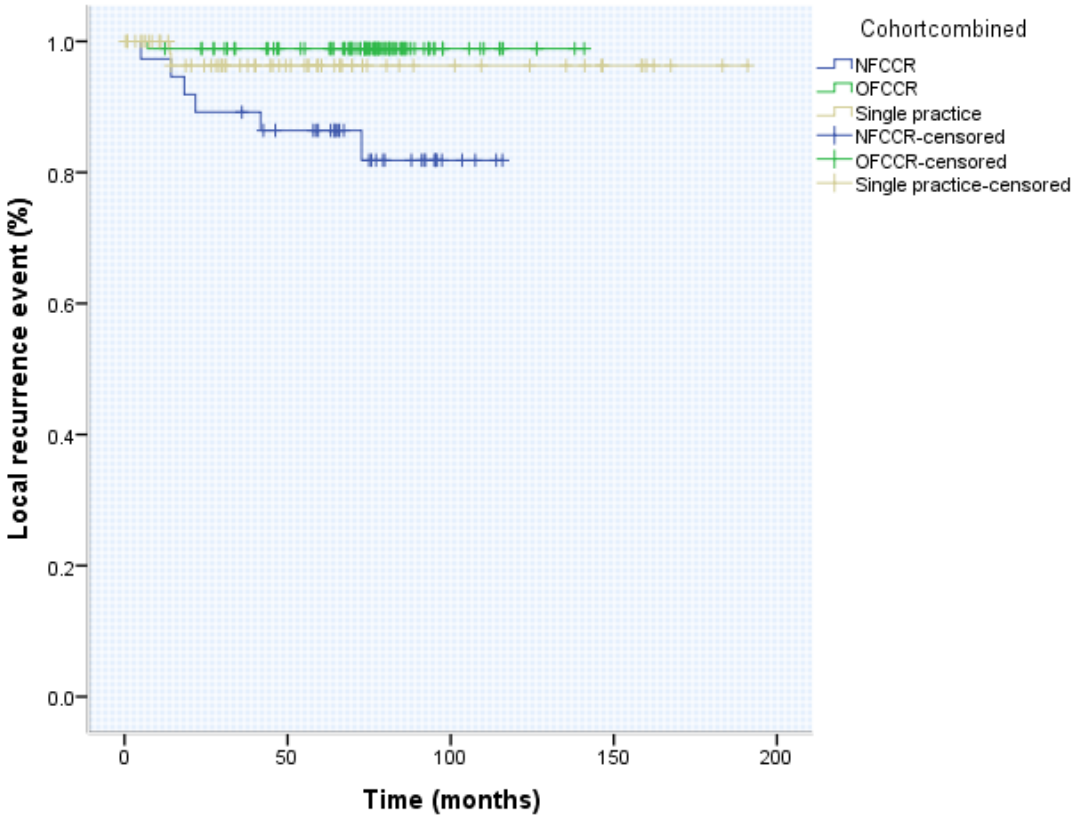
Figure 5: Kaplan-Meier curves of overall survival by cohort for patients with stage I rectal cancer

Subsequently, a local recurrence-free time to event analysis was performed for stage I patients among each cohort. In terms of events, the NFCCR, the OFCCR, and the single practice had six, one, and two local recurrences, respectively. Given that neither cohort resulted in 50% of the stage I patients having a local recurrence, median time to event estimates could not be calculated. At 10-years of follow up, the NFCCR cohort had a significantly lower percentage (81.9% vs. 98.9% vs. 96.3%; NFCCR, OFCCR, Single practice, respectively) of stage I patients remain without locally recurrent disease (log rank (mantel cox) = 12.648; df = 2; p = 0.002).

Table 15: Time to local recurrence-free time to event by cohort for patients with stage I rectal cancer

Cohort	N	N of events	Time to event (% with no event at follow-up)				
			2 years	4 years	6 years	8 years	10 years
NFCCR	37	6	89.2	86.4	86.4	81.9	81.9
OFCCR	90	1	98.9	98.9	98.9	98.9	98.9
Single practice	66	2	96.3	96.3	96.3	96.3	96.3

Figure 6 shows the corresponding Kaplan-Meier survival curves for the local recurrence-free time to event analysis of stage I patients. As shown in the figure, the time to event curve of the NFCCR is separated from that of the other cohorts, suggesting a worsened prognosis in terms of locally recurrent disease.



Chi = 12.648; df = 2; p = 0.002

Figure 6: Kaplan-Meier curves of local recurrence-free time to event by cohort for patients with stage I rectal cancer

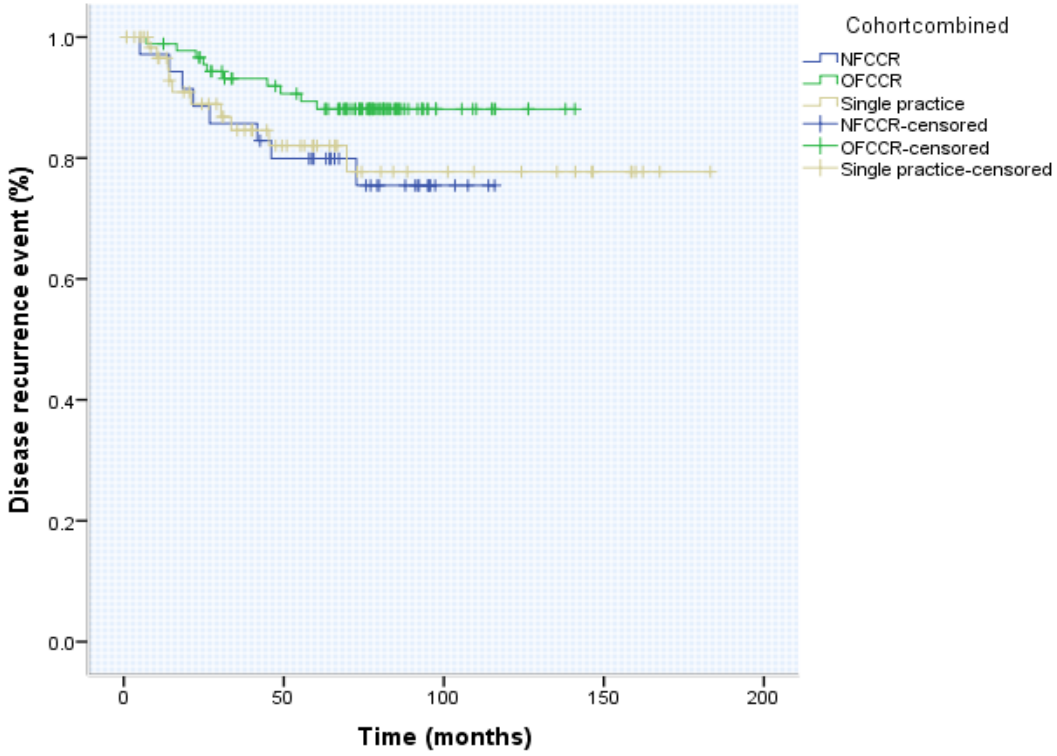
Similarly, a disease-free time to event analysis was performed for patients with stage I rectal cancer. In terms of events, the NFCCR, the OFCCR, and the single practice had 8, 10, and 10 disease recurrences among stage I patients, respectively. Given that neither cohort had 50% of its patients suffer a recurrence, median time to event estimates could not be provided. At 10 years of follow-up, the NFCCR, the OFFCR, and the single practice had 75.5%, 88.1%, and 77.7% of their respective cohorts remain recurrence free. With that said, neither cohort was significantly different from the other in terms of disease recurrence among stage I patients (log rank (mantel-cox) = 3.532; df = 2; p = 0.171).

Table 16: Disease-free time to event by cohort for patients with stage I rectal cancer

Cohort	N	N of events	Time to event (% with no event at follow-up)				
			2 years	4 years	6 years	8 years	10 years
NFCCR	35	8	88.6	79.9	79.9	75.5	75.5
OFCCR	90	10	96.6	91.9	88.1	88.1	88.1
Single practice	65	10	88.9	82	77.7	77.7	77.7

Figure 7 shows the Kaplan-Meier curves corresponding to disease-free time to event for patients with stage I disease. The results, stratified by cohort, show a noticeable

improvement in the rate of recurrent disease among patients of the OFCCR. However, this result did not reach statistical significance. The NFCCR and OFCCR cohorts intersect and therefore are similar in time to disease recurrence.



Chi = 3.532; df = 2; p = 0.171

Figure 7: Kaplan-Meier curves of disease-free time to event by cohort for patients with stage I rectal cancer

4.5.2 Analysis of outcomes for stage IV patients

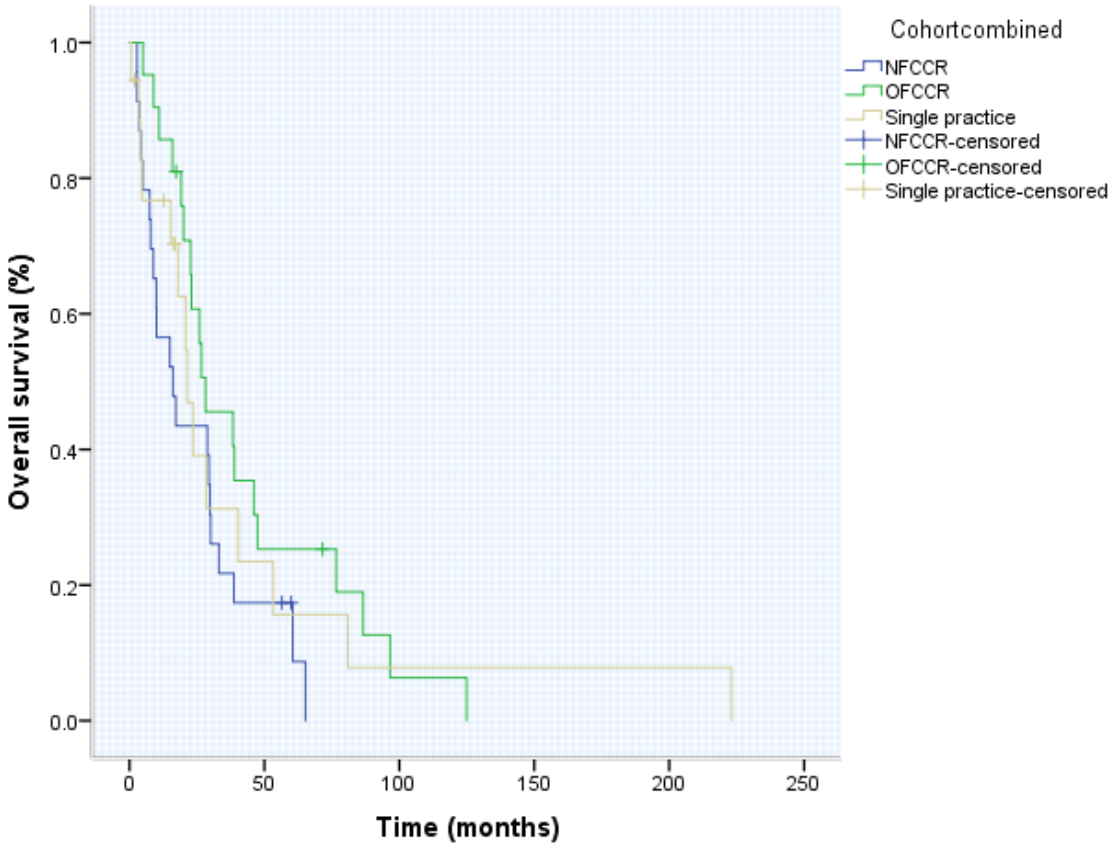
A survival analysis was performed for advanced staged rectal cancer patients separated by cohort. The NFCCR, the OFCCR, and the single practice had 23, 21, and 18

stage IV patients, respectively. Of the 23 patients in the NFCCR cohort, 21 had expired during the 10-year follow up. During this period, 19 of the 21 patients in the OFCCR cohort and 14 of the 18 patients in the single practice cohort had died. Given that more than 50% of the sample had passed away, median survival estimates could be calculated for each cohort. The median overall survival for the NFCCR, the OFCCR, and the single practice cohorts were 16.1 months, 28.2 months, and 21.3 months, respectively. With that said, there was no statistically significant difference in survival among the three cohorts for stage IV patients (Log rank (Mantel-Cox = 2.911; df = 2; p = 0.233).

Table 17: Overall survival by cohort for patients with stage IV rectal cancer

Cohort	N	N of events	Overall Survival (% alive at follow-up)					Median time to event (months)	95% CI
			2 years	4 years	6 years	8 years	10 years		
NFCCR	23	21	43.5	17.4	0	0	0	16.11	(4.943, 27.276)
OFCCR	21	19	60.7	25.3	25.3	12.6	6.3	28.175	(10.351, 46.000)
Single practice	18	14	39.1	23.4	15.6	7.8	7.8	21.337	(15.218, 27.456)

Figure 8 shows the Kaplan-Meier curves comparing the overall survival of the three cohorts. As depicted in the figure the three lines intersect, suggesting that there is no statistically significant difference between the three cohorts in terms of overall survival for patients with stage II and III rectal cancer.



Log rank (Mantel-Cox) = 2.911; df = 2; p = 0.233

Figure 8: Kaplan-Meier curves of overall survival by cohort for patients with stage IV rectal cancer

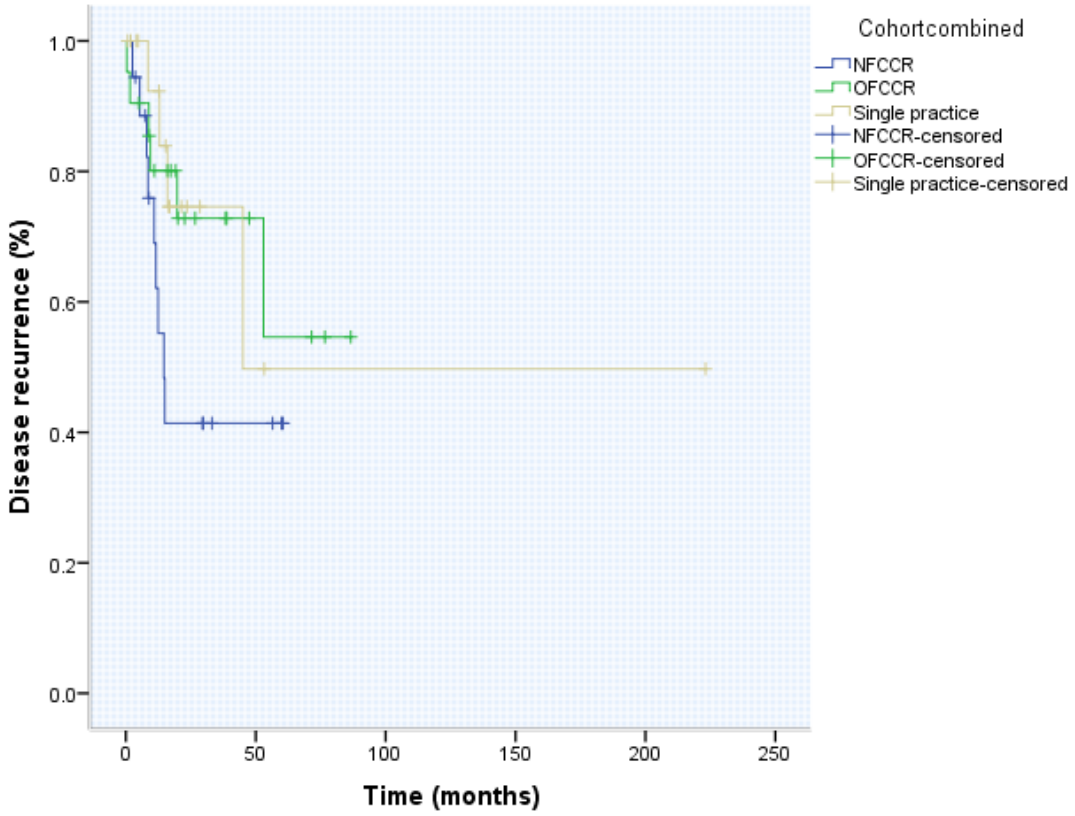
Table 18 shows the results of a disease-free time to event analysis performed for stage IV patients compared between each cohort. In terms of the NFCCR, the OFCCR, and the single practice, there were 9, 6, and 4 events of recurrent disease within the 10-year follow up. At the 10-year follow up, the respective proportions of patients without recurrent disease for the NFCCR, the OFCCR, and the single practice cohorts were

41.4%, 54.6%, and 49.7%, respectively. There was no statistically significant difference in terms of time to disease recurrence between each cohort (Log rank (Mantel-Cox) = 3.356; df = 1; p = 0.187).

Table 18: Disease-free time to event by cohort for patients with stage IV rectal cancer

Cohort	N	N of events	Time to event (% without recurrence at follow-up)				
			2 years	4 years	6 years	8 years	10 years
NFCCR	18	9	41.4	41.4	41.4	41.4	41.4
OFCCR	21	6	72.8	72.8	54.6	54.6	54.6
Single practice	17	4	74.6	49.7	49.7	49.7	49.7

Figure 9 shows the Kaplan-Meier curves comparing the disease-free time to event of the three cohorts. Given that each line intersects, one can conclude that there is no statistically significant difference between the three cohorts in terms of disease-free time to event among patients with stage II and III disease.



