THE ASSOCIATION BETWEEN PREHABILITATION AND ONCOLOGIC OUTCOMES IN PATIENTS UNDERGOING CURATIVE-INTENT SURGERY FOR COLORECTAL CANCER

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ABSTRACT (ENGLISH)

Introduction: Preoperative multimodal exercise and nutritional programs (prehabilitation) decrease postoperative morbidity and improve functional capacity and recovery following colorectal surgery. The effect of prehabilitation on cancer outcomes is however unknown. The objectives of this thesis were to investigate the effect of prehabilitation on survival after colorectal cancer surgery and to determine the effect of longer time from diagnosis to surgical treatment on survival after colorectal cancer surgery.

Methods: First, a pooled analysis of three previous prehabilitation trials (2 RCTs, 1 cohort) in patients undergoing elective, biopsy-proven, primary non-metastatic colorectal cancer surgery from 2009-2014 within an enhanced recovery program was performed. Second, a retrospective cohort of all adult patients undergoing elective resection of primary non-metastatic colorectal adenocarcinoma from 2009-2014 were reviewed. Treatment delays were defined as time from tissue diagnosis to definitive surgery, categorized as <4, 4 to <8 and ≥8weeks. In both studies, the primary outcomes were 5-year disease-free(DFS) and overall survival(OS). DFS and OS were analyzed using Kaplan-Meier curves and multiple Cox regression.

Results: A total of 202 patients were included in the pooled study(+prehab 104, -prehab 98). Median prehabilitation duration was 29 days(IQR20-40). Patient and tumor characteristics were well-balanced (33% stage III). Postoperative complications and time to adjuvant chemotherapy were similar. Mean duration of follow-up was 60.3 months (SD26.2). DFS was similar for the combined group of stage I-III patients (p=0.244). For stage III patients, prehabilitation was associated with improved DFS (73.4% vs. 50.9%, p=0.044). There were no differences in OS

(p=0.226). Prehabilitation independently predicted improved DFS (HR 0.45, 95%CI: 0.21-0.93), adjusting for stage and other confounders. Prehabilitation did not independently predict OS. In the second study, 408 patients were included (83.2%colon;15.8%rectal) with a mean follow-up of 58.4 months(SD29.9). Fourteen percent(14.0%) of patients underwent resection <4weeks, 40.0% 4 to <8weeks and 46.1% ≥8weeks. More rectal cancer patients had treatment delay ≥8weeks compared to colonic tumors(69.8% vs. 41.4%,p<0.001). Cumulative 5-year DFS and OS were similar between groups(p=0.558;p=0.572). After adjusting for confounders, surgical delays were not independently associated with DFS and OS.

Conclusion: In this thesis, prehabilitation is associated with improved 5-year DFS in stage III colorectal cancer and independently predicted improved 5-year DFS in all stages. Treatment delays >4 weeks were not associated with worse oncologic outcomes. Delaying surgery to optimize patients can safely be considered without compromising survival. These promising findings should be confirmed in larger studies.

RÉSUMÉ (FRENCH ABSTRACT)

Introduction: Les programmes multimodaux préopératoires d'exercice et de nutrition (préadaptation) diminuent l'incidence de morbidité postopératoire et améliorent la capacité fonctionnelle ainsi que la récupération suite à une chirurgie colorectale. L'effet de la préadaptation sur les résultats oncologiques est toutefois inconnue. Les objectifs de ce mémoire étaient d'investiguer l'effet de la préadaptation sur le taux de survie après un chirurgie pour le cancer du côlon et rectum et de déterminer l'effet de délais prolongés entre le diagnostic et la résection sur ce même taux de survie après un chirurgie pour le cancer du côlon et rectum.

Méthode: En premier lieu, une analyse combinée de trois études publiées (2 études randomisée et 1 cohorte) incluant les patients subissant une résection colorectale élective pour un cancer du côlon ou rectum non-métastatique entre 2009 et 2014 a été conduite. En deuxième lieu, tous les patients adultes ayant subi un résection colorectale pour un cancer non-métastatique entre 2009 et 2014 a été revue rétrospectivement. Les délais de traitement correspondent au temps entre le diagnostic et la date de résection et ont été catégorisés comme suit: <4, 4 to <8 and ≥8 semaines. Dans ces deux études, les résultats primaires étaient la survie en temps rémission (TSR) ainsi que la survie globale (TSG) à 5 ans. Ces deux taux de survie ont été analysés utilisant les courbes de Kaplan-Meier et un régression multiple de Cox.

Résultats: Un total de 202 patients ont été inclus dans l'étude combinée(+préad 104, -préad 98). La durée de préadaptation médiane était de 29 jours (IIQ20-40). Les caractéristiques

démographiques et tumorales étaient bien balancées (33% stade 3). Les complications postopératoires et l'intervalle entre la chirurgie et l'initiation de la chimiothérapie adjuvante étaient similaires. La durée moyenne de suivi était 60.3 mois (DS26.2). Les TSR étaient similaires entre les deux groupes pour les stades 1-3 combinés(p=0.244). Chez les patients avec un stade 3, la préadaptation était associée avec un TSR amélioré (73.4% vs. 50.9%, p=0.044). Aucune différence n'a été observée pour le TSG (p=0.226). Les résultats de la régression multiple ont démontrés que la préadaptation était indépendamment associée avec un TSR amélioré (HR ajusté 0.45, IC à 95%: 0.21-0.93). Aucune association entre la préadaptation et le TSG n'a été trouvée. Dans la deuxième étude, 408 patients ont été inclus (83.2%côlon;15.8%rectum) avec un suivi moyen de 58.4 mois (DS29.9). Quatorze pourcents (14.0%) des patients ont subi une résection <4 semaines, 40.0% 4 to <8 semaines and 46.1% ≥8 semaines. Plus de patients ayant un cancer du rectum ont connu des délais ≥8 semaines comparativement à ceux ayant une tumeur au côlon dans notre cohorte(69.8% vs. 41.4%,p<0.001). Le TSR et TSG cumulatifs étaient similaires dans les trois groupes (p=0.558;p=0.572). Lorsque les facteurs confusionnels ont été examinés, les délais chirurgicaux n'étaient pas indépendamment associés avec TSR ni TSG.

Conclusion: Dans ce mémoire, la préadaptation était associée avec un taux survie en temps de rémission améliorée à 5 ans chez les patients avec un cancer du côlon et rectum de stade 3. La préadaptation a aussi indépendamment prédit une survie en temps de rémission améliorée à 5 ans lorsque tous les stades étaient combinés. Les délais de traitement de >4 semaines n'étaient pas associés avec des résultats oncologiques réduits. Retarder la résection colorectale pour optimiser les patients dans la période préopératoire peut être considéré de façon sécuritaire

sans compromettre le taux de survie. Ces résultats prometteurs devraient être confirmés dans des études de plus grande envergure.

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CONTRIBUTION OF AUTHORS

Maude Trepanier (MT) wrote this thesis and was the principal author both of the manuscripts included in this thesis. For both manuscripts, MT was directly involved in the study design, data collection, analysis and interpretation of results, as well as drafting of the manuscripts. Kevin Schwartzman (KS) was the primary thesis supervisor. Liane S. Feldman (LSF) was the thesis co-supervisor. KS and LSF are co-authors on both papers, and contributed greatly in every step of the research process. Lawrence Lee (LL) was the primary investigator of the research program and provided great mentorship and support throughout.

Contributions of the co-authors published manuscripts is shown below.

Manuscript 1

Trépanier M, Minnella EM, Paradis T, Awasthi R, Kaneva P, Schwartzman K, Carli F, Fried GM, Feldman LS, Lee L. Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. Ann Surg. 2019 Sep;270(3):493-501.

- Study conception and design: MT, GMF, LSF, LL
- Data acquisition: MT, TP, EMM, RA
- Analysis and interpretation of data: MT, PK, KS, GMF, LSF, LL
- Drafting of manuscript: MT, GMF, LSF, LL
- Critical revision: MT, EMM, PK, KS, FC, GMF, LSF, LL

Manuscript 2

Trépanier M, Paradis T, Kouyoumdjian A, Dumitra T, Charlebois P, Stein BL, Liberman AS, Schwartzman K, Carli F, Fried GM, Feldman LS, Lee L. The Impact of Delays to Definitive Surgical Care on Survival in Colorectal Cancer Patients. J Gastrointest Surg. 2019 Jul 31. doi: 10.1007/s11605-019-04328-4. [Epub ahead of print]

- Study conception and design: MT, GMF, LSF, LL
- Data acquisition: MT, TP, AK, TD
- Analysis and interpretation of data: MT, GMF, LSF, LL
- Drafting of manuscript: MT, GMF, LSF, LL
- Critical revision: MT, PC, BLS, ASL, KS, FC, GMF, LSF, LL

CHAPTER 1 – Introduction and Literature Review

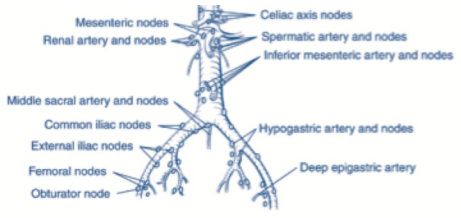
1.1 Epidemiology, diagnosis, prognosis and treatment strategies of colorectal cancer

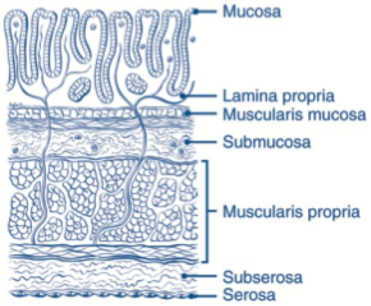
According to the Canadian Cancer Society, colorectal cancer is the third most common cancer in Canada in 2019.[1] It is estimated that a total of 26,300 Canadians will be diagnosed with colorectal cancer and 9,500 will die from it this year, making it the second leading cause of cancer death in men and the third in women.[1] It is currently estimated that about 1 in 14 Canadian men and 1 in 18 women will develop this disease during their lifetime and 1 in 32 men and 1 in 37 women will die from it.[1] Despite the recent decline in incidence due to the widespread implementation of screening programs allowing the detection and removal of precancerous polyps, colorectal cancer remains common and represents an important public health issue.

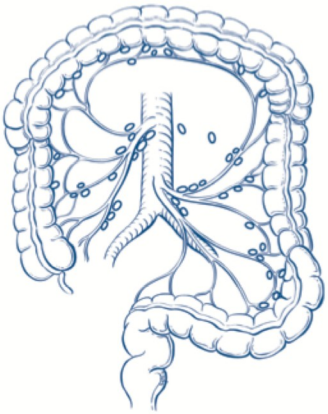
The diagnosis of colorectal cancer is usually made by screening colonoscopy or with the development of symptoms, such as bleeding and changes in bowel habits. The presence of symptoms typically signifies larger and more advanced tumors. During colonoscopy, several tissue biopsies are taken. Once a diagnosis of colorectal adenocarcinoma is established after pathological evaluation of the biopsied lesion, patients undergo imaging studies to rule out the presence of metastatic spread to other organs, such as liver and lungs.

The current treatment strategies for non-metastatic colon cancer include surgical resection of the primary tumor, followed by systemic adjuvant chemotherapy to reduce the risk of cancer recurrence. Adjuvant therapy is typically reserved for patients with stage 3 disease or those with high-risk stage 2 disease. The TNM classification is used to determine the stage of

the tumor. It is determined by the depth of tumor invasion (T stage), the number of lymph nodes involved (N stage) and the presence of metastatic disease (M stage) during final pathological assessment of the surgical specimen and is presented in Figure 1.1 below.







Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into pericolorectal tissues
- T4a Tumor penetrates to the surface of the visceral peritoneum[2]
- T4b Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1–3 regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in 2–3 regional lymph nodes
- N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 Metastasis in 4 or more regional lymph nodes
- N2a Metastasis in 4–6 regional lymph nodes
- N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (for example, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).
* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Figure 1.1 – American Joint Committee on Cancer 7th Edition, Colon and Rectal Cancer Staging[2]

For rectal cancer, the treatment strategy can be more complex and may include the delivery of neoadjuvant radiotherapy with or without systemic chemotherapy depending on several factors determined by preoperative imaging studies. When detected prior to metastatic spread to other organs such as the liver, colorectal cancer is potentially curable with surgery.

However, despite advancements in surgical techniques and adjuvant therapies, it is estimated that 25-40% of colorectal cancer patients experience disease recurrence in the first 5 years following definitive curative surgical treatment, highlighting the clinical importance of this problem.[3, 4] The recurrence rate highly depends on tumor stage. A recent retrospective cohort study of the Swedish Colorectal Cancer Registry involving 14,325 patients reported that the 5-year recurrence rates in their cohort were: 5% in stage I, 12% in stage II and 33% in stage III.[5] The National Comprehensive Cancer Network (NCCN) however reports higher stage-specific recurrence rates, but these are based on data published several years ago and may therefore not reflect current treatment modalities.[6] Nevertheless, a significant proportion of patients experience recurrence despite curative surgical resection of their primary tumor.

1.2 Risk factors for cancer recurrence

Several risk factors predicting recurrence have been identified over the years. These can be broadly classified into tumor-, treatment-, system- and patient-related factors.

Tumor biology plays an important role in the prognosis of colorectal cancer. The decision to administer adjuvant systemic therapy is mainly based on tumor-specific variables. Higher T and N stages, poor differentiation, and presence of lymphovascular or perineural invasion, and desmoplastic reaction have been identified as predictors of poor outcomes and are considered high-risk features.[7-14] Amongst these variables, lymph node involvement is associated with the highest risk for disease recurrence.[15] In the presence of any of those high-risk features, adjuvant chemotherapy is recommended for stage 2 disease (i.e. without nodal involvement).[6, 16-18] Additionally, there are several tumor-specific genetic mutations and

molecular markers that have been found to be associated with worse disease-free and overall survival, such as K-RAS and BRAF mutations.[19] However, while tumor variables may be used for risk stratification and decisions regarding delivery of adjuvant systemic therapies, they are non-modifiable risk factors for poor oncologic outcomes.

Several treatment aspects may also influence long-term oncologic outcomes. The quality of surgical resection, often determined by resection margin status and lymph node harvest, may be an important element to consider.[20] It is well established that positive margins (i.e. resection margins involved by cancer cells) are associated with worse disease-free and overall survival.[21] In addition, there is increasing evidence showing an association between lymph node yield and oncologic outcomes.[22] Recent studies have reported that a higher lymph node harvest beyond the minimum of 12 lymph nodes required for staging is, in fact, independently associated with improved survival irrespectively of N stage, lymph node ratio and receipt of adjuvant systemic therapy.[22] Whether lymph node yield is a marker of surgical quality or experienced pathologists is unclear. The postoperative course may also affect long-term cancer outcomes. Postoperative complications have been shown to delay the initiation of adjuvant chemotherapy and activate the systemic inflammatory response, both predictors of adverse long-term cancer prognosis.[23-33] Many studies have also reported that the timely delivery and completion of adjuvant chemotherapy is independently associated with improved survival when other risk factors are also considered.[34] Therefore, other risk factors for poor outcomes include adjuvant chemotherapy omission as well as cycle interruption. The timing of initiation of chemotherapy may also play a role.[34]

Additionally, system-related factors may also influence cancer outcomes. Timely access to care and quality of care received have been shown to affect cancer outcomes.[35] Several studies have reported better short- and long-term outcomes for colon and rectal cancer patients treated in high-volume specialized centers.[36, 37] High-volume surgeons, specialized/experienced pathologists and multidisciplinary approach all contribute to optimal cancer care.[38, 39] There are currently few data on the effect of delays to surgery on survival and it remains unclear whether achieving wait-time benchmarks for surgery significantly impacts survival.[40] This will be discussed in Chapter 4.