Chi = 3.356; df = 1; p = 0.187

Figure 9: Kaplan-Meier curves of disease-free time to event by cohort for patients with stage IV rectal cancer

4.6 Analysis of patients with stage II and III rectal cancer

4.6.1 Baseline demographics by patient cohort

Table 19 shows the baseline clinical and pathological differences at baseline among the three cohorts for patients with stage II and III disease. This sample comprises 488 patients with stage II and III disease. Of these, 30.3% (148) of participants come

from the NFCCR, 33.4% (163) come from the OFCCR, and another 36.2% (177) come from the records of the colorectal surgeon's single practice. Given that this is a non-randomized trial, the SPSS 23 computer program was used to investigate potential differences at baseline between each of the three cohorts. Pearson chi-square tests were performed to investigate patient factors, such as gender, cell type, neoadjuvant therapy, surgery type, staging, surgical margins, tumor grade, and presence of invasion. For the continuous variable, age, a non-parametric Kruskal-Wallis test was performed to assess differences between the three cohorts.

As depicted in the table, no statistically significant difference exists between each cohort in terms of the rate of adenocarcinoma cell type, abdominoperineal resection surgery, or poorly differentiated disease. In addition, there was no significant difference among the proportion of stage II or III cancers in either cohort. In contrast, significant differences existed between the cohorts in terms of clinical characteristics, including age, gender, neoadjuvant therapy, and the rate of AR surgery. The median age for the NFCCR, the OFCCR, and the single practice was 60 vs. 62 vs. 62 years, respectively ($p = 0.021$). In regards to male gender, the OFCCR had a significantly lower proportion of males in comparison to both the NFCCR and the single practice (56% vs. 71% vs. 69%; $p = 0.01$). In addition, there was a significantly increased rate of neoadjuvant CRT in the single practice (36%) in comparison to both the NFCCR (5%) and the OFCCR (7%). With respects to the type of surgical procedure performed, the rate of AR was significantly higher in the single practice cohort than the rates of AR in the NFCCR and OFCCR cohorts (69% vs. 55% vs. 51%, respectively; $p < 0.001$). Patients of the single practice had a much lower rate of complete tumor excision than both the NFCCR and the OFCCR

(81% vs. 93% vs. 96%, respectively; $p < 0.001$). In terms of grade, the OFCCR had a significantly lower rate of well-differentiated tumors in comparison to the NFCCR and the single practice (6% vs. 10% vs. 14%, respectively). In contrast, the single practice had a significantly lower proportion of moderately differentiated tumors when compared with the NFCCR and the OFCCR (55% vs. 79% vs. 77%; $p < 0.001$). There were significantly different rates of invasion between the three cohorts in terms of vascular invasion (36% vs. 14% vs.19%; NFCCR vs. OFCCR vs. Single practice), lymphatic invasion (36% vs. 17% vs. 29%; NFCCR vs. OFCCR vs. Single practice) and perineural invasion (30% vs. 4% vs 19%; NFCCR vs. OFCCR vs. Single practice).

Table 19: Baseline clinical & pathological characteristics by cohort for stage II and III patients

	Total	NFCCR	OFCCR	Single practice	P - value
n	488	148	163	177	
Age; median (SD)	62 (10)	60 (9)	62 (10)	62 (12)	0.021
Male gender; n (%)	320 (66)	105 (71)	92 (56)	123(69)	0.01
Cell-type; n (%)					
Adenoncarcinoma, NOS; n (%)	413 (85)	131(89)	139 (85)	143 (81)	NS
Neo-adjuvant therapy; n (%)	83 (17)	8 (5)	12 (7)	63 (36)	< 0.001
Type of surgery performed; n (%)					
Anterior resection; n (%)	288 (59)	82 (55)	83 (51)	123 (69)	0.001
Abdominoperineal resection; n (%)	144 (30)	47 (32)	50 (30)	47 (27)	NS
Pathological staging (pTNM); n (%)					
Stage 2; n (%)	213 (44)	68 (46)	74 (45)	71 (40)	NS
Stage 3; n (%)	275 (56)	80 (54)	89 (55)	106 (60)	NS
Tumor entirely resected; n (%)	437 (90)	138 (93)	156 (96)	143 (81)	< 0.001
Grade of primary tumor					
Well differentiated; n (%)	49 (10)	15 (10)	10 (6)	24 (14)	0.041
Moderately differentiated ; n (%)	340 (70)	117 (79)	125 (77)	98 (55)	< 0.001
Poorly differentiated; n (%)	63 (13)	15 (10)	22 (13)	26 (15)	NS
Presence of invasion; n (%)					
Vascular invasion; n (%)	110 (23)	53 (36)	23 (14)	34 (19)	< 0.001
Lymphatic invasion; n (%)	133 (27)	53 (36)	28 (17)	52 (29)	0.001
Perineural invasion; n (%)	85 (17)	45 (30)	7 (4)	33 (19)	< 0.001

4.6.2 Outcome measurement by patient cohort

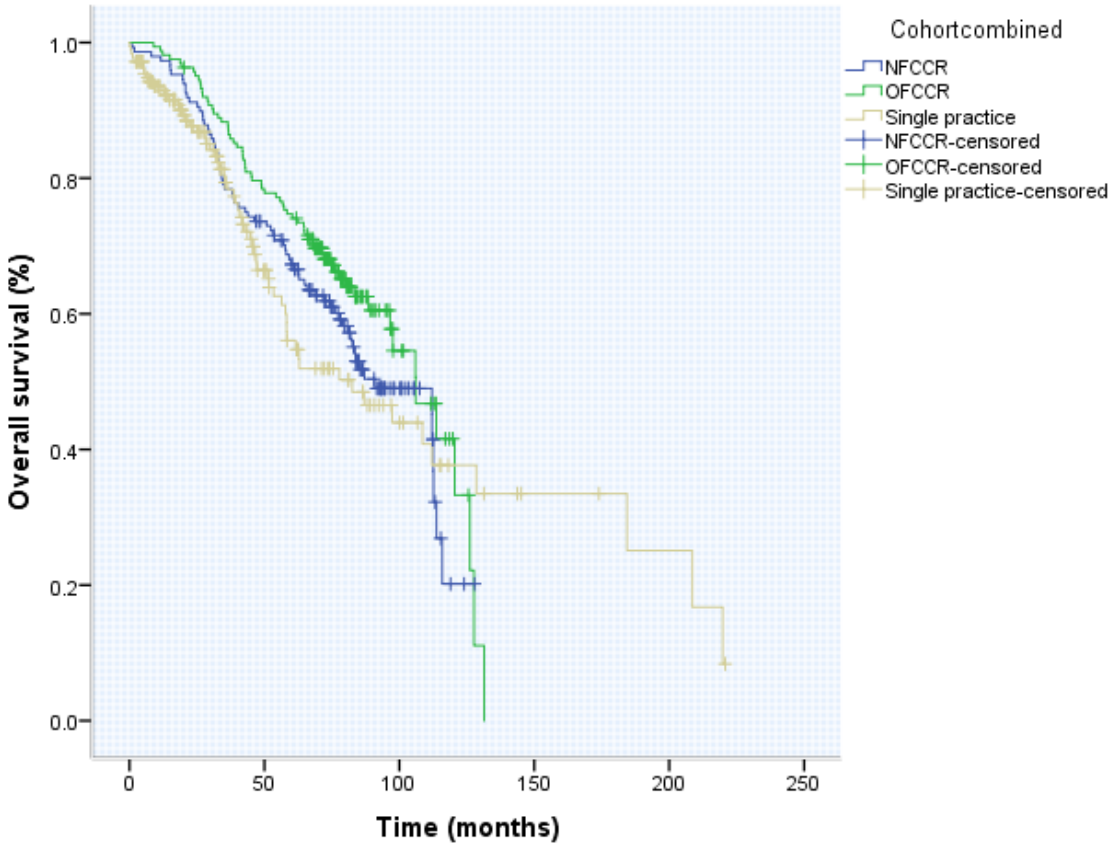
Table 20 shows the results of the survival analysis performed for stage II and III patients across cohorts. In the NFCCR cohort, 73 of the 148 stage II and III patients had expired within the 10-year follow up. During this period, 66 of the 163 stage II and III

patients in the OFCCR cohort, and 61 of the 177 stage II and III patients in the single practice cohort had passed. Median survival estimates for the NFCCR, the OFCCR, and the single practice were 90.7 months, 106.0 months, and 82.6 months, respectively. Given that each confidence interval overlaps, there was no statistically significant difference in survival between cohorts for these patients (Log rank (Mantel-Cox) = 3.532; df = 2; p = 0.171).

Table 20: Overall survival by cohort for patients with stage II & III rectal cancer

Cohort	N	N of events	Overall survival (% alive at follow-up)					Median time to event (months)	95% CI
			2 years	4 years	6 years	8 years	10 years		
NFCCR	148	73	91.2	73.6	61.9	49	20.2	90.74	(70.942, 110.537)
OFCCR	163	66	95.7	79.6	68.1	60.5	41.6	105.995	(91.337, 120.652)
Single practice	177	61	87.7	66.4	51.9	46.5	37.7	82.586	(48.225, 116.947)

Figure 10 shows Kaplan-Meier curves comparing the results of each cohort. Given that each line intersects, one can conclude that there is no statistically significant difference between each cohort in terms of overall survival among patients with stage II and III disease.



Chi = 3.532; df = 2; p = 0.171

Figure 10: Kaplan-Meier curves of overall survival by cohort for patients with stage II & III rectal cancer

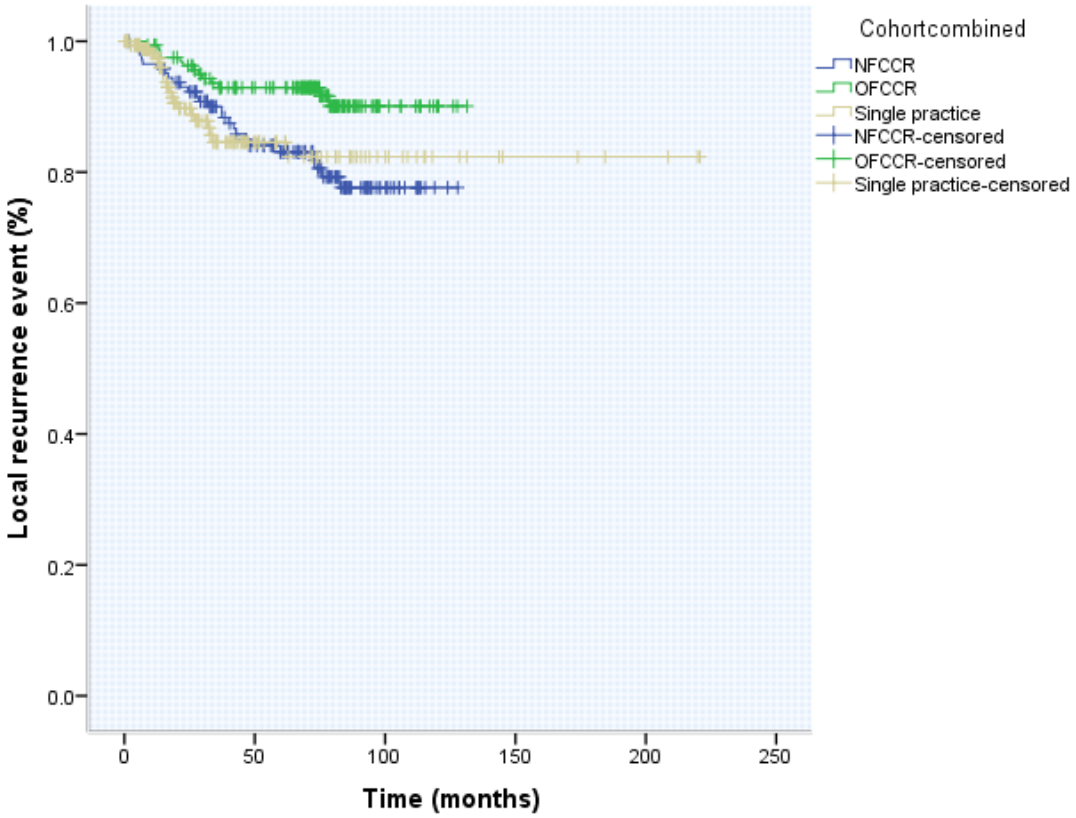
A local recurrence-free time to event analysis was performed for patients with stage II and III rectal cancer. As shown in table 21, the NFCCR had 26 patients with local recurrences, while the OFCCR had 13 patients with local recurrence during the 10-year period. The single practice had 20 events of local recurrence during this time. Given that the rate of patients without a local recurrence at follow up did not reach < 50%, median

time to local recurrence estimates could not be calculated. At 10 years of follow up, the proportion of stage II and III patients without local recurrence was 77.6%, 90.1%, and 83.2%, respectively. The OFCCR had a significantly better prognosis in terms of proportion without local recurrence when compared to the other cohorts during the 10-year follow up (Log rank (Mantel-Cox) = 7.773; df = 2; p = 0.021).

Table 21: Local recurrence-free time to event by cohort for patients with stage II & III rectal cancer

Cohort	N	N of events	Time to event (% without local recurrence at follow-up)				
			2 years	4 years	6 years	8 years	10 years
NFCCR	146	26	93	84.1	83.1	77.6	77.6
OFCCR	163	13	96.2	92.9	92.9	90.1	90.1
Single practice	176	20	89.7	84.6	82.3	82.3	83.2

Figure 11 shows the corresponding Kaplan-Meier curves of local recurrence-time to event for patients with stage II and III rectal cancer. As shown in the graph, there is a significant separation in the Kaplan-Meier curves, as patients of the OFCCR experienced a significantly improved time to local recurrence in comparison to both the NFCCR and the single practice.



Log rank (mantel-cox) = 7.773; df = 2; p = 0.021

Fig 11: Kaplan-Meier curves of local recurrence-free time to event by cohort for patients with stage II & III rectal cancer

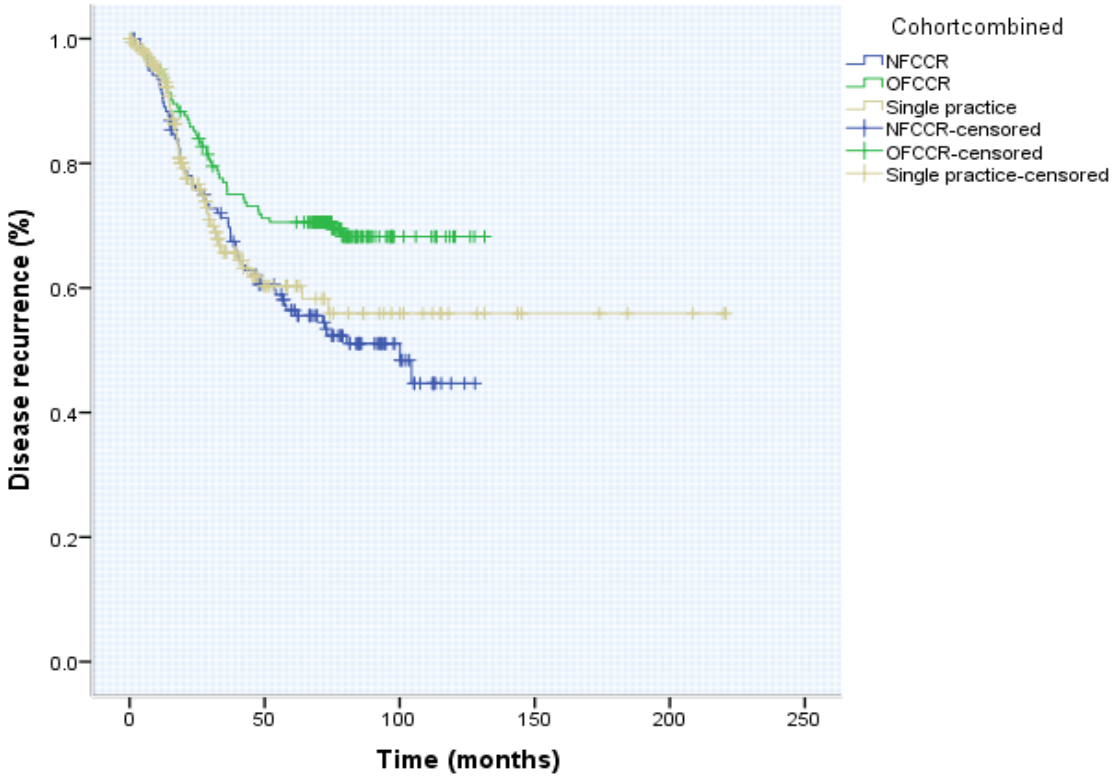
Table 22 shows the results of a disease-free time to event analysis performed for patients with stage II and III disease. In terms of event, there were 65 disease recurrences in the NFCCR cohort, 49 disease recurrences in the OFCCR cohort, and 49 disease recurrences in the single practice cohort. As shown in the table, the OFCCR had a significantly improved rate of disease recurrence during the 10-year follow up. Given that

the proportion of patients without recurrent disease did not reach 50% in most cohorts, median time to event estimates could not be calculated. With that said, stage II and III patients of the OFCCR experienced a significantly improved disease-free time to event in comparison to patients of the NFCCR and the OFCCR (Log rank (Mantel-Cox = 9.053; df = 2; p = 0.011).

Table 22: Disease-free time to event by cohort for patients with stage II & III rectal cancer

Cohort	N	N of events	Time to event (% without recurrence at follow-up)				
			2 years	4 years	6 years	8 years	10 years
NFCCR	139	65	76.5	60.5	54.5	51.1	44.7
OFCCR	163	49	85.2	71.8	70.5	68.2	68.2
Single practice	175	49	76.7	61.8	58.2	55.9	55.9

Figure 12 shows the time to Kaplan-Meier curves corresponding to disease-free time to event for patient with stage II and III disease. As shown in the figure, there is a clear separation between the Kaplan-Meier curve corresponding to patients of the OFCCR and the curves corresponding to both the NFCCR and the OFCCR. As a result, stage II and III patients of the OFCCR had a statistically significant improvement in disease-free recurrence in comparison to those of the NFCCR and the single practice.



Chi = 9.053; df = 2; p = 0.011

Figure 12: Kaplan-Meier curves of disease-free time to event by cohort for patients with stage II & III rectal cancer

4.7 Analysis of stage II and III patients by neoadjuvant therapy

4.7.1 Overall survival and recurrence outcomes

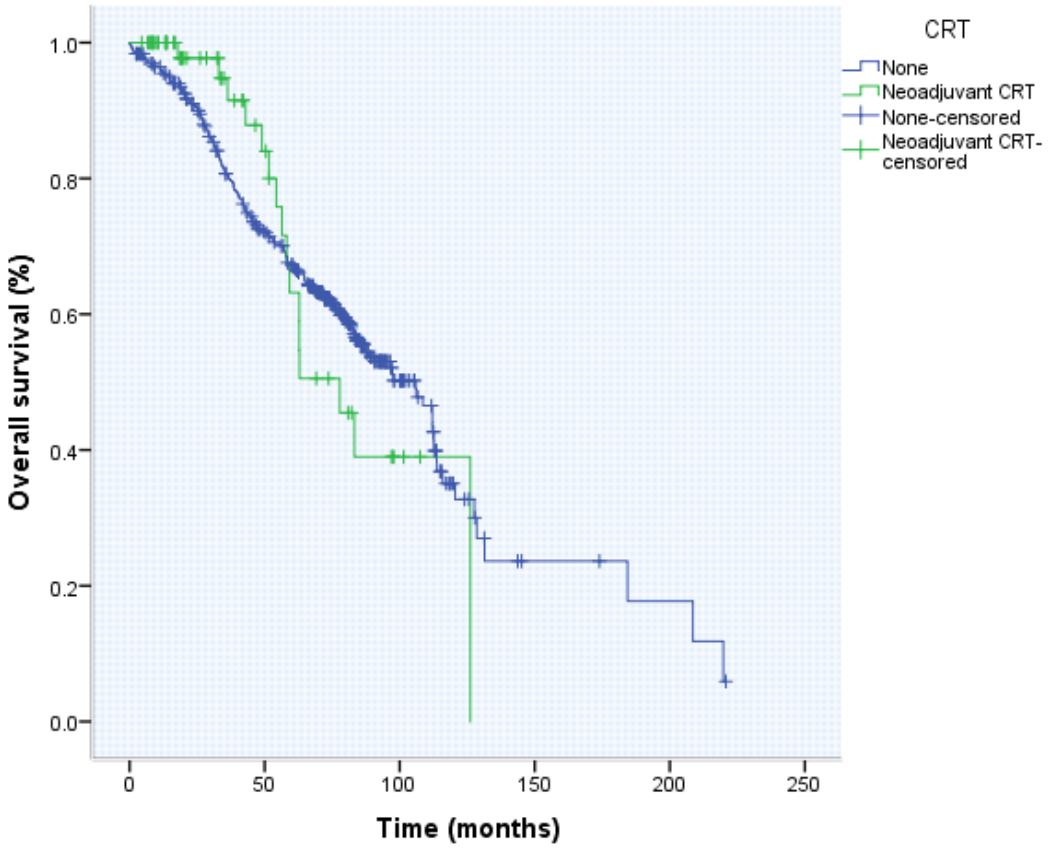
Subsequently, an overall survival analysis was performed to compare patients with stage II and III disease based on neoaduvant CRT status. Table 23 shows that of the 62 patients with locally advanced disease that had neoadjuvant therapy, 15 expired within

a 10-year follow up. Of the 415 patients who did not receive neoadjuvant therapy, 148 had passed away within this period of time. Of patients with stage II and III disease, the median overall survival estimates for those receiving neoadjuvant CRT was just 77.8 months (57.3 – 98.4), whereas the estimate for individuals without neoadjuvant therapy was 106 months (90.8 – 121.1). At 10-years of follow up, the proportion of patients still alive was 39.0% for those receiving neoadjuvant CRT and 35.1% for patients who did not receive this therapy.

Table 23: Overall survival by neoadjuvant therapy status for patients with stage II & III rectal cancer

Therapy	N	N of events	Overall survival (% alive at follow-up)					Median time to event (months)	95% CI
			2 years	4 years	6 years	8 years	10 years		
Neoadjuvant CRT	63	16	97.7	87.8	50.5	39	39	77.819	(57.267, 98.371)
None	425	184	90.7	72.5	62.6	53	35.1	105.962	(90.812, 121.112)

Figure 13 shows the Kaplan-Meier curves corresponding to overall survival for patients with stage II and III disease. Given that both curves overlap significantly, there is no statistically significant difference in survival between patients with stage II and III disease that receive neoadjuvant therapy and those who do not (Log rank (Mantel-Cox) = 0.012; df = 2; p = 0.913).



Chi = 0.012; df = 1; p = 0.913

Fig. 13: Kaplan-Meier curves of overall survival by neoadjuvant therapy status for patients with stage II & III rectal cancer

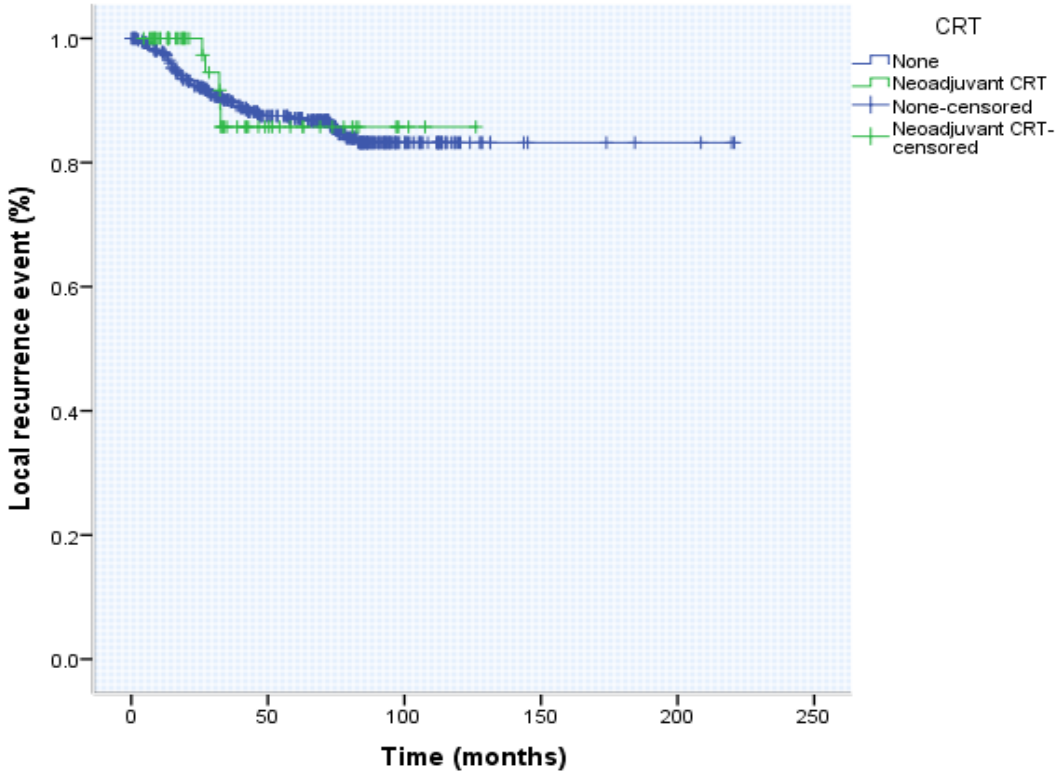
Table 24 shows the results for local recurrence-free time to event for stage II and III patients comparing those who received neoadjuvant CRT and those who did not receive neoadjuvant therapy. Of the 63 stage II and III patients who received neoadjuvant CRT, 5 had a local recurrence within 10 years of follow up. Of the 422 patients who did not receive neoadjuvant therapy, 54 had a local recurrence event during the same period.

From the table, one can note that the time to event at each point of follow up is fairly similar between both groups. At 10 years of follow up, the proportion of patients with stage II and III disease without local recurrence was 85.7% and 83.2% for those receiving neoadjuvant CRT therapy and those without this therapy, respectively. There was no statistically significant difference in overall survival between the two groups (Log rank (Mantel-Cox = 0.106; df = 1; p = 0.745)).

Table 24: Local recurrence-free time to event by neoadjuvant therapy status for patients with stage II & III rectal cancer

Therapy	N	N of events	Time to event (% without local recurrence at follow-up)				
			2 years	4 years	6 years	8 years	10 years
Neoadjuvant CRT	63	5	100	85.7	85.7	85.7	85.7
None	422	54	92.4	87.5	86.7	83.2	83.2

Figure 14 shows the Kaplan-Meier curves corresponding to the local recurrence – free time to event analysis by neoadjuvant therapy status. As depicted in the graph, both curves overlap significantly, suggesting that there is no statistically significant difference in overall survival for patients with stage II and III rectal cancer based on neoadjuvant therapy.



Log rank (Mantel-Cox) = 0.106; df = 1; p = 0.745

Figure 14: Kaplan-Meier curves of local recurrence-free time to event by neoadjuvant therapy status for patients with stage II & III rectal cancer

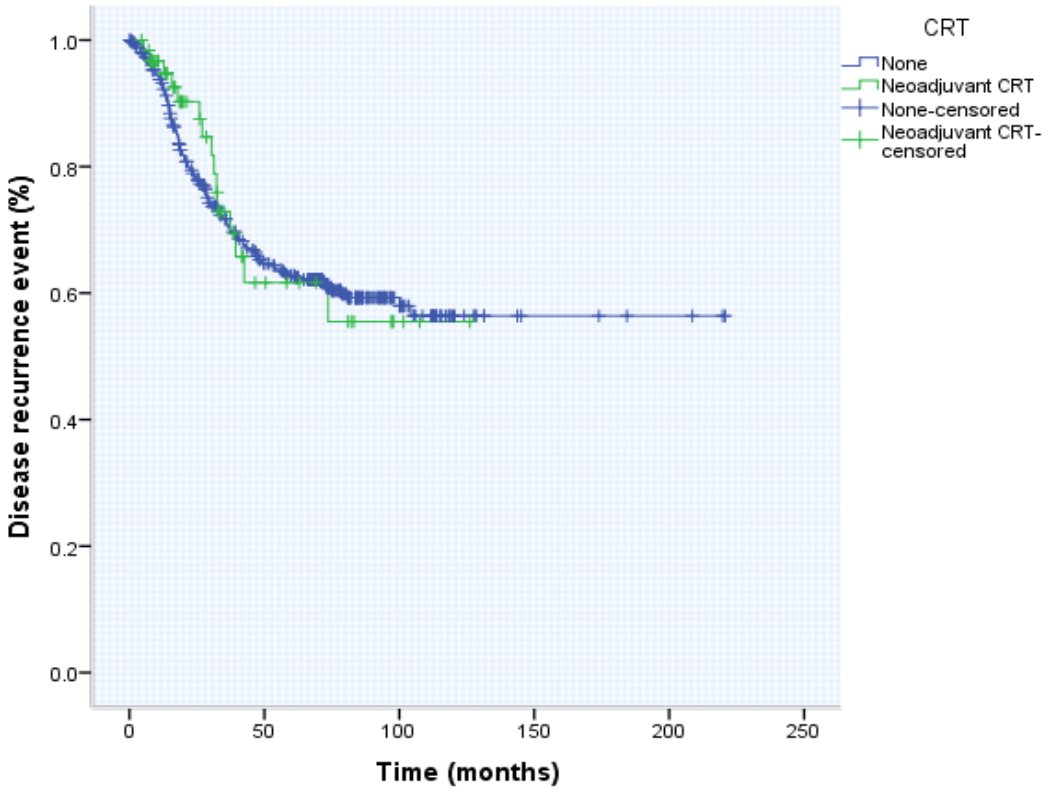
A disease-free time to event analysis was performed for patients with stage II and III disease in order to compare the recurrence rate of patients based on status of neoadjuvant therapy. Table 25 shows that 15 of the 62 patients receiving neoadjuvant CRT included in the analysis had either a local or distant recurrence. Of the 415 patients not receiving neoadjuvant CRT, there were 148 events of disease recurrence. At 10 years of follow up, the proportion of individuals without disease recurrence was 55.5% and

56.4% for patients receiving neoadjuvant CRT and those receiving treatment without neoadjuvant therapy, respectively. There was no statistically significant difference in disease-free time to event for patients with stage II and III disease based on neoadjuvant therapy (Log rank = 0.074; df = 1; p = 0.786).

Table 25: Disease-free time to event by neoadjuvant therapy status for patients with stage II & III rectal cancer

Therapy	N	N of events	Time to event (% without disease recurrence at follow-up)				
			2 years	4 years	6 years	8 years	10 years
Neoadjuvant CRT	62	15	90.2	61.7	61.7	55.5	55.5
None	415	148	78.6	65.3	61.7	59.3	56.4

Figure 15 shows the Kaplan-Meier graphs of the disease-free time to event analysis comparing outcome by neoadjuvant therapy status. As depicted, there is significant overlap between the curves of those receiving neoadjuvant therapy and those not receiving neoadjuvant therapy. This suggests that there was no significant difference in disease recurrence based on receiving neoadjuvant CRT.



Chi = 0.074; df = 1; p = 0.78

Figure 15: Kaplan-Meier curves of disease-free time to event by neoadjuvant therapy status for patients with stage II & III rectal cancer

4.7.2 Univariate predictors of outcome

Table 26 shows the results of the univariate analysis of overall survival for patients with stage II and III rectal cancer. Age at diagnosis was found to be a significant predictor of survival. For every additional year, there was a 3.1% increase in risk of

mortality. In addition, the presence of AR surgery was associated with a 46% decreased relative risk of mortality (Exp (B) = 0.539; 0.408 – 0.713). In addition, complete excision was a significant predictor of overall survival. The results suggest that complete excision of the primary tumor can decrease the relative risk of mortality by 50% (Exp (B) = 0.497; 0.311 – 0.792. Poorly differentiated tumors were associated with a 2 -fold increase in relative risk for patients (Exp (B) = 2.009; 1.386 – 2.913). Both vascular invasion (Exp (B) = 1.642; 1.212 – 2.226) and perineural invasion (Exp (B) = 1.858; 1.343 – 2.571) were associated with poor prognosis in terms of overall survival for patients with locally advanced disease. Similarly, stage III patients were 1.4 times more likely to have expired than stage II patients during follow-up (Exp (B) = 1.355; 1.017 – 1.806). In terms of neoadjuvant chemo-radiation therapy, there was no significant effect on overall survival for patients with stage II and III disease. Other patient variables that had no statistically significant effect on overall survival included male sex, adenocarcinoma cell type, lymphatic invasion, and cohort.

Table 26: Results of univariate analysis of overall survival for patients with stage II & III rectal cancer

		n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)		488 (100)	1.031	1.016 - 1.046	< 0.001
Male Sex		320 (66)	1.301	0.965 - 1.753	NS
Adenocarcinoma, NOS		413 (85)	0.836	0.569 - 1.227	NS
Neoadjuvant CRT		63 (13)	1.029	0.616 - 1.720	NS
Combined neoadjuvant therapy group		83 (17)	1.232	0.834 - 1.820	NS
Anterior resection		288 (59)	0.539	0.408 - 0.713	< 0.001
Tumor completely excised		437 (90)	0.497	0.311 - 0.792	0.003
Grade of tumor, poorly differentiated		63 (13)	2.009	1.386 - 2.913	< 0.001
Vascular invasion		110 (23)	1.642	1.212 - 2.226	0.001
Lymphatic invasion		133 (27)	1.316	0.978 - 1.771	NS
Perineural invasion		85 (17)	1.858	1.343 - 2.571	< 0.001
Stage					
	II	213 (44)	1		
	III	275 (56)	1.355	1.017 - 1.806	0.038
Cohort					
	NFCCR	148 (30)	1		
	OFCCR	163 (33)	0.781	0.560 - 1.090	NS
	Single practice	177 (36)	1.075	0.755 - 1.530	NS

Subsequently, a univariate analysis of local recurrence-free time to event was performed. As depicted in table 27, AR surgery was shown to be associated with 44% reduction in relative risk of local recurrence (Exp (B) = 0.558; 0.334 – 0.931). Poorly differentiated grade of tumors suggested a 2.4 fold increase in the risk of acquiring a local recurrence (Exp (B) = 2.397; 1.292 – 4.448). Both vascular invasion (Exp (B) = 2.582; 1.536 – 4.341) and lymphatic invasion (Exp (B) = 2.072; 1.236 – 3.473) were associated with significantly increased risk of developing a local recurrence. Similarly, patients of

the OFCCR cohort had a 58% reduced risk of developing a local recurrence in comparison to patients of the NFCCR (Exp (B) = 0.423; 0.217 – 0.823). The results of the local recurrence-free time to event analysis suggest neoadjuvant CRT to have no significant effect on time to local recurrence. Other non-significant patient variables in the univariate analysis included age at diagnosis, male sex, adenocarcinoma cell type, complete excision, perineural invasion, and stage.