Finally, several patient-related factors independently predict survival following curative-intent surgery for colorectal cancer. Older age at diagnosis is associated with worse outcomes.[41] However, age is a non-modifiable risk factor, but numerous other potentially modifiable risk factors for cancer recurrence have been recently identified. Poor lifestyle habits, especially lack of physical activity and low-fiber diet, are well-known risk factors for the development of colorectal cancer. There have also been increasing data suggesting beneficial effects of exercise on long-term cancer outcomes following curative resection.[32, 42-47] In addition, the current body of literature suggests that poor baseline functional status and frailty, which are markers for low levels of physical activity and poor cardiovascular fitness, are associated with worse long-term cancer outcomes.[42, 48] These data suggest that functional capacity may therefore be a potentially modifiable risk factor for poor oncologic outcomes.

1.3 Functional capacity as a modifiable risk factor

Functional capacity is the extent to which a person can increase their exercise intensity, which largely depends on cardiovascular fitness and proper functioning of the cardiovascular, respiratory and circulatory systems. The assessment of functional capacity can provide important diagnostic and prognostic information.[49] In recent years, functional capacity has been commonly evaluated preoperatively in order to identify patients who are at a higher risk of perioperative cardiovascular events and who may require further preoperative testing or medical optimization.[49] Traditionally, functional capacity is subjectively assessed by asking patients to report whether they can climb two flights of stairs without dyspnea; this is thought to correspond to 4 metabolic equivalents (METs), which is the threshold used for perioperative cardiovascular risk stratification.[49] However, this subjective assessment is not an accurate predictor postoperative morbidity.[50] In contrast, the Duke Activity Status Index (DASI) is a validated questionnaire including activities of daily living and recreational activities that can more accurately measure functional status and predict postoperative complications.[50, 51]

In addition, there are several objective methods to measure functional capacity, of which cardiopulmonary exercise testing (CPET) is the gold standard. CPET provides a "global assessment of the integrative exercise response involving the pulmonary, cardiovascular, hematopoietic, neuropsychologic and skeletal muscle systems that is not adequately reflected through the measurement of individual organ system function".[52] A CPET is an incremental symptom-limited exercise test, on a treadmill or stationary cycle ergometer, during which simultaneous non-invasive measurements of pulmonary gas exchange, analysis of blood pressure, heart rate, and peripheral oxygen saturation are conducted. Several measures are

obtained during this test, of which the maximal oxygen consumption (VO2 max) and anaerobic threshold have been shown to predict postoperative complications.[53-56] The main limitation of CPET is the cost associated with the equipment required to perform the test. The six-minute walk test (6MWT) is a less expensive alternative to CPET and is commonly used to assess functional capacity. It involves the measurement of the distance walked in 6 minutes at a brisk pace set by the patient and provides a valid assessment of functional capacity in patients with cardiopulmonary disease.[57-59] Evidence supports the 6MWT as a valid measure of recovery after abdominal surgery.[60]

A large number of studies have reported that poor baseline functional capacity is associated with an increased risk of perioperative morbidity and prolonged recovery.[61-63] Furthermore, evidence supports frailty as an independent predictor of perioperative morbidity and longer recovery even when comorbid medical conditions are considered.[63] A recent substudy of the published METS trial[50] examined the capacity of the 6MWT to predict postoperative recovery and disability compared to DASI, CPET and plasma biomarker N-terminal pro-B-type natriuretic peptide.[64] The authors reported that DASI was the overall most significant predictor of postoperative disability. However, when they looked at high-risk patients only, 6MWT was a better predictor when the distance walked was less than 370 meters.

Furthermore, there is some evidence showing that patients with lower baseline functional status have worse long-term oncologic outcomes.[42, 48] Several mechanisms are thought to be involved. Poor functional capacity has been associated with longer recovery and

increased perioperative morbidity, which may trigger a systemic inflammatory response that can alter disease-free survival through a variety of biochemical processes, as well as delay initiation and/or tolerability of adjuvant therapies..[32, 42-47] In addition, functional capacity and cardiovascular fitness are closely related to level of exercise. Multiple studies have reported that exercise may affect disease-free survival through several mechanisms. First of all, excess visceral adipose tissue, which may be reduced with exercise, has been found to be independently associated with disease recurrence and mortality among colon cancer patients.[46] A recent study showed that aerobic exercise reduced visceral adipose tissue in a dose-response fashion in patients with stage I–III colon cancer.[47] It is however unclear whether this translates into a dose-response effect on oncologic outcomes. Furthermore, while the presence of systemic inflammation predicts recurrence and overall survival in patients with colorectal cancer[30], a previous study reported that exercise inhibits inflammatory cytokine production in adipose tissue.[65, 66] In addition, exercise may affect serum insulin concentrations and insulin-like growth factor-I bioavailability, an important promoter of cell proliferation and inhibitor of apoptosis in colon cancer cells.[67] Circulatory shear flow induced by exercise may also alter the viability, proliferation and metastatic potential of circulating colon cancer cells.[68] Functional capacity and exercise may thus play an important role in cancer recurrence and disease progression.

While the vast majority of risk factors for disease recurrence and adverse outcomes following curative surgical resection of colorectal cancer include non-modifiable tumor- and surgery-dependent characteristics as described above[7-14], baseline preoperative functional capacity is a potentially modifiable risk factor for poor outcome.[69] Current practice focuses on

rehabilitation after surgery with different strategies such as physiotherapy and occupational therapy, but this might not be the optimal time to intervene. Postoperative complications and prolonged recovery to baseline may impact rehabilitation. The preoperative period might thus be a better time to engage patients in activities to prepare for their upcoming surgery. In fact, the preoperative setting has been successfully used to optimize patients' baseline functional status to better tolerate surgery, reduce perioperative morbidity and hasten recovery.[43-45, 70] There is increasing evidence demonstrating that a significant improvement in preoperative baseline functional capacity can be achieved with the use of multimodal prehabilitation programs.[43-45, 71]

1.4 Prehabilitation

Multimodal prehabilitation is an intervention that aims to improve patient health status in the preoperative period in order to mitigate perioperative functional decline and its consequences on recovery, quality of life, and cancer care. Trimodal prehabilitation programs consist of a combination of exercise, nutritional and psychosocial counseling. Three published studies will be reviewed: Li et al. (2013), Gillis et al. (2014), and Bousquet-Dion et al.(2018)[43-45], as data from these trials were used in this thesis. The specific components of trimodal prehabilitation programs have evolved over time and will be presented below (Table 1.2).

Li et al.[45] first published a prospective pre- and post-intervention study investigating the effect of trimodal prehabilitation on postoperative recovery, measured using 6MWT. The study included adult patients with a colonic or rectal malignancy planned for curative-intent resection. Patients with metastatic disease, any medical condition precluding the safe use of

physical activity and those unable to understand English or French sufficiently to complete the questionnaires were excluded. Care was provided by one of three fellowship-trained colorectal surgeons, and perioperative care was guided by a mature standardized enhanced recovery pathway (ERP).[72] Patients in the control group were assessed at three time points: at 1 week preoperatively, at 4 weeks and 8 weeks postoperatively. After implementation of the prehabilitation intervention, patients were referred to the program from colorectal clinic after the decision to proceed with surgery was made. At the initial visit, the prehabilitation program was explained, and informed consent was obtained. After a medical examination, the patients met with a kinesiologist, a nutritionist, and a psychologist for baseline measures to be obtained and for an individualized home-based program to be designed. The patients then initiated the prehabilitation intervention at home and were reassessed at the same three time points as the patients in the control group. The length of prehabilitation was determined by the wait time until surgery.

In this study, the prehabilitation program consisted of moderate intensity aerobic exercise for 30 minutes three times a week with a target intensity set at half the calculated maximal heart rate (220 - age). Resistance exercises were also performed three times a week. In addition, whey protein isolate supplements were given to provide intake of 1.2 g/kg body weight of protein per day. A global nutritional assessment was carried out during the initial visit and one or two modifiable dietary behaviors such as excess alcohol or fat intake were identified and discussed with the patient. In addition, relaxation exercises and breathing exercises were taught to patients at their initial visit. A compact disc reviewing these anxiety-reducing techniques was provided for home practice.

The authors found that, during the prehabilitation period, functional walking capacity significantly improved in the intervention group. However, the postoperative complication rates and the hospital length of stay did not differ. Compared to controls, patients in the prehabilitation program had better postoperative walking capacity at both 4 weeks and 8 weeks postoperatively. At 8 weeks, 81% of the prehabilitated patients had recovered to or above their preoperative walking capacity compared with 40% of the control group, suggesting a significant benefit from prehabilitation. The study was limited by its observational design and lack of randomization, which may have introduced possible confounding and bias. Another weakness of the pre- and post-intervention design is the possibility of other changes in practice that could have impacted outcomes in the latter group.

A randomized controlled trial was performed by Gillis et al. to overcome these limitations.[44] The study objective was to quantify the effect of prehabilitation on pre- and postoperative functional walking capacity. In this trial, consecutive adult patients scheduled for curative-intent resection of colorectal cancer were approached at their initial office visit, and consent was obtained in eligible patients. The same inclusion and exclusion criteria described above for Li et al. were applied.

An initial assessment was conducted approximately 4 weeks preoperatively during which patients completed baseline questionnaires, as well as biochemical, functional, and anthropometric measurements. Upon completion of the baseline assessment, patients were randomized to the intervention or control group in a 1:1 ratio using computer-generated randomization. Group allocation was concealed. Patients in the prehabilitation group were seen

by a kinesiologist, dietitian, and psychologist at the baseline visit, and a home-based program was designed. Patients were instructed to begin the trimodal prehabilitation program at home immediately. The home-based prehabilitation program was similar to the intervention implemented by Li et al. described above. Patients in the rehabilitation (control) group participated in an identical consultation scheduled within 1 week of their surgery. Control patients were instructed to initiate the program at home after surgery. The postoperative program was carried out by all participants, regardless of group assignment, for 8 weeks after hospital discharge. Patients were re-assessed before surgery, and at 4 and 8 weeks. 6MWT was measured at each visit. All patients received perioperative care according to a standardized ERP.[72] The authors found that, while awaiting surgery, preoperative functional walking capacity increased in a significantly higher proportion of patients in the prehabilitation group compared with the control group. Complication rates and duration of hospital stay were similar. The difference between baseline (at enrolment) and 8-week 6MWT was significantly higher in the prehabilitation compared with the rehabilitation group (+23.7 m vs. −21.8 m; mean difference 45.4 m (95% CI, 13.9 to 77.0)). In addition, a significantly higher proportion of prehabilitated patients had recovered to or above baseline functional capacity at 8 weeks compared to the rehabilitation group. The mean self-reported compliance with this unsupervised prehabilitation program was 78% and declined in the postoperative period.

A third study by Bousquet-Dion et al. was conducted to determine whether a weekly supervised exercise session could provide further benefit to our current prehabilitation program compared to standard post-surgical rehabilitation by improving adherence and patient engagement.[43] A randomized controlled trial was designed similarly to the previously described

trial. Identical study settings, inclusion and exclusion criteria, recruitment and randomization were applied. Patients underwent a similar baseline assessment during which they were randomized to the intervention or control group. Patients randomized to prehabilitation met with the multidisciplinary team and a similar individualized home-based program was designed. In this trial, patients were also required to attend once a week in-laboratory exercise sessions supervised by a trained kinesiologist during the preoperative period. Postoperatively, patients in both groups were instructed to continue their home-based program for an additional 8-week period. The authors reported that changes in 6MWT distance were similar in both groups preoperatively and postoperatively, suggesting that the addition of a weekly supervised exercise session to prehabilitation program did not further enhance postoperative walking capacity. The methodology and prehabilitation programs of the three studies discussed are summarized in Tables 1.1 and 1.2 below.

Table 1.1 – Methodology of the three studies

Characteristics	**Li et al. (2013)**	**Gillis et al. (2014)**	**Bousquet-Dion et al. (2018)**
Study design	Prospective pre- and post-intervention study	Parallel-arm single-blind randomized controlled trial	Parallel-arm single-blind randomized controlled trial
Study period	July 2009 – September 2011	November 2011 – March 2013	December 2013 – August 2015
Study settings	One tertiary care center with ERP	One tertiary care center with ERP	One tertiary care center with ERP
Inclusion criteria	Adult patients with colon or rectal malignancy undergoing curative-intent resection	Adult patients with colon or rectal malignancy undergoing curative-intent resection	Adult patients with colon or rectal malignancy undergoing curative-intent resection
Exclusion criteria	- Metastatic disease - Medical condition precluding safe use of physical activity - Unable to understand French or English	- Metastatic disease - Medical condition precluding safe use of physical activity - Unable to understand French or English	- Metastatic disease - Medical condition precluding safe use of physical activity - Unable to understand French or English
Primary outcome	Functional walking capacity, measured by 6MWT 8 weeks after surgery	Functional walking capacity, measured by 6MWT 8 weeks after surgery	Functional walking capacity, measured by 6MWT
Secondary outcomes	- Complication rate (using Clavien-Dindo classification) - Self-reported physical activity - Health-related quality of life (using the Medical Outcomes Study 36-Item Short-Form Health Sur- vey (SF-36))	- Complication rate (using Clavien-Dindo classification) - Self-reported physical activity - Health-related quality of life (using the SF-36) - Anxiety and depression (using the Hospital Anxiety and Depression Scale (HADS))	- Self-reported physical activity - Weekly energy expenditure (using the Community Healthy Activity Model Program for Seniors (CHAMPS) questionnaire)

Table 1.2 – Prehabilitation programs

Intervention	Li et al. (2013)	Gillis et al. (2014)	Bousquet-Dion et al. (2018)
Exercise	Home-based Moderate-intensity aerobic exercise for 30 min 3 times/week; Resistance exercise (calisthenics and elastic band movements) 3 times/week to volitional fatigue	Home-based Exercise for up to 50 min at least 3 times/week alternating between moderate-intensity aerobic and resistance exercise; Participants were provided with a set of three resistance bands	Supervised Weekly session with trained kinesiologist; Moderate-intensity exercise NuStepVR T5 (NuStep Inc., Ann Arbor, MI) recumbent stepper or standard treadmill for 30 minutes; Resistance exercise program for 25 minutes; Feedback provided Home-based Moderate-intensity aerobic exercise for 30 min 3-4 times/week; Resistance training: 8 exercises targeting major muscle groups 3–4 times/week in up to 2 sets of 8–15 repetitions, dependent on volitional fatigue; Patients were given an elastic resistance band and a pedometer
Nutrition	One or 2 modifiable dietary behaviors (e.g. excess alcohol or fat intake) identified and discussed; Whey protein isolate to reach 1.2g/kg/d	Whey protein isolate to reach 1.2g/kg/d; Further nutritional counseling given to help with bowel movements regularity, body composition optimization and glycemic control	Whey protein isolate to reach 1.2g/kg/d; Further nutritional counseling given to help with bowel movements regularity, body composition optimization and glycemic control
Psychosocial	90-minute session with trained psychologist; Anxiety- reduction techniques (e.g. relaxation and breathing exercises), mirrored on a compact disk for home	60-minute session with trained psychologist; Anxiety- reduction techniques (e.g. relaxation and breathing exercises), mirrored on a compact disk for home	60-minute session with trained psychologist; Anxiety- reduction techniques (e.g. relaxation and breathing exercises), mirrored on a compact disk for home; Instruction booklets

In summary, patients in the prehabilitation groups achieved significant improvements in baseline functional capacity during the preoperative period (Table 1.3).[44, 45]

Table 1.3 – Main study findings

Characteristics	Li et al. (2013)	Gillis et al. (2014)	Bousquet-Dion et al. (2018)
6MWT, m, control vs. prehab (p-value)			
Preoperative	402 (SD57) vs. 464 (92) (<0.01)	Mean Δ −16.4(SD46.0) vs. +25.2(50.2)(<0.01)	471 (SD108) vs.470 (118)
4 weeks postop.	356 (71) vs. 407 (111) (0.01)	-	444 (116) vs. 441 (120)
8 weeks postop.	375 (58) vs. 459 (101) (<0.01)	−21.8 (80.7) vs. +23.4 (54.8) (0.020)	472 (108) vs. 468 (118)

Furthermore, a greater proportion of patients recovered to baseline functional capacity at 8 weeks postoperatively than among patients who did not receive the intervention (Figure 1.2).