Table 27: Results of univariate analysis of local recurrence-free time to event for patients with stage II & III rectal cancer

	n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)	488 (100)	1.011	0.985 - 1.038	NS
Male Sex	318 (65)	1.133	0.660 - 1.942	NS
Adenocarcinoma, NOS	411 (84)	0.592	0.320 - 1.095	NS
Neoadjuvant CRT	63 (13)	0.859	0.343 - 2.152	NS
Combined neoadjuvant therapy group	83 (17)	0.847	0.384 - 1.866	NS
Anterior resection	288 (59)	0.558	0.334 - 0.931	0.026
Tumor completely excised	435 (89)	0.545	0.246 - 1.203	NS
Grade of tumor, poorly differentiated	63 (13)	2.397	1.292 - 4.448	0.006
Vascular invasion	109 (22)	2.582	1.536 - 4.341	< 0.001
Lymphatic invasion	132 (27)	2.072	1.236 - 3.473	0.006
Perineural invasion	85 (17)	1.6	0.878 - 2.916	NS
Stage				
II	212 (43)	1		
III	273(56)	1.537	0.902 - 2.619	NS
Cohort				
NFCCR	148 (30)	1		
OFCCR	163 (28)	0.423	0.217 - 0.823	0.011
Single practice	176 (36)	0.977	0.544 - 1.757	NS

Table 28 shows the results of the univariate analysis of disease-free time to event for patients with stage II and III disease. The presence of male sex was shown to be associated with a 1.4 fold increase in relative risk of developing either a local or distant recurrence. The use of AR surgery suggested a 39% decreased likelihood of having a disease recurrence during follow up. Poorly differentiated tumors were associated with a 1.6 fold increase in developing recurrence. Similarly, presence of invasion was associated with an increased risk of disease recurrence, whether it was vascular invasion (Exp (B) = 1.953; 1.411 – 2.703), lymphatic invasion (Exp (B) = 1.851; 1.350 – 2.539), or perineural invasion (2.368; 1.686 – 3.327). In terms of disease staging, stage III patients were approximately twice as likely to suffer recurrent disease in comparison to stage II patients (Exp (B) = 1.997; 1.434 – 2.781). In comparison to the NFCCR cohort, the OFCCR cohort was 42% less likely to have recurrent disease (Exp (B) = 0.579; 0.399 – 0.839). The results of the univariate analysis of disease-free time to event suggest that neoadjuvant CRT has no significant effect on time to disease recurrence. Other non-significant patient variables in the univariate analysis included age at diagnosis, adenocarcinoma cell type, and complete excision.

Table 28: Results of univariate analysis of disease-free time to event for patients with stage II & III rectal cancer

	n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)	488 (100)	0.996	0.981 - 1.012	NS
Male Sex	312 (64)	1.425	1.018 - 1.997	0.039
Adenocarcinoma, NOS	404 (83)	0.905	0.591 - 1.386	NS
Neoadjuvant CRT	62 (13)	0.929	0.545 - 1.582	NS
Combined neoadjuvant therapy group	82 (17)	1.11	0.719 - 1.714	NS
Anterior resection	284 (58)	0.607	0.447 - 0.826	0.001
Tumor completely excised	428(88)	0.609	0.368 - 1.010	NS
Grade of tumor, poorly differentiated	62 (13)	1.571	1.025 - 2.408	0.038
Vascular invasion	108 (22)	1.953	1.411 - 2.703	< 0.001
Lymphatic invasion	131 (27)	1.851	1.350 - 2.539	< 0.001
Perineural invasion	84 (17)	2.368	1.686 - 3.327	< 0.001
Stage				
II	208 (43)	1		
III	269 (55)	1.997	1.434 - 2.781	< 0.001
Cohort				
NFCCR	139 (28)	1		
OFCCR	163 (33)	0.579	0.399 - 0.839	0.004
Single practice	175 (36)	0.898	0.618 - 1.305	NS

4.7.3 Multivariate models of outcomes

Table 29 shows the results of a multivariate analysis used to assess the impact of neoadjuvant CRT on overall survival for patients with stage II and III rectal cancer. Neoadjuvant CRT was removed from the model, suggesting no significant effect on patient survival for this sample when controlled for other variables. With that said, age at diagnosis, AR, complete excision, poorly differentiated grade, perineural invasion, and stage were all shown to be significant independent predictors of overall survival. For example, both AR and complete excision were shown to decrease the risk of mortality by

47% (0.402 – 0.706; p < 0.001) and 58% (0.259 – 0.670; p > 0.001), respectively. In contrast, poorly differentiated tumors were associated with a 1.8 fold increase (1.207 – 2.565; p = 0.003) in relative risk of mortality when controlled for other variables in the model. In addition, the presence of perineural invasion was associated with 1.7 fold increase in relative risk (1.219 – 2.348; p = 0.02) of mortality. Stage III patients were 1.4 times more likely to have expired when compared to patients with stage II disease (1.030 – 1.843; p = 0.031).

Table 29: Results of multivariate analysis of overall survival for patients with stage II & III rectal cancer

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age (per year)	.033	.008	19.462	1	.000	1.034	1.019	1.049
Anterior resection	-.630	.144	19.161	1	.000	.533	.402	.706
Complete excision	-.877	.243	13.054	1	.000	.416	.259	.670
Poorly differentiated	.565	.192	8.622	1	.003	1.759	1.207	2.565
Perineural invasion	.526	.167	9.867	1	.002	1.692	1.219	2.348
Stage3	.320	.148	4.653	1	.031	1.377	1.030	1.843

Table 30 shows the results of the multivariate model of local recurrence-free time to event for patients with stage II and III disease. Neoadjuvant CRT was removed from the model, suggesting no significant effect on local recurrence for this sample when

controlled for other variables. Both the adenocarcinoma cell type and AR surgery were shown to decrease the relative risk of local recurrence by 47% (Exp (B) = 0.532; 0.284 – 0.994) and 50% (Exp (B) = 0.503; 0.298 – 0.847), respectively. In addition, patients of the OFCCR were 52% less likely to develop local recurrence (Exp (B) = 0.483; 0.242 – 0.962). In contrast, the presence of vascular invasion was associated with a 2.4 fold increase in relative risk of local recurrence during follow-up (Exp (B) = 2.362; 1.372 – 4.066).

Table 30: Results of multivariate analysis of local recurrence-free time to event for patients with stage II & III rectal cancer

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Adenocarcinoma, NOS	-.632	.319	3.912	1	.048	.532	.284	.994
Anterior resection	-.687	.266	6.666	1	.010	.503	.298	.847
Vascular invasion	.859	.277	9.613	1	.002	2.362	1.372	4.066
NFCCR			6.818	2	.033			
OFCCR	-.728	.352	4.285	1	.038	.483	.242	.962
Single practice	.194	.312	.388	1	.534	1.214	.659	2.237

Table 31 shows the results of the multivariate model of disease free time to event for patients with stage II and III disease. Neoadjuvant CRT was not included in the final model, as it was not a significant predictor of disease-free time to event for this sample when controlled for other variables. With that said, AR and complete excision reduced

the risk of disease recurrence by 34% (Exp B) = 0.655; 0.480 – 0.894) and 49% (Exp (B) = 0.514; 0.309 – 0.856), respectively. In contrast, male sex, vascular invasion, perineural invasion, and stage were all independent significant predictors of poor disease recurrence prognosis. Specifically, male patients were 1.4 times (Exp (B) = 1.436; 1.024 – 2.013) more likely to have a recurrence in comparison to their female counterparts. Similarly, the presence of vascular invasion was associated with a 1.4 fold (Exp (B) = 1.003 – 2.054) increase in relative risk of developing recurrent disease, whereas perineural invasion was associated with a 1.9 fold (Exp (B) = 1.864; 1.280 – 2.716) increase in risk. Patients with stage III disease were 1.9 times (Exp (B) = 1.920; 1.373 – 2.686) more likely to develop recurrence than those with stage II disease.

Table 31: Results of multivariate analysis of disease-free time to event for patients with stage II & III rectal cancer

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Sex, male	.362	.172	4.405	1	.036	1.436	1.024	2.013
Anterior resection	-.422	.159	7.102	1	.008	.655	.480	.894
Complete excision	-.666	.260	6.542	1	.011	.514	.309	.856
Vascular invasion	.362	.183	3.912	1	.048	1.436	1.003	2.054
Perineural invasion	.623	.192	10.527	1	.001	1.864	1.280	2.716
Stage 3	.652	.171	14.512	1	.000	1.920	1.373	2.686

4.8 Analysis of patients with stage II and III disease following December 2003

4.8.1 Baseline demographics

Table 32 shows the predictors of neoadjuvant CRT for patients with stage II and III rectal cancer diagnosed after December 2003. Of the 118 patients with locally advanced disease diagnosed after 2003, 38.9% received neoadjuvant CRT while 61% of patients did not receive this therapy despite a universal shift in clinical practice. As depicted in the table, no significant difference exists between patients receiving neoadjuvant CRT and those without neoadjuvant therapy in terms of age, adenocarcinoma cell type, type of surgery performed, stage, tumor grade, vascular invasion, and perineural invasion. In contrast, the patients who received neoadjuvant CRT differed from those not receiving this therapy in terms of the proportion of males, complete resection, and lymphatic invasion. Specifically, 85% of the sample receiving neoadjuvant CRT were males, whereas only 64% of those without neoadjuvant CRT were males ($p = 0.014$). The proportion of patients with complete tumor resection for those receiving neoadjuvant CRT and those without neoadjuvant CRT was 54% and 89%, respectively ($p < 0.001$). Of the 46 patients in the neoadjuvant CRT group, 9% had lymphatic invasion, whereas 29% of patients without neoadjuvant CRT had lymphatic invasion ($p = 0.012$).

Table 32: Predictors of neoadjuvant chemo-radiation therapy for patients with stage II & III rectal cancer post December 2003

	Total	Preoperative chemoradiation	No preoperative therapy	P - value
n	118	46	72	
Age; median (SD)	62 (11)	61 (10)	63 (12)	NS
Male gender; n (%)	85 (72)	39 (85)	46 (64)	0.014
Adenocarcinoma, NOS; n (%)	94 (80)	35 (76)	59 (82)	NS
Type of surgery performed; n (%)				
Anterior resection; n (%)	84 (71)	30 (65)	54 (75)	NS
Abdominoperineal resection; n (%)	34 (29)	16 (35)	16 (22)	NS
Stage; n (%)				
Stage 2; n (%)	49 (42)	18 (39)	31 (43)	NS
Stage 3; n (%)	69 (58)	28 (61)	41 (57)	NS
Tumor entirely resected; n (%)	89 (75)	25 (54)	64 (89)	< 0.001
Grade of primary tumor				
Well differentiated; n (%)	11 (9)	3 (7)	8 (11)	NS
Moderately differentiated ; n (%)	63 (53)	17 (37)	46 (64)	NS
Poorly differentiated; n (%)	16 (14)	4 (9)	12 (17)	NS
Presence of invasion; n (%)				
Vascular invasion; n (%)	17 (14)	4 (9)	13 (18)	NS
Lymphatic invasion; n (%)	25 (21)	4 (9)	21 (29)	0.012
Perineural invasion; n (%)	20 (17)	9 (20)	11 (15)	NS

4.8.2 Overall survival and recurrence outcomes

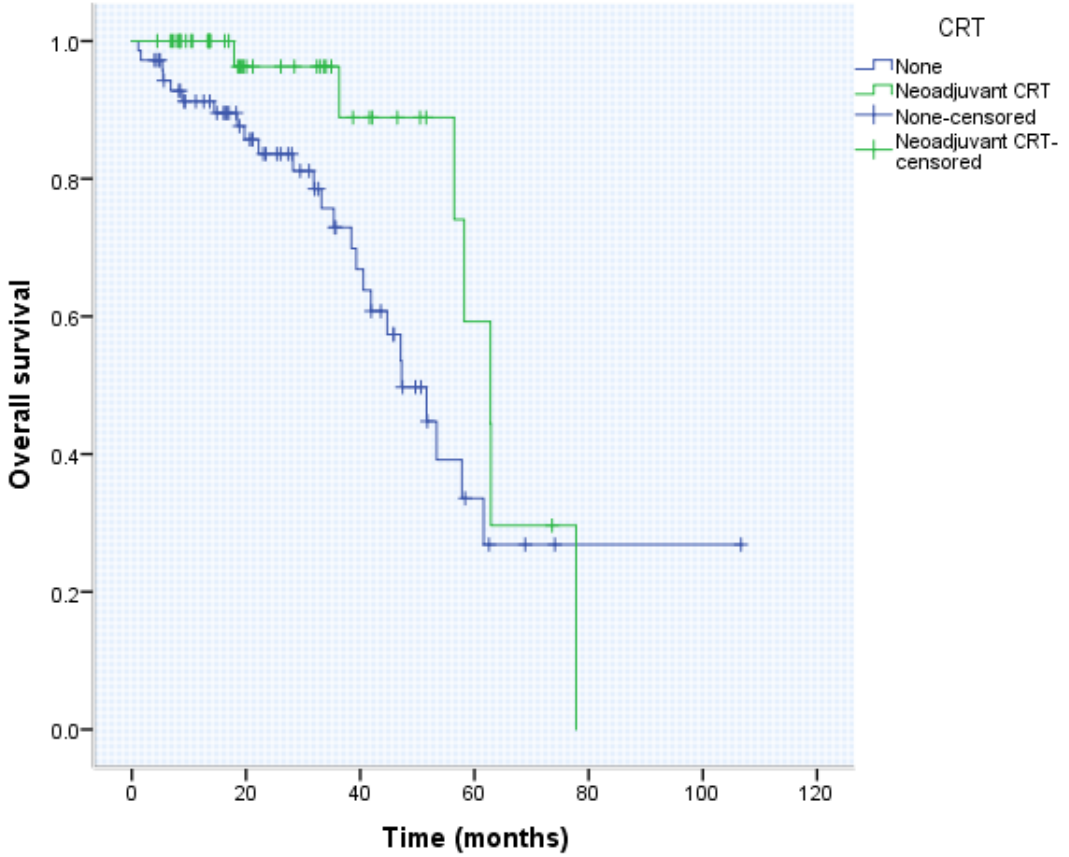
Table 33 shows the results of the overall survival analysis for patients with stage II and III rectal cancer diagnosed following December 2003. Of the 46 patients who received neoadjuvant CRT, 7 had expired within the 10-year follow up. Of the 72 patients with stage II and III disease who did not receive neoadjuvant therapy, 25 of those individuals had died within the same period. Median survival estimates were calculated, as the percentage of patients alive at follow-up reached less than 50% in both groups. The

median survival estimate for patients receiving neoadjuvant CRT was 62.8 months (51.6 – 74.0), whereas the median survival for patients who did not receive neoadjuvant therapy was 47.2 months (38.0 – 56.5). Patients in the neoadjuvant CRT group experienced a significantly improved overall survival rate in comparison to those receiving treatment without neoadjuvant therapy (Log rank (Mantel-Cox) = 3.889; df = 1; p = 0.049).

Table 33: Overall survival for patients with stage II & III rectal cancer diagnosed post-December 2003

Therapy	N	N of events	Overall survival (% alive at follow-up)					Median survival (months)	95% CI
			2 years	4 years	6 years	8 years	10 years		
Neoadjuvant CRT	46	7	96.3	88.9	29.6	0	0	62.795	(51.570, 74.019)
None	72	25	83.6	49.7	26.9	26.9	26.9	47.244	(38.025, 56.463)

Figure 16 shows the Kaplan-Meier curves corresponding to the overall survival analysis performed for patients with stage II and III disease diagnosed after December 2003. As shown in the graph, two patient survival curves are present based on status of receiving neoadjuvant CRT. There is clear separation between the overall survival curves, suggesting that there is a statistically significant difference in overall survival between the two groups.



Chi = 3.889; df = 1; p = 0.049

Figure 16: Kaplan-Meier curves of overall survival for patients with stage II & III rectal cancer diagnosed post-December 2003

Table 34 shows the results of the local recurrence-free time to event for patients with stage II and III rectal cancer. Of the 46 patients receiving neoadjuvant CRT, just 3 individuals suffered locally recurrent disease during the 10-year follow up. Of the 72 patients without neoadjuvant therapy, 8 individuals had a local recurrence event during this time. Given that the percentage of patients without local recurrence in either group

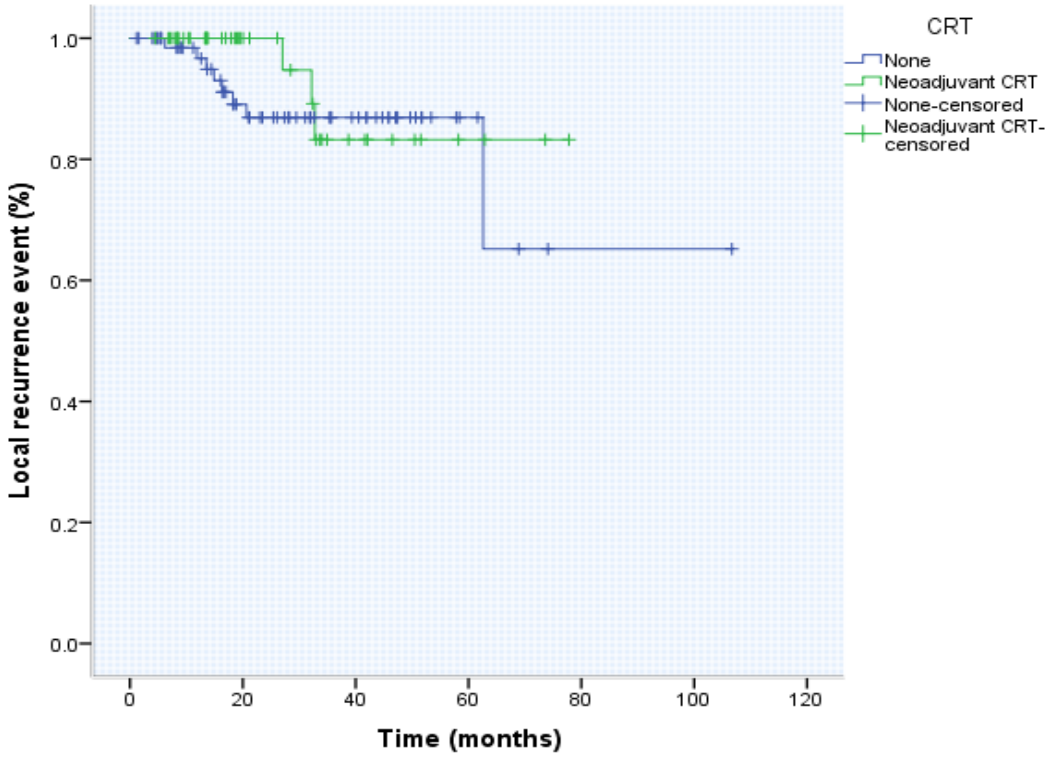
did not drop below 50%, median time to event estimates could not be calculated. At 10 years of follow-up, 83.2% of the patients receiving neoadjuvant CRT were without local recurrence. In comparison, just 65.2% of the patients who did not receive neoadjuvant therapy were without local recurrence. With that said, there was no statistically significant difference between the two groups in terms of local recurrence-free time to event (Log rank (Mantel-Cox) = 0.508; df = 1; p = 0.476)).

Table 34: Local recurrence-free time to event for patients with stage II and III rectal cancer diagnosed post-December 2003

Therapy	N	N of events	Overall time to event (% without local recurrence at follow-up)				
			2 years	4 years	6 years	8 years	10 years
Neoadjuvant CRT	46	3	100	83.2	83.2	83.2	83.2
None	72	8	86.9	86.9	65.2	65.2	65.2

Figure 17 shows the Kaplan-Meier curves corresponding to the local recurrence-free time to event analysis for patients with locally advanced disease diagnosed after December 2003. As shown in the graph, the results have been separated into two curves in order to determine if a difference exists, regarding time to local recurrence for patients receiving neoadjuvant CRT and those treated without neoadjuvant CRT. Both of the

Kaplan-Meier curves intersect, suggesting no statistically significant difference between the two groups.



Chi = 0.508; df = 1; p = 0.476

Figure 17: Kaplan-Meier curves of local recurrence-free time to event for patients with stage II and III rectal cancer post-December 2003

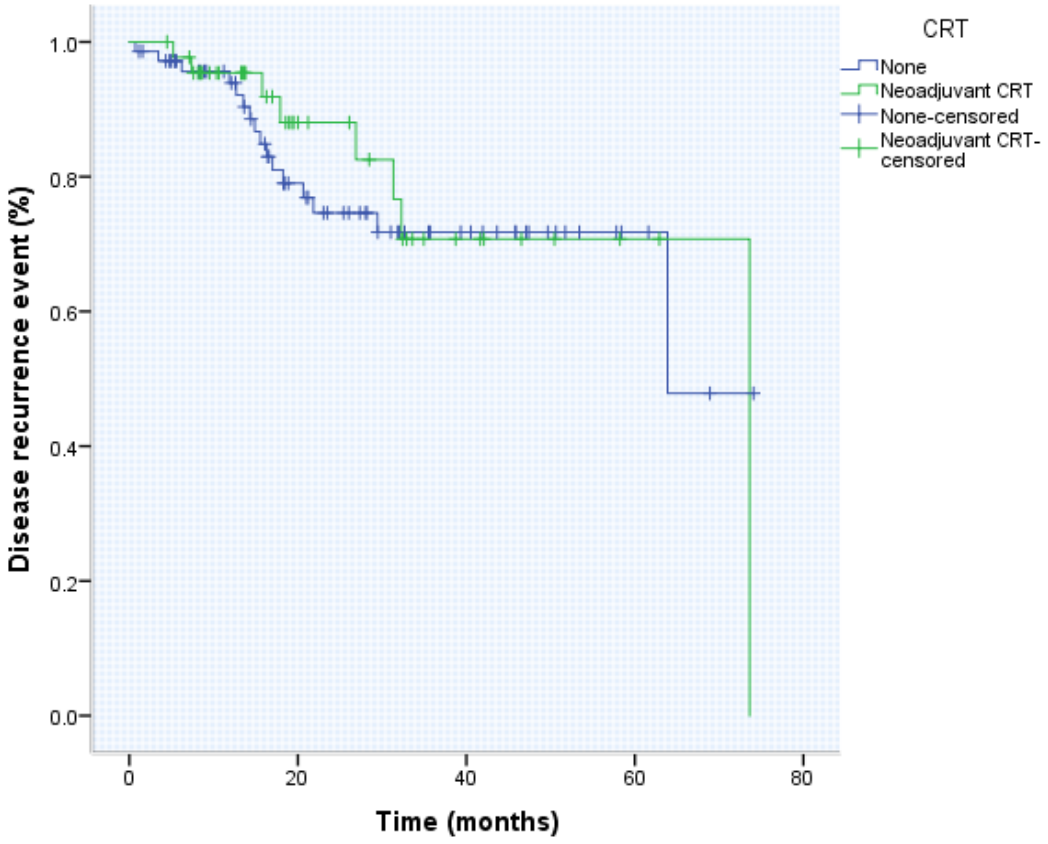
Table 35 shows the results of disease-free time to event of patients with stage II and III rectal cancer diagnosed following December 2003. Of the 45 patients receiving neoadjuvant CRT, 8 individuals had either a local or distant recurrence during the 10-year follow up. Of the 72 patients who received treatment without neoadjuvant CRT, 16

patients suffered recurrent disease within this period. Given that the percentage of patients without recurrence in either group did not reach 50%, median time to event estimates could not be calculated. At 10 years of follow up, there were no patients without recurrent disease in the group that received neoadjuvant CRT, whereas 47.8% of the patients who did not receive neoadjuvant therapy were without recurrence. Still, no statistically significant difference in disease-free time to event was observed between the two groups (Log rank (Mantel-Cox = 0.143; df = 1; p = 0.705)).

Table 35: Time to disease-free time to event for patients with stage II and III rectal cancer diagnosed post-December 2003

Therapy	N	N of events	Overall time to event (% withough recurrence at follow-up)				
			2 years	4 years	6 years	8 years	10 years
Neoadjuvant CRT	45	8	88	71	71	0	0
None	72	16	74.6	71.8	47.8	47.8	47.8

Figure 18 shows the Kaplan-Meier curves corresponding to disease-free time to event for stage II and III patients diagnosed following December 2003. The results are stratified based on neoadjuvant CRT status, creating two separate curves. Both curves intersect, suggesting that there is no significant difference between patients receiving neoadjuvant CRT and those receiving treatment without neoadjuvant therapy.



Log-rank (Mantel-Cox) = 0.143; df = 1; p = 0.705

Figure 18: Kaplan-Meier curves of disease-free time to event for patients with stage II and III rectal cancer diagnosed post-December 2003

4.8.4 Univariate predictors of outcome

Subsequently, a univariate analysis of overall survival was performed for patients with stage II and III rectal cancer. As depicted in table 36, age at diagnosis was shown to be associated with overall survival. For every additional year of age, the relative risk of mortality increased by 5.6% (1.022 – 1.092; p = 0.001). Similarly, poorly differentiated

tumor grade was associated with 2.9 fold increase (1.233 – 6.933; p = 0.015) in the relative risk of mortality. In addition, vascular invasion was shown to be associated with 2.3 fold increase in relative risk for this sample (1.030 – 5.177; p = 0.042). In contrast, male sex, adenocarcinoma cell type, AR, complete excision, poorly differentiated grade, stage, lymphatic invasion, and perineural invasion had no significant effect on overall survival for this sample. Neoadjuvant CRT was shown to have no statistically significant effect on overall survival for patients with stage II and III rectal cancer diagnosed following December 2003.

Table 36: Results of univariate analysis of overall survival for patients with stage II & III rectal cancer diagnosed post-December 2003

		n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)		118 (100)	1.056	1.022 - 1.092	0.001
Male sex		85 (72)	0.47	0.230 - 0.959	NS
Adenocarcinoma, NOS		94 (80)	0.967	0.414 - 2.259	NS
Neoadjuvant chemoradiation therapy		46 (39)	0.438	0.188 - 1.018	NS
Anterior resection		84 (71)	0.867	0.407 - 1.844	NS
Tumor completely excised		89 (75)	2.435	0.845 - 7.014	NS
Grade of tumor, poorly differentiated		16 (14)	2.937	1.233 - 6.993	0.015
Vascular invasion		17 (14)	2.309	1.030 - 5.177	0.042
Lymphatic invasion		25 (21)	1.716	0.833 - 3.534	NS
Perineural invasion		20 (17)	2.169	0.992 - 4.742	NS
Stage					
	II	49 (42)	1		
	III	69 (58)	1.432	0.673 - 3.047	NS

Table 37 shows the results of the univariate analysis of local recurrence-free time to event for patients with stage II and III rectal cancer diagnosed after December 2003. As depicted in the table, no association was found between any patient variables included in this analysis and one's risk of developing local recurrence. Of note, neoadjuvant CRT had no significant effect on local recurrence-free time to event for this cohort of patients.

Table 37: Results of univariate analysis of local recurrence-free time to event for patients with stage II & III rectal cancer diagnosed post-December 2003

		n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)		118 (100)	1.043	0.989 - 1.100	NS
Male sex		85 (72)	1.062	0.280 - 4.029	NS
Adenocarcinoma, NOS		94 (80)	0.811	0.215 - 3.062	NS
Neoadjuvant chemoradiation therapy		46 (39)	0.62	0.164 - 2.340	NS
Anterior resection		84 (71)	0.712	0.208 - 2.436	NS
Tumor completely excised		89 (75)	3.524	0.447 - 27.796	NS
Grade of tumor, poorly differentiated		16 (14)	2.484	0.512 - 12.044	NS
Vascular invasion		17 (14)	1.641	0.354 - 7.609	NS
Lymphatic invasion		25 (21)	0.75	0.162 - 3.478	NS
Perineural invasion		20 (17)	1.618	0.428 - 6.118	NS
Stage					
	II	49 (42)	1		
	III	69 (58)	3.329	0.719 - 15.410	NS

Table 38 shows the results of the univariate analysis of disease-free time to event for patients with stage II and III rectal cancer diagnosed post-December 2003. As depicted in the table, the presence of vascular invasion was associated with a 4.8 fold

(2.043 – 11.384; $p < 0.001$) increase in relative risk of developing recurrent disease. Similarly, patients with lymphatic invasion were suggested to be three times more likely (1.308 – 6.688; $p = 0.009$) to suffer recurrent disease. Perineural invasion was associated with a 4.1 fold increase (1.805 – 9.226; $p = 0.001$) in the relative risk of disease recurrence. Patients with stage III disease were 9.3 times more likely (2.169 – 40.294; $p = 0.003$) to suffer recurrence in comparison to patients with stage II disease. In contrast, age at diagnosis, male sex, adenocarcinoma cell type, neoadjuvant CRT, AR, complete resection, and tumor grade had no statistically significant association with disease recurrence among this cohort of patients. Of note, no association was found between neoadjuvant CRT and disease-free time to event.

Table 38: Results of univariate analysis of disease-free time to event for patients with stage II & III rectal cancer diagnosed post-December 2003

		n; (%)	Exp (B)	95% Confidence interval	P-value
Age at diagnosis (per year)		118 (100)	1.001	0.964 - 1.039	NS
Male sex		84 (71)	0.974	0.400 - 2.370	NS
Adenocarcinoma, NOS		94 (80)	0.726	0.286 - 1.842	NS
Neoadjuvant chemoradiation therapy		45 (38)	0.848	0.362 - 1.988	NS
Anterior resection		84 (71)	1.04	0.409 - 2.641	NS
Tumor completely excised		89 (75)	1.118	0.415 - 3.014	NS
Grade of tumor, poorly differentiated		16 (14)	1.919	0.639 - 5.763	NS
Vascular invasion		17 (14)	4.822	2.043 - 11.384	< 0.001
Lymphatic invasion		25 (21)	2.958	1.308 - 6.688	0.009
Perineural invasion		20 (17)	4.08	1.805 - 9.226	0.001
Stage					
	II	48 (41)	1		
	III	69 (58)	9.348	2.169 - 40.294	0.003

4.8.4 Multivariate predictors of outcome

A multivariate analysis of overall survival was performed for patients with stage II and III rectal cancer diagnosed after December 2003 (see table 39). When controlling for all other variables included in the analysis, neoadjuvant CRT was not significantly associated with overall survival. With that said, the magnitude of benefit was a 58.2% reduction in relative risk of mortality.

Table 39: Preliminary results of multivariate analysis of overall survival for patients with stage II & III rectal cancer diagnosed post-December 2003

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age (per year)	.055	.020	7.465	1	.006	1.056	1.016	1.099
Sex, male	-.857	.432	3.929	1	.047	.424	.182	.990
Adenocarcinoma, NOS	.038	.511	.005	1	.941	1.038	.381	2.830
Neoadjuvant CRT	-.871	.540	2.603	1	.107	.418	.145	1.206
Anterior resection	.279	.450	.386	1	.534	1.322	.548	3.191
Complete excision	.169	.627	.072	1	.788	1.184	.346	4.047
Poorly differentiated	1.327	.611	4.715	1	.030	3.771	1.138	12.497
Vascular invasion	1.544	.797	3.752	1	.053	4.682	.982	22.328
Lymphatic invasion	-1.409	.720	3.829	1	.050	.244	.060	1.002
Perineural invasion	.923	.760	1.476	1	.224	2.518	.568	11.168
Stage 3	1.080	.508	4.513	1	.034	2.945	1.087	7.979

Table 40 shows the final results of the multivariate model used to describe overall survival for patients with locally advanced disease diagnosed post-December 2003. Following the removal of non-statistically significant variables in the model, only age at diagnosis, male sex, vascular invasion, and stage were independent predictors of overall survival. Specifically, each additional year of age was associated with a 6.8% increase (1.032 – 1.105; < 0.001) in the relative risk of mortality. Male patients had a 64% reduced risk (0.165 – 0.778; p = 0.009) of mortality in comparison to their female counterparts. In addition, the presence of vascular invasion was associated with a 3.3 fold increase (1.410 – 7.766; p = 0.006) in the relative risk of mortality. In terms of stage of disease, stage III patients were 2.9 times more likely (1.210 – 6.780; p = 0.017) to expire during the 10-year follow up in comparison to patients with stage II disease.

Table 40: Final model of multivariate analysis of overall survival for patients with stage II & III rectal cancer diagnosed post-December 2003

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Age (per year)	.065	.017	14.039	1	.000	1.068	1.032	1.105
Sex, male	-1.026	.395	6.733	1	.009	.358	.165	.778
Vascular invasion	1.197	.435	7.560	1	.006	3.309	1.410	7.766
Stage 3	1.052	.440	5.730	1	.017	2.865	1.210	6.780

Given that no variables were associated with local recurrence-free time to event in the previous univariate analysis of patients with locally advanced disease following

December 2003, one would expect that no multivariate regression model would be able to describe a relationship with local recurrence-free time to event for this cohort of patients. A multivariate analysis was performed and there were no statistically significant predictors of local recurrence-free time to event for patients with stage II and III rectal cancer diagnosed post-December 2003.

Table 41 shows the results of the multivariate analysis performed for patients with stage II and III disease diagnosed post-December 2003. As depicted in the table, only vascular invasion and stage of disease were found to be associated with disease recurrence for this cohort of patients. Specifically, the presence of vascular invasion was associated with a 4.1 fold increase (1.751 – 9.721; p = 0.001) in the relative risk of developing either a local or distant recurrence. Similarly, stage III patients were 9.3 times more likely to suffer recurrent disease in comparison to patients with stage II disease. Of note, neoadjuvant CRT was not found to be associated with disease-free time to event for patients of this cohort.

Table 41: Results of multivariate analysis of disease-free time to event for patients with stage II & III rectal cancer diagnosed post-December 2003

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Vascular invasion	1.417	.437	10.503	1	.001	4.126	1.751	9.721
Stage 3	2.226	.762	8.528	1	.003	9.261	2.079	41.248

Chapter 5: DISCUSSION

Most evidence from the current literature suggests that neoadjuvant CRT improves the local recurrence-free time to event for patients with stage II and III rectal cancer, while offering no significant improvement in patient survival. Still, there is an ongoing need to evaluate the effect of neoadjuvant CRT on patient prognosis. Our objective was to determine if neoadjuvant CRT independently predicts improved patient survival for patients with stage II & III rectal cancer. By evaluating the change in clinical practice from post-operative to neoadjuvant CRT in three separate cohorts of patients, this study provides an interpretation of the prognostic factors that predict disease recurrence and overall survival of patients with locally advanced rectal cancer.