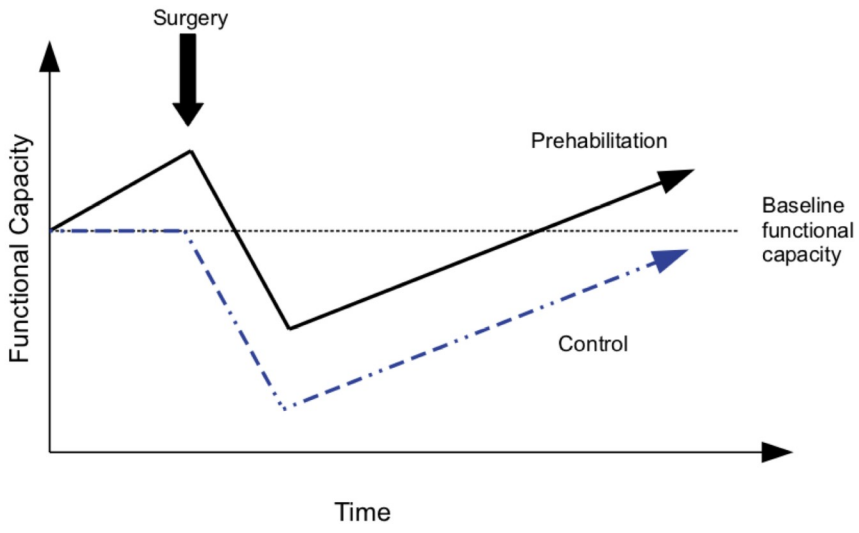


Figure 1.2 – Functional capacity with prehabilitation

In addition to these three trials, short-term outcomes of trimodal prehabilitation have been reported by other studies.[73, 74] While most trials have been conducted in patients undergoing major abdominal surgery, they differ significantly in terms of their prehabilitation elements and protocols. A recent systematic review that included 20 studies published between January 2006 and September 2016 found that most programs were unimodal.[75] There were only two trials identified in this review that assessed a multimodal prehabilitation program that included exercise, nutrition, and psychological support (Li et al.[45] and Gillis et al.[44] described above). The current body of evidence supports an improvement in functional capacity with multimodal prehabilitation. Furthermore, a recent metanalysis including trials in high-risk patients reports a significant reduction in overall and pulmonary complications.[73, 74, 76, 77] However, it is unclear whether the changes achieved with prehabilitation have an impact beyond the perioperative period. A potential favourable effect on cancer outcome has been described for individual elements of prehabilitation programs, such as exercise and immunonutrition, for the reasons described above (section 1.3). Behavioural changes are more likely to be continued postoperatively if they were initiated in the preoperative period compared to after surgery.[44] Yet no previous studies have investigated the synergistic effects of a trimodal prehabilitation program on long-term oncologic outcomes.[78]

CHAPTER 2 - Thesis Objectives

1. The primary objective of this thesis is to investigate the effects of multimodal prehabilitation (exercise, nutrition and psychology) on oncologic outcomes after elective curative-intent colorectal cancer surgery.
2. The secondary objective of this thesis is to determine the effect of delaying curative-intent surgical resection (to allow for preoperative optimization) on survival in colorectal cancer patients undergoing curative-intent resection.

CHAPTER 3- Improved Disease-Free Survival After Prehabilitation For Colorectal Cancer Surgery

3.1 Preamble to Manuscript 1

While early postoperative outcomes and recovery may be improved with prehabilitation in some studies, it is unknown whether this translates into better colorectal cancer outcomes.[4, 5, 8, 9] There is increasing evidence that patients with poorer baseline functional status have worse long-term oncologic outcomes.[11, 12] The improvement of functional status through targeted prehabilitation may thus result in better cancer outcomes, either by influencing the timing of initiation and/or tolerability of adjuvant therapies, or through the effect of exercise, which has been recognized to alter oncologic outcomes through several physiologic and biochemical processes.[4, 6, 7, 12-17] In addition, several studies have linked poorer psychological state and baseline quality of life to early postoperative morbidity and worse long-term oncologic outcomes.[79, 80] Other studies have also reported that severe malnutrition predicts greater chemotherapy toxicity and reduced overall survival in colorectal cancer patients.[81, 82] The improvement of psychological and nutritional states with prehabilitation may thus potentially lead to better cancer outcomes, especially if these changes persist throughout the continuum of cancer care.[83]

The potential favourable effects on cancer outcomes have been described for individual elements, but the long-term synergistic effects of trimodal prehabilitation on cancer outcomes have not yet been assessed. Therefore, the objective of manuscript 1 is to investigate the effect of trimodal prehabilitation on long-term oncologic outcomes after elective colorectal cancer surgery, which will address objective 1 of this thesis.

MANUSCRIPT 1: Improved Disease-Free Survival After Prehabilitation For Colorectal Cancer Surgery

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3.2 Abstract

Objective: The objective of this study was to investigate the effect of prehabilitation on survival after colorectal cancer surgery.

Summary Background Data: Preoperative multimodal exercise and nutritional programs (prehabilitation) improve functional capacity and recovery following colorectal surgery. Exercise may also affect cancer outcomes by mediating the systemic inflammatory response. The effect of prehabilitation on cancer outcomes is unknown.

Methods: Pooled data from three prehabilitation trials (2 RCTs, 1 cohort) in patients undergoing elective, biopsy-proven, primary non-metastatic colorectal cancer surgery from 2009-2014 within an enhanced recovery program were analyzed. Patients were grouped into +prehab or -prehab. The primary outcomes were 5-year disease-free(DFS) and overall survival(OS). DFS and OS were analyzed using Kaplan-Meier curves and multiple Cox regression.

Results: A total of 202 patients were included (+prehab 104, -prehab 98). Median prehabilitation duration was 29 days(IQR20-40). Patient and tumor characteristics were well-balanced (33% stage III). Postoperative complications and time to adjuvant chemotherapy were similar. Mean duration of follow-up was 60.3 months (SD26.2). DFS was similar for the combined group of stage I-III patients (p=0.244). For stage III patients, prehabilitation was associated with improved DFS (73.4% vs. 50.9%, p=0.044). There were no differences in OS (p=0.226). Prehabilitation independently predicted improved DFS (HR 0.45, 95%CI: 0.21-0.93), adjusting for stage and other confounders. Prehabilitation did not independently predict OS.

Conclusion: In this report, prehabilitation is associated with improved 5-year DFS in stage III colorectal cancer. This finding should be confirmed in future trials.

3.3 Introduction

Despite advances in surgical techniques and implementation of enhanced recovery pathways, the incidence of postoperative complications following colorectal surgery remains high.[1] Functional capacity (physical and nutritional status as well as psychosocial factors) has been identified as a potentially modifiable risk factor for poor surgical outcomes.[2] Several studies have demonstrated an improvement in preoperative baseline functional capacity with targeted trimodal prehabilitation, which includes exercise, nutritional and psychological interventions.[3-6] Prehabilitation before surgery aims at improving patient physiological reserve to attenuate the risk of postoperative functional decline, and potentially decrease the incidence of postoperative complications and hasten recovery.[4, 6-10]

While early postoperative outcomes may be improved with prehabilitation, it is unknown whether this translates into better colorectal cancer outcomes.[4, 5, 8, 9] There is some evidence that patients with lower baseline functional status have worse long-term oncologic outcomes.[11, 12] Therefore, improvement of functional status through targeted prehabilitation may result in better cancer outcomes, either by influencing the timing of initiation and/or tolerability of adjuvant therapies, or through the effect of exercise, which may alter disease-free survival through a variety of biochemical and physiologic processes.[4, 6, 7, 12-17] The long-term effects of trimodal prehabilitation on cancer outcomes have not yet been characterized. Therefore, the objective of this study is to investigate the effect of trimodal prehabilitation on long-term oncologic outcomes after elective colorectal cancer surgery.

3.4 Methods

3.4.1 Study population

A follow-up pooled analysis of three previous prospective studies conducted at a single high-volume specialist-referral center from July 2009 to August 2015 was performed.[4, 6, 7] These included one prospective pre- and post-intervention cohort study[6] and two randomized controlled trials[4, 7] investigating the effect of the implementation of a trimodal prehabilitation program on postoperative outcomes and recovery in colorectal cancer patients. Detailed methodology regarding patient enrolment, randomization and group allocation have been previously reported.[4, 6, 7] In brief, adult patients undergoing colorectal surgery for non-metastatic colorectal adenocarcinoma, including rectal tumors, were eligible to participate in those studies. Eligible patients were referred to the prehabilitation program by their treating surgeon. Subjects were excluded if they had metastatic disease at the time of diagnosis, if they were diagnosed with any medical condition precluding the safe use of physical activity or if they were unable to understand English or French sufficiently to accurately complete the study questionnaires. The study protocol was approved by the local institutional review board.

In the present study, patients were further excluded if they underwent surgery for locally recurrent cancer, had in-situ disease on pathology specimen, unresectable primary tumors or appendiceal tumors. Patients with pulmonary nodules, liver lesions or retroperitoneal lymphadenopathy noted on preoperative imaging with low initial suspicion for metastatic disease, but recognized to be malignant in the early postoperative period were also excluded from this study and labelled as having metastatic disease at the time of surgery. None

of the included patients were found to have an inherited colorectal cancer syndrome, such as Lynch syndrome and familial adenomatous polyposis (FAP).

3.4.2 Trimodal Prehabilitation

The trimodal prehabilitation program consisted of a combination of preoperative exercise, nutritional and psychosocial counseling. Patients randomized to the intervention group initially met with a kinesiologist, nutritionist and trained psychologist for a global assessment. During this first visit, an individualized home exercise program (30 minutes of moderate aerobic activity 3-4 times per week with resistance training with[7] or without supervision[4, 6]), nutritional counselling, whey protein isolate supplements and anxiety-reduction techniques were provided to patients. Patients were instructed to follow their program until the day of their surgery. Duration of prehabilitation was mainly determined by the wait time until surgery and averaged 4 weeks in all studies. In 2 of the 3 included studies, control patients underwent a similar initial assessment preoperatively, but were instructed to follow their program in the postoperative period only (rehabilitation). Patients in the intervention and control groups were encouraged to continue their program for 8 weeks postoperatively. All three studies were conducted within a mature enhanced recovery program after colorectal surgery.[18]

3.4.3 Outcomes and Variable Definitions

Prospectively collected data from previous studies included baseline patient demographics (age, gender, body mass index, comorbidities classified using the American Society of Anesthesiologists score), prehabilitation program compliance, surgical procedure,

length of stay and perioperative outcomes (postoperative complications were measured using the Clavien-Dindo (CD) classification with severe complications defined as CD ≥ 3).[19] After obtaining institutional research ethics review board approval, tumor-related variables were retrospectively collected from electronic medical records and included tumor location, grade, lymphovascular invasion, perineural invasion, margin status, pathological TNM stage, lymph node harvest, and number of positive lymph nodes. Lymph node ratio was calculated from available data and dichotomized as <0.10 and ≥0.10.[20] Date of initiation of adjuvant systemic therapy was also recorded.

The primary outcomes of this study were 5-year disease-free (DFS) and overall survival (OS). Last date of contact and vital status at last contact were used to determine OS. Recurrence was determined from the review of all surveillance computed tomography scan and colonoscopy reports performed as per routine surveillance guideline schedule following curative resection of colorectal cancer.[21] DFS was defined as the time interval between surgery and the date of imaging/endoscopic test revealing the presence of metastatic disease or local recurrence. Secondary outcomes included receipt of adjuvant systemic therapy and time to initiation of systemic chemotherapy (oral or intravenous) from the day of surgery.

3.4.4 Statistical analysis

Data are represented as n (%) for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables. The prehabilitation and control groups were compared. Univariate analyses were performed using student t-test to compare means and two-sample Wilcoxon rank-sum (Mann-Whitney) test for medians of

continuous variables. Two-sided Fisher's exact and $\chi 2$ test were used for categorical variables. A subgroup analysis of stage III disease was performed to assess and compare chemotherapy-related outcomes between groups. Kaplan–Meier survival curves were generated to describe 5-year DFS and OS, and log-rank tests to compare the cumulative survival distributions. Multiple regression analyses were performed using Cox proportional hazard models to identify independent predictors of 5-year DFS and OS, adjusting for potential confounders. A multiple regression analysis using Cox proportional hazard model was completed for the subgroup of patients with stage III disease. A subgroup analysis was also performed for rectal cancer patients. All analyses were performed using STATA 12.1 (StataCorp, College Station, TX).

3.5 Results

A total of 244 patients were reviewed, of which 202 were included. The prehabilitation group included 104 patients and the control group 98 (Figure 3.1). A total of 42 patients were excluded and these were evenly distributed across studies. Baseline demographics, tumor and operative characteristics as well as perioperative outcomes were well balanced between groups (Tables 3.1-3.2). Mean age was 68.0 years (SD 11.0) and 26.7% of patients had ASA score≥ 3. Seventy-five patients (37.7%) had rectal tumors and 66 (32.7%) stage III disease. Median prehabilitation duration was 29 days (IQR 20-40) and median compliance with trimodal prehabilitation program was 80% (IQR 50-100). For the rectal cancer patients, prehabilitation took place during the wait time after neoadjuvant therapy. Mean duration of follow-up was 60.3 months (SD 26.2). Receipt of adjuvant therapy and timing of initiation of systemic chemotherapy were similar between groups (Table 3.2).

On Kaplan-Meier survival analysis, 5-year cumulative OS and DFS did not significantly differ between patients who underwent prehabilitation and controls (96.4% vs. 91.7% for OS and 85.3% vs. 79.3% for DFS) (Figures 3.2A and 3.3). However, in the subgroup analysis of stage III disease, prehabilitation was associated with higher 5-year DFS compared to control group (73.4% vs. 50.9%, log-rank p=0.045) (Figure 3.2B). 5-year DFS and OS were similar between groups in the subgroup analysis of rectal cancer patients (100% in the prehabilitation vs. 94.5% in the control group for OS, log-rank test p=0.173; 86.9% vs. 79.9% for DFS, log-rank test p=0.366) (Figure 3.4).

Results of adjusted multiple Cox proportional hazard regression for DFS for all stages combined and for stage III disease are shown in Table 3.3. After adjusting for possible confounders, trimodal prehabilitation independently predicted improved DFS in all stages combined and in the subgroup of patients with stage III disease. In the OS models, prehabilitation was not significantly associated with the outcome. In addition, none of the covariates independently predicted OS as shown in Table 3.4. In the subgroup analysis of rectal cancer patients, prehabilitation independently predicted improved DFS (HR 0.22; 95% CI 0.05-0.91, p=0.036) when confounders were adjusted for (Table 3.5). Details regarding neoadjuvant therapy and wait times to surgery can be found in Table 3.6. Subgroup analyses of stage III disease and rectal cancer were not performed for OS owing to the lack of events (i.e. death).

3.6 Discussion

Trimodal prehabilitation is associated with an improvement in preoperative functional capacity and short-term postoperative recovery after major abdominal surgery, and may also

decrease the incidence of postoperative complications.[3-6, 8-10, 22] Multiple recent studies have also reported that exercise may alter disease-free survival, but the long-term effects of trimodal prehabilitation on oncologic outcomes have, however, not yet been characterized.[13-17] The objective of this study was thus to investigate the effect of trimodal prehabilitation on survival after colorectal cancer surgery.

In the present study, prehabilitation was associated with an improved 5-year DFS in patients with stage III disease. A similar result was not observed when all stages were combined likely due to the low numbers of recurrences in stage I and II patients. In our multivariate analysis, prehabilitation was identified as an independent predictor of better DFS in all stages after adjusting for possible confounders. Although the literature is limited, our results compare to a recent study by West et al., in which a greater proportion of subjects included in the prehabilitation group were found to have pathological tumor regression when compared to the control group.[23] In addition, their study reported that exercise prehabilitation reversed the fall in functional capacity seen as a result of neoadjuvant therapy in patients with locally advanced rectal cancer.[23] Although we detected a statistically significant difference in 5-year DFS, we did not see any difference in 5-year OS. Our study may have been underpowered to detect a difference in overall survival owing to the small number of events and a type 2 error may have been introduced. However, it is very difficult to demonstrate statistically significant difference in overall survival in colorectal cancer studies given the high 5-year survival rate. In addition, disease-free survival has been shown to be a good surrogate marker for overall survival.[24-28] Furthermore, since improvements in DFS were only identified in the subgroup analysis of stage III disease, concerns about multiple comparisons could be raised. However, the same effect was

identified for the entire study group when confounders were adjusted for, which argues against multiple comparison problems.