5.1 Predictors of survival and recurrence by patient cohort

Firstly, the prognostic variables pertinent to rectal cancer were examined between the three patient cohorts. The results of the analysis shown in Table 1 suggest that the cohorts differ at baseline significantly, especially with respects to the patients of the NFCCR and the single practice cohorts. Given that a portion of the single practice sample was accrued following 2004, these individuals were much more likely than those of the NFCCR to have received neoadjuvant CRT (27% vs. 6%; $p < 0.001$). Other studies show a similar change in clinical practice supporting neoadjuvant therapy following the publishing of the Sauer et al. paper in 2004. For example, a 2014 trial by Wiegering et.al examined treatment outcomes in rectal cancer between two decades. Their results

suggested that the usage of neoadjuvant CRT had increased from 5.3% throughout 1993-2001 to 35.3% during 2002 -2010 ($p < 0.001$). Similarly, Law et al. examined treatment outcomes in rectal cancer between two decades using the periods 1993-2001 and 2002-2011. With respects to all stages of the disease, the rates of neoadjuvant radiation without chemotherapy had increased from 4.4% during 1993-2001 to 17.4% throughout 2002 – 2011 ($p < 0.001$).

In addition, the single practice had a higher rate of AR surgery in comparison to both that of the NFCCR and the OFCCR (68% vs. 54% vs. 47%, respectively; $p < 0.001$). AR surgery is often performed for tumors located within the proximal one-third of the rectum and this level of tumor tends to have a better prognosis in terms of lower recurrence and mortality rates. With that said, the surgeon of the single practice completed fellowship training in colorectal surgery. The higher rate of AR in the single practice of this study reflects the surgeon's experience and comfort performing low lying ARs for tumors past the proximal one-third of the rectum, thus avoiding permanent colostomy for patients with more challenging procedures. In addition, the single practice had a higher rate of well-differentiated cancers than both the NFCCR and the OFCCR (16% vs 10% vs 10%, respectively; $p = 0.01$). The main surgeries performed in this study comprise AR and APR. With that said, a subset of patients received a local excision, which is associated with a higher rate of incomplete margins and worse prognosis. Of note, there were 0, 18, and 3 local excisions in the NFCCR, OFCCR, and single practice, respectively. These cases were included in the analysis and we acknowledge this as a limitation to our study design.

In addition, there was a baseline difference between the numbers of rectal adenocarcinomas between the three cohorts, with the patients of the single practice having a significantly lower rate of adenocarcinomas (81% vs. 89% vs. 87%, single practice vs. NFCCR & OFCCR, respectively). As mentioned, the other options of cell type included in this study were tumors of either mucinous or signet ring cell origin. Each of these cell types are associated with a significantly worse prognosis than non-specified adenocarcinoma and as a result, our study group decided to focus solely on the non-specified adenocarcinoma cell type vs. subtype adenocarcinoma. An analysis of the mucinous cell type was performed, suggesting no statistically significant difference in the proportion of this poor prognostic indicator between cohorts (10.6% vs. 8.7% vs. 14.7%; p = NS).

The single practice actually had a lower proportion of complete tumor excision in comparison to both the NFCCR and the OFCCR (85% vs. 90% vs. 93%, respectively; p = 0.002). There are many predictors that could potentially account for this result, including tumor stage (T4 vs. T2-T3 tumor), neoadjuvant CRT, poor differentiation, Type of surgery (AR vs. APR), cohort, previous local excision, and mucinous cell type. A multivariate model of complete excision was proposed for this project, but ultimately our group decided against performing this analysis given that the number of cases with incomplete excision was so small. With a larger sample of patients, we suspect that the discrepancy of incomplete excision between cohorts would become statistically non-significant. Lastly, the NFCCR had a statistically higher proportion of vascular, lymphatic, and perineural invasion.

In terms of overall survival, no statistically significant difference was found between the three cohorts. With that said, the OFCCR experienced improvements in both disease-free time to event and local recurrence-free time to event. This could partly be explained by the methodology employed by OFCCR, as this cohort did not enroll proxy consent when ascertaining their sample. As a result, the patients of the OFCCR likely include a larger proportion of individuals who had favorable prognostic factors in comparison to other cohorts.

In terms of univariate predictors of survival for all patients included in the study, table 5 shows that age, male sex, AR, complete excision, poorly differentiated grade, vascular invasion, lymphatic invasion, perineural invasion, stage, and the OFCCR cohort were all significant predictors of mortality. This is interesting given the favorable prognostic baseline of the OFCCR cohort. When controlling for all other factors included in the analysis, the OFCCR cohort, as well as male sex and lymphatic invasion were no longer significantly associated with worsened survival. Neoadjuvant CRT had no significant effect on overall survival for patients in both the univariate and multivariate models during this phase of the experiment. With that said, this portion of our analysis comprised the total sample of patients with disease of all stages, whereas neoadjuvant CRT is a therapy specific to stage II and III rectal cancer. In contrast, the 2016 paper by Law et al. also performed a multivariate analysis including patients with all stages of rectal cancer. Their multivariate analysis showed neoadjuvant radiation without chemotherapy to improve overall survival (exp (B) =0.688; p = 0.011) for patients of all stages when controlling for all other variables in their model.

With regards to locally recurrent disease for all stages, table 6 summarizes the univariate predictors of local recurrence, including adenocarcinoma cell type, complete tumor excision, poorly differentiated grade, vascular invasion, lymphatic invasion, perineural invasion, stage, and the OFCCR cohort. When controlled for all factors included in the analysis, the presence of vascular, lymphatic and perineural invasion was no longer significantly associated with locally recurrent disease. Again, neoadjuvant CRT was not a significant independent predictor of local recurrence in both univariate and multivariate analyses for patients of all stages. Interestingly, the OFCCR cohort was a significant independent predictor of local recurrence-free time to event, but not overall survival or disease-free time to event. The improved prognosis of this cohort can be partly explained by the absence of proxy consent. The multivariate analysis suggests patients of the OFCCR to have a 69% reduction in relative risk of developing locally recurrent disease, yet this had a limited effect on the overall survival of this cohort when considering all stages.

In terms of disease-free time to event, the univariate analysis describes the predictors of recurrence for all stages of disease across three different cohorts of patients. Male sex, AR, complete resection, poorly differentiated grade, vascular invasion, lymphatic invasion, perineural invasion, stage, and the OFCCR cohort were all significant predictors of disease recurrence. However, when each variable was tested in the multivariate model, only male sex, stage, and perineural invasion remained as significant independent predictors of disease recurrence. Again, neoadjuvant CRT had no significant effect on disease-free time to event for this sample. Although the current body of evidence suggests neoadjuvant CRT to improve the rates of both distant and local

recurrence, this was not shown for patients of all stages in this phase of our analysis. Furthermore no mortality benefit was demonstrated when considering this broad sample.

5.2 Predictors of survival and recurrence by stage of disease

A sub-group analysis for patients with stage I rectal cancer was performed, comparing the rates of overall survival between the three cohorts. As expected, table 14 shows a relatively low mortality rate for these patients with early staged disease. Median survival estimates could be calculated for only the OFCCR and single practice, which were 115.0 and 167.5 months, respectively. The overall survival at 10 years for patients with stage I disease in the NFCCR, OFCCR, and single practice was 79.9%, 40.1%, 72.2%, respectively. The Memorial Sloan Kettering cancer group reported a 10-year disease free time to event rate of 83% for patients with T1 rectal cancer, which is similar to our results for early-staged rectal cancers. The 2016 Law et al. paper found that at 5 years of follow up, the cancer-specific survival for stage I patients was 92.0% from 1993 - 2001 and 92.9% from 2002 – 2011. These estimates are similar to the results of our study, as the 4-year overall survival rate for the NFCCR, OFCCR, and single practice were 91.7%, 95.1%, and 89.9%. Although these estimates are neither cancer-specific nor measure the same time of follow up as the study by Law et al, the estimates between studies loosely reflect each other. Our study found no significant difference in the overall survival for patients diagnosed with stage I rectal cancer between cohorts.

In addition, the rate of local recurrence for stage I disease was compared across cohorts. The proportion of patients alive without local recurrence at 10 years of follow-up

was 81.9%, 98.9%, and 96.3%, respectively. Although median survival estimates could not be calculated, patients of the NFCCR experienced a significantly higher rate of local recurrence (Chi = 12.648; p value = 0.002). The NFCCR had 6 events of local recurrence compared to 1 event and 2 events in the OFCCR and single practice, respectively. This may be due to the fact that stage I rectal cancers are usually managed by local excision with good recurrence outcome. Alternatively, error could have occurred in data collection given the retrospective design of our study. With respects to the study by Law et al., local recurrence free time to event for patients with stage I disease at 5 years of follow up was 92.6% from 1993-2001 and 96.6% from 2002-2011, which reflects the results of our study at 4 years of follow up (86.4%, 98.9%, and 96.3%; NFCCR, OFCCR, single practice, respectively). Similarly, a study by Kajiwara in 2010, which examined the local recurrence rates of stage I rectal cancers, demonstrated a rate of 5 – 26% in cases treated with local excision and adjuvant therapy (Kajiwara et al.; 2010).

The rate of disease-free time to event for patients with stage I disease for our study was calculated for each cohort. At 10 years of follow up, the percentage of stage I patients without recurrence were 75.5%, 88.1%, and 77.7% for the NFCCR, the OFCCR, and single practice, respectively. The Memorial Sloan Kettering cancer group reported a 10-year recurrence rate of 83% for patients with T1 rectal cancer, which is similar to our results for early-staged rectal cancers (Paty, 2002).

Subsequently, a subgroup analysis was then performed for patients with stage IV rectal cancer. Table 17 compares the respective overall survival rates for patients of each cohort. Due to the progressive nature of rectal cancer, the survival for patients with stage IV disease would be expected to be the poorest in comparison to earlier-staged rectal

cancer. The median overall survival estimates for patients with stage IV rectal cancer in our analysis were 16.11 months, 28.175 months, and 21.337 months for the NFCCR, the OFCCR, and the single practice, respectively. There was no statistically significant difference in the time to death between each cohort for patients with stage IV cancer. The 2016 paper by Law et al. demonstrates a median survival of 14.2 months from 1993 – 2001 and 20.4 months from 2002 – 2011, indicating a statistically significant improvement among stage IV patients in the latter decade (Law, 2016). At four years of follow up, the percentage of stage IV patients who were still alive was 17.4%, 25.3%, and 23.4% for the NFCCR, the OFCCR, and the single practice, respectively. The 2014 study by Wiegering et al. reported a 5-year survival rate of nearly 30% (Wiegering, 2014). With respects to disease free time to event for stage IV rectal cancers, median time to event estimates could not be calculated. However, the percentage of patients without an event at 6 years of follow-up was 41.4%, 54.6%, and 49.7% for the NFCCR, OFCCR, and single practice cohorts, respectively. There is limited data in the literature that has calculated disease-free time to event for stage IV patients, likely due to the poor survival and subsequent low rate of further metastasis in this group.

5.3 Predictors of survival and recurrence of patients with stage II & III rectal cancer by cohort

Subsequently, a sub-group analysis was performed for patients with stage II and III rectal cancer, as our primary objective is to evaluate neoadjuvant CRT for patients with locally advanced disease. The baseline clinical and pathological characteristics of

each cohort were similar to table 1 after removing patients with stages I and IV of the disease. Still, the greatest differences were noted between the NFCCR and single practice cohorts. Given that the majority of patients from the single practice were recruited following December 2003, this cohort had a higher rate of patients treated with neoadjuvant CRT (36% vs. 5% vs. 7%; $p > 0.001$). With the exception of complete resection, the single practice cohort had more favorable prognostic indicators for patients with stage II and III rectal cancer. For example, the single practice cohort had an increased rate of AR in comparison to both the NFCCR and the OFCCR cohorts (69% vs. 55% vs. 51%; $p = 0.001$). In addition, the single practice had a significantly lower proportion of moderately differentiated tumors in comparison to the NFCCR and the OFCCR (55% vs. 79% vs. 77%; $p > 0.001$). In comparison to the single practice cohort, the NFCCR had much higher rates of vascular invasion (36% vs. 19%), lymphatic invasion (36% vs. 29%), and perineural invasion (30% vs. 19%). In contrast, the single practice was significantly worse than other cohorts in terms of obtaining complete margins, which has been shown to be one of the most significant predictive factors of recurrent disease. Ultimately, none of these prognostic differences translated to any significant difference in overall survival between the three patient cohorts for stage II and III disease. Patients of the OFCCR cohort experienced significantly improved disease-free and local recurrence-free time to event. However, this may be attributed to the absence of proxy consent when collecting this sample of patients. When analyzed in terms of neoadjuvant CRT status, no differences existed among the three main outcomes between patients receiving neoadjuvant CRT and those managed without this therapy.

The univariate analysis shown that AR surgeries were beneficial for patients with stage II and III disease in terms of overall survival, locally recurrence-free time to event and disease-free time to event. Complete excisions had no effect on the rate of recurrent disease, whether local or distant metastasis, however, it was associated with a survival benefit. Poorly differentiated disease was associated with poor prognosis regarding all three outcomes examined. As expected, vascular invasion was shown to worsen local recurrence, distant recurrence, and overall survival. Lymphatic invasion was a poor prognostic factor for local recurrence-free time to event and disease-free time to event, but this did not worsen patient survival. Perineural invasion was associated with both recurrent disease and mortality. Although, stage III patients were associated with recurrent disease, there was no association with local recurrence specifically. As expected, stage III patients had a greater relative risk for mortality. Although, patients of the OFCCR had improved disease-free, and local recurrence-free time to event, this did not translate to a survival benefit for stage II and III patients.

When controlled for all other factors in the analysis, age, AR, complete excision, poorly differentiated grade, perineural invasion, and stage were all significant independent predictors of overall survival. Each of these prognostic factors had the expected individual effect on overall survival that is documented in the literature. Interestingly, vascular invasion no longer had an effect on overall survival when controlling for other variables in the analysis and this result differs from the current body of literature. In terms of a multivariate model for local recurrence-free time to event, adenocarcinoma cell type, AR, vascular invasion, and the OFCCR cohort were all significant independent predictors of event. When controlling for all prognostic factors

included in the analysis, poorly differentiated grade and lymphatic invasion were no longer significantly associated with local recurrence.

For the multivariate model of disease-free time to event, male sex, AR, complete excision, vascular invasion, perineural invasion, and stage were all significant independent predictors of event. Interestingly, poorly differentiated grade, lymphatic invasion, and the OFCCR cohort were no longer significant predictors of disease recurrence after controlling for all variables in the analysis. With that said, patients of the OFCCR cohort may have been less likely to have a local recurrence, but this result did not affect disease-free time to event or overall survival for patients with stage II and III disease.

5.4 Predictors of survival and recurrence of patients with stage II and III rectal cancer by neoadjuvant therapy

The main portion of the analysis focused on patients with stage II and III rectal cancer who were diagnosed following December 2003, which approximates the time period that neoadjuvant CRT was incorporated in clinical practice. Of the total 63 stage II and III patients of the single practice who were treated with neoadjuvant CRT, 46 were diagnosed post December-2004. In comparison, the 2004 seminal paper by Sauer et al. had 62 patients who received neoadjuvant CRT. From table 32, it is apparent that there were limited clinicopathological differences at baseline between those receiving neoadjuvant CRT and those who did not receive neoadjuvant CRT. Firstly, there were a higher proportion of male patients in the neoadjuvant CRT group in comparison to the

group not receiving neoadjuvant CRT (85% vs. 64%; p = 0.014), which can be attributed to a non-randomized sample. In addition, there were a significantly lower percentage of patients with complete excisions in the group who received neoadjuvant CRT (54% vs. 89%; p > 0.001). This is a counterintuitive result, as the literature suggests that neoadjuvant CRT may reduce the size of the primary tumor before surgery, increasing the probability of achieving complete surgical margins. Another potential explanation includes CRT perhaps being given selectively to patients with clinically larger tumors, which had lower probability for complete excision. Lastly, the rate of lymphatic invasion was much higher in the group that did not receive neoadjuvant CRT (29% vs. 9%; p = 0.012). Again, one would hypothesize that neoadjuvant CRT would be preferentially offered to patients with lymphatic invasion, but this result may be due to non-randomized sampling.

In terms of overall survival in our study, there was a statistically significant improvement for the group that received neoadjuvant CRT (p = 0.049). At the 4-year follow up, patients of the neoadjuvant CRT group had a survival of 88.9% compared with the adjuvant CRT group having 49.7% of patients remain. With that said, our study was retrolective in nature, including many different types of chemotherapy agents and radiation regimes without knowing the specific type of chemotherapeutic agent or radiation course. This may somewhat account for the differences in our overall survival estimates, which tend to be higher in the treatment arm and lower in the control arm when compared to other previous positive findings.

Most of the published randomized trials deny any association between neoadjuvant CRT and overall survival for locally advanced rectal cancers. For example,

the German Rectal Cancer Study Group found a 5-year overall survival of 76% in their group receiving neoadjuvant CRT vs. an overall survival rate of 74% in those without neoadjuvant CRT (p=0.8). The study enrolled 823 patients with either stage II or stage III disease and subsequently randomized those individuals to receive 5,040 cGy per week and concurrent 5-fluorouracil. Patients in the neoadjuvant CRT group then received radical surgery with TME six weeks following their CRT. The post-operative group received a similar treatment with the exception of a small boost of radiotherapy. The study was designed to have 80% power in order to detect a 10% difference in the primary end-point, 5-year overall survival. The results of the study prompted a change in clinical management due to local control rather than overall survival, which was statistically similar between groups. However, the authors note that the benefit in recurrence outcomes may have been due to improved compliance, as neoadjuvant radiotherapy was more tolerable to patients than the postoperative regime (92% vs. 54%; $p < 0.001$). A similar effect was observed for chemotherapy (89% vs. 50%; $p < 0.001$).

With that said, a 2009 randomized controlled trial by Roh et al. did show a non-significant trend towards improved overall survival for patients receiving neoadjuvant CRT when compared with postoperative CRT. The investigators demonstrated a 5-year overall survival rate of 74.5% vs. 65.6% in favor of patients receiving neoadjuvant CRT ($p = 0.065$). The Investigators randomized 254 patients with T3 or T4 and/or node positive rectal cancers to receive either neoadjuvant CRT consisting of flurouracil and leucovorin with 45 Gy in 25 fractions with a 5.40 boost in the original margins or the same regime postoperatively no later than four weeks. The neoadjuvant therapy group

received surgery after eight weeks post completion of CRT. The primary end points were disease-free survival and overall survival.

A 2013 retrospective study by Tural et al. compared neoadjuvant CRT with postoperative CRT in patients with stage II and III rectal cancer. Tural et al. found no significant difference between each arm of the intervention, reporting a median overall survival of 43.3 months and 47.6 months for both neoadjuvant and postoperative CRT, respectively. The 5-year overall survival for this study approximated the estimate published in the German Rectal Cancer Study Group paper (71.4% vs. 64.4%; $p = 0.9$). Similar to our study, the data collection was retrospective in design, allowing for error in recording and labeling data. Unlike our recruitment strategy, patients were excluded from the analysis if positive margins occurred during surgery. Furthermore, no attempt was made to control for confounding variables, though the study design was retrospective in nature (Tural, 2013).

A 2014 retrospective cohort study by Wiegering et al., with methodology similar to our experiment, analyzed two time periods comparing overall survival between 1993-2001 and 2002-2010 for patients with locally advanced rectal cancer. The authors reported an improved overall survival rate of 79.8% vs. 50.5% ($p < 0.0001$). This result was attributed to neoadjuvant therapy, but also new chemotherapeutic agents and changes in surgical method between the two time periods. Another retrospective study published in 2016 by Law et al. comparing overall survival over two time periods, 1993-2001 and 2002 -2011. The study reported an improved overall survival rate of 68.1% in the latter period vs. an overall survival rate of 60.2% between 1993-2001 ($p = 0.003$).

In terms of constructing a multivariate model for overall survival in the present study, neoadjuvant CRT was removed from the model for patients with stage II and III rectal cancer diagnosed after 2003, as it did not provide a survival benefit with all other factors controlled. From the Kaplan Meier plot, the magnitude of the relative risk for neoadjuvant CRT suggests benefit (58.2% reduction in mortality), but it failed to achieve statistical significance because of inadequate power due to the small sample size of the study. To elaborate, the landmark randomized controlled trial by Sauer et al. estimated that 680 patients would be required in order to achieve a power of 0.80 and detect a 10% difference in overall survival between groups. Our research included 757 patients and it is known that observational studies require much larger samples than randomized trials. More objectively, the hazard estimates from our results show very wide confidence intervals, reflecting that our study is underpowered. Given that an effect size of 58.2% reduction in mortality was observed for the group receiving neoadjuvant CRT, one may hypothesize that this result could become statistically significant with a much larger sample size.

With respects to the aforementioned retrospective studies, the 2013 Tural paper did not perform a multivariate analysis, limiting the quality of the group's results. The 2014 Wiegering paper reported improved overall survival in the latter decade of rectal cancer management, but the multivariate model did not include neoadjuvant therapy as a significant predictor. Interestingly, the 2016 study by Law et al. found that neoadjuvant radiation therapy significantly improved overall survival independent of the time period 2002- 2011(HR = 0.688; p = 0.011) when included in their multivariate analysis.

In terms of the local recurrence-free time to event in our study, there was no statistical improvement for individuals receiving neadjuvant CRT, which does not match the results observed in the current literature. At 4 years of follow-up, 83.2% of patients treated with neoadjuvant CRT were without local recurrence. In comparison, the 4-year local recurrence-free time to event for patients not receiving neoadjuvant CRT was 86.9% (Log rank (Mantel-Cox) = 0.508; df = 1; p = 0.476). This differs from the findings reported in the literature, as the 2004 Sauer et al paper found neoadjuvant CRT to improve the rate of local recurrence. The authors reported a 5-year cumulative incidence of local recurrence of 13% in the neoadjuvant CRT group vs. 6% in the post-operative group (p=0.006). Similar to the German Rectal Cancer group, the 2013 study by Tural et al. found a significant improvement in local recurrence rates for patient receiving neoadjuvant CRT. The authors found a 5-year local recurrence-free time to event rate of 89.2% compared to 74.8% in the post-operative CRT group (p = 0.04). As mentioned, this study removed patients with positive margins from it's analysis and despite being retrospective in design, the authors made no effort to control for third variables.

With respects to retrospective studies, the 2009 Roh et al. paper reported a cumulative incidence of local recurrence of 10.7% for both neoadjuvant and postoperative CRT groups (p = 0.693. In 2014, Wiegering et al. analyzed two time periods, finding a lower local recurrence-free time to event rate of 5.3% during 2002 - 2010 compared to 14.3% during 1993-2001 (p = 0.029). Lastly, Law et al. reported a significantly lower rate of local recurrence-free time to event for the period of 2002 – 2011 in comparison to 1993 – 2001 (5.9% vs. 11.9%; p = 0.002). Neither of the aforementioned retrospective studies

performed a multivariate model to rule out third variables to local recurrence free time to event.

With respects to disease-free time to event, our study found no significant benefit for neoadjuvant CRT for patients with locally advanced disease diagnosed after 2003 (Log-rank (Mantel-Cox) = 0.143; df = 1; p = 0.705). At 4 years of follow up, the neoadjuvant CRT group had a disease-free time to event rate of 71% whereas the post-operative group had a disease-free time to event rate of 71.8%. This finding is similar to the results of the 2004 Sauer et al. paper resulting in a disease-free time to event rates of 68% for patients randomized to receive neoadjuvant CRT and 65% for patients given post-operative CRT (p = 0.32). Similarly, the 2013 paper by Tural et al. reports no statistical benefit for disease-free time event, with rates of 81.7% in the neoadjuvant CRT group in comparison to 68.5% in the post-operative CRT group (p = 0.1). In contrast, the study by Roh et al. reported an improved disease-free time to event rate of 64.7% for patients receiving neoadjuvant CRT verses 53.4% for post-operative CRT patients (P = 0.011). The 2014 Wiegering study reported an improved disease-free time to event rate of 19% during 1993 – 2001 in comparison to 32% during 2002 – 2010 (p = 0.0035). The 2016 study by Law et al. did not perform a disease-free time to event analysis. As mentioned, these latter two studies did not perform multivariate models for disease-free time to event.

5.5 Conclusions of study and future directions

With respects to our study, a portion of the data were collected from retrospective chart audits. A criticism of this research would be that retrospective methods are prone to error when recording information from patient files. Specifically, there is potential for human error whenever patient information is being read from a chart that may be illegible or documented incorrectly by hospital staff. In addition, this experiment involved three different patient samples with multiple individuals involved in data entry, which can lead to discrepancy in the recording and accuracy of said information. Similarly, any data collector could potentially input an incorrect value when transferring this information collected from the chart into our dataset. Although the same chart abstraction form was incorporated at all sites, incongruent labeling of variables in datasets could lead to error when combining data. A further limitation of the study is the fact that only 1 of 3 data sources includes patients treated during the entire timespan of interest when the research question is to evaluate the changes in treatment over time.

Another notable limitation is that the OFCCR cohort did not incorporate proxy consent when recruiting patients to the study. As a result, post-mortem file abstraction could not be performed. The patient sample that was accrued had a higher proportion of stage I disease in comparison to other cohorts with low rates of lymphovascular and perineural invasion. In addition, the observational study design does not account for general improvements in medical care over time, including surgical advancements related to locally advanced rectal cancer. Ultimately, this makes it difficult to examine differences in survival due to neoadjuvant CRT without the use of a control group. Although our analysis provided regression accounting for stage and invasion status,

patients of the OFCCR cohort may have favorable prognostic factors that were not accounted for in the survival and time to event analyses leading to bias among our results. Ultimately, this bias would not affect those patients diagnosed with locally advanced staged disease, which is the main group of interest.

A major weakness of this study would be the lack of information collected with respects to CRT regime and timing of surgery post therapy in our cohorts. Many other studies ensure that a standardized regime is followed, though these studies are also prospective design. With our analysis, it is difficult to identify how many patients received a certain chemotherapeutic agent and the duration that drug during treatment. In addition, the results suggest that patients who received neoadjuvant CRT were less likely to have complete excisions. As mentioned previously, this result could be due to the possibility of selective use of neoadjuvant CRT in stage II and III patients with worse prognosis and this could have made it more difficult to demonstrate a survival benefit for neoadjuvant CRT. In addition, measures of overall survival incorporate all cause mortality with no adjustment for cancer-specific death. Although overall survival provides an estimation of cancer-specific death for this patient population, the rate of rectal cancer, comorbid disease, and incidental death will underestimate the rate of cancer-specific survival. With that said, overall survival is the outcome used in many studies to address this research question, but some papers do also analyze cancer-specific mortality, somewhat limiting the generalizability of our findings. Furthermore, the results suggest that there is a significant difference between the single practice cohort and the cancer registry cohorts with respects to the both the rate of anterior resection surgeries and complete resections. This may further limit the generalizability of our results to other

studies in the available literature. This patient sample comes from a single person's practice and differences in survival may be due to surgeon-specific variables not accounted for in our analysis. Another issue is related to the data of the surgeon's practice, which would suggest that prior to December 2003, a significant proportion of the patients in the single practice were already receiving neoadjuvant CRT (29% vs. 39%; prior to December 2003 vs. after December 2003). This would certainly make it more difficult to demonstrate significant changes in the rate of neoadjuvant CRT over time. Many other variables exist that were not incorporated in our analysis, such as the rate of surgical complications and adherence to CRT regime, which could act as confounding variables. Lastly, multiple tests were included in this study, which increases the probability of finding a significant result in at least one of the many analyses performed; the probability of type 1 error increases with the number of tests included in the analysis. This is particularly important as the survival curve showing potential benefit for neo-adjuvant CRT in stage II/III disease just reaches statistical significance at $p=0.049$. The higher p-value in the setting of multiple tests could potentially result from an increased probability of type I error and this is a limitation of the findings of this research.

Our research suggests a trend in improved survival for patients with stage II and III rectal cancer who received neoadjuvant CRT. However, this study was not able to achieve a statistically significant result due to a small sample size lacking the appropriate power to make such a conclusion. Studies exist that evaluate CRT directly (neoadjuvant CRT vs. postoperative CRT) in randomized controlled trials and by comparing the decades before and after the implementation of neoadjuvant regimes in cohort designs. While most direct comparisons of CRT suggest that neoadjuvant therapy offers no

survival benefit for stage II and III patients with rectal cancer, there are mixed findings when comparing survival between the decades before and after implementation of neoadjuvant regimes. With that said, there is still a need for further evaluation of clinical practice before and after the implementation of neoadjuvant therapy, especially when considering that our study was able to show a survival result trending towards significance. Future studies should include cohort designs with adequate sample size to detect significant mortality benefit or meta-analyses of existing findings. An attempt should be made to standardize proxy consent status between participating samples and documenting the specific type of chemotherapeutic agents used. The strengths of our study includes a representative sample of patients with rectal cancer enrolled from multiple population-based registries, the standardization and quality assurance involved in our data collection, and the level of comparison involved in describing results across multiple cohorts and time periods. Again, neoadjuvant CRT had no statistically significant effect on mortality related to stage II and III rectal cancer. However, the relative risk of death was 57% lower for patients with locally advanced disease receiving neoadjuvant CRT, suggesting benefit had our study been adequately powered.

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Appendix A: Health Research Ethics Authority Approval

Health Research Ethics Authority

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

September 27, 2013

Mr. Ian Short
C/O Elizabeth Dicks
29 Lunenburg Street
St. John's, NL

Dear Mr. Short

Reference # 13.231

Re: Optimal timing of chemoradiotherapy & total meso-rectal excision for stage II and III rectal cancer patients

Your application received an expedited review by a Sub-Committee of the Health Research Ethics Board and **full approval** was granted effective **September 27, 2013.**

This approval will lapse on **September 26, 2014**. It is your responsibility to ensure that the Ethics Renewal form is forwarded to the HREB office prior to the renewal date. *The information provided in this form must be **current to the time of submission** and submitted to the HREB **not less than 30 nor more than 45 days** of the anniversary of your approval date.* The Ethics Renewal form can be downloaded from the HREB website http://www.hrea.ca.

This is to confirm that the following documents have been reviewed and approved or acknowledged (as indicated):

- Application, approved
- Proposal, approved
- Extraction Form Variables for Deidentified Patients, approved
- Letter to Dr. Green, acknowledged
- Letter from Dr. Green, acknowledged

The Health Research Ethics Board advises THAT IF YOU DO NOT return the completed Ethics Renewal form prior to date of renewal:

- *Your ethics approval will lapse*
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

Lapse in ethics approval may result in interruption or termination of funding

It is **your responsibility to seek the necessary approval from the Regional Health Authority or other organization as appropriate**.

Modifications of the protocol/consent are not permitted without prior approval from the Health Research Ethics Board. Implementing changes in the protocol/consent without HREB approval may result in the approval of your research study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HREB website) and submitted to the HREB for review.
This research ethics board (the HREB) has reviewed and approved the research protocol and documentation as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*; *ICH Guidance E6: Good Clinical Practice* and applicable laws and regulations. The membership of this research ethics board is constituted in compliance with the membership requirements for research ethics boards as defined by *Health Canada Food and Drug Regulations Division 5; Part C*
Notwithstanding the approval of the HREB, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,

HREB meeting date: October 3, 2013

Ontario Familial Colon Cancer Registry Treatment and Outcome Study

CLINICAL DIAGNOSIS AND TREATMENT FORM

OFCCR # _____

OCGN # _____

OCR Group # _____

_____

_____

Name: _____,

_____

LAST FIRST

Sex:

☐	Male
☐	Female
☐	Unknown

Date of Birth:

DD	
MM	
YYYY	

CLINICAL DIAGNOSIS AND TREATMENT - BASELINE

1. Place of Diagnosis:

Name	City or Town	MOH Code

2. Site of Cancer(s):

Cancer	Site Name	4-Digit ICD-9 Code
1.		
2.		
3.		
4.		
5.		

3. Date of initial diagnosis of colorectal cancer (please use histological date i.e. Date of pathology report):

DD	
MM	
YYYY	
□	Unknown

4. Preoperative symptoms (please check all that apply):

□	None, asymptomatic (detected by screening)
□	Bleeding
□	Constipation
□	Diarrhea
□	Pain
□	Weight Loss
□	Other Please Specify: _____
□	Unknown

5. Method of colorectal cancer diagnosis:

□	Colonoscopy
□	Rigid sigmoidoscopy
□	Flexible sigmoidoscopy
□	Sigmoidoscopy NOS
□	Barium enema
□	Chest x-ray
□	Chest CT scan
□	Abdominal/Pelvic CT scan
□	Ultrasound
□	Other Please Specify: _____
□	Unknown

6. Type of definitive surgery for colorectal cancer (SEER coding used) (please attach all pathology and operative reports for this colorectal cancer):

□	None
□	Local tumour destruction, i.e. laser, electrocautery
□	Local surgical excision with specimen i.e. polypectomy, snare
□	Segmental resection, not hemi-colectomy i.e. cecectomy, appendectomy, sigmoidectomy, partial resection of transverse colon and flexures, iliocolectomy, enterocolectomy, partial colectomy, NOS □ Low Anterior
□	Hemi-colectomy, but not total. Right or left, must include a portion of transverse colon
□	Abdominoperineal resection
□	Total or subtotal colectomy, not rectum
□	Colectomy NOS
□	Segmental colectomy + other organs (*Please specify below)
□	Hemi-colectomy + other organs (*Please specify below)
□	Total or subtotal colectomy or + other organs (*Please specify below)
□	Abdominoperineal resection + other organs (*Please specify below)
□	Other Please Specify: _____
□	Unknown

*If Other Organs were removed:

☐	Spleen
☐	Gallbladder
☐	Appendix (not a part of colon resection)
☐	Stomach
☐	Pancreas
☐	Small intestine
☐	Liver
☐	Abdominal Wall, Retroperitoneum
☐	Adrenal
☐	Kidney
☐	Bladder
☐	Urethra
☐	Ovary
☐	Uterus
☐	Vagina
☐	Prostate
☐	Other Please Specify: _____
☐	Unknown

7. If no surgery was performed, reason:

☐	Patient Refusal
☐	Antecedent Death
☐	Medical Contraindication
☐	Other Please Specify: _____
☐	Unknown

8. Summary of disease from pathology report only:

pT	
pN	
pM	
☐	Unknown

9. If pN1 or greater (*if pN0 pls. go to #14)*:

Number of Nodes Reported	
Number of Nodes Positive	

10. Pathological Stage of disease (from all information available):

T	
N	
M	
□	Unknown

11. Stage of disease at initial diagnosis (from all information available)

□	Stage 0
□	Stage 1
□	Stage 2
□	Stage 3
□	Stage 4
□	Unknown

12. Other Pathology Identified:

Yes	**Type:**	**No**	**Unknown**
□	□ Crohn's Disease □ Ulcerative colitis □ Diverticulosis/it is □ Perforation □ Other Please Specify: _____	□	□

13. Preoperative CEA (carcinoembryonic antigen):

□	Yes _____ ug/L
□	No
□	Unknown

14. Date of Blood Test for Preoperative CEA:

DD	
MM	
YYYY	
☐	Unknown

15. Date of surgery:

DD	
MM	
YYYY	
☐	Unknown

16. Primary surgery hospital:

Name	City or Town	MOH Code

17. Operating Surgeon:

18. Operative findings, local (residual tumour) (please obtain information from the operative report and/or the discharge summary)

☐	Tumour *not entirely* resected
☐	Tumour *entirely* resected
☐	Unknown

19. Operative findings, Distant (pls. obtain info. from the operative report &/or the discharge summary):

No Metastatic Disease	Metastatic Disease Found	Type of Metastatic Disease Found:	Unknown
□	□	□ Ascites □ Mesenteric nodes, other than in mesentery of planned resection □ Liver □ Lung □ Omentum □ Abdominal wall □ Ovaries □ Bone □ Peritoneum □ Mesentery □ Other Please Specify: _____	□

20. Margins:

Negative	Positive	Unknown
□	□ Proximal □ Distal □ Radial □ Other Please Specify: _____	□

(CONCURRENT) PRIMARY DIAGNOSIS #_____ Please see Ques.#2 to identify Site #.
(Please complete a separate form for each primary diagnosis).