Predictors of disease recurrence and adverse outcomes following curative surgical resection of colorectal cancer mainly include non-modifiable tumor- and surgery-dependent characteristics.[21, 29-35] It is estimated that 25-40% of colorectal cancer patients experience disease recurrence in the first 5 years following definitive surgical treatment, highlighting the clinical importance of this problem.[36, 37] In our study, we identified a potentially risk-modifying intervention for long-term oncologic outcomes in patients undergoing curative-intent surgical resection of primary non-metastatic colorectal cancer. The implementation of prehabilitation programs is feasible and may have other health benefits.[38, 39] Nevertheless, there are concerns about the impact of delaying definitive surgical care to allow for adequate prehabilitation. However, a recent study by Curtis et al. revealed that a delay of more than 12 weeks from diagnosis to resection did not impact overall survival.[40] This suggests that there is, in fact, a safe preoperative window for adequate prehabilitation without significantly affecting cancer outcomes as a result of disease progression.

Several different mechanisms may potentially explain the results observed in our study. Exercise may alter disease-free survival through a variety of biochemical and physiologic processes.[13-17] Aerobic exercise may affect cancer outcomes by reducing excess visceral adipose tissue, an independent predictor of disease recurrence and mortality among colon cancer patients.[13, 14] Furthermore, physical activity inhibits inflammatory cytokine production in adipose tissue, which has been associated with recurrence and mortality in individuals with colorectal cancer.[15] Evidence supports the presence of other independent anti-inflammatory

effects of exercise beyond the reduction of visceral fat alone.[41] Circulatory shear flow induced by aerobic activity may also alter the viability, proliferation and metastatic potential of circulating tumor cells.[17]

While this evidence suggests a beneficial effect on survival with exercise, it is unclear if prehabilitation results in long-term lifestyle changes that are significant enough to explain our results. In our study, data on levels of physical activity beyond 8 weeks postoperatively were not available and the long-term effects of prehabilitation on exercise pattern could not be assessed. However, patients who initiated the program in the preoperative period had a higher adherence immediately after surgery compared to those beginning the program postoperatively.[4] It is also unknown if a dose-response relationship exists between the degree of compliance with prehabilitation programs and cancer outcomes. Furthermore, the additional roles of nutritional optimization and psychological counselling cannot be ruled out as essential contributors to the observed improvement in disease-free survival.[42] Protein supplementation enhances muscle protein synthesis by providing adequate substrates for the anabolic effects of exercise resulting in increased lean body mass, muscle strength and functional capacity.[43] Nevertheless, exercise, with nutritional optimization, is likely to play an important role in the recurrence rate decrease identified in the present study.

In addition, the improved preoperative baseline functional capacity achieved with prehabilitation may contribute to our results. Prior studies have reported that patients with a lower baseline functional status have poorer long-term oncologic outcomes, suggesting that an improvement in functional status may result in better survival.[11, 12] Patients with higher functional capacity may have earlier initiation of adjuvant systemic therapy. However,

prehabilitation was not associated with shorter time to initiation of adjuvant systemic therapy in our study. Other hypotheses include improved tolerance of systemic therapy since patients with higher functional capacity experience less clinically significant chemotherapy-related side-effects and complications that may affect cycle completion and dose reduction rate.[12] Improving preoperative baseline functional capacity may thus optimize chemotherapy regimen completion and survival.

Furthermore, prehabilitation may improve survival by decreasing the incidence of postoperative complications. The current body of literature, however, does not strongly support a decrease in postoperative morbidity with prehabilitation likely owing to the fact that most studies in colorectal cancer were underpowered to detect a significant difference.[8-10] In our study, prehabilitation did not reduce the incidence of postoperative complications. Nonetheless, postoperative complications have been associated with worse oncologic outcomes by delaying initiation of adjuvant therapy, and by mediating the systemic inflammatory response, an important predictor of adverse long-term prognosis.[15, 44-53] Targeted prehabilitation may mediate a decrease in postoperative morbidity by increasing functional capacity and result in better oncologic outcomes by decreasing delays in initiation to adjuvant therapy.[44, 45]

The findings of our study should be interpreted in light of several other limitations. First, the heterogeneity of prehabilitation programs in the three pooled studies may have affected our results. It is possible that the survival benefit seen with prehabilitation was greater in patients who participated in supervised exercise sessions compared to those who were randomized to the home-based regimen. However, the sample size did not allow for a subgroup analysis. In

addition, since controls also underwent a preoperative multidisciplinary assessment, they may have implemented lifestyle changes as a result of their awareness of the study (Hawthorne effect). This phenomenon may have resulted in exposure misclassification in the control group and reduced the effect size of the association identified in our study.

Furthermore, while validated frailty measurement tools or questionnaires were not used in patient selection in the initial studies, patients with lower baseline functional capacity seem to benefit the most from prehabilitation; a greater effect on long-term oncologic outcomes may be observed in this subgroup of frail patients.[54] However, in our study, data were not available to compare frailty indices between groups. Similarly, a subgroup analysis of frail patients could not be performed. Nevertheless, since our study population may have included healthy patients who are at low-risk of post-operative complications and functional decline, the beneficial effect of prehabilitation could simply reflect the beneficial properties of physical activity rather than the reduction in postoperative morbidity and improvement in functional recovery. Additionally, both colon and rectal cancer patients were included in this study and oncologic outcomes may differ between these two subgroups. In our study, we identified a possibly better DFS in prehabilitation patients with rectal cancer, but the effect did not demonstrate statistical significance, perhaps reflecting our small sample size. Lastly, in the present study, we conducted a post hoc analysis of three pooled trials. Initial power calculation and randomization were therefore not conducted to assess long-term outcomes, which may impact our results.

3.7 Conclusion

In this report, prehabilitation was not associated with improvement in OS, which may be reflect the presence of type 2 error. However, despite the small sample size and heterogeneous study population, trimodal prehabilitation was associated with improved 5-year DFS in stage III colorectal cancer and independently predicted 5-year DFS for all stages on multiple regression analysis. This study may thus provide very preliminary evidence supporting the use of routine prehabilitation as an important adjunct in the treatment of primary non-metastatic colorectal cancer, but should be confirmed in larger prospective trials. Future studies examining the cost implications of this intervention should be conducted to better assess prospects for scale-up, and optimize cancer care.

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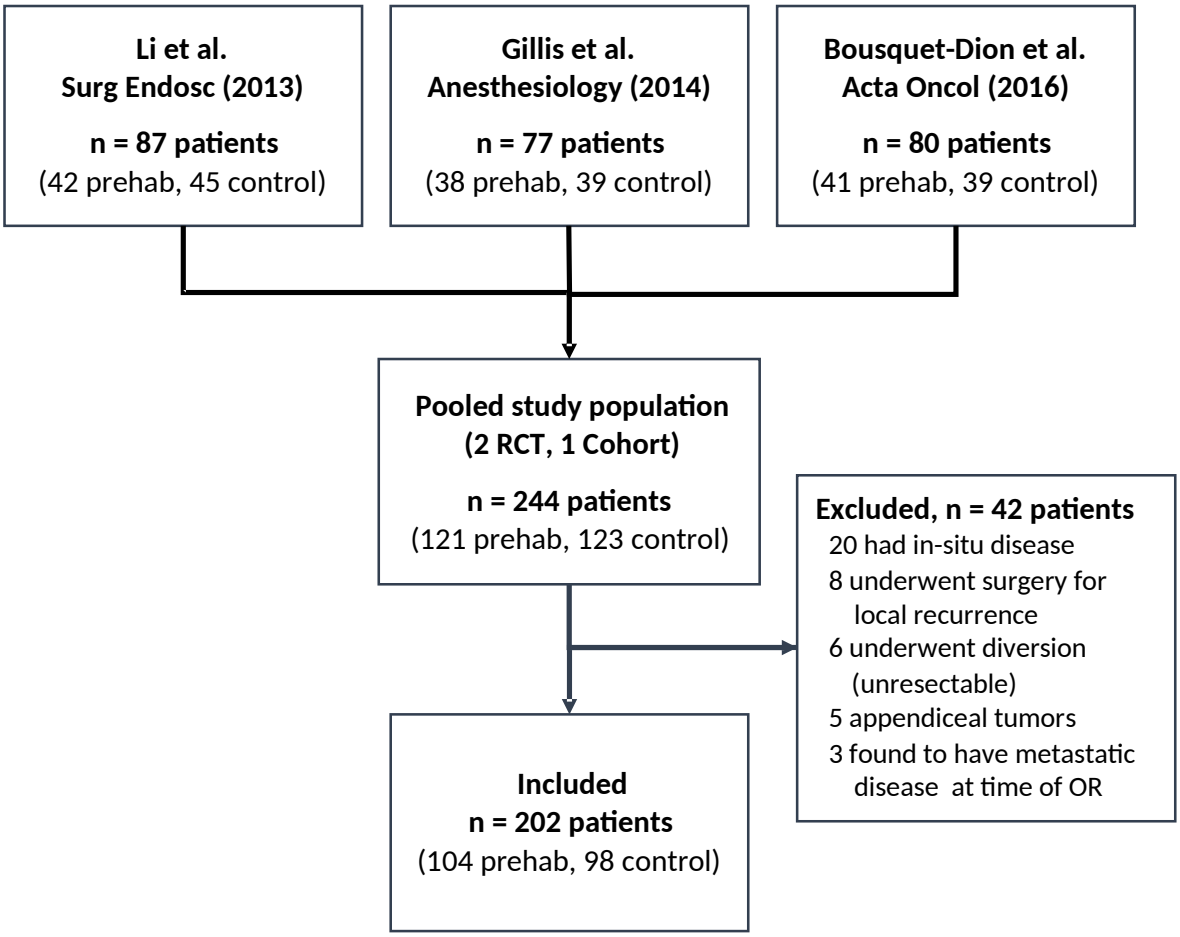
Li et al.
Surg Endosc (2013)
n = 87 patients
(42 prehab, 45 control)
Gillis et al.
Anesthesiology (2014)
n = 77 patients
(38 prehab, 39 control)
Bousquet-Dion et al.
Acta Oncol (2016)
n = 80 patients
(41 prehab, 39 control)
Pooled study population
(2 RCT, 1 Cohort)
n = 244 patients
(121 prehab, 123 control)
Excluded, n = 42 patients
20 had in-situ disease
8 underwent surgery for local recurrence
6 underwent diversion (unresectable)
5 appendiceal tumors
3 found to have metastatic disease at time of OR
Included
n = 202 patients
(104 prehab, 98 control)

Table 3.1 – Baseline characteristics and perioperative outcomes
Data presented as n(%) unless otherwise specified

Variables	**Prehab group n = 104**	**Control group n = 98**	**p-value**
Mean age, years (sd)	68.8 (11.3)	67.1 (10.6)	0.278
Male gender	61 (58.7)	63 (64.3)	0.411
Mean body mass index (sd)	27.3 (4.4)	27.6 (4.8)	0.606
ASA			
1	11 (10.6	12 (12.2)	0.598
2	68 (65.4)	57 (58.2)	
3	25 (24.0)	28 (28.6)	
4	0	1 (1.0)	
Procedure*			
RHC	33 (31.7)	25 (25.5)	0.295
LHC	10 (9.6)	6 (6.1)	
AR/SR	21 (20.2)	26 (26.5)	
LAR	29 (27.9)	31 (31.6)	
Subtotal	0	3 (3.1)	
APR	10 (9.6)	5 (5.1)	
Transverse	1 (1.0)	2 (2.0)	
Surgical approach			
Open	8 (7.7)	5 (5.1)	0.603
Laparoscopic	91 (87.5)	90 (91.8)	
Converted to open	5 (4.8)	3 (3.1)	
Stoma creation	28 (26.9)	33 (33.7)	0.296
Median length of stay, days (IQR)	4 (3-6.5)	4 (3-6)	0.777
30-day complications	40 (38.5)	32 (32.7)	0.389
Superficial SSI†	8 (7.7)	7 (7.1)	0.882
Deep SSI	4 (3.9)	6 (6.1)	0.528
Ileus	19 (18.3)	15 (15.3)	0.574
Cardiovascular	4 (3.9)	2 (2.0)	0.684
Respiratory	7 (6.7)	4 (4.1)	0.539
Severe 30-day complications (Clavien-Dindo ≥ 3)	6 (5.8)	5 (5.1)	0.835
30-day ER visits	17 (16.4)	15 (15.3)	0.840
30-day readmissions	10 (9.6)	12 (12.2)	0.549
30-day reoperation	1 (1.0)	2 (2.0)	0.612

*Procedure: RHC=right hemicolectomy, LHC=left hemicolectomy, AR/SR=anterior/sigmoid resection, LAR=low anterior resection, Subtotal=subtotal colectomy, APR=abdominoperineal resection, Transvers=transverse colectomy
†SSI=surgical site infection

Table 3.2 – Tumor characteristics
Data presented as n(%) unless otherwise specified

Variables	**Prehab group n = 104**	**Control group n = 98**	**p-value**
Tumor location			
Right-sided	34 (32.7)	27 (28.4)	0.766
Left-sided	31 (29.8)	32 (33.7)	
Rectal	39 (37.5)	36 (37.9)	
Neoadjuvant therapy	23 (59.0)	24 (66.7)	0.491
(y)pTNM			
0/1	36 (34.6)	37 (37.8)	0.910
2	32 (30.8)	31 (31.6)	
3	36 (34.6)	30 (30.6)	
(y)pT			
0/1	22 (21.2)	22 (22.5)	0.963
2	22 (21.2)	22 (22.5)	
3	52 (50.0)	47 (48.0)	
4	8 (7.7)	7 (7.1)	
(y)pN			
0	69 (66.4)	68 (69.4)	0.891
1	25 (24.0)	21 (21.4)	
2	10 (9.6)	9 (9.2)	
Total nodes, median (IQR)	19 (13-28)	19 (13-25)	0.989
Positive nodes, median (IQR)	0 (0-1)	0 (0-1)	0.565
Lymph node ratio ≥ 0.10	15 (48.4)	14 (56.0)	0.571
High-grade tumor	8 (7.7)	10 (10.3)	0.516
Lymphovascular invasion	38 (36.9)	35 (36.1)	0.905
Perineural invasion	35 (34.3)	28 (28.9)	0.409
Positive margins	4 (3.9)	3 (3.1)	1.000
Receipt of adjuvant chemotherapy	35 (33.7)	29 (29.6)	0.535
Timing of initiation of adjuvant chemotherapy in stage III	(n = 36)	(n = 30)	0.537
None	6 (16.7)	3 (10.0)	
≤ 56 days	24 (66.7)	19 (63.3)	
> 56 days	6 (16.7)	8 (26.7)	
Mean follow-up duration, months (sd)	59.2 (24.4)	63.0 (28)	0.179

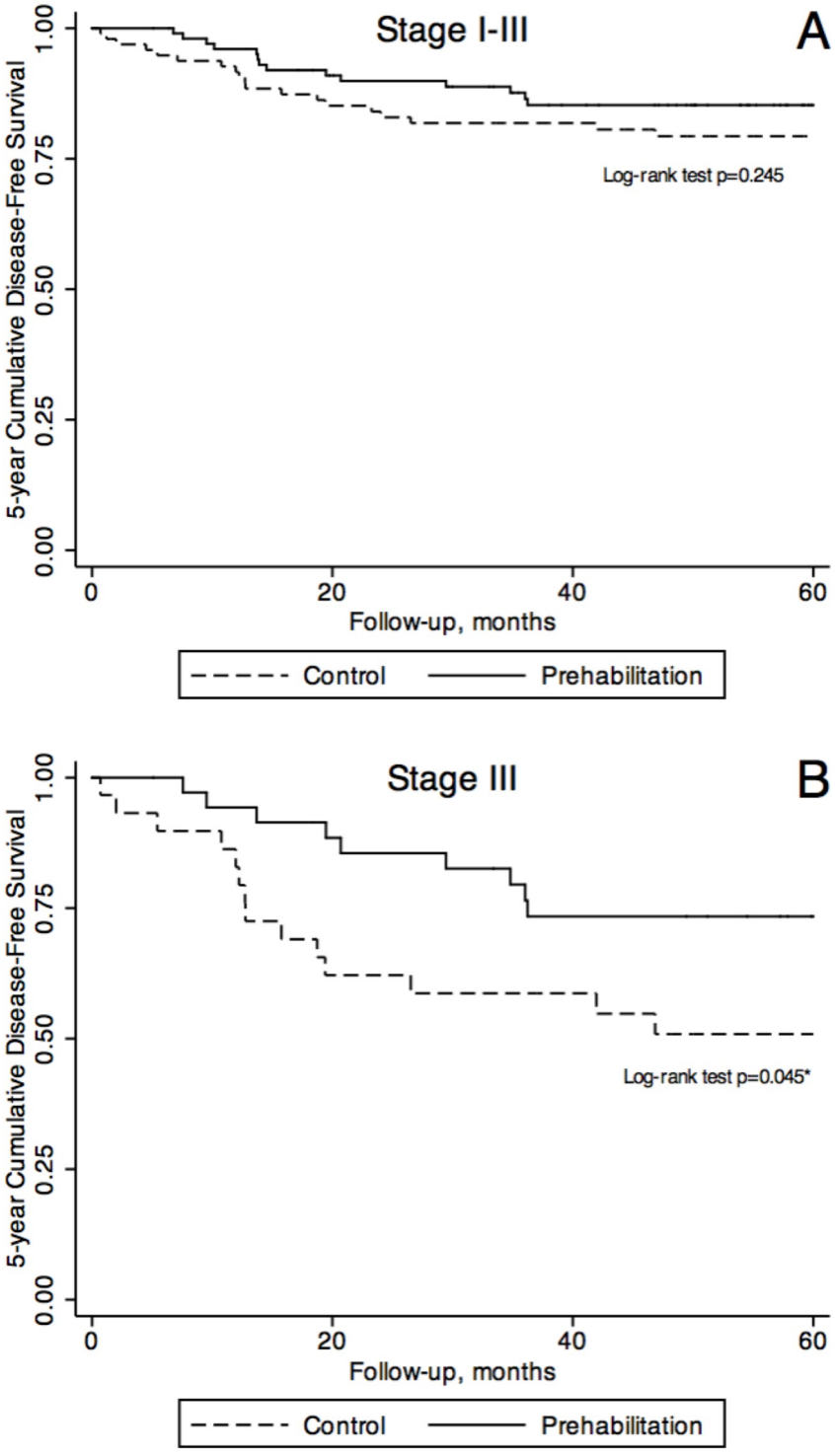

Figure 3.2 – Kaplan-Meier survival curves of 5-year disease-free survival in patients undergoing prehabilitation vs. control for A) all stages and B) stage III disease

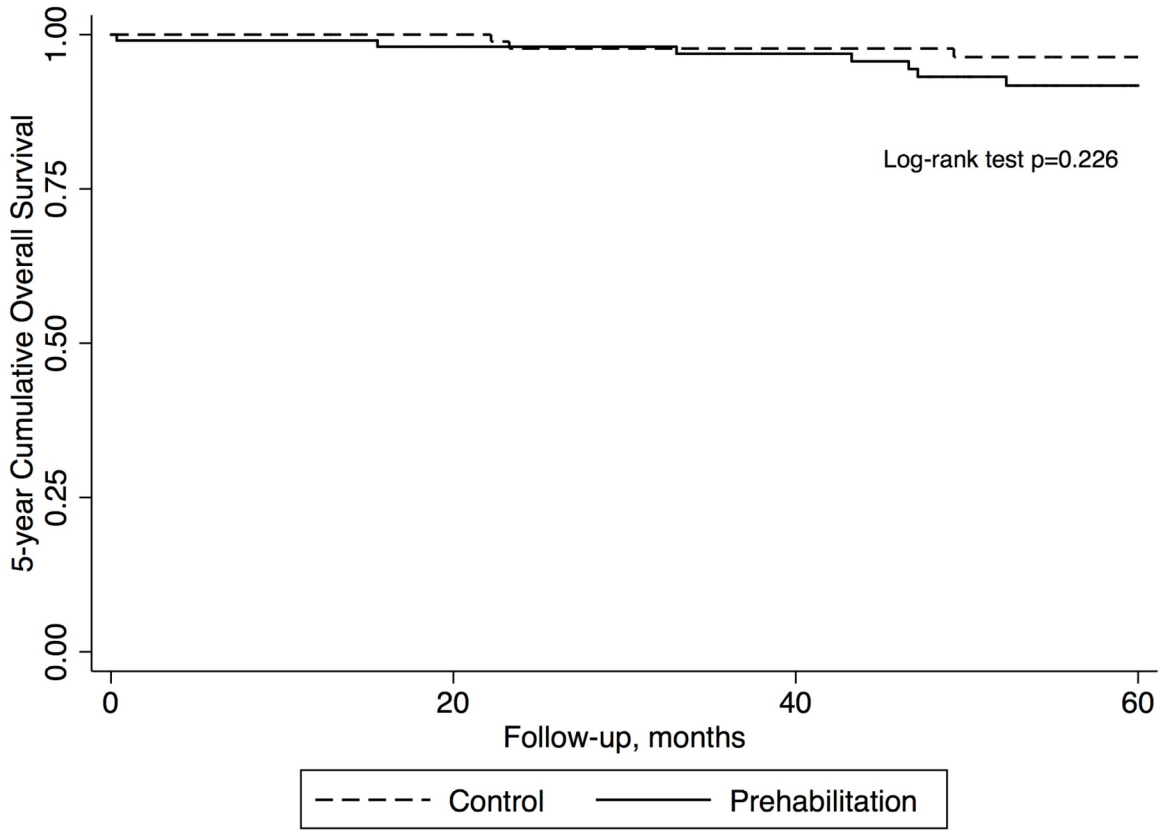

Figure 3.3 – Kaplan-Meier survival curves of 5-year overall survival in patients undergoing prehabilitation vs. control for all stages

Table 3.3 – Multivariate analysis of disease-free survival all stages and stage III*

Variables	**All stages** Hazard ratio (95% CI)	**Stage III** Hazard ratio (95% CI)
Age, per additional year	1.03 (1.00-1.07)	1.04 (0.99-1.08)
Male gender	1.23 (0.58-2.59)	1.16 (0.46-2.90)
ASA ≥ 3	0.65 (0.28-1.52)	0.46 (0.14-1.47)
Rectal surgery	0.78 (0.35-1.75)	1.01 (0.38-2.67)
Laparoscopy	0.43 (0.12-1.52)	0.36 (0.07-1.83)
Severe 30-day complications (Clavien-Dindo ≥ 3)	1.17 (0.15-9.24)	3.10 (0.34-28.19)
(y)pTNM stage		
1	ref	-
2	4.61 (0.97-21.89)	-
3	32.33 (5.81-179.94)	-
Positive margins	3.99 (1.22-13.06)	3.71 (1.09-12.70)
Adjuvant chemotherapy	0.40 (0.13-1.24)	0.32 (0.09-1.14)
Prehabilitation	0.45 (0.21-0.93)	0.26 (0.10-0.68)

*All covariates included the model are mentioned in the table

Table 3.4 – Multivariate analysis of Overall Survival for all stages*

Variables	**Hazard ratio**	**95% Confidence Interval**
Age	1.04	0.97-1.11
Male gender	1.10	0.31-3.93
ASA ≥ 3	0.65	0.13-3.11
Prehabilitation	1.99	0.50-8.02
Rectal cancer	0.38	0.08-1.86
Node-positive disease	1.37	0.16-11.88
Adjuvant chemotherapy	0.77	0.09-6.66

*All covariates included the model are mentioned in the table

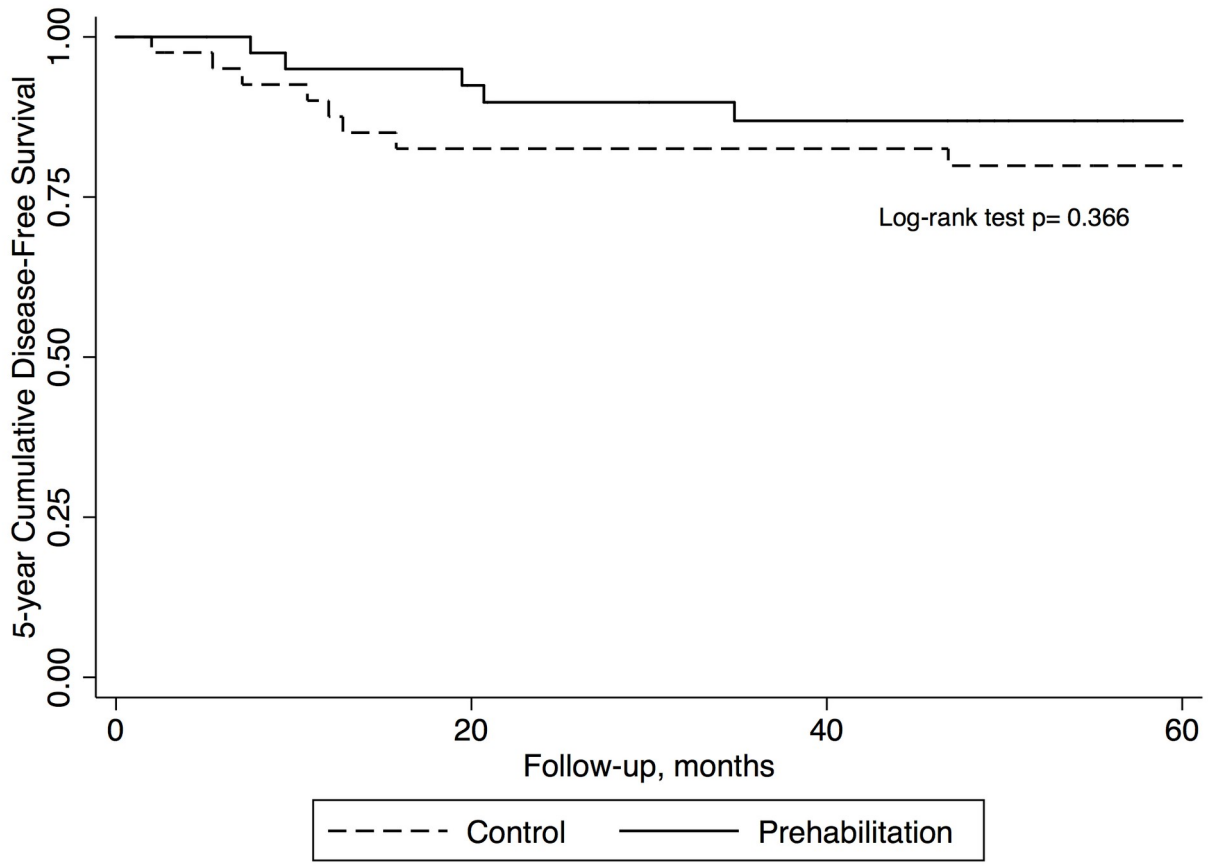

Figure 3.4 – Kaplan-Meier survival curves of 5-year disease-free survival in rectal cancer patients undergoing prehabilitation vs. control for all stages

Table 3.5 – Multivariate analysis of survival for subgroup of rectal cancer patients*

Variables	**DFS** Hazard ratio (95% CI)
Age, per additional year	1.03 (0.97-1.10)
Male gender	0.99 (0.28-3.46)
ASA ≥ 3	0.20 (0.01-2.73)
Severe 30-day complications (Clavien-Dindo ≥ 3)	2.96 (0.28-31.38)
(y)pTNM stage	
1	ref
2	omitted, no events
3	134.43 (7.81-2314.94)
Neoadjuvant therapy	0.68 (0.16-2.95)
Positive margins	4.26(0.77-23.52)
Adjuvant chemotherapy	0.10 (0.01-0.63)
Prehabilitation	0.20 (0.05-0.86)

*All covariates included the model are mentioned in the table

Table 3.6 – Treatment characteristics of rectal cancer patient subgroup
Data presented as n(%) unless otherwise specified

Variables	**Prehab group n = 39**	**Control group n = 36**	**p-value**
cTNM			
1	7 (18.0)	5 (13.9)	0.471
2	11 (28.2)	15 (41.7)	
3	21 (53.9)	16 (44.4)	
Receipt of neoadjuvant therapy			
Overall	23 (59.0)	24 (66.7)	0.491
cTNM 2	10 (90.9)	12 (80.0)	0.614
cTNM 3	13 (61.9)	12 (75.0)	0.491
Type of neoadjuvant therapy			
Brachytherapy	1 (4.4)	5 (20.8)	0.015
Short-course	7 (30.4)	13 (54.2)	
Long-course	15 (65.2)	6 (25.0)	
Mean time-to-surgery following neoadjuvant therapy, days (SD)	58.5 (14.5)	60.8 (13.5)	0.574

CHAPTER 4 – The Impact of Delays to Definitive Surgical Care on Survival in Colorectal Cancer Patients

4.1 Preamble to Manuscript 2

The study presented in chapter 3 identified a potential disease-free survival benefit from prehabilitation for patients undergoing curative colorectal cancer resection, especially those with stage 3 disease. In this pooled secondary analysis, the median duration of the program was 29 days (IQR 20-40) from enrolment to surgery and was mainly determined by the wait time to surgery, which largely depends on healthcare resources.

In 2007, the Cancer Reform Strategy published by the National Health Service (NHS) Cancer Plan in the United Kingdom provided updated guidelines on wait-time benchmarks that included a maximum 1-month wait from diagnosis to first treatment for all cancers.[84] Similar guidelines have been adopted in several other countries to ensure timely access to care and treatment. In Canada, a 28-day interval between diagnosis and surgery is targeted for colon cancer while the initial treatment of rectal cancer should be initiated within 6–8 weeks.[85]

In the study presented in chapter 3, the interval between cancer diagnosis and surgery in the pooled trials was not reported. It was thus unclear whether patients enrolled in prehabilitation programs comply with the wait-time benchmarks, although the median prehabilitation time was longer than the 28-day benchmark. There is conflicting evidence on the effect of delays to surgery on colorectal cancer outcomes.[40, 86-89] By corollary, there exist concerns about the consequences of prolonging the preoperative period to allow for prehabilitation on overall and disease-free survival that should be investigated prior to

implementation of prehabilitation programs as adjuncts to cancer care. This will be examined in manuscript 2 presented below, which addresses objective 2 of this thesis.

MANUSCRIPT 2: The Impact Of Delays To Definitive Surgical Care On Survival In Colorectal Cancer Patients

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4.2 Abstract

Introduction: Treatment delay may have detrimental effects on cancer outcomes. The impact of longer delays on colorectal cancer outcomes remains poorly described. The objective of this study was to determine the effect of delays to curative-intent surgical resection on survival in colorectal cancer patients.

Methods: All adult patients undergoing elective resection of primary non-metastatic colorectal adenocarcinoma from 01/2009-12/2014 were reviewed. Treatment delays were defined as time from tissue diagnosis to definitive surgery, categorized as <4, 4 to <8 and ≥8weeks. Primary outcomes were 5-year disease-free(DFS) and overall survival(OS). Statistical analysis included Kaplan-Meier curves and Cox regression models.

Results: A total of 408 patients were included(83.2%colon;15.8%rectal) with a mean follow-up of 58.4 months(SD29.9). Fourteen percent(14.0%) of patients underwent resection <4weeks, 40.0% 4 to <8weeks and 46.1% ≥8weeks. More rectal cancer patients had treatment delay ≥8weeks compared to colonic tumors(69.8% vs. 41.4%,p<0.001). Cumulative 5-year DFS and OS were similar between groups(p=0.558;p=0.572). After adjusting for confounders, surgical delays were not independently associated with DFS and OS.

Conclusions: Treatment delays >4 weeks were not associated with worse oncologic outcomes. Delaying surgery to optimize patients can safely be considered without compromising survival.

4.3 Introduction

Despite advances in surgical techniques, perioperative care and adjuvant systemic therapies, it is estimated that 25-40% of colorectal cancer patients experience disease recurrence in the first 5 years following definitive surgical treatment.[1, 2] Efforts at identifying modifiable risk factors for poor oncologic outcomes are thus needed to improve cancer outcomes, and delays to definitive surgical resection have recently been recognized as a target for improvement.[3-5] In fact, several studies conducted in breast and lung cancer patients have reported that treatment delays have detrimental effects on survival.[3-5]

For colorectal cancer, current standards target 28 days from date of diagnosis to definitive treatment. However, several patient-level and healthcare system factors may influence the time interval between colorectal cancer diagnosis and surgical resection, and delays are not uncommon.[6] Several previous studies have assessed the effect of treatment delays on long-term colorectal cancer outcomes, but reported conflicting results.[6-10] The majority of these studies did not include data on disease-free survival and did not adjust for postoperative complications, a well-known predictor of poor oncologic outcomes.[7, 11-21]

Given the equivocal data on the impact of treatment delays, the optimal time to surgery is unknown. The preoperative setting may be used to optimize patients' baseline functional status to better tolerate surgery and hasten recovery.[22-25] In addition, there is evidence showing that poor baseline functional status is associated with worse long-term cancer outcomes.[26, 27] Consequently, there might be a role for preoperative optimization programs in colorectal cancer care. However, these programs may require longer preoperative intervals to maximize effect and may thus delay time to definitive resection. It is unknown whether longer treatment

delays will impact oncologic outcomes. Therefore, the objective of this study was to determine the effect of delays to curative-intent surgical resection on disease-free and overall survival in colorectal cancer patients.

4.4 Materials and Methods

4.4.1 Study design and population

A retrospective cohort study including all adult patients undergoing elective resection of primary, biopsy-proven, non-metastatic colorectal cancer from January 2009 to December 2014 was conducted at a single high-volume specialist referral centre. The cohort included both colon and rectal cancer patients. Emergency surgeries performed for bleeding, obstruction, and perforation were excluded, defined as patients who were admitted from the emergency department and operated on during the same admission. Subjects with in-situ disease or histology other than colonic adenocarcinoma were excluded from the study. Patients who received neoadjuvant therapy were also excluded. Patients with pulmonary nodules, liver lesions or retroperitoneal lymphadenopathy noted on preoperative imaging with low initial suspicion for metastatic disease, but recognized to be malignant in the early postoperative period, were also excluded from this study. The study protocol was approved by the local institutional review board.

4.4.2 Outcomes and Variables

Patient charts and electronic medical records were reviewed by the study team. Baseline demographics (age, gender, comorbidities measured using the American Society of Anesthesiologists score, body mass index), operative characteristics, perioperative outcomes

(30-day emergency department visits, readmissions and complications scored using the Clavien-Dindo (CD) classification[28] with severe complications defined as a CD score ≥3), TNM staging, tumor characteristics (location, grade, margin status, lymphovascular and perineural invasion), receipt of systemic adjuvant therapy and survival data were collected retrospectively. Lymph node ratio was calculated based on available data and dichotomized as <0.10 and ≥0.10.[29] Treatment delays were defined as the time between tissue diagnosis (date of initial biopsy) and definitive surgery, and grouped into <4 weeks, 4 to <8 weeks and ≥8 weeks, based on the 28-day target for surgery.

The primary outcomes of this study were 5-year disease-free (DFS) and overall survival (OS). Last date of contact and vital status at last contact were used to measure OS. Recurrence was determined from the review of all surveillance computed tomography scan and colonoscopy reports performed as per routine surveillance guidelines following curative resection of colorectal cancer.[30] DFS was defined as the time interval from surgery to the date of imaging/endoscopic test revealing metastatic disease or local recurrence.

4.4.3 Statistical Analysis

Data are represented as n (%) for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables. The three groups (<4 weeks, 4 to <8 weeks and ≥8 weeks) were compared. Univariate analyses were performed using one-way analysis of variance to compare means of continuous variables, Kruskal-Wallis rank test for medians of continuous variables and $\chi 2$ test for categorical variables. A subgroup comparison of stage III disease patients was performed to assess and compare chemotherapy-related

outcomes between groups, including time to initiation of systemic therapy from date of surgery, which we analyzed using Kaplan–Meier survival analysis. Kaplan–Meier survival curves were generated to describe 5-year DFS and OS, and log-rank tests were used to compare the cumulative survival distributions. Multiple regression analyses were performed using Cox proportional hazard models to identify independent predictors of 5-year DFS and OS, adjusting for potential confounders (age, gender, ASA ≥ 3, laparoscopic approach, rectal tumor, TNM stage, severe postoperative complications and receipt of adjuvant systemic therapy). All analyses were performed using STATA 12.1 (StataCorp, College Station, TX).

4.5 Results

A total of 408 patients were included (84.2% colon;15.8% rectal), with a mean interval from tissue diagnosis to surgery of 56 days(SD 28) (median of 53 days (IQR 37-70)). The mean follow-up duration was 58.4 months (SD29.9). Fifty-seven patients (14.0%) underwent resection <4 weeks, 163 (40.0%) at 4 to <8 weeks and 188 (46.1%) ≥8 weeks. Baseline demographics are shown in Table 4.1. Age and gender were similar between groups, but patients included in the <4 and ≥8 weeks groups were more comorbid when compared to the 4 to <8 weeks group.

Tumor characteristics were well-balanced between groups (Table 4.1). Lymph node harvest as well as lymph node ratio were also similar between groups. However, patients with right-sided tumors were more likely to undergo surgical resection within 4 weeks of tissue diagnosis. Conversely, a significantly larger proportion of rectal cancer patients had treatment delay ≥8 weeks when compared to patients with colonic tumors (69.8% vs. 41.4%, p<0.001). This difference was also reflected in the type of procedures and proportion of patients

undergoing stoma creation with a significantly higher proportion of low anterior resections, abdominoperineal resections and new stomas in the ≥8 weeks group. Furthermore, TNM stages did not differ between groups and a similar proportion of patients received adjuvant systemic therapy in all three groups. The mean time to initiation of adjuvant chemotherapy from date of surgery was 70.8 days (SD 22.9) for stage III disease and did not differ between groups, as illustrated in Figure 4.1.

On Kaplan-Meier survival analysis, there were no differences in cumulative 5-year DFS between groups for the overall cohort (<4 weeks 77.7% vs. 4-8 weeks 82.5% vs. ≥8 weeks 83.9%, log-rank p=0.432)(Figure 4.2A). OS was also similar between the three groups (94.1% vs. 89.0% vs. 90.4%, log-rank p=0.572)(Figure 4.3A). Similar results were observed for patients with stage III disease (Figures 4.2B and 4.3B). After adjusting for possible confounders, surgical delays were not independently associated with DFS and OS (Table 4.3). Older age and higher TNM stages predicted worse DFS and OS in all regression models. Conversely, laparoscopic approach and receipt of adjuvant systemic chemotherapy were independently associated with improved survival. Subgroup analysis reported comparable results for patients with stage 3 disease.

4.6 Discussion

In colorectal cancer, the current body of literature evaluating the effect of treatment delays on overall and disease-free survival is limited. Published studies have measured treatment delays inconsistently and reported conflicting results.[6-10] A significant proportion of patients experience disease recurrence following curative surgical resection of colorectal

tumors and the impact of treatment delays on oncologic outcomes needs to be defined as it may represent a modifiable risk factor for poor cancer outcomes.[1, 2] The objective of this study was therefore to determine the effect of delays to curative-intent surgical resection on disease-free and overall survival in colorectal cancer patients.

In our cohort, only 14% of patients met current colorectal cancer care benchmarks. This represents a significantly lower proportion of patients than previously reported. Flemming et al. reported a median time to surgery of 24 days[6] while other studies reported that 40-44% of included patients underwent surgery within 4 weeks of diagnosis.[8, 9] However, the definition used for date of diagnosis was heterogeneous between studies, varying from date of first investigation identifying the malignancy to date of multidisciplinary meeting confirming diagnosis.[6, 8, 9] In our data, it is unclear if treatment delays primarily occurred prior to initial colorectal surgical assessment, reflecting delays in referral, or whether healthcare resource allocation or timeliness of preoperative staging and investigations also played a role in delaying receipt of definitive care. It is also worth mentioning that these previously published studies were conducted in different countries with different healthcare systems which may limit comparisons. Nevertheless, in the present study, patients who experienced treatment delays of 4 to <8 weeks and ≥8 weeks did not have inferior 5-year DFS or OS than those who received prompt surgical treatment. These data are concordant with several other studies that found no association between time to surgery and survival in colorectal cancer patients.[6, 8, 10, 31] Additionally, cumulative survival in our cohort was similar to what is reported in the literature.[6, 8, 10, 31, 32] Moreover, treatment delays did not predict worse survival after adjustment for

confounders, including severe postoperative complications, a known confounder that has not often been considered in previous studies.[7, 13-21]

Furthermore, in our cohort, rectal cancer patients experienced longer treatment delays than those with colonic tumors, which may also explain the higher stoma creation rate in that group. These findings may explained by the fact that rectal cancer patients often undergo additional imaging with magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS). They are also often presented preoperatively at multidisciplinary tumor boards since the surgical decision making process for rectal tumors is more complex and requires more multidisciplinary input than colonic tumors. This may explain some of the treatment delays observed in our cohort.

The results of our study may be explained by the relatively slow growth of colorectal adenocarcinomas. Most colorectal cancers arise from the adenoma-adenocarcinoma sequence, which may take more than 10 years to progress to malignancy.[33, 34] This contrasts with the biology of certain other malignancies, such as lung cancer, that are recognized to progress significantly faster.[35] Therefore, delaying definitive surgical care by several weeks in colorectal cancer patients may not have a significant impact on long-term outcomes, as observed in the present study. However, the current body of literature investigating the effect of treatment delay on colorectal cancer upstaging and resectability is very limited and tumor biology heterogeneity may challenge this hypothesis.

A previous study by Flemming and colleagues examined factors influencing the interval from colorectal cancer diagnosis to surgery and identified many elements responsible for treatment delays, including healthcare resources and patient-related factors.[6] In their study,

older age and comorbid illnesses both predicted longer time to surgery.[6] Although these findings were not reproduced in our study, longer times to surgery in a frail patient population may offer the opportunity for preoperative optimization without significantly altering our practice. There is evidence suggesting that improving preoperative baseline functional status may improve long-term cancer outcomes, either by reducing postoperative morbidity or by influencing the timing of initiation and tolerability of adjuvant chemotherapy.[17, 18, 27, 36] In our cohort, treatment delays ≥8 weeks did not lead to worse outcomes suggesting that there is a safe preoperative window to optimize patients preoperatively without negatively impacting cancer outcomes as a result of disease progression. Our study findings may minimize concerns about the use of preoperative optimization programs in the context of colorectal cancer[22-24], as any associated delay in surgery has limited impact and is outweighed by benefits such as better ability to tolerate adjuvant systemic therapy.

However, treatment delays may result in significant psychological distress and decreased perceived health state and quality of life for patients.[37] It is well established that patients with colorectal cancer have a high prevalence of psychological distress and depression.[38] The heightened psychological distress induced by added treatment delays may be a driver for faster time to surgery in healthcare systems that are less constrained by operative room availability. However, the potential benefit of delaying surgery to optimize performance status and improve postoperative outcomes must be balanced with the negative impact of decreased patient satisfaction with care and quality of life.

The results of our study should be interpreted in light of several limitations. First of all, it may be underpowered to detect small survival differences due to the small number of events

observed in our cohort. Furthermore, data related to chemotherapy regimen completion, cycle interruption and chemotherapy-related complications that may affect oncologic outcomes were not available and therefore could not be considered in the analysis. Additionally, indication for initial colonoscopy (screening vs. presence of symptoms) was not obtainable, because many patients underwent initial endoscopic evaluation at other institutions before surgical referral. Therefore, we could not assess lead-time bias. Furthermore, the indication for surgery was not available for this study, and therefore we could not determine if the patients in the <4 week group were symptomatic and may have had more advanced tumors, although TNM stage distribution and other tumor characteristics between the three study groups were similar.

Lastly, our study population was somewhat heterogeneous in that both colon and rectal cancer patients were included. The rectal cancers were largely upper rectal and rectosigmoid cancers, which have the same prognosis as colon cancer.[39] In our study, a subgroup analysis could not be conducted for rectal cancer patients given the small number of observed events (recurrences and deaths) in this subgroup. Furthermore, since patients who received neoadjuvant therapy were excluded, our study population did not include patients with locally advanced rectal cancer. Hence, our results are not generalizable to all rectal cancer patients.

4.7 Conclusion

In this study, delays longer than 28 days from time of colorectal cancer diagnosis to surgery were not associated with worse oncologic outcomes, even in stage 3 disease. Furthermore, patients who underwent definitive surgical resection ≥ 8 weeks from date of

tissue diagnosis did not experience poorer cancer outcomes. It is likely that the time to definitive resection may not necessarily need to be within 28 days of diagnosis, so that the preoperative period may be safely prolonged, when needed, to optimize patient preoperative status though prehabilitation programs. However, in the absence of potential patient benefit from preoperative optimization programs, unwarranted delays should still be avoided.

4.8 References

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Table 4.1 – Baseline demographics and tumor characteristics
Data presented as n(%) unless otherwise specified

Variables	**Overall n=408**	**<4 weeks n=57**	**4 to <8 n=163**	**≥8 weeks n=188**	**p-value**
Mean age, years (SD)	69.8 (11.2)	71.0 (12.1)	69.0 (10.9)	70.1 (11.1)	0.646
Male gender	224 (54.9)	26 (45.6)	88 (54.0)	110 (58.5)	0.220
ASA† score ≥ 3	149 (36.5)	23 (40.4)	45 (27.6)	81 (43.1)	0.009
Body mass index(BMI), kg/m^2	27.0 (4.8)	26.2 (4.6)	27.0 (4.1)	26.1 (5.4)	0.003
Tumor location					
Right	215 (53.6)	38 (69.1)	92 (56.8)	85 (46.2)	0.000
Left	123 (30.7)	16 (29.1)	52 (32.1)	55 (29.9)	
Rectal	63 (15.7)	1 (1.8)	18 (11.1)	44 (23.9)	
TNM stage					0.123
I	122 (29.9)	11 (19.3)	44 (27.0)	67 (35.6)	
II	149 (36.5)	24 (42.1)	65 (39.9)	60 (31.9)	
III	137 (33.6)	22 (38.6)	54 (33.1)	61 (32.5)	
T stage					0.214
T1	62 (15.2)	5 (8.8)	21 (12.9)	36 (19.2)	
T2	81 (19.9)	9 (15.8)	29 (17.8)	43 (22.9)	
T3	204 (50.0)	33 (57.9)	88 (54.0)	83 (44.2)	
T4	61 (15.0)	10 (17.5)	25 (15.3)	26 (13.8)	
N stage					0.352
N0	271 (66.4)	35 (61.4)	109 (66.9)	127 (67.6)	
N1	90 (22.1)	18 (31.6)	32 (19.6)	40 (21.3)	
N2	47 (11.5)	4 (7.0)	22 (13.5)	21 (11.2)	
Lymph node harvest ≥ 12	357 (87.5)	50 (87.7)	144 (88.3)	163 (86.7)	0.897
Lymph node ratio ≥ 0.10 (N+ disease)	77 (56.2)	8 (36.4)	35 (64.8)	34 (55.7)	0.076
High grade/poorly differentiated	46 (12.5)	8 (14.8)	17 (11.7)	21 (12.5)	0.842
Lymphovascular invasion	150 (40.9)	23 (41.8)	60 (41.1)	67 (40.4)	0.980
Perineural invasion	132 (36.2)	18 (32.7)	57 (39.3)	57 (34.6)	0.580
Positive margins	7 (1.9)	2 (3.6)	3 (2.0)	2 (1.2)	0.381
Receipt of adjuvant chemotherapy (overall)	111 (27.2)	18 (31.6)	44 (27.0)	49 (26.1)	0.713
Receipt of adjuvant chemotherapy (stage III)	105 (76.6)	17 (77.3)	41 (75.9)	47 (77.1)	0.987
Mean follow-up duration, months (SD)	58.4 (29.9)	66.1 (29.2)	55.5 (30.2)	58.6 (29.7)	0.953

†ASA=American Society of Anesthesiologists

Table 4.2 – Perioperative characteristics and outcomes
Data presented as n(%) unless otherwise specified

Variables	Overall n=408	<4 weeks n=57	4 to <8 n=163	≥8 weeks n=188	p-value
Procedure†					0.004
RHC	212 (52.0)	38 (66.7)	91 (55.8)	83 (44.2)	
LHC	38 (9.3)	6 (10.5)	14 (8.6)	18 (9.6)	
AR/SR	85 (20.8)	10 (17.5)	38 (23.3)	37 (19.7)	
LAR	56 (13.7)	1 (1.8)	17 (10.4)	38 (20.2)	
Subtotal	4 (1.0)	2 (3.5)	1 (0.6)	1 (0.5)	
Total	3 (0.7)	0	0	3 (1.6)	
APR	7 (1.7)	0	1 (0.6)	6 (3.2)	
Transverse	3 (0.7)	0	1 (0.6)	2 (1.1)	
Surgical approach					0.154
Laparoscopic	334 (81.9)	41 (71.9)	133 (81.6)	160 (85.1)	
Conversion to open	8 (2.0)	2 (3.5)	2 (1.2)	4 (2.1)	
Open	66 (16.2)	14 (24.6)	28 (17.2)	22 (12.8)	
Stoma creation	35 (8.6)	0	9 (5.5)	26 (13.8)	0.000
30-day complications					
Total	177 (43.5)	23 (41.1)	73 (44.8)	81 (43.1)	0.879
Severe complications (Clavien-Dindo ≥ 3)	35 (8.6)	5 (8.8)	16 (9.8)	14 (7.5)	0.737
Cardiac	18 (4.5)	1 (1.8)	6 (3.7)	11 (5.9)	0.423
Respiratory	26 (6.5)	1 (1.8)	10 (6.2)	15 (8.1)	0.248
Ileus	67 (16.7)	10 (18.1)	21 (13.0)	36 (19.6)	0.247
Superficial SSI‡	23 (5.7)	3 (5.5)	13 (8.0)	6 (3.8)	0.237
Deep SSI‡	25 (6.1)	3 (5.3)	13 (8.0)	9 (4.8)	0.489
30-day Emergency Room visits	61 (16.4)	7 (15.2)	30 (19.9)	23 (13.1)	0.295
30-day readmissions	43 (11.6)	5 (10.9)	22 (14.6)	16 (9.1)	0.312
30-day reoperations	11 (2.9)	1 (1.8)	6 (4.0)	4 (2.3)	0.700
Median LOS§, days (IQR)	4 (4)	4 (5)	4 (4)	4 (5)	0.826

†Procedure: RHC=right hemicolectomy, LHC=left hemicolectomy, AR/SR=anterior/sigmoid resection, LAR=low anterior resection, Subtotal=subtotal colectomy, Total=total, APR=abdominoperineal resection, Transverse=transverse colectomy
‡SSI=surgical site infection
§LOS=length of stay

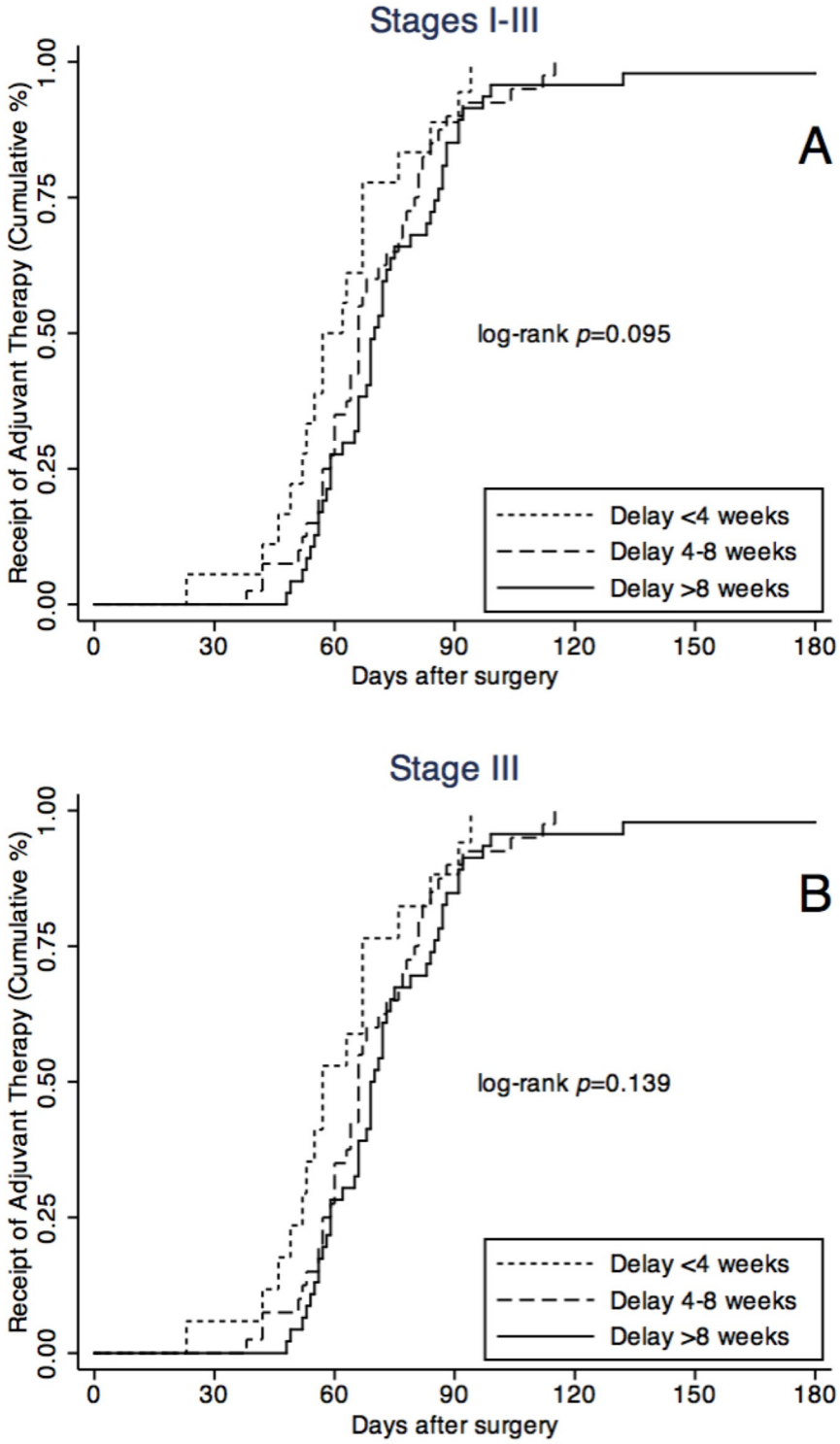

Figure 4.1 – Time to initiation of adjuvant systemic therapy from date of surgery in A) all stages combined and B) stage III disease

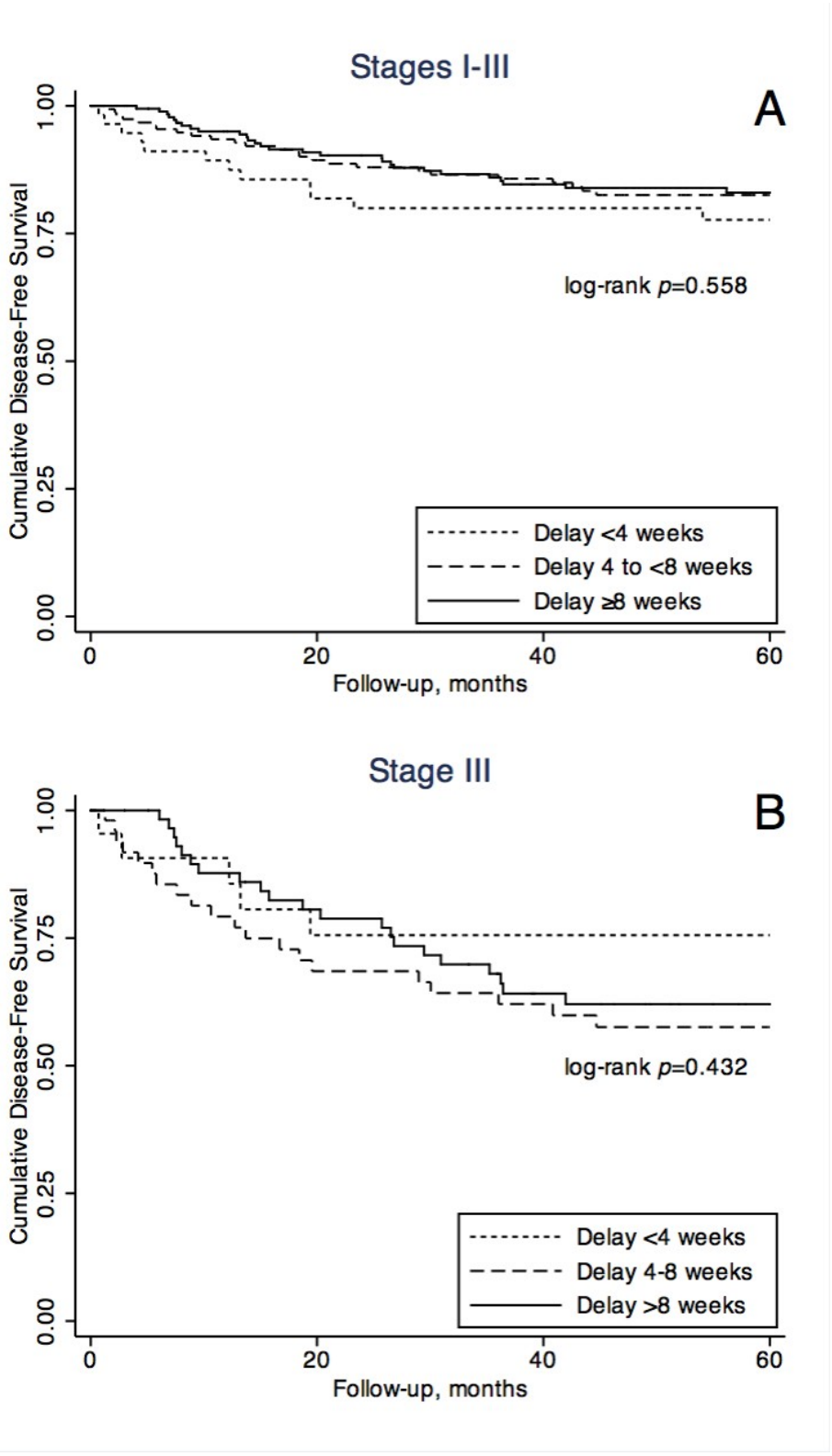

Figure 4.2 – Disease-free survival in A) all stages combined and B) stage III disease

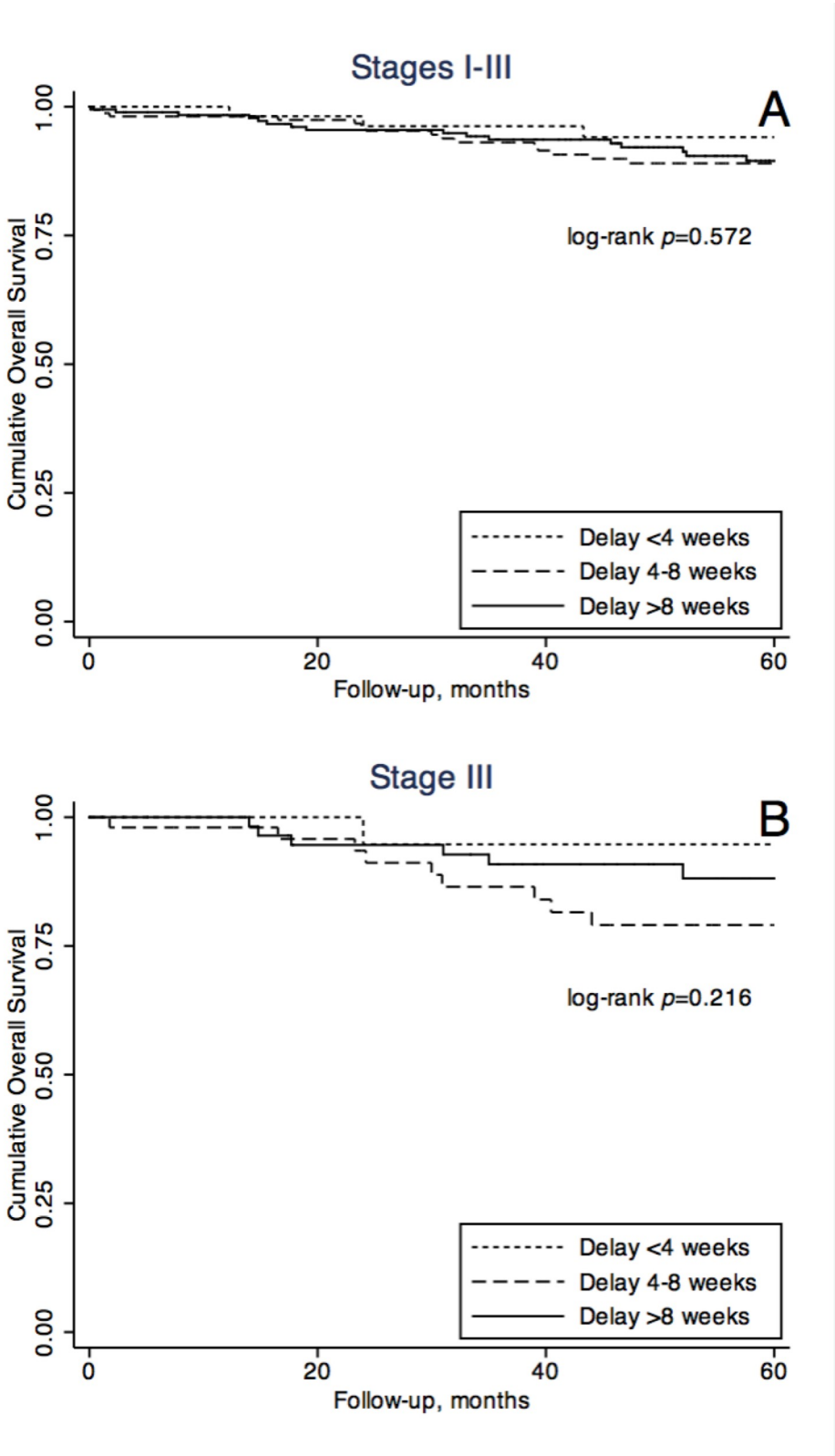

Figure 4.3 – Overall survival in A) all stages combined and B) stage III disease

Table 4.3 – Multivariate analysis of disease-free survival and overall survival, all stages combined*

	Disease-free survival HR (95%CI)	**Overall survival HR (95% CI)**
Delay to surgery		
<4 weeks (ref.)	–	–
4 to <8 weeks	0.96 (0.47-1.95)	2.51 (0.70-9.03)
≥ 8 weeks	0.86 (0.42-1.78)	2.15 (0.59-7.81)
Age, per additional year	1.03 (1.00-1.05)	1.07 (1.02-1.11)
Male gender	1.34 (0.80-2.26)	1.81 (0.84-3.87)
ASA† score ≥ 3	0.96 (0.55-1.67)	1.96 (0.96-4.01)
Rectal tumors	1.23 (0.63-2.38)	2.23 (0.90-5.53)
Laparoscopy	0.61 (0.33-1.11)	0.34 (0.15-0.75)
TNM stage		
Stage I (ref.)	–	–
Stage II	3.13 (1.03-9.53)	4.58 (1.29-16.33)
Stage III	23.25 (7.49-72.13)	16.38 (4.22-63.53)
Severe complications (Clavien-Dindo ≥ 3)	1.18 (0.24-2.87)	1.36 (0.51-3.62)
Adjuvant systemic therapy	0.48 (0.24-0.97)	0.21 (0.07-0.63)

*All covariates included the model are mentioned in the table

†ASA=American Society of Anesthesiologists

CHAPTER 5 – Discussion

5.1 General Findings

This thesis investigated the effect of trimodal prehabilitation on long-term oncologic outcomes in a population of patients undergoing curative colorectal resection for non-metastatic colorectal cancer. Evidence supports the use of prehabilitation to improve functional capacity, complications and recovery after major abdominal surgery. There is also increasing evidence to support the association of physical activity, nutrition and psychosocial factors with long-term cancer outcomes.[32, 42-47, 67, 68, 80, 90] However, previous studies have not assessed the synergistic effect of a trimodal prehabilitation program on colorectal cancer outcomes. In this thesis, we did not observe an association between prehabilitation and overall survival, likely owing to type 2 error given sample size. However, we demonstrated that trimodal prehabilitation is associated with improved disease-free survival in stage 3 disease patients and was an independent predictor of decreased recurrence for all stages combined, after adjusting for other risk factors. This effect was most significant in the stage 3 disease subgroup.

However, functional changes with prehabilitation require several weeks. In response to concerns about prolonging wait time to surgery due to prehabilitation, we investigated the effect of delays to curative colorectal cancer resection on long-term oncologic outcomes. As presented in manuscript 2, we did not identify a significant association between surgical delays beyond current wait-time benchmarks and disease-free as well as overall survival. We concluded that there may in fact be a safe preoperative window for prehabilitation programs.

This thesis provides preliminary evidence to support the use of routine prehabilitation as an adjunct to cancer care and adds to the body of literature suggesting that the time to definitive surgery may not necessarily need to be within 28 days of colorectal cancer diagnosis.

5.2 Discussion of Methodology

5.2.1 Study Designs

Although study designs and their limitations were briefly addressed in both manuscripts presented in chapters 3 and 4, a more thorough discussion will be presented below.

It is first important to highlight the limitations of a pooled analysis as presented in manuscript 1 and how these may affect the interpretation of our results. First of all, we pooled data from three trials for the analysis and it can be questioned whether the studies were too heterogenous to be combined. In this thesis, the pooled studies shared identical inclusion and exclusion criteria and the study populations did not differ significantly. Nevertheless, while the prehabilitation program components were similar across studies, the most recent study included a weekly supervised exercise session, which may have resulted in improved compliance with the program and therefore introduced heterogeneity between intervention groups.[43] However, adherence (or compliance) was measured differently across studies and can therefore not be statistically compared. The most recent trial by Bousquet-Dion et al. used attendance at supervised sessions as a surrogate measure of compliance while the other two studies asked patients to report compliance with the home-based program. Despite possible differences in compliance with the intervention, the mean preoperative change in 6MWT was similar between intervention groups in all three studies: 40 (SD40) meters in Li et al.[45], 25.2

(50.2) in Gillis et al.[44] and 21 (47) in Bousquet-Dion et al.[43] The minimal clinically important difference for 6-minute walk test distance of adults has been reported to range between 14.0 and 30.5 meters.[91] This suggests that the effect of prehabilitation was similar across the included studies, and therefore that the addition of a supervised component may not have resulted in significant heterogeneity. The most significant difference between studies lies in the study design. Li et al. was an observational study whereas the other two studies were randomized controlled trials. With an observational design, patients are not randomized to the intervention, which may introduce an imbalance in confounding variables. However, Li et al was designed as a pre- and post-intervention study, and the majority of patient baseline characteristics were similar between the pre- and post-intervention groups and comparable to the other two trials. These data suggest that only very minimal imbalance was introduced and pooling was reasonable.

Since the study presented in manuscript 1 is a secondary analysis of previous trials, our sample size was limited by the size of the initial trials. Certainly, the three pooled studies were not conducted to evaluate long-term cancer outcomes and were instead powered primarily to assess the impact of prehabilitation on functional capacity, functional recovery and 30-day postoperative morbidity. Therefore, it is possible that our study was underpowered to detect a significant difference in overall survival between groups. We did not perform an a priori sample size or power calculations since additional patients could not be added to our cohort to improve power. However, post-hoc power calculation yielded a power of 0.53 (with 35 deaths in 202 patients with an adjusted HR of 1.99 for prehabilitation). We thus recognize that there may be concerns about possible type 2 error in our study, especially given our limited sample

size. However, it is very difficult to demonstrate statistically significant difference in overall survival in colorectal cancer studies given the high 5-year survival rate and low number of events. In fact, many landmark studies in colorectal cancer management have failed to show significant differences in overall survival, but reported improved disease-free survival.[92-96] A small number of trials, such as the MOSAIC trial, have demonstrated a difference in overall survival, but these included thousands of patients.[97] Moreover, disease-free survival has been shown to be a good surrogate marker for overall survival and we believe that our conclusion is supported by our data.[98-102]

It is also important to address the fact that the pooled trials were not designed to answer the research question of interest. Since the present analysis was not pre-specified in the original protocols, it could be considered post hoc. However, in this thesis, the research question and statistical analysis were specified before the data were acquired. In addition, data from previous studies were pooled prior to outcome ascertainment, which was retrospectively performed, minimizing any possible concerns about data dredging. Data dredging involves the misuse of data during which many statistical tests are performed after data collection to identify any possible significant results that are then kept and published.[103]

Furthermore, as briefly mentioned in the discussion of the first manuscript, concerns about multiple testing may be raised. This phenomenon typically arises when several subgroups analyses or a set of different hypotheses are tested simultaneously. The greater the number of statistical inferences tested, the more likely it is to observe a statistically positive result due to chance and introduce type 1 error. In this thesis, subgroup analyses for stage 3 and rectal

cancer patients were performed for disease-free survival. A significantly better 5-year disease-free survival was observed with prehabilitation in the stage 3 disease subgroup, while other analyses did not reveal statistically meaningful differences. Although this should be cautiously interpreted in the context of multiple comparison bias, the results of our multiple regression analysis argue against such bias. In fact, our Cox proportional hazard regression model identified an independent association between prehabilitation and recurrences for all stages combined. Although we recognize the risk of introducing type 1 error when performing multiple subgroup analyses, the results of our multiple regression analysis for the overall cohort compare to those of our stage 3 subgroup univariate survival analysis. In addition, there are several plausible hypotheses to explain our findings that make us confident that the interpretation of our results is not subject to multiple comparison bias. For instance, the improved functional capacity achieved with prehabilitation may potentially improve timely delivery and tolerance of adjuvant systemic chemotherapy, which may result in better oncologic outcomes.[34] However, data on chemotherapy was not reliably available and this hypothesis could not be tested in our cohort.

It is also important to emphasize that the first manuscript presented in this thesis was a hypothesis-generating study that will need to be reproduced in larger cohorts. With the growing evidence supporting the use of prehabilitation to hasten recovery and reduce perioperative morbidity, the interest for prehabilitation programs is increasing. However, despite promising results, the existing body of literature does not provide enough evidence to reallocate healthcare resources to this type of intervention, especially given the lack of cost-utility analysis of such programs. For this reason, most patients are not currently routinely

enrolled in a prehabilitation program and most studies focus on frail patients and not necessarily cancer patients. Therefore, the implications of designing an appropriately powered prospective study to assess long-term oncologic outcomes are substantial and must take into account the cost associated with prehabilitation, perioperative care, rehabilitation and survivorship. The ideal study design to answer our research question would be a multicenter randomized controlled trial to allow for the recruitment of a large number of cancer patients to achieve adequate sample size and statistical power to detect a clinically relevant difference in overall survival as well as disease-free survival over a relatively short period of time to account for changes in treatment modalities over time. However, the healthcare resources and cost required to design such study are substantial and are likely the limiting factors in its realization.

With regards to the second manuscript presented, the ideal study design would also be a randomized controlled trial to account for baseline differences between groups that also impact the timing of resection. However, despite our study showing no association between surgical delays and survival, other studies have shown contradictory results suggesting that the true effect has yet to be determined.[40, 86-89] Therefore, given the possible risk of worse outcomes with added delays and the psychological distress associated with longer cancer treatment wait times, it would be unethical to randomize patients to longer delays.[104-106] Furthermore, surgical delays are heterogeneously defined in the literature and there are no accepted standard definitions. In our study, cutoff values were chosen according to governmental benchmarks for cancer care.

5.2.1 Analysis

Some elements of the statistical analyses presented in manuscripts 1 and 2 will be discussed in further details below.

First of all, in this thesis, both studies presented assessed 5-year disease-free and overall survival. In addition to univariate comparisons, Kaplan-Meier survival curves were used to describe and compare cumulative survival distributions between groups. This approach was favoured over the life table since timing of events were precisely known in our cohort and prespecified time intervals were not required. Kaplan-Meier survival analyses have two main assumptions: 1) censoring (i.e. loss to follow-up) is not related to the event of interest (either death or cancer recurrence in this thesis); and 2) the risk of events is stable over time within each time interval.[107] In this thesis, the reasons for loss to follow-up were not known, but were assumed to be independent of cancer outcomes. Furthermore, the risk of recurrence or death may vary over time in our cohort of patients with colorectal cancer. In fact, it has been recognized that the risk of disease recurrence is highest in the first two years following curative colorectal cancer resection.[108-110] However, the Kaplan-Meier model allows intervals with different survival rates while assuming that survival is constant within each interval.[111] In this thesis, significantly more events were observed in the first 2 years following resection. Since events were more frequently observed, the time intervals between each event computed in our Kaplan-Meier analysis were shorter during the initial two person-years of follow-up. This can be observed in figure 3.2. With the time intervals being shorter, it is less likely that the rate of events varied significantly within those intervals. For this reason, we believe that the second assumption is met in this thesis. In addition, we do not believe there were significant secular

trends that could have impacted survival rates. There were no major changes in practice, surgical management or adjuvant systemic therapies over the study time periods. In summary, the use of Kaplan-Meier survival analysis was appropriate in this thesis and its assumptions were not violated.

A Cox proportional hazard model was also used in both manuscripts presented in this thesis to identify independent predictors of recurrence and death. This regression model follows a semi-parametric distribution and is commonly used to investigate the simultaneous effect of several variables on survival time. In a Cox proportional hazards regression model, the measure of effect is the hazard rate, which is the risk of "failure" (i.e. the risk of experiencing the event of interest), given that the patient has survived up to a specific time. However, in most cases, this model is used to compare groups and reporting the hazard ratio between groups is more relevant. One of the main advantages of using a Cox proportional hazard model is that it does not require or assume knowledge of the baseline hazard rate and estimates relative rather than absolute rates for the different levels of the covariates. In this thesis, a Cox proportional hazard model was chosen over other regression models to account for the fact that the primary outcomes were measured as time intervals (i.e. time to death for overall survival and time to recurrence for disease-free survival). Furthermore, comparing mean time-to-event between groups using a t-test or linear regression would ignore censoring. In addition, comparing proportion of events in our groups using odds (risk) ratios via logistic (binomial) regression would ignore impact of time on the outcomes and would assume that time-at-risk was similar for all patients included in the cohort.

There are several important assumptions for appropriate use of the Cox proportional hazards regression model, including 1) independent survival times between subjects, 2) multiplicative relationship between the predictors and the hazard, and 3) a constant hazard ratio over time. We believe that all assumptions were met in both analyses performed. Although the hazard rate for recurrence may be higher in the first two years following curative resection, it should be similarly higher in both groups so that the ratio between groups remain constant over the follow-up period.

The choice of model covariates should also be discussed. There are different ways to build a multiple regression model and choose predictors to include. In this thesis, specific covariates for our model were chosen based on a priori knowledge about colorectal cancer, especially risk factors for cancer recurrence. Accordingly, baseline demographics and previously described risk factors for oncologic outcomes, such as tumor stage, receipt of adjuvant systemic therapy, margin status, etc. were included.[21, 34, 41] It is important to note that not all previously described predictors were significant in our analysis, which is likely related to our sample size and presence of type 2 error. Using subject matter knowledge to build a multivariate model is the approach most widely accepted among epidemiologists and is preferred over the stepwise identification of confounders or the change-in-estimate method. Furthermore, it is important to acknowledge that the number of covariates adjusted for in our regression models was limited by our sample size and the low rates of events in our cohorts. A larger number of events may result in a more accurate and precise estimation of regression coefficients and confidence intervals, but we are still confident that the model selection used in both manuscripts was appropriate.

5.3 Future Directions

Despite the increasing evidence showing that prehabilitation can improve functional status, recovery, postoperative outcomes and long-term oncologic outcomes, there are still several gaps in our understanding of the optimal program (duration, components, effectiveness, etc.) and how to appropriately select patients who may benefit most from the intervention. Patients with frailty, malnutrition, multiple comorbidities, major depression, planned extensive surgery or cancer treatments seem to benefit the most from such programs, at least in terms of short term outcomes.[112, 113] The ideal assessment method has not yet been clearly defined. Physicians' subjective assessment of functional capacity and frailty before surgery has been shown to have very poor accuracy, highlighting the need for objective risk assessment tools.[50] Yet the available surgical risk prediction scores remain inaccurate.[114] Furthermore, the findings of manuscript 1, where there were potentially long-term impacts on cancer outcomes in an unselected group suggests that there may be wider benefits in the cancer care continuum beyond the frail patient.[83]

While most prehabilitation studies focus on short-term clinical and functional outcomes, it remains unclear whether this is the appropriate outcome measure. The most relevant short- and long-term outcomes that truly matter to patients may not be captured by current studies.[115] As we shift towards patient-centered care, patient-reported outcomes such as disability-free survival should be taken into account. Furthermore, we should investigate patient preferences as they may consider cancer outcomes more important than short-term functional recovery. Identifying patients who may benefit from multimodal prehabilitation

programs may thus go beyond functional recovery and short-term outcomes and may need to be individualized according to patient needs and preferences. Our understanding of patient preferences in the context of recovery and outcome measures after prehabilitation thus need to be further expanded.

Finally, cost implications of prehabilitation programs need to be assessed in future studies. Prehabilitation has the potential to decrease hospital length of stay and postoperative complications and hasten functional recovery allowing patients to return to their normal daily activities, including work, sooner after surgery. This thesis has also shown that it may decrease cancer recurrence, which may result in fewer patients requiring surgical re-intervention, radiotherapy or additional systemic therapy. The improved outcomes achieved with prehabilitation are promising and may have the potential to reduce healthcare costs. However, prehabilitation programs are costly and require a dedicated multidisciplinary team. Cost-utility analyses should be to be conducted to determine if healthcare resources should be specifically allocated to this intervention and identify efficient strategies to implement programs. It is possible that some patient subgroups benefit most from the intervention, such as frail elderly subjects. It will be interesting to assess whether prehabilitation is most cost-effective in this group of patients at higher risk of poor perioperative and long-term oncologic outcomes.

CHAPTER 6 – Conclusions

To our knowledge, this thesis was the first to report the association between preoperative trimodal prehabilitation programs and colorectal cancer outcomes following curative resection of colorectal adenocarcinoma. In manuscript 1, we reported an improved 5-year disease-free survival in colorectal cancer patients with stage 3 disease. Prehabilitation also independently predicted lower recurrence in all stages. In manuscript B, we reported that surgical delays beyond current wait time benchmarks did not negatively impact survival in colorectal cancer patients undergoing curative resection. Our findings provide intriguing, but nonetheless preliminary, evidence supporting the use of trimodal prehabilitation programs in non-metastatic colorectal cancer patients scheduled for resection.

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