21. Grade of Primary:

Well Differentiated	Moderately Differentiated	Poorly Differentiated	Undifferentiated	Unknown
☐	☐	☐	☐	☐

22. Cell Type:

	Adenoca.
☐	NOS
☐	Mucinous
☐	Signet ring cell
☐	Other Please specify: _____
☐	Unknown

23. Vascular Invasion:

☐	Yes
☐	No
☐	Unknown

24. Lymphatic Invasion:

☐	Yes
☐	No
☐	Unknown

25. Perineural Invasion:

☐	Yes
☐	No
☐	Unknown

26. Patient Enrolled in a clinical trial:

□	Yes Please Specify: _____
□	No
□	Unknown

27. Oncologist(s): □ Not assessed

1.	3.
2.	4.

28. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #32)	Unknown
□	□ Adjuvant □ Palliative	□	□

Height	**Weight**	**B.S.A.**
_____.___ cm □ Unknown	_____.___ kg □ Unknown	___.___ m2 □ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR BASELINE DIAGNOSIS

First Course Only. **Flow sheet attached**

Y/N: _____

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
___	_____	_____	_____	_____	_____	□ Progression
___	_____	_____	_____	_____	_____	□ Stable
___	_____	_____	_____	_____	_____	□ Minor
___	_____	_____	_____	_____	_____	□ Partial
___	_____	_____	_____	_____	_____	□ Complete
___	_____	_____	_____	_____	_____	□ Unknown
___	___				_____	
					_____	
					_____	

						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

						□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown
						□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown
						□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown

32. Radiation given (*please attach all flow sheets, where available)*:

Yes	Type	No	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

CLINICAL FOLLOW-UP SINCE BASELINE DIAGNOSIS

33. **New** cancer event in the four years following the initial diagnosis:

Yes	Check off as many that apply and complete the corresponding section.	None	Unknown
☐	☐ Locoregional Recurrence ☐ Distant Recurrence ☐ Other Non-Colorectal Primary ☐ Colorectal Primary ☐ Death	☐	☐

34. Patient Enrolled in a clinical trial since baseline:

☐	Yes Please Specify: _____
☐	No
☐	Unknown

FIRST LOCOREGIONAL RECURRENCE

☐ None (go to #43)

If applicable, please attach copies of documentation (i.e. radiology reports, clinic notes, pathology reports, operative reports, etc.) with the date of first detection of site(s) of first locoregional recurrence(s).

35. Sites of involvement at time of first locoregional recurrence *(please check off all that apply):*

	Site	First Diagnosed Day	First Diagnosed Month	First Diagnosed Year
☐	Anastomosis			
☐	Mesentery			
☐	Abdominal Wall (not incisional)			
☐	Incisional			
☐	Pelvis			
☐	Other Please specify: _____ _____ _____			
☐	Unknown			

36. Surgery for locoregional recurrence:

☐	Yes Please specify: _____ ___
☐	No
☐	Unknown

37. Treatment for locoregional recurrence:

☐	Yes
☐	No
☐	Unknown

38. Oncologist(s): ☐ Not assessed

1.	3.
2.	4.

39. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #A6)	Unknown
□	□ Adjuvant □ Palliative	□	□

Height	**Weight**	**B.S.A.**
_____.___ cm □ Unknown	_____.___ kg □ Unknown	___.___ m2 □ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR FIRST LOCOREGIONAL RECURRENCE

First Course. **Flow sheet attached**

Y/N: _____

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
___ __	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____	□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown
___ __	_____ _____ _____ _____ _____ ___	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____	□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown

						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

					_____ _____ _____ _____	
_____	_____ _____ _____ _____ _____ ___	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
_____	_____ _____ _____ _____ _____ ___	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

40. Radiation given (*please attach all flow sheets, where available)*:

Yes	Type	No	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

41. Other treatment given (*please attach all documents)*:

☐	Yes
☐	No
☐	Unknown

42. Other Locoregional recurrence sites after the first site was identified *(please check off all that apply):*

	Site	Diagnosed Day	Diagnosed Month	Diagnosed Year
☐	Anastomosis			
☐	Mesentery			
☐	Abdominal Wall (not incisional)			
☐	Incisional			
☐	Pelvis			
☐	Other Please specify: _____ _____ _____			
☐	Unknown			

FIRST DISTANT RECURRENCE

☐ None (go to #51)

If applicable, please attach copies of documentation (i.e. radiology reports, clinic notes, pathology reports, operative reports, etc.) with the date of first detection of site(s) of first distant recurrence(s).

43. Sites of involvement at time of first distant recurrence *(please check off all that apply):*

	Site	First Diagnosed Day	First Diagnosed Month	First Diagnosed Year
☐	Liver			
☐	Lung			
☐	Bone			
☐	Ascites			
☐	Non-mesenteric lymph nodes (except supraclavicular) Please specify: _____ _____ _____			
☐	Supraclavicular nodes			
☐	Brain			
☐	Skin, except incision Please specify: _____			
☐	Adrenal gland			
☐	Other Please specify: _____			

44. Surgery for distant recurrence:

☐	Yes Please specify: _____ ___
☐	No
☐	Unknown

45. Treatment for distant recurrence:

☐	Yes
☐	No
☐	Unknown

46. Oncologist(s): ☐ Not assessed

1.	3.
2.	4.

47. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #B6)	Unknown
□	□ Adjuvant □ Palliative	□	□

Height	**Weight**	**B.S.A.**
_____.___ cm □ Unknown	_____.___ kg □ Unknown	___.___ m2 □ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR FIRST DISTANT RECURRENCE

First Course. **Flow sheet attached**

Y/N: _____

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
_____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____	□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown
_____	_____ _____ _____ _____ _____ ___	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____	□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown
	_____ _____	_____ _____	_____ _____	_____ _____	_____ _____	□ Progression □ Stable

______ _	____________________ ____________________ ____________________ ____	__________ __________ __________ _______	______ ______ ______ ______	__________ __________ __________ _______	_______ _______ _______ _______ _______ _______ ______	☐ Minor ☐ Partial ☐ Complete ☐ Unknown
______ _	____________________ ____________________ ____________________ ____________________ ____________________ ____	__________ __________ __________ __________ __________ _______	______ ______ ______ ______ ______ ______	__________ __________ __________ __________ __________ _______	_______ _______ _______ _______ _______ _______ _______ _______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
______ _	____________________ ____________________ ____________________ ____________________ ____________________ ____	__________ __________ __________ __________ __________ _______	______ ______ ______ ______ ______ ______	__________ __________ __________ __________ __________ _______	_______ _______ _______ _______ _______ _______ _______ _______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
______ _	____________________ ____________________ ____________________ ____________________ ____________________ ____	__________ __________ __________ __________ __________ _______	______ ______ ______ ______ ______ ______	__________ __________ __________ __________ __________ _______	_______ _______ _______ _______ _______ _______ _______ _______ ______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
______ _	____________________ ____________________ ____________________ ____________________ ____________________ ____	__________ __________ __________ __________ __________ _______	______ ______ ______ ______ ______ ______	__________ __________ __________ __________ __________ _______	_______ _______ _______ _______ _______ _______ _______ _______	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

_____	_____ _____ _____ _____ _____ ___	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____	□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown

48. Radiation given (*please attach all flow sheets, where available)*:

Yes	Type	No	Unknown
□	□ Adjuvant □ Palliative	□	□

49. Other treatment given (*please attach all documents)*:

□	Yes
□	No
□	Unknown

50. Other Distant recurrence sites after the first site was identified *(please check off all that apply):*

	Site	Diagnosed Day	Diagnosed Month	Diagnosed Year
☐	Liver			
☐	Lung			
☐	Bone			
☐	Ascites			
☐	Non-mesenteric lymph nodes (except supraclavicular) Please specify: _____ _____ _____			
☐	Supraclavicular nodes			
☐	Brain			
☐	Skin, except incision Please specify: _____			
☐	Adrenal gland			
☐	Other Please specify: _____			

OTHER NON-COLORECTAL PRIMARY(S)

☐ None (go to #55)

51. Hospital of Diagnosis:

Name	City or Town	MOH Code

52. Sites of new Non-Colorectal Primary Cancer(s) since the initial diagnosis of Colorectal cancer:

Cancer	Site	4-Digit ICD-9 Code
1.		
2.		
3.		
4.		
5.		

53. Date(s) of diagnosis of new Non-Colorectal Primary Cancer(s) (please use histological date):

Cancer	Day	Month	Year
1.			
2.			
3.			
4.			
5.			

54. Stage(s) of new Non-Colorectal Primary Cancer(s):

Cancer	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Unknown
1.	□	□	□	□	□	□
2.	□	□	□	□	□	□
3.	□	□	□	□	□	□
4.	□	□	□	□	□	□
5.	□	□	□	□	□	□

NEW COLORECTAL PRIMARY(S)

□ None (go to #80)

55. Site of Cancer(s):

Cancer	Site Name	4-Digit ICD-9 Code	Diag. Day	Diag. Month	Diag. Year	Unknown
1.						□
2.						□
3.						□
4.						□
5.						□

56. Preoperative symptoms (please check all that apply):

□	None, asymptomatic (detected by screening)
□	Bleeding
□	Constipation
□	Diarrhea
□	Pain
□	Weight Loss
□	Other Please Specify: _____
□	Unknown

57. Method of colorectal cancer diagnosis (check all that apply):

□	Colonoscopy
□	Rigid sigmoidoscopy
□	Flexible sigmoidoscopy
□	Sigmoidoscopy NOS
□	Barium enema
□	Chest x-ray
□	Chest CT scan
□	Abdominal CT scan
□	Ultrasound
□	Other Please Specify: _____
□	Unknown

58. Type of definitive surgery for colorectal cancer (SEER coding used) (please attach all pathology and operative reports for this colorectal cancer):

□	None (please go to #18)
□	Local tumour destruction, i.e. laser, electrocautery
□	Local surgical excision with specimen i.e. polypectomy, snare
□	Segmental resection, not hemi-colectomy i.e. cecectomy, appendectomy, sigmoidectomy, partial resection of transverse colon and flexures, iliocolectomy, enterocolectomy, partial colectomy, NOS □ Low Anterior
□	Hemi-colectomy, but not total. Right or left, must include a portion of transverse colon
□	Abdominoperineal resection
□	Total or subtotal colectomy, not rectum
□	Colectomy NOS
□	Segmental colectomy + other organs (*Please specify below)
□	Hemi-colectomy + other organs (*Please specify below)

☐	Total or subtotal colectomy or + other organs (*Please specify below)
☐	Abdominoperineal resection + other organs (*Please specify below)
☐	Other Please Specify: _____
☐	Unknown

*If Other Organs were removed:

☐	Spleen
☐	Gallbladder
☐	Appendix (not a part of colon resection)
☐	Stomach
☐	Pancreas
☐	Small intestine
☐	Liver
☐	Abdominal wall, Retroperitoneum
☐	Adrenal
☐	Kidney
☐	Bladder
☐	Urethra
☐	Ovary
☐	Uterus
☐	Vagina
☐	Prostate
☐	Other Please Specify: _____
☐	Unknown

59. If no surgery was performed, reason:

☐	Patient Refusal
☐	Antecedent Death
☐	Medical Contraindication
☐	Other Please Specify: _____
☐	Unknown

60. Summary of disease from pathology report only:

pT	
pN	

pM	
☐	Unknown

61. If pN1 or greater (*if pN0 pls. go to #D8)*:

Number of Nodes Reported	
Number of Nodes Positive	

62. Pathological Stage of disease (from all information available):

T	
N	
M	
☐	Unknown

63. Stage of disease at initial diagnosis (from all information available)

☐	Stage 0
☐	Stage 1
☐	Stage 2
☐	Stage 3
☐	Stage 4
☐	Unknown

64. Other Pathology Identified:

Yes	**Type:**	**No**	**Unknown**
☐	☐ Crohn's Disease ☐ Ulcerative colitis ☐ Diverticulosis/it is ☐ Perforation ☐ Other Please Specify: _____	☐	☐

65. Preoperative CEA (carcinoembryonic antigen):

☐	Yes _____ ug/L
☐	No
☐	Unknown

66. Date of Blood Test for Preoperative CEA:

DD	
MM	
YYYY	
□	Unknown

67. Date of surgery:

DD	
MM	
YYYY	
□	Unknown

68. Primary surgery hospital:

Name	City or Town	MOH Code

69. Operating Surgeon:

70. Operative findings, local (residual tumour) (please obtain information from the operative report and/or the discharge summary)

□	Tumour *not entirely* resected
□	Tumour *entirely* resected
□	Unknown

71. Operative findings, Distant (pls. obtain info. from the operative report &/or the discharge summary):

No Metastatic Disease	Metastatic Disease Found	Type of Metastatic Disease Found:	Unknown
□	□	□ Ascites □ Mesenteric nodes, other than in mesentery of planned resection □ Liver □ Lung □ Omentum □ Abdominal wall □ Ovaries □ Bone □ Peritoneum □ Mesentery □ Other Please Specify: _____	□

72. Margins:

Negative	Positive	Unknown
□	□ Proximal □ Distal □ Radial □ Other Please Specify: _____	□

(CONCURRENT) PRIMARY DIAGNOSIS #_____ Please see Ques.#5 to identify Site #.
(Please complete a separate form for each primary diagnosis).

73. Grade of Primary:

Well Differentiated	Moderately Differentiated	Poorly Differentiated	Undifferentiated	Unknown
☐	☐	☐	☐	☐

74. Cell Type:

	Adenoca.
☐	NOS
☐	Mucinous
☐	Signet ring cell
☐	Other Please specify: _____
☐	Unknown

75. Vascular Invasion:

☐	Yes
☐	No
☐	Unknown

76. Lymphatic Invasion:

☐	Yes
☐	No
☐	Unknown

77. Perineural Invasion:

☐	Yes
☐	No
☐	Unknown

78. Oncologist(s): □ Not assessed

1.	3.
2.	4.

79. Chemotherapy given (If yes, pls. complete Treatment table below & attach all flow sheets):

Yes	Type	No (Pls. go to #D28)	Unknown
□	□ Adjuvant □ Palliative	□	□

Height	**Weight**	**B.S.A.**
_____.___ cm □ Unknown	_____.___ kg □ Unknown	___.___ m2 □ Unknown

CHEMOTHERAPY TREATMENT (For cyclic chemo., pls. report each cycle *separately* e.g. 1, 2, 3, 4)

FOR NEW CRC PRIMARY

First Course **Flow sheet attached**

Y/N: _____

Cycle #	Name	Drug Dosage	IV/PO	Days Given	Date Given	Palliative Therapy Response
_____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____	□ Progression □ Stable □ Minor □ Partial □ Complete □ Unknown
_____	_____ _____ _____ _____ _____	_____ _____ _____ _____ _____	_____ _____ _____ _____ _____	_____ _____ _____ _____ _____	_____ _____ _____ _____ _____	□ Progression □ Stable □ Minor □ Partial □ Complete

						☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
						☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

______ _	________________ ________________ ________________ ________________ ________________ ____	_________ _________ _________ _________ _________ ______	_____ _____ _____ _____ _____ _____	_________ _________ _________ _________ _________ ______	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
______ _	________________ ________________ ________________ ________________ ________________ ____	_________ _________ _________ _________ _________ ______	_____ _____ _____ _____ _____ _____	_________ _________ _________ _________ _________ ______	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown
______ _	________________ ________________ ________________ ________________ ________________ ____	_________ _________ _________ _________ _________ ______	_____ _____ _____ _____ _____ _____	_________ _________ _________ _________ _________ ______	_____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____	☐ Progression ☐ Stable ☐ Minor ☐ Partial ☐ Complete ☐ Unknown

79. Radiation given (*please attach all flow sheets, where available)*:

Yes	Type	No	Unknown
☐	☐ Adjuvant ☐ Palliative	☐	☐

DEATH

80. Date of Death:

DD	
MM	
YYYY	

81. Cause of Death *(please attach copy of death certificate if available):*

☐	Colorectal cancer
☐	Other, No colorectal present Please specify: _____
☐	Other, colorectal present Please specify: _____
☐	Unknown

82. Autopsy performed *(please attach copy of report if available)*:

☐	Yes
☐	No
☐	Unknown

83. Location of Death:

☐	Hospital Please specify: _____
☐	Home
☐	Hospice Please specify: _____
☐	Other Please specify: _____
☐	Unknown

DATE OF FINAL CHART NOTE: _____

PATIENT HAS BEEN REFERRED TO THE CARE OF: DR. _____

ADDITIONAL FOLLOW-UP REQUIRED (Y/N): _____

Date form Completed: _____ _____ _____ (dd/mmm/yyyy)

Abstractor's Initials: _____ _____

ADDITIONAL NOTES: