Understanding the impact of bowel dysfunction and permanent colostomy on health related quality of life in patients with rectal cancer

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A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Masters of Science in Epidemiology

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Abstract

Introduction:

The surgical treatment of rectal cancer involves either Permanent Colostomy (PC) or Restorative Proctectomy (RP). Both of which have been found to have a negative impact on health-related quality of life (HRQOL) for their own reasons. Patients with PC suffer the long term consequences of living with a stoma and patients with RP can have varying degrees of bowel dysfunction that can be debilitating. Current studies evaluating HRQOL and predicting bowel dysfunction lack relevance to patients and providers.

Objectives:

1) identify patients at highest risk of severe bowel dysfunction following RP and 2) compare HRQOL in patients treated with PC versus those with varying degrees of bowel dysfunction after RP.

Methods:

Following institutional ethics approval, and using a mixed methods approach in which both quantitative and qualitative data were collected and analyzed, patients were prospectively recruited into the institution's rectal cancer registry starting in 2018. Patients who were treated in the preceding 5 years were also eligible for inclusion. 1) In patients undergoing RP pre-treatment bowel dysfunction was measured using the Low Anterior Resection Syndrome (LARS) score at initial referral to colorectal surgery. The LARS score is a 5-item weighted questionnaire that categorizes patients as having no LARS, minor LARS or major LARS. Predicted pretreatment LARS scores were then calculated using normative data from the general public for each patient. Observed pretreatment LARS categories were then compared to predicted and post-treatment LARS categories (collected at least one year from final operation)

using Pearson's chi-square. Multiple multinomial regression was also performed to evaluate pre-treatment LARS category as a predictor of post treatment categories. 2) Patient with tumors within 10cm of the anal-verge treated with either RP or PC were administered the Patient-Generated Index (PGI) at least 1 year following their final operation. The PGI is an individualized HRQOL measure that consists of identifying up to 5 HRQOL domains most affected by a given condition then weighting their importance based on individual patient values to generate a score of 0 (poor HRQOL) to 100 (best HRQOL). PGI scores were compared between a) PC and RP and b) PC and LARS subgroups using multiple linear regression. Qualitative analysis of HRQOL domains was done through linking verbatim patient reports to the International Classification of Functioning. Proportions and frequencies were compared using Z-test of proportions.

Results:

1) 121 patients were included with 58 = no LARS, 34 = minor LARS and 29 = major LARS prior to treatment. Overall, patients with rectal cancer were more likely to have bowel dysfunction than the general public with male patients and older patients being the most affected (Table 2). Further, pre-treatment LARS category was significantly associated with post-treatment LARS category (p=0.037). When evaluating pre-treatment LARS category as a predictor of post-treatment LARS category pre-treatment LARS category was found to be a significant predictor of post-treatment LARS (table 4). 2) 121 patients were included with PC = 39 and RP = 82 (53% no/minor LARS and 47% major LARS). Overall, patients with PC had significantly lower quality of life scores than those with RP (Table 2). However, patients with major LARS scored similarly to those with PC (Table 2). On content analysis, PC patients reported more problems with sexual function, body image, and sports (Table 3). RP patients reported more problems with sleep, using transportation, and taking care of oneself (Table 3).

Conclusion:

Overall, patients treated with RP tend to have higher overall HRQOL scores. However, patients with major LARS appear to have no significant HRQOL benefit over those with PC. Therefore, using pre-treatment LARS scores and individual patient values, the shared decision making process can help guide patients and providers in making an informed choice in the treatment of rectal cancer.

Résumé

Introduction:

Le traitement chirurgical du cancer du rectum implique soit une colostomie permanente (CP), soit une proctectomie réparatrice (PR). Il a été constaté que ces deux interventions ont un impact négatif sur la qualité de vie liée à la santé (QVLS) pour leur propres raisons. Les patients ayant subi une CP souffrent des conséquences à long terme de la vie avec une stomie et les patients ayant subi une PR peuvent présenter des degrés divers de dysfonctionnement intestinal qui peuvent être débilitants. Les études actuelles évaluant la QVLS et prédisant le dysfonctionnement intestinal manquent de pertinence pour les patients et les prestataires.

Objectifs:

1) identifier les patients présentant le risque le plus élevé de dysfonctionnement intestinal sévère après une PR et 2) comparer la QVLS chez les patients traités par CP par rapport à ceux présentant divers degrés de dysfonctionnement intestinal après une PR.

Méthodes:

Après approbation éthique institutionnelle, et en utilisant une approche de méthodes mixtes dans laquelle des données quantitatives et qualitatives ont été collectées et analysées, les patients ont été recrutés prospectivement dans le registre du cancer du rectum de l'institution à partir de 2018. Les patients qui ont été traités au cours des 5 années précédentes étaient également éligibles pour l'inclusion. 1) Chez les patients subissant une PR, la dysfonction intestinale avant traitement a été mesurée à l'aide du score du syndrome de résection antérieure basse (LARS) lors de l'orientation initiale vers la chirurgie colorectale. Le score LARS est un questionnaire pondéré en 5 points qui classe les patients selon qu'ils n'ont pas de LARS, qu'ils ont un LARS mineur ou un LARS majeur. Les scores LARS prédits avant traitement ont

ensuite été calculés en utilisant des données normatives du grand public pour chaque patient. Les catégories de LARS observées avant traitement ont ensuite été comparées aux catégories de LARS prédites et post-traitement (recueillies au moins un an après l'opération finale) à l'aide du chi-carré de Pearson. Une régression multinomiale multiple a également été réalisée pour évaluer la catégorie LARS avant traitement comme prédicteur des catégories après traitement. 2) Les patients présentant des tumeurs à moins de 10 cm de la verge anale et traités par PR ou CP ont été soumis à l'indice généré par le patient (IGP) au moins un an après leur opération finale. L'IGP est une mesure individualisée de la QVLS qui consiste à identifier jusqu'à 5 domaines de QVLS les plus affectés par une condition donnée, puis à pondérer leur importance en fonction des valeurs individuelles du patient pour générer un score de 0 (mauvaise QVLS) à 100 (meilleure QVLS). Les scores IGP ont été comparés entre a) les sous-groupes CP et PR et b) CP et LARS en utilisant la régression linéaire multiple. L'analyse qualitative des domaines de la QVLS a été réalisée en reliant les rapports verbatim des patients à la Classification Internationale du Fonctionnement. Les proportions et les fréquences ont été comparées à l'aide du test Z des proportions.

Résultats:

1) 121 patients ont été inclus avec 58 = pas de LARS, 34 = LARS mineur et 29 = LARS majeur avant le traitement. Dans l'ensemble, les patients atteints d'un cancer du rectum étaient plus susceptibles de souffrir de dysfonctionnement intestinal que le grand public, les hommes et les patients plus âgés étant les plus touchés (tableau 2). De plus, la catégorie de LARS avant traitement était significativement associée à la catégorie de LARS après traitement (p=0,037). Lorsque l'on évalue la catégorie de LARS avant traitement comme prédicteur de la catégorie de LARS après traitement, on constate que la catégorie de LARS avant traitement est un prédicteur significatif du LARS après traitement (tableau 4). 2) 121 patients ont été inclus avec CP = 39 et PR = 82 (53% de LARS non/mineur et 47% de LARS majeur). Dans l'ensemble, les

patients avec CP avaient des scores de qualité de vie significativement plus bas que ceux avec PR (tableau 2). Cependant, les patients souffrant d'un LARS majeur ont obtenu un score similaire à celui des patients atteints de PR (tableau 2). Dans l'analyse de contenu, les patients atteints de CP ont signalé plus de problèmes liés à la fonction sexuelle, à l'image corporelle et aux sports (tableau 3). Les patients atteints de PR ont signalé plus de problèmes de sommeil, d'utilisation des transports et de prise en charge de soi (tableau 3).

Conclusion:

Dans l'ensemble, les patients traités par PR ont tendance à avoir des scores globaux de QVLS plus élevés. Cependant, les patients présentant un LARS majeur ne semblent pas bénéficier d'un avantage significatif en termes de QVLS par rapport aux patients traités par PR. Par conséquent, en utilisant les scores LARS avant traitement et les valeurs individuelles des patients, le processus de prise de décision partagée peut aider à guider les patients et les prestataires à faire un choix éclairé dans le traitement du cancer du rectum.

Acknowledgements

I would like to thank Dr. Lawrence Lee the principal investigator for both studies included in this thesis for his mentorship in both the context of research and in surgery. Throughout the process of study design, data collection, data analysis, manuscript drafting and thesis writing he has been consistently available to offer guidance and constructive feedback. I am very grateful to have had the opportunity to learn from him and this thesis would not have been possible without his ongoing support and mentorship.

I would also like to thank Dr. Julio F. Fiore Jr. and Dr. Liane S. Feldman for their mentorship, feedback and support throughout the course of study design and writing. Their feedback has been incredibly valuable and has helped me substantially in the process of carrying out these projects and writing this thesis. I feel very fortunate to have had the opportunity to be included in the Steinberg-Bernstein Centre for Minimally Invasive Surgery.

Lastly, I would like to thank Dr. Anna Wang, Michael F. Maalouf and Zoe Atsaidis for their contributions to data collection, literature review and manuscript editing. Their help has made the research process organized and efficient.

Contribution to original knowledge

The work presented in this thesis contributes two main findings to the field of rectal cancer. First, in Chapter 2 we describe and test a novel approach to predicting LARS following the treatment of rectal cancer with surgery. Previous prediction models lack accuracy and therefore, there is significant room for improvement. Therefore, we evaluate the use of pre-treatment symptoms as a predictor of post-treatment symptoms based on the hypothesis that the patient and tumor characteristics that contribute to pre-treatment bowel dysfunction may be related to those that contribute to LARS following treatment. Second, in Chapter 3, we evaluate HRQOL outcomes using a patient-centric HRQOL measure that has not been previously used to compare HRQOL in patients treated with the two main surgical treatments for rectal cancer. Ultimately, Chapter 3 contributes an understanding of HRQOL outcomes from the patient perspective which has not been done in this population.

Contribution of Authors

Thesis

Stephan Robitaille (SR) was the primary author for both manuscripts included in this thesis and was the principal author of the thesis itself. For all components of this thesis SR was the primary author responsible for data collection and analysis. SR was also the primary author responsible for review of literature and writing. Dr. Lawrence Lee (LL) was the principle thesis supervisor and the primary investigator for the rectal cancer research program at the McGill University Health Centre. LL contributed significantly in each component of this thesis including but not limited to study design, review of statistical analyses and evaluating written work. Further, LL provided great mentorship and support throughout the process of application to the Masters program to completion of the final thesis.

Manuscript 1

Predictors of pre- and post-treatment bowel dysfunction severity in patients with rectal cancer

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Study conceptualization and design: SR, JFF, LSF, LL Data collection: SR, AW Data analysis: SR, LL Writing: SR, AW, LL Revision: SR, AW, SL, PC, BS, JFF, LSF, LL

Manuscript 2

The impact of restorative proctectomy vs. permanent colostomy on health related quality of life following rectal cancer surgery

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Study conceptualization and design: SR, JFF, LSF, LL

Data collection: SR, MFM, RP, TGJ

Data analysis: SR, LL

Writing: SR, LL

Revision: SR, MFM, SL, JFF, LSF, LL

Chapter 1: Introduction

Epidemiology

In 2021 there were an estimated 24,800 new cases of colorectal cancer (CRC) in Canada, accounting for 10-12% of new cancer diagnoses making it the third leading cause of cancer nationwide.¹ More importantly, CRC is associated with the second highest mortality rate after cancers of the lung and bronchi and is responsible for 11-12% of all cancer related deaths in Canada.¹ Generally, cancers of the colon and rectum are grouped together under the umbrella term CRC largely because they share many similarities in their histopathologic characteristics.² However, there are different anatomic and embryologic considerations between cancers that arise from the colon and those that arise from the rectum that ultimately drive differences in treatment and prognosis.^{2,3} Overall, 29-35% of new CRC cases will originate in the rectum and therefore will require a different approach from the treating team when compared to colon cancer.^{4,5}

Anatomy

The rectum is the distal-most segment of the gastro-intestinal tract, commonly measures approximately 15 centimeters in length and is characterized by the absence of bands of longitudinal muscle called "taenia coli".³ Furthermore, the rectum has distinct differences in the make up of capillary network, blood supply and lymphatic drainage when compared to the colon which is thought to be related to the different physiologic functions and embryologic development of the organs.^{6,7} Specifically, the colon is primarily an absorptive organ and the rectum primarily serves as a storage vesicle.^{2,8} In addition to these structural and physiologic differences, the rectum also resides deep in the pelvis, is mostly extraperitoneal and is in close

proximity to urogenital organs, pelvic nerves and major blood vessels.⁷ Moreover, in the context of rectal cancer, the rectum is subdivided into low, middle or high based on distance to the anal verge in which the tumor is located.⁷ This distance is colloquially referred to as "tumor height" by healthcare providers who treat rectal cancer. This subclassification is critical as the distal most aspect of the rectum merges with the anal canal which contains the anal sphincter muscles - the major contributors to fecal continence.³ As a result, these anatomic features are central to the symptoms, management and side-effects of rectal cancer treatment.

Symptoms and diagnosis

Overall, the majority of patients with newly diagnosed rectal cancer initially present with symptoms of new rectal bleeding, change in bowel habits or pain in the abdomen or rectum.⁹ In particular, patients with low tumors also report symptoms of tenesmus which is the sensation of incomplete evacuation of the rectum.¹⁰ Importantly, many individuals in the general public may experience some degree of bowel dysfunction at baseline.¹¹ However, the understanding of the degree of symptomatic change in bowel function for those with rectal cancer is limited.⁹ As a result, the contribution of a rectal tumor on bowel dysfunction may be difficult to interpret without examination, investigation or further research. During a physical exam, the initial identification of a lesion can be made using a digital rectal exam in the case of low tumors.⁵ However, formal diagnosis of rectal cancer is made using the combination of endoscopy and biopsy for histopathologic confirmation of disease.⁵ Following the diagnosis of rectal cancer, the staging process typically includes pelvic imaging in the form of endo-rectal ultrasound or pelvic magnetic resonance imaging to evaluate loco-regional spread and computed tomography of the chest and abdomen to evaluate for distant metastases.⁵ Combined with a thorough history, physical exam and interdisciplinary discussion, these investigations can help guide the potential

treatment strategies available to the patient.⁵ In particular, sphincter function, frailty and patient preferences should be considered in the shared decision making process.

Management

Following the appropriate staging and work-up of a patient, treatment typically involves one of or a combination of surgery, radiotherapy or chemotherapy.¹² With surgery being the mainstay of treatment.¹³ The surgical management of rectal cancer has evolved extensively over the last century with Dr. Ernest Miles describing the first abdominal perineal excision (also referred to as abdominal perineal resection) in 1908 (Figure 1).¹⁴ Modern iterations of this procedure although technically advanced are associated with significant morbidity largely secondary to permanent colostomy (PC) or perineal wound issues since the procedure involves excision and closure of the perineum and externalization of the bowel through the abdominal wall with a PC.¹⁵⁻¹⁷ As a result, most patients would prefer the alternative surgical approach of restorative proctectomy (RP) which involves reconnecting the bowel to the remnant rectum or anus if feasible in a given case (Figure 2).¹⁸ Ultimately, many RP patients will be given a temporary stoma to allow the bowel connection to heal by diverting effluent through the abdominal wall into a bag rather than through the new bowel connection in order to reduce the risk of complication or reoperation.¹⁹ However, most patients have this temporary stoma reversed within months of the initial surgery and therefore have the chance to avoid a permanent stoma.²⁰ The feasibility of RP is largely dependent on tumor height and the presence of invasion into adjacent structures such as the external anal sphincter.²¹ The absence of invasion into the external anal sphincter allows the surgeon to perform an intersphincteric resection where the tumor is excised while both preserving the external anal sphincter and achieving a negative resection margin (Figure 3).²¹ The ability to offer RP rather than PC in patients with low rectal cancers has principally been

afforded by advancements in neoadjuvant chemotherapy and radiotherapy that contribute to tumor downstaging and ultimately the potential for a negative resection margin required for RP.^{21,22} Importantly, these two operative approaches have comparable oncologic outcomes in several propensity matched studies.^{23–25} Therefore, it is important to consider patient values and patient experience in the decision making process if both options are available. Similar to PC, RP is associated with its own set of issues that are well documented in the literature with most patients developing bowel dysfunction (BD) in the form of Low Anterior Resection Syndrome (LARS) after surgery.²⁶



Figure 1: Abdominal perineal resection with permanent colostomy.²⁷



Figure 2: Restorative proctectomy with reconnection of the bowel continuity.²⁷



Figure 3: Anatomy of the sphincter muscles and planes of intersphincteric resection.²⁸

Low Anterior Resection Syndrome

LARS constitutes a constellation of symptoms including incontinence to liquid and solid stool. frequency of bowel movements, urgency, and a phenomenon known as clustering where patients need to evacuate their bowel shortly after having done so already.²⁶ Several methods have been used to evaluate bowel dysfunction in this context including the LARS score, the Wexner score and the Memorial Sloan Kettering Bowel Function Instrument.^{26,29,30} However, the LARS score has been considered superior in the context of clinical research as the Wexner score predominantly measures incontinence and neglects other key components of bowel dysfunction experienced by patients with LARS.²⁹ Whereas the Memorial Sloan Kettering Bowel Function Instrument although more complete in terms of addressing the symptoms of LARS it takes more time to administer to patients making it unfavorable for a screening tool.³⁰ Despite the benefits of the LARS score, it too has its own limitations and may miss important components of bowel dysfunction that can impact QOL such as constipation.³¹ Ultimately, LARS is most commonly measured using the LARS score, a 5-item weighted guestionnaire that is scored from 0-42 and categorizes patients as having no LARS (0-20), minor LARS (21-29) and major LARS (30-42) (Figure 4).²⁶ After RP for rectal cancer, LARS can occur in up to 70-90% of patients and has been associated with significant impairments in guality of life (QOL).^{32,33} Although some patients may experience improvement in their symptoms over time, most experience persistent LARS for many years after surgery.^{34,35} Different mechanisms that contribute to the development of LARS have been described such as, loss of a true rectum, decreased compliance of the neo-rectum, a change in motility, denervation leading to change in sensory feedback loops as well as underlying poor sphincter function.^{36–40} Given the prevalence of LARS among patients undergoing RP and its associated impairment in QOL, a number of studies have evaluated which factors may be associated with developing LARS.⁴¹ The factors most strongly associated with LARS are, the use of neoadjuvant radiotherapy, low tumor height

and more extensive surgery referred to as total mesorectal excision.⁴¹ Based on the identification of factors associated with the development of LARS, tools such as the "Pre-operative LARS score" (POLARS) score have been developed in an attempt to predict which patients were most likely to suffer from LARS following surgery.⁴² Later studies evaluating the POLARS tool found that it was only able to categorize 39% of patients in the correct LARS category.⁴³ As a result, our ability to reliably predict LARS following RP and inform patients of their likely trajectory in the shared decision making process is limited.

APPENDIX 2. LARS Score: Scoring Instructions	
Add the scores from each 5 answers to one final score. Do you ever have occasions when you cannot control your flatus (wind)?	
□ No, never	0
□ Yes, less than once per week	4
\Box Yes, at least once per week	7
Do you ever have any accidental leakage of liquid stool?	
□ No, never	0
□ Yes, less than once per week	3
\Box Yes, at least once per week	3
How often do you open your bowels?	
More than 7 times per day (24 hours)	4
4–7 times per day (24 hours)	2
1-3 times per day (24 hours)	0
Less than once per day (24 hours)	5
Do you ever have to open your bowels again within one hour of the last bowel opening?	
No. never	0
□ Yes, less than once per week	9
\Box Yes, at least once per week	11
Do you ever have such a strong urge to open your howels that you have to rush to the toilet?	
No. never	0
Yes, less than once per week	11
☐ Yes, at least once per week	16
-	
lotal Score:	
Intermetation	

Interpretation:	
0-20:	No LARS
21–29:	Minor LARS
30-42:	Major LARS

Figure 4: The Low Anterior Resection Syndrome Score²⁶

Quality of life

Since the introduction of advanced imaging techniques and neoadjuvant therapies, there has been increasing deliberation over the best surgical approach for low rectal cancer - either the traditional approach of abdominal perineal resection (APR) with the creation of a PC or RP in conjunction with modern neoadjuvant therapies.^{44,45} With modern studies unable to identify an oncologic benefit of one approach over the other, many patients are presented with the choice of an APR with PC or a RP.^{23,24} Therefore, significant efforts have been made to evaluate HRQOL outcomes between these procedures in order to better guide patients and providers in the decision making process.⁴⁶ Overall, there has been no clear benefit of one procedure over the other in terms of global HRQOL.⁴⁶ However, there is a lack of high quality studies comparing these procedures and significant risk of bias has been identified among published data.⁴⁶ Similarly, a Cochrane review in 2012 found no significant difference between these two procedures in overall HRQOL.⁴⁷ Although most studies show no significant difference in overall HRQOL there are some studies that favor RP and others that favor PC.^{48–52} Despite the lack of overall difference in HRQOL, there have been some important distinctions in affected HRQOL domains with PC patients having worse body image and RP patients having more issues with bowel dysfunction.⁴⁶ As previously discussed, LARS is a phenomenon experienced by most patients who undergo RP and increasing LARS severity appears to be associated with worse overall HRQOL.³³ Ultimately, not all RP patients experience the same HRQOL impairment and therefore LARS severity should be considered in the comparison of PC vs RP when discussing HRQOL outcomes. The majority of studies comparing HRQOL outcomes in rectal cancer use the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and its colorectal specific subscales.^{46,53–55} These tools, although thoroughly developed through interviews with a diverse group of patients may lack relevance to the individual patient, their concerns and their values.^{54,56} In some cases, standardized instruments may lack relevance to

individual patients as the result of excess "noise" in the form of including "average" issues reported by a population and lack of emphasis on individual values or concerns.⁵⁷ Many other instruments used to evaluate HRQOL in this population are considered generic and not developed to assess HRQOL impairments in this context and therefore may be difficult to interpret in the clinical setting.⁵⁸ In 1994, Ruta et al. described a novel approach to evaluating HRQOL called the Patient Generate Index (PGI) that focuses on HRQOL outcomes from the patient perspective.⁵⁹ An individualized approach to the evaluation of HRQOL is based on the premise that only the patient themself is fit to judge their HRQOL.⁶⁰ With this in mind, the focus of the PGI is to allow patients to describe the aspects of their lives that are most affected, to rate the importance of their impact and to be simple for patients to understand and complete.⁵⁹ The administration of the PGI involves 4 steps: First, patients are asked to list up to 5 areas of their lives most affected by their condition, second, patients are then asked to score how severely these areas are affected (0 = completely debilitating, 10 = ideal level of function) to generate a weight for each area and third, patients are offered 12 hypothetical "tokens" in which they're told they can spend as they please to improve the affected areas of life they reported.⁶¹ Finally, a score is calculated by multiplying the assigned weight of each HRQOL domain by the allocated proportion of tokens assigned by the patient to generate a score of 0-100 (0 = worst, 100 =best).⁶¹ Several studies have been conducted to assess the reliability, validity and responsiveness of the PGI in different contexts with overall success.⁵⁷ In patients with rectal cancer the PGI has been shown to be valid and more responsive than other standardized HRQOL instruments designed for use in this population.⁵⁶ In fact, the PGI has been able to detect patient concerns that would have otherwise been missed by other standardized HRQOL instruments.⁶² Overall, the impact of rectal cancer treatment on HRQOL is poorly understood and comparisons made between treatment strategies should consider factors such as LARS and use instruments that are patient-centric in order to provide reliable information to guide the shared decision making process.46,58

Description of the problem

The SDM process in rectal cancer is complex and in order to appropriately inform the patient we need to be able to more accurately predict LARS severity and characterize HRQOL domains affected by differences in LARS severity or PC. Therefore, we sought to evaluate the role of pre-treatment bowel dysfunction in predicting post-treatment bowel dysfunction and to evaluate HRQOL from the patients perspective.

Thesis objectives

- The primary objective of this thesis is to evaluate a novel approach to predict postoperative bowel function using pre-treatment bowel dysfunction in patients undergoing restorative proctectomy for rectal cancer.
- The secondary objective of this thesis is to evaluate health-related quality of life outcomes between permanent colostomy and restorative proctectomy using the PGI for patients treated for rectal cancer.

Chapter 2- Predicting Low Anterior Resection Syndrome

Preamble

Low anterior resection syndrome (LARS) following the treatment of rectal cancer can be associated with significant impairments of an individual's HRQOL.³³ As a result, patients with major LARS can experience a substantial deterioration in their HRQOL when compared to those with more mild symptoms.⁵⁸ In order to better understand which patients will develop LARS several studies have retrospectively evaluated patient, tumor and treatment characteristics and their association with LARS.⁶³ Some of the factors associated with developing LARS are, diverting stomas, radiotherapy, older age, post-operative chemotherapy, total-mesorectal excision and anastomotic leak.^{63,64} Based on these findings, researchers have developed predictive models in an attempt to prospectively identify which patients are at the highest risk for developing LARS.⁴² However, accuracy is limited as only 39% of patients appear to be categorized in the correct LARS category.⁴³ As a result, the use of such tools are limited in guiding the shared decision making process. This disconnect between true LARS category and predicted category may be the result of a lack of generalizability of the normative data or due to unidentified covariates that are intrinsic to the patient or tumor.⁴³ Moreover, factors such as an individual's underlying sphincter function, comorbidity or pelvic floor strength may be contributors to LARS severity.^{40,65} Ultimately, the development of LARS appears to be multifactorial and identifying each individual contributing factor appears difficult.

Considering these findings, we sought to evaluate a patient-centric approach to determine the risk of developing LARS. The majority of patients diagnosed with colorectal cancer initially present with a change in bowel habits.⁶⁶ However, there are few studies that specifically evaluate rectal cancer symptoms or characterize the prevalence of bowel dysfunction in rectal

cancer patients compared to the general public. Notably, a significant proportion of individuals within the general public experience varying degrees of bowel dysfunction.¹¹ We hypothesized that bowel function at the time of referral to a colorectal surgeon could provide an indication of post-operative bowel function in patients who undergo RP. Moreover, lower tumors appear to have more significant bowel dysfunction and may also be associated with some previously identified factors such as radiotherapy or diverting stomas in the context of low anastomoses.^{10,65} Furthermore, an individual's underlying sphincter function, pelvic floor strength and comorbidity may influence bowel dysfunction prior to treatment and subsequently LARS after treatment. Therefore, pre-treatment bowel dysfunction may provide insight into not only factors known to be associated with the development of LARS but also may allow these factors to be interpreted in the context of an individual's capacity to compensate for bowel dysfunction. The following study "Predictors of pre- and post-treatment bowel dysfunction severity in patients with rectal cancer" investigated the impact of rectal cancer on bowel function and evaluates pre-treatment bowel function as a predictor of LARS and has been published in "Surgery" 2022.⁶⁷

Predictors of pre- and post-treatment bowel dysfunction severity in patients with rectal cancer

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Presented at: 79th annual meeting – Central Surgical Association June 2nd-4th, 2022 in Milwaukee, Wi. Oral presentation in scientific session #4.

Abstract:

Objective:

Treatment of rectal cancer is frequently associated with Low Anterior Resection Syndrome (LARS). However, data concerning the contribution rectal tumors have on pre-treatment bowel-dysfunction (BD) is scarce. We sought to evaluate the impact of the untreated rectal cancer on BD and the relationship of pre-treatment and post-treatment function.

Methods:

A prospective database of adult rectal cancer patients at a single university-affiliated colorectal referral center from 08/2018 to 03/2022 was queried. BD was measured using the LARS score questionnaire (categorized as no, minor, or major LARS) which was provided to patients at their primary visit, and after treatment. Patients were included if they underwent rectal cancer treatment and had pre- and post-treatment LARS measurements. Observed LARS scores were

compared to normative LARS data for age and sex-specific distributions from published data. Multiple multinomial regression compared pre- and post-treatment LARS scores.

<u>Results:</u>

Overall, 121 patients were included with mean age 62.0years (SD12.3), 74% male, and mean tumour height 8.7cm (SD5.72). The proportion of pre-treatment observed LARS were 48% no LARS, 28% minor, and 24% major. Male and older patients were more likely to have worse than predicted LARS categories (p<0.05). On average, LARS category did not change following treatment (p=0.618) and pre-treatment LARS category was a significant independent predictor of post-treatment category (p=0.037).

Conclusion:

Pre-treatment BD in rectal cancer patients is common and significantly worse than predicted for older and male patients. Importantly, pre-treatment BD predicted postoperative function. These results may better inform the shared decision-making process.

Introduction:

Advances in the treatment of rectal cancer and surgical technique have led to increasing trends toward sphincter preserving surgery.¹ However, one of the major disadvantages to sphincter preservation is that up to 80-90% of patients can suffer from bowel dysfunction and impaired quality of life.² Bowel dysfunction in this context is often measured using the Low Anterior Resection Syndrome (LARS) score, which encompasses the most problematic areas reported by these patients including symptoms of frequency, urgency, clustering, incontinence, or diarrhea.³ Many patients are willing to accept varying degrees of LARS following treatment whereas other patients have a lower tolerance for severe LARS and may rather opt for permanent colostomy.⁴ Therefore, reliable prediction of LARS severity would significantly contribute to the shared decision making process by informing patient expectations.

In a recent review, a number of factors predisposing patients to postoperative LARS were identified.⁵ Specifically, the factors most highly associated with postoperative LARS were found to be low tumor height, fecal diversion, neoadjuvant radiotherapy, and total mesorectal excision.⁵ Moreover, another study developed a nomogram to predict LARS based on patient, tumor, and treatment factors associated with postoperative LARS.⁶ Although the elements that comprise this model have been associated with the development of LARS, the model appears to have limited accuracy, correctly predicting LARS category in only 39% of patients.^{5,7} Given the limitations of currently available tools to predict the likelihood and severity of postoperative LARS, patients may lack the necessary information to make an informed decision about their treatment.

Symptoms of bowel dysfunction can exist in the general public to varying degrees.⁸ However, many patients with rectal cancer may have LARS-like symptoms at the time of diagnosis and there is currently little data characterizing the impact of rectal cancer on bowel function.⁹ If these symptoms can be appropriately measured and their relationship to post-treatment LARS can be elucidated, pretreatment LARS may serve as a realistic reference point for patients to understand bowel dysfunction and possibly to gain insight into their post-treatment trajectory. Therefore, we sought to evaluate how rectal cancer impacts pre-treatment severity of bowel dysfunction and determine if bowel function changes following sphincter preserving treatment.

Methods:

Study population and setting: A prospective functional outcomes database of adult patients evaluated for new rectal cancer at a single university-affiliated colorectal referral center in Montreal, Quebec, Canada from 08/2018 to 03/2022 was queried. Patients were included in the study if they had a new rectal cancer diagnosis and had completed the LARS score prior to treatment initiation where treatment was defined as either surgery or neoadjuvant therapy.

Demographic data including patient, tumor and treatment characteristics were recorded. Treatment was defined as surgical resection or complete clinical response to neoadjuvant therapy. The study protocol was approved by our institutional ethics review board and informed consent was obtained for study participation.

Outcomes: Bowel dysfunction was measured using the LARS score, a 5-item weighted questionnaire scored 0-42.3 Based on the results of the LARS score patients were categorized as no LARS (0-20), minor LARS (21-29) and major LARS (30-42).³ The LARS score was administered by a dedicated research nurse and a senior general surgery resident at initial visit prior to treatment (which was on average 2-3 weeks following diagnosis) and at follow-up visits between 6 months to 1 year post-treatment or ileostomy reversal when appropriate. Predicted LARS scores were calculated using normative data obtained from the administration of the LARS score to the general public.⁸ The normative data represents the degree of bowel dysfunction present in the general public and is subclassified in age and sex or physical disease-specific distributions.⁸ Predicted LARS categories were then generated by matching the proportions of the LARS severity (no, minor or major LARS) reported in the normative data. Differences in predicted and observed pretreatment LARS score were evaluated based on age, sex and tumor characteristics. Any change in LARS categories before and after treatment were also recorded and known factors associated with post-operative bowel dysfunction were evaluated. LARS trajectory was defined as the change in LARS category before and after treatment and patients were grouped according to same, worse or improved bowel function. Patients with permanent colostomy were included in the analysis for predicted and observed pre-treatment LARS and were excluded for the post-treatment analysis.

Analysis: Demographic data was presented as mean with standard deviation or median with interquartile range and categorical data was reported as frequency and percentage were appropriate. Pre and post-treatment, observed and predicted, and age and gender subgroup LARS categories were compared using Pearson Chi-square or Fisher's exact tests. Category

specific proportions were analyzed using standard two-sample proportion Z-test. Mean differences between observed and predicted LARS scores were presented and analyzed using multiple linear regression adjusting for tumor height and size. Multinomial logistic regression was used to evaluate pre-treatment LARS as a predictor of post-treatment LARS categories. Covariates included, age and sex. Other known risk factors for post-treatment LARS were excluded as covariates due to significant co-linearity. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using Stata software package (Stata v16.0, StataCorp, College Station, Tx)

Results:

Overall, 121 patients were included (60.5% response rate), 104 (86%) underwent rectal resection, 62 (51.2%) received neoadjuvant therapy and 10 (8.3%) had complete clinical response. Patients with major LARS prior to treatment tended to be older, otherwise there were no differences in patient demographics or tumor characteristics between patients with different pre-treatment LARS category (Table 1). Other known risk factors associated with the development of LARS were also the same between groups (Table 1). However, fecal diversion was associated with a deterioration of LARS category (p= 0.0162). Conversely, age (p=0.1625), sex (p=1.000), ASA score (p= 0.1325), stage (p= 0.2139), distance to anal-verge (p= 0.7144), and neoadjuvant therapy (p= 0.204) were not. Pretreatment predicted and observed LARS categories and are summarized in Table 2 along with sex and age specific subgroups. In each LARS category, predicted age and gender specific distribution underestimated observed LARS categorization (Table 2). Larger tumor size (B1.70, 95%CI: 0.37, 3.03) and shorter distance to anal-verge (B - 0.68, 95%CI: -1.17, -0.18) were independently associated with increased mean difference between predicted and observed LARS scores.

Overall, 13 (11%) patients underwent permanent colostomy and 32 (26%) had not completed the post-treatment LARS questionnaire (4 participants died, 9 were lost to follow-up, and 19 had not reached minimum follow-up time) and were therefore 76 (63%) patients were

included in the post-treatment analysis. Pretreatment and post-treatment LARS categories were compared and outlined in Table 3. Overall, pretreatment LARS score was comparable to post-treatment score (*p*=0.618). Of patients who had room for improvement of their bowel function 14 (37%) improved and of those who had room for their LARS to worsen 23 (37%) worsened. Overall, 82% (95%CI: 73%, 91%) were categorized as the same or worse LARS category following treatment. Trajectory of LARS category before and after treatment is outlined in Table 3. Notably, patients with minor LARS were just as likely to end up in any LARS category following treatment whereas half of patients with major LARS improved and 39% of patients with no LARS got worse (Table 3). Pretreatment LARS category was a significant predictor of post-treatment category when evaluated with multinomial logistic regression, estimates of odds ratios are presented in Table 4.

Discussion:

The presence of severe bowel dysfunction after sphincter preserving surgery for rectal cancer is significantly associated with impaired quality of life.¹⁰ Interestingly, certain patients may prefer permanent colostomy over sphincter preservation if severe residual bowel dysfunction were anticipated.⁴ Therefore, when feasible, the option to proceed with sphincter preserving surgery is discussed with patients as part of the shared decision making process. However, our ability to reliably predict post treatment bowel dysfunction is limited and communicating the degree of expected impairment lacks a realistic patient specific reference point.

The disruption of bowel function in patients with a rectal tumor is a known phenomenon.^{11,12} To better understand the predictors and degree of bowel dysfunction in this population, we compared the observed pretreatment LARS scores to predicted normative values for age and sex or physical disease.⁸ Unsurprisingly, patients with rectal cancer had significantly worse symptoms of bowel dysfunction compared to the general public. This difference was more pronounced in men and patients aged 50 to 80 years-old for equivalent

tumor size and location. Conversely, female rectal cancer patients did not have worse bowel function compared to normative values. Predicted scores classified 62% of patients as having no LARS while only 47% of patients were observed as having no LARS at their initial visit (Table 2). Therefore, over half of rectal cancer patients have bowel dysfunction consistent with LARS and as a result, many may have impaired quality of life.¹⁰ However, whether this is worse than expected highly depends on age and sex. When looking at tumor characteristics, we found that larger tumors and tumors located closer to the anal-verge tended to be associated with significantly worse observed scores compared to predicted scores. We hypothesize that these effects are due to larger and lower tumors causing a disruption of the normal anatomic and physiologic function of the rectum. Interestingly, lower tumors are associated with an increased risk of postoperative LARS, whereas male sex and older age are associated with decreased LARS severity when using current prediction tools.⁶

Pretreatment LARS categories were, on average, the same as post treatment categories with 82% of patients classified in the same LARS category or worse following treatment (Table 3). Moreover, based on multinomial regression, pretreatment LARS category appeared to be a significant predictor of post treatment LARS category (Table 4). This suggests that pre-treatment LARS is a good predictor of post-treatment function. We suspect this may be due lower and larger tumours not only being associated with pre-treatment LARS but also having a higher likelihood of being treated with neoadjuvant therapy and/or having a lower anastomosis, both of which have been associated with worse post-treatment function.⁵ Interestingly, although there are various available tools to measure bowel dysfunction, many do not address the variety of symptoms experienced by patients with LARS.¹³ Furthermore, differences in reporting results make it difficult to compare and interpret results between studies.¹³ Whereas, the validity and reliability of the LARS score in this context has been demonstrated and LARS categorization has been associated with important differences in quality of life.^{2,3,14,15} Therefore, our prediction of LARS categorization may provide patients and providers with meaningful information

regarding post treatment bowel dysfunction. Certainly, elucidating whether patients with pre-treatment bowel dysfunction are affected differently after treatment than those that have new bowel dysfunction following treatment remains unclear and would be an important target for new research.

Understanding expected changes in bowel function with respect to pretreatment function can provide patients with a relevant reference point in the shared decision-making process. We found that approximately one-third of patients who had LARS prior to treatment improved their LARS category. Similarly, one-third of patients with no LARS or minor LARS prior to treatment were classified in a more severe category following treatment (Table 3). Fecal diversion appeared to be associated with a change of LARS category, whereas age, sex, ASA score, stage, distance to anal-verge, and neoadjuvant therapy were not. Interestingly, although neoadjuvant therapy has been associated with increased odds of major LARS, our study did not identify a significant association with a change in LARS category after treatment.¹⁷ We suspect these findings are likely due to many patients already having LARS at the initial visit. Regarding the trajectory of patients in each LARS category, 39% of patients with no LARS developed LARS after treatment. Meanwhile, 33% of patients with minor LARS transitioned to major LARS and 29% of these patients improved to no LARS. Furthermore, half of the patients with major LARS improved following treatment (Table 3). Although an important proportion of patients have major LARS following treatment, a subset may actually improve over time suggesting that further follow-up in this cohort could contribute further to our understanding of the trajectory of bowel function following rectal cancer diagnosis and treamtent.¹⁸

Limitations: Tumor size was evaluated at pathology and therefore may not be representative of the size at initial diagnosis due to neoadjuvant therapy or further growth. This may have impacted our analysis of the relationship between pretreatment tumor size and LARS score. However, we suspect that our results with respect to tumor size may still be reliable. Further, normative data used was based on a Danish registry and did not contain any Canadian

patients and therefore there is potential for cultural differences limiting the application of normative data on our population. However, we have no reason to believe the Canadian population would be significantly different in terms of bowel function. There are other aspects of bowel dysfunction (especially constipation) that are not captured on the LARS score and may contribute to the impact of bowel function on quality of life.¹⁵ In addition, post treatment LARS scores were collected on average at 12 months following the collection of pretreatment LARS scores. Therefore, bowel function in some patients may still improve with time.¹⁸ Lastly, data was collected from a voluntary cancer registry at a single colorectal referral center. As a result, we recognize the potential for limited generalizability as well as volunteer or response biases.

Conclusion: Patients with rectal cancer have significant bowel dysfunction compared to the general population. These pre-treatment bowel dysfunction symptoms can be used by patients as a reference point that when combined with our findings can allow patients to have meaningful insight into what can be anticipated in terms of post treatment bowel function. Further, the relationship between pretreatment and post treatment LARS may allow providers to predict the trajectory of LARS throughout rectal cancer treatment more reliably and better inform the shared decision-making process.

Conflict of Interest/Disclosure:

L Lee is supported by a Career Development Award from the American Society of Colon & Rectal Surgeons (CDA-019) and reports an investigator-initiated operating grant from Johnson & Johnson as well as, speaker fees from Stryker. LS Feldman reports an investigator-initiated grant from TheatOR, and speaker fees from Abbott and Merck. JF Fiore Jr reports an investigator-initiated grant from Merck and consulting fees from Shionogi. AS Liberman is on the advisory board for Novadaq, Merck, and Servier, and receives speaker fees from Ippen. The other co-authors have nothing to report.

Funding/Financial Support:

S. Robitaille is supported by Canadian Institute of Health Research bursary for students with a professional degree (CGS-M), the McGill Clinical Investigator program and the McGill Surgeon Scientist program and L. Lee is supported by Fonds de Recherche – Santé Quebec career award. There was no other funding associated with this project.

Acknowledgements:

The Canadian Institute of Health Research (CGS-M), the McGill Clinical Investigator and Surgeon Scientist programs as well as Fonds de Recherche – Santé Quebec (Quebec Health Science Research Fund).

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Figures:

<u>Table 1</u>: Patient demographics, tumor characteristics and LARS risk factors by pre-treatment LARS category.

	Pre-treatment LARS category				
	Total	No LARS	Minor LARS	Major LARS	P-value
	N=121	N=58	N=34	N=29	
Age, mean	61.8 (12.3)	60.8 (13.5)	58.9 (11.0)	67.8 (9.75)	0.0107*
(SD)					
Female	32 (26.4%)	19 (32.8%)	8 (23.5%)	5 (17.2%)	0.2937
BMI, mean	61.8 (12.3)	27.7 (5.5)	27.4 (3.88)	25.3 (3.41)	0.0923
(SD)					
ASA					
1 to 2	78 (64.5%)	40 (69.0%)	21 (45.6%)	16 (55.2%)	
3 to 4	43 (35.5%)	18 (31.0%)	13 (38.2%)	12 (41.3%)	0.5307
T-stage					
0 - 2	24 (21.5%)	13 (22.4%)	5 (14.7%)	8 (27.5%)	
3 - 4	95 (78.5%)	45 (77.6%)	29 (85.3%)	21 (72.5%)	0.4274
N-stage					

N-	61 (50.4%)	30 (51.7%)	16 (47.1%)	15 (51.7%)	
N+	57 (48.8%)	28 (48.2%)	18 (52.9%)	13 (44.8%)	0.9157
M-stage					
M-	104 (86.0%)	52 (89.7%)	26 (76.5%)	26 (89.7%)	
M+	15 (12.4%)	5 (8.6%)	7 (20.6%)	3 (10.3%)	0.2465
Distance to	8.70 (5.72)	9.34 (6.65)	7.75 (4.31)	8.55 (5.18)	0.4389
Anal-Verge					
(cm), mean					
(SD)					
0-5cm	36 (29.8%)	16 (27.6%)	10 (29.4%)	10 (34.5%)	
>5cm	85 (70.2%)	42 (72.4%)	24 (70.6%)	19 (65.5%)	0.7492
Tumor size	3.71 (2.12)	3.17 (1.5)	4.30 (2.90)	3.92 (1.88)	0.0714
(cm) , mean					
(SD)					
Stoma					
No	59 (48.7%)	34 (58.6%)	14 (41.2%)	11 (37.9%)	
Yes	62 (51.2%)	24 (41.4%)	20 (58.8%)	18 (62.1%)	0.1108
Neoadjuvant					
No	60 (48.8%)	31 (53.4%)	13 (38.2%)	15 (51.7%)	

Yes 62 (51.2%) 27 (46.6%) 21 (61.8%) 14 (48.3%) U	0.3465
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LARS, Low Anterior Resection Syndrome; SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiology. *P<0.05

Table 2: Predicted categories vs. observed pre-treatment categories

	Γ	Male (N=8	39)	50 to 80 years-old (N=91)		Т	otal (N=1	21)	
	Obser	Predic	95%CI	Obser	Predic	95%CI	Obser	Predic	95%CI
	ved	ted		ved	ted		ved	ted	
No	39	64%	34%,54	42	69%	36%,56	58	62%	38%,56
LARS	(44%)		%	(46%)		%	(48%)		%
			P<0.00			P<0.00			P<0.00
			1			1			1
Minor	26	16%	20%,38	25	16%	18%,36	34	19%	20%,36
LARS	(29%)		%	(27%)		%	(28%)		%
			P<0.00			P=0.00			P=0.011
			1			4			
Major	24	9%	18%,36	24	14%	17%,35	29	19%	16%,31
LARS	(27%)		%	(26%)		%	(24%)		%
			P<0.00			P=0.00			P=0.16
			1			1			1

LARS, Low Anterior Resection Syndrome; CI, Confidence interval.

Table 3: Trajectory of LARS category, pre-treatment vs. change in LARS

	Pre- and	Pre- and post-treatment LARS		Post-treatment			
		category		(categorie	S	
Pre-treatme	Same	Improved	Worse	No	Minor	Major	P-value
nt	(N=39)	(N=14)	(N=23)	LARS	LARS	LARS	
categories							
No LARS	23 (61%	0	15 (39%	23	7	8	
	CI: 45%,		CI: 23%,				
	77%)		55%)				
Minor LARS	9 (38% CI:	7 (29% CI:	8 (33% CI:	7	9	8	
	19%, 57%)	11%, 47%)	14%, 52%)				
Major LARS	7 (50% CI:	7 (50% CI:	0	3	4	7	0.037*
	23%, 76%)	23%, 76%)					

LARS, Low Anterior Resection Syndrome; CI, Confidence interval.

Table 4: Multinomial regression: Pre-treatment LARS vs. Post-treatment LARS

Post-treatment LARS category

Pre-treatment	No LARS	Minor LARS	Major LARS
category	(reference)		
No LARS (intercept)		0.02	0.03
		(95% CI: 0.00, 1.36)	(95% CI: 0.00, 1.38)
Minor LARS		4.86*	3.83
		(95% CI: 1.24, 19.13)	(95% CI: 0.99, 14.73)
Major LARS		3.75	6.05*
		(95% CI: 0.65, 21.60)	(95% CI: 1.23, 29.75)

LARS, Low Anterior Resection Syndrome; CI, Confidence interval. Adjusted for age and gender,

*P<0.05.

Chapter 3 - Health-Related Quality of Life in Patients with Rectal Cancer

Preamble

Shared-decision making is important in rectal cancer particularly when deciding between RP and PC. Each of these treatment strategies can have important impacts on an individuals HRQOL.⁴⁶ Although traditional measures of successful post-operative recovery such as absence of complications, readmissions or prolonged hospitalization may be important to patients, most patients value recovery of their HRQOL.⁶⁸ As a result, several studies have evaluated HRQOL in the context of post-operative recovery following the treatment of rectal cancer.^{46,58} This approach is often referred to as evaluating patient-reported outcomes and has become ubiquitous in the surgical community.^{69–71} However, many instruments used to evaluate HRQOL in this context are considered generic or have been criticized for their lack of an individualized HRQOL assessment.^{57–60} In chapter 2 we demonstrated that postoperative bowel dysfunction can be reliably predicted using pre-treatment bowel dysfunction.⁶⁷ However, it is important to characterize overall HRQOL and the specific HRQOL domains that are affected by bowel dysfunction versus PC and to do so from the patient perspective, in order to be able to provide an accurate assessment of the potential HRQOL outcomes following low rectal cancer surgery.^{56,59}

When evaluating outcomes in rectal cancer, RP and PC have been extensively compared in terms of oncologic outcomes and HRQOL outcomes.^{23,24,46} Ultimately, the standardized tools used to evaluate HRQOL in rectal cancer have failed to detect an important overall difference between PC and RP.⁴⁶ Although there may not be a true difference in overall HRQOL between

these procedures, the instruments used to evaluate HRQOL lack sensitivity when compared to an individualized assessment tool such as the Patient Generated Index.⁵⁶ Furthermore, when considering individual patient values, patients who undergo RP may not all experience the same trajectory of HRQOL outcomes and this heterogeneity appears to be linked to LARS severity.^{34,58} Therefore, a patient-centric approach to evaluate HRQOL outcomes that considers both symptom severity and individual values and concerns may provide insight for both patients and providers in the shared decision making process. Our study "The impact of restorative proctectomy vs. permanent colostomy on health related quality of life following rectal cancer surgery" aims to evaluate the impact of rectal cancer treatment on HRQOL in patients treated with PC and RP while considering LARS severity. These data were presented at the 23rd annual Steinberg-Bernstein minimally-invasive surgery visiting professor day at McGill University in November 2022 and the manuscript currently under review with the journal "Diseases of the Colon and Rectum". The impact of restorative proctectomy vs. permanent colostomy on health related quality of life following rectal cancer surgery

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Abstract:

Background: The impact of bowel dysfunction vs. colostomy on quality of life after rectal cancer surgery is poorly understood.

Objective: Evaluate quality of life after rectal cancer surgery in patients with colostomy vs. restorative proctectomy.

Patients: Participants were eligible if they underwent restorative proctectomy or permanent colostomy for rectal cancer.

Main outcome measures: A mixed-methods study where quality of life was measured using the Patient-Generated Index. Patients were asked to list up to 5 areas of their life affected by their surgery. Areas were then weighted according to patients' preferences for improvement to generate a score from 0-100. The areas reported by patients were linked to the International Classification of Functioning for content analysis. Bowel dysfunction was measured using the low anterior resection syndrome score, and patients were then grouped according to 1) colostomy or 2) no/minor or 3) major low anterior resection syndrome. Quality of life was compared between groups.

Results: Overall, 121 patients were included (colostomy n=39, restorative proctectomy n=82). There were no differences in demographics, neoadjuvant radiotherapy, or time to follow-up between groups. In the restorative proctectomy group, 53% had no/minor and 47% major low anterior resection syndrome. Overall, patients with colostomy had significantly lower quality of life scores than those with restorative proctectomy (Table 2). However, patients with major low anterior resection syndrome scored similarly to those with colostomy (Table 2). On content analysis, colostomy patients reported more problems with sexual function, body image, and sports (Table 3). Sphincter preservation patients reported more problems with sleep, using transportation, and taking care of oneself (Table 3).

Limitations: single-centre, volunteer

Conclusions: Colostomy has a more detrimental impact on quality of life than restorative proctectomy. However, bowel dysfunction severity is important to consider. Patients with colostomy are affected differently than those with restorative proctectomy.

Introduction:

The combination of modern surgical techniques and advances in neoadjuvant therapies has led to sphincter-preserving surgery becoming more widely suitable in the treatment of rectal cancer.¹ Traditionally, patients with low or locally advanced tumors that would have been treated with abdominal perineal resection and permanent colostomy (PC) have the potential to be downstaged and undergo restorative proctectomy (RP) with good oncologic outcomes.^{2,3} However, RP in these cases can be associated with severe postoperative bowel dysfunction in

up to 80-90% of patients which can subsequently have a negative impact on health-related quality of life (HRQOL).^{4,5} Most commonly referred to as Low Anterior Resection Syndrome (LARS) in this context, bowel dysfunction appears to have an increasingly detrimental impact on HRQOL as severity increases.^{6,7} Similarly, PC is associated with changes in HRQOL through its own set of challenges.^{8,9} When comparing RP to PC, there is no clear benefit of one approach over the other in terms of overall HRQOL outcomes.^{10,11} However, most studies evaluating HRQOL following rectal cancer treatment use generic HRQOL instruments that may omit concepts valued by patients treated for rectal cancer.^{5,12}

More recently studies evaluating HRQOL in cancer patients have used the Patient-Generated Index (PGI) which is an individualized measure to evaluate HRQOL.^{13–15} In the context of rectal cancer, the PGI has been shown to be both responsive and valid in evaluating outcomes and has been shown to be beneficial when compared to other HRQOL measures. ¹⁶

Our current understanding of the impact of rectal cancer treatment on HRQOL is largely based on generic measures.⁵ With advancements in treatment options, providers need to be better equipped to inform patients during the shared decision making process regarding what to expect following surgery. Both RP and PC have been shown to have a meaningful impact on HRQOL but little is understood about how patients are affected and how bowel dysfunction contributes to these differences.^{10,17} Therefore, the objectives of this study are to 1) evaluate patient reported outcomes following rectal cancer treatment from the patient perspective, 2) compare outcomes in HRQOL between RP and PC and 3) define the areas of life most affected by bowel dysfunction and PC.

Materials & Methods:

This was a mixed-methods study carried out at a single university-affiliated colorectal referral center in Canada. Patients were eligible for inclusion if they were enrolled in our institution's prospective rectal cancer database and were treated for rectal cancer with either RP

or PC. This registry was initiated in 10/2018 and enrolled all new rectal cancer patients starting this date, as well as those treated within the past 5 years and were still undergoing active surveillance. As a result, most patients were prospectively recruited with some patients being retrospectively recruited. Patients were excluded if their tumors were >10cm from the anal verge on pre-operative endoscopy or MRI, they developed metastatic disease during follow-up, had a simultaneous procedure, underwent a trans-anal resection or were operated on at an outside institution. Following ethics approval from our institutional review board, patients were called by a trained research student (MFM or RP) or a general surgery resident (SR) and administered the PGI at least 12 months following PC or restoration of bowel continuity (RP without diversion or following reversal of diverting loop ileostomy). During the PGI interview patients were asked to 1) identify up to 5 of the most important areas of their life (HRQOL domains) affected by their bowel function or their colostomy 2) patients were then asked to score how severely each of these areas were affected (0 = completely debilitating, 10 = ideal level of function) and then 3) patients were offered 12 hypothetical "tokens" that they could spend as they please to improve the areas that affect them most.^{13,14} The total weighted PGI score was obtained by multiplying the rating for each identified HRQOL domain by the proportion of "tokens" allocated to that domain, these values were then summed to generate a score from 0 (worse) to 100 (best).¹⁴

The QOL domains reported by patients on the PGI were then coded according to the World Health Organization's International Classification of Functioning, Disability and Health (ICF) using established linking rules.¹⁸ The process of coding HRQOL domains to the ICF allows standardization on an internationally recognized framework previously used in HRQOL research and aids in facilitating interdisciplinary communication.¹⁹ For example, if one patient reported "At work, I worry that I may soil myself" it would be linked to the ICF categories "b152 Emotional functions," "b525 Defecation functions", and "d850 Remunerative employment". Linking of ICF domains was performed by 3 independent reviewers (SR), (TGJ) and (MFM). Domains reported at least 4 times were considered significantly affected: P=0.0407 (no/minor LARS), P=0.0402

(major LARS) and P=0.0396 (Permanent Colostomy). Therefore, only domains reported at least 4-times in a single group were included in our analysis.

Patients were grouped according to whether they underwent RP or PC. In those who underwent RP, bowel dysfunction was measured using the LARS score at least 1 year following re-establishment of bowel continuity (RP without diversion or following reversal of diverting loop ileostomy).²⁰ The LARS score is a 5-item weighted questionnaire that categorizes patients as having no, minor or major LARS based on bowel dysfunction symptom severity.²⁰ Two subgroups within the RP group were then formed based on LARS categorization 1) no/minor LARS or 2) major LARS.

Primary outcome measures were 1) mean PGI between groups and 2) frequency of reported HRQOL domains between groups and subgroups. Multiple linear regression adjusting for age, sex, neoadjuvant radiation, tumor height, minimally invasive approach and time to follow-up (in months) was performed to evaluate mean difference in PGI between all RP patients, LARS subgroups and PC groups. Frequency and percent of reported ICF categories were compared between groups using the Z-test for proportions. Patient, treatment and tumor characteristics were also recorded and compared using Student's T-test, Pearson's Chi-Square or Kruskal–Wallis rank test where appropriate. Sample size was determined from similar studies where 38 patients were required in each group to detect the minimally clinical important difference of 13 (SD 17) points in the PGI in a similar patient population.¹⁶ A p-value <0.05 was considered as statistically significant. Statistical analyses were performed using Stata software package (Stata v16.0, StataCorp, College Station, Tx).

Results:

Overall, 249 of 335 (74%) patients were eligible to participate (26 patients did not meet minimum follow up time, 30 patients developed metastasis or were palliative, 6 patients were awaiting ileostomy closure, 21 patients were on a watch and wait protocol, 3 patients were operated on at outside institutions). In total, 182 of 249 (73%) patients agreed to participate

however, 61 patients were excluded after further review (48 patients had a tumor >10cm from the anal verge, 1 patient had a simultaneous esophagectomy, 1 patient was given a diverting stoma in the context of necrotizing fasciitis, 9 underwent a trans-anal approach, and 2 patients were missing operative details in the chart). Finally, 121 patients were included in the final analysis with 39 (33%) colostomy patients and 82 (67%) RP patients (42 with no/minor LARS and 40 with major LARS). Anastomotic configuration in RP patients were side-to-end in 58 (71%) patients, end-to-end in 15 (18%) patients and colonic J-pouch in 9 (11%) patients. Further, a stapled anastomosis was performed in 66 (80%) patients and a hand-sewn anastomosis in 16 (20%) patients. In total, 7 (9%) RP patients had an anastomotic leak and 66 (80%) had a diverting loop ileostomy. Median time to ileostomy reversal was 4.8 [IQR 4] months.

Interviews were conducted at a mean of 35.1 (SD 26.2) months following restoration of bowel continuity or PC. Overall, there was no difference in age, sex, body mass index, use of neoadjuvant therapy, surgical approach (laparoscopy vs. open), tumor size or mean time to interview between the RP group and the PC group. There was also no difference in 30-day readmissions, complications or emergency visits. Patients who received a PC had higher ASA scores, lower tumors, higher T-stage on final pathology and longer length of stay (Table 1).

Unadjusted mean PGI score was lower in the PC group when compared to the RP group (Table 1). Adjusted PGI scores were significantly lower in patients who received PC when compared to RP patients (Table 2). When comparing LARS subgroups, patients with PC had a significantly lower PGI score when compared to those with no or minor LARS (Table 2). When comparing PC to those with major LARS, patients with PC scored lower than those with major LARS (Table 2). However, this difference was not statistically significant.

In total, there were 324 individual responses to the PGI among all 121 patients equaling on average 2.7 HRQOL domains identified per patient and 33 unique HRQOL domains identified. The final analysis included 13 HRQOL domains once domains reported less than 4 times were excluded. Patients with RP had significantly more issues with B134 "Sleep

functions", D470 "Using transportation" and D570 "Looking after one's health" than patients with PC (Table 3). Whereas patients with PC had significantly more issues with B1801 "Body image", and D9201 "Sports" (Table 3). When comparing only those with major LARS to those with PC, patients with major LARS had significantly more issues with D470 "Using transportation", D570 "Looking after one's health" and D850 "Remunerative employment" (Table 3). Patients with PC had significantly more issues with B1801 "Body image" than those with major LARS (Table 3). Patients with B1801 "Body image" than those with major LARS (Table 3). Patients with major LARS had more frequently reported issues with D850 "Remunerative employment" than those with no or minor LARS (Table 3). Other frequently reported HRQOL domains were no different between the groups (Table 3).

Discussion:

Bowel dysfunction and PC and their associated impairment of HRQOL following rectal cancer treatment is a known phenomenon.^{5,8} However, most studies evaluating the impact of rectal cancer on HRQOL use generic HRQOL instruments that may lack relevance to rectal cancer patients.⁵ Similarly, studies evaluating differences in HRQOL between RP and PC are largely based on comparisons made with these generic measures.^{10,11,21} The major advantages to the PGI are that it allows patients to report important HRQOL domains that may be unaddressed by generic instruments and weigh them according to their own personal values.^{14,22}

Overall, the mean PGI score in our population was 45.9 (SD 26.3) which is comparable to previous literature.¹⁶ In several studies comparing abdominal perineal resection to RP beyond 1-year of follow-up, overall HRQOL was comparable between groups when evaluated with a generic HRQOL instrument.^{10,11,21} However, there were some key differences in subscales suggesting that patient experience between the groups may be different.¹⁰ In our study, when comparing overall HRQOL between the groups, patients with PC had significantly lower PGI scores, and therefore worse HRQOL, when compared to all RP patients with an adjusted mean difference of 15.3 points (Table 2). These findings contrast with previous literature and indicate

that there likely is an important difference in overall HRQOL between these treatment groups when assessed from the patients' perspective and accounting for their own specific preferences and values.^{10,11,21} When comparing the adjusted PGI scores of LARS subgroups, patients with no/minor LARS scored, on average, 20.6 points higher than patients with PC which translates to significantly better overall HRQOL (Table 2). Patients with major LARS scored 10.7 points higher than those with PC. However, this result was not statistically significant nor did it reach the minimal clinical important difference (Table 2).¹⁶ Overall, these findings align with the notion that PC has a more detrimental impact on HRQOL than RP.²¹ However, when comparing those with major LARS to those with PC the overall HRQOL benefit appears less pronounced.

In the context of modern multimodal protocols, abdominal perineal resection and PC does not appear to confer significant survival benefit over RP.²³ Moreover, previous studies demonstrate that patients favor preservation of HRQOL in the process of selecting therapeutic strategies even at the expense of worse survival.^{24–26} Therefore, knowledge of the overall HRQOL benefit of RP over PC may assist patients in the pre-operative decision making process. Although overall HRQOL appears to be better in the RP group, there are significant differences in HRQOL between LARS subgroups and differences in the affected HRQOL domains between RP and PC. When evaluating affected HRQOL domains, our results are congruent with previously identified observed differences in body image, sexual function and remunerative employment between treatment groups (Table 3).¹⁰ Notably, when considering specific HRQOL domains and individual patient values, patients with PC had significantly better reported sleep function, use of transportation and ability to look after one's own health at the expense of worse body image, sexual function and involvement in sports than patients with RP (Table 3). Further, patients with major LARS had significantly more issues with remunerative employment than those with PC and those with no or minor LARS (Table 3). Patients with major LARS are known to have delayed return to work, prolonged medical leave and increased financial impact than those with more mild symptoms.²⁷ As a result, the effect on remunerative

employment can have a significant impact on global HRQOL.²⁷ Patients with PC tend to suffer more from issues with body image, sexual function and physical activities.²⁸ These issues although likely multifactorial and interconnected have been linked to dissatisfaction with appearance and stigma associated with having a stoma leading to negative body image and impaired sexual function.^{28–30} Ultimately, dissatisfaction with sexual function due to ostomy related issues is associated with worse HRQOL.³¹ Understanding these factors and how they impact HRQOL is very important to consider for individualized patient care as some patients may assign more value to certain areas than others. For example, patients may accept an overall decrease in HRQOL to preserve a more valued HRQOL domain. Moreover, patients may prefer one treatment strategy over the other based on their own personal values. Therefore, the use of strategies to predict LARS severity such as pretreatment LARS or the POLARS score may assist in the shared decision making process by informing patients of what they may expect in terms of symptoms and in-turn HRQOL.^{32,33} However, further research into this topic is needed.

Limitations: This study was conducted at a single Canadian colorectal referral center and therefore may not be generalizable to all patients. Interviews were conducted at a mean of 35.1 (26.2) months following surgery and therefore may not fully represent patient experiences in the immediate post-operative phase. Further, as some patients are further from their date of operation they may have had more time to recalibrate their internal reference of HRQOL potentially resulting in a response shift when compared to those who were more recently treated.³⁴ In order to adjust for the potential response shift our regression analysis included follow-up time as a covariate. In addition, bowel dysfunction begins to stabilize 12 months following restoration of bowel continuity suggesting a longer follow-up time may provide insight into living with long term sequelae of treatment.^{5,35} When accounting for non-participants and deaths we were only able to include 39 colostomy patients. Although this number was sufficient for our primary outcome, more patients could have provided more information about affected

HRQOL domains. Therefore, we focused on the most frequently reported domains in order to make comparisons. Although there are differences in HRQOL between LARS categories, the LARS score does not capture all aspects of bowel dysfunction following RP and there may be further heterogeneity of HRQOL within LARS categories.³⁶ Lastly, 27% of patients were unreachable by phone or did not want to participate. As a result, there is potential for response bias.

Conclusions: Both restorative proctectomy and permanent colostomy have an important impact on the HRQOL of individuals treated for rectal cancer. In general, patients treated with restorative proctectomy tend to have better health-related quality of life than those with permanent colostomy, especially when their symptoms of bowel dysfunction are less severe. However, there are significant differences in the aspects of life affected in these populations such as, sleep, sexual function, remunerative employment, body image, transportation, self-care, and physical activity. Therefore, a personalized approach must be made in the shared decision-making process using this information to guide patients with their values in mind.

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	Overall	Restorative	Permanent	P-Value
	(n=121)	Proctectomy	Colostomy	
		(n=82)	(n=39)	
Age, mean (SD)	65.9 (11.0)	0) 65.1 (10.7) 67.5 (11.6)		0.250
Sex, female	33% (40)	29% (24)	41% (16)	0.189
BMI, mean (SD)	26.9 (5.2)	26.8 (5.5)	27.0 (4.7)	0.900
ASA				0.017
1 to 2	80 (66%)	60 (73%)	20 (51%)	
3 to 4	41 (34%)	22 (27%)	19 (49%)	
Neoadjuvant	65% (79)	62% (51)	72% (28)	0.280
radiotherapy				
Distance from anal	6.2 (2.8)	7.1 (2.4)	4.3 (2.6)	<0.001*
verge (cm), mean (SD)				
Tumor size (cm), mean	4.6 (2.3)	4.3 (2.1)	5.2 (2.8)	0.076
(SD)				
MIS approach	88% (106)	90% (74)	82% (32)	0.215

Table 1: Patient, tumor and treatment characteristics

pT-stage				0.010*
0 to 2	64 (53%)	50 (61%)	14 (36%)	
3 to 4	57 (47%)	32 (39%)	25 (64%)	
LOS, median [IQR]	4 (4.5)	3 (3.0)	6 (8.5)	<0.001*
Complications	35% (42)	32% (26)	41% (16)	0.332
Readmission	16% (19)	16% (13)	15% (6)	0.888
Emergency visits	22% (27)	23% (19)	21% (8)	0.805
PGI score, mean (SD)	45.9	50.8 (24.5)	35.5 (27.3)	0.002*
	(26.3)			
Follow-up time, mean in	35.1	38.2 (26.6)	28.5 (24.3)	0.059
months (SD)	(26.2)			

MIS, Minimally Invasive Surgery; LOS, Length of Stay; SD, Standard Deviation; BMI, Body

Mass Index; and ASA, American Society of Anesthesiology. *P<0.05

Table 2: Adjusted mean difference in PGI score between patients with restorative proctectomy

vs. permanent colostomy using multiple linear regression

	Mea		
	Estimate	95% Confidence Interval	P-Value
Colostomy (reference)	-	-	-
Restorative Proctectomy	15.3	(3.3, 27.3)	0.0130*

No/Minor LARS	20.6	(7.1, 34.2)	0.0032*
Major LARS	10.7	(-2.5, 23.8)	0.1109

LARS, Low Anterior Resection Syndrome; PGI, Patient Generated Index.

Adjusted for age, sex, tumor height, time to administration of the PGI in months, neoadjuvant radiotherapy, and minimally-invasive approach. *P<0.05

Table 3: ICF linked HRQOL domains identified on the PG
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	No/Minor	Major	Permanent	P-Value (major
	LARS (n=42)	LARS	Colostomy	LARS vs.
		(n=40)	(n=39)	colostomy)
B134 "Sleep	7 (17%)	5 (13%)	1 (3%)	0.1027†
functions"				
B152 "Emotional	6 (14%)	5 (13%)	5 (13%)	1.000
functions"				
B1801 "Body image"	2 (5%)	1 (3%)	8 (21%)	0.0135*†
B455 "Exercise	4 (10%)	1 (3%)	1 (3%)	1.000
tolerance functions"				
B525 "Defecation	9 (21%)	4 (10%)	4 (10%)	1.000
functions"				

B640 "Sexual	3 (7%)	7 (18%)	14 (36%)	0.0712†
functions"				
D470 "Using	9 (21%)	8 (20%)	2 (5%)	0.0445*†
transportation"				
D510 "Washing	1 (2%)	2 (5%)	5 (13%)	0.2130
oneself"				
D570 "Looking after	14 (33%)	13	5 (13%)	0.0350*†
one's health"		(33%)		
D640 "Doing	4 (10%)	1 (3%)	0 (0%)	0.2757
housework"				
D850 "Remunerative	4 (10%)	15	6 (15%)	0.0208*‡
employment"		(38%)		
D9201 "Sports"	9 (21%)	11	18 (46%)	0.0974†
		(28%)		
D9205 "Socializing"	27 (64%)	24	17 (44%)	0.1547
		(60%)		

LARS, Low Anterior Resection Syndrome; ICF, International Classification of Functioning; HRQOL, Health Related Quality of Life; PGI, Patient Generated Index; RP, Restorative Proctectomy; PC, Permanent Colostomy. * = P<0.05 Major LARS vs. Permanent Colostomy, † = P<0.05 Restorative Proctectomy vs. Permanent Colostomy and ‡ = P<0.05 no/minor LARS vs. Major LARS

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Chapter 4 - Discussion

The Shared Decision Making Process

The process of incorporating shared-decision making (SDM) into clinical practice has led to more well informed patients, increased patient involvement and in some cases, less invasive treatment.⁷² Overall, most patients prefer to be involved in the decision-making process regarding their care and incongruence between patient preferences for their role in decision making and their actual role can contribute to decisional regret.^{73,74} Furthermore, increased patient involvement in their own care has been associated with better outcomes such as decreased readmission, complications or length of hospital stay.⁷⁵ As a result, studies have evaluated the optimal approach to incorporating the SDM process into practice.⁷⁶ The process of SDM involves three key components, 1) "Choice talk" where patients are made aware of treatment options, 2) "Option talk" where details about each treatment option are explored in detail, and 3) "Decision talk" where the emphasis is on supporting patients as they incorporate their own values.⁷⁶ This process is particularly important in the context of rectal cancer as there appears to be a disconnect between patients and providers in terms of what symptoms matter most.⁷⁷ Ultimately, providing information about outcomes within the realm of what patients can envision or understand can help facilitate their evaluation of risks with respect to their personal values.⁷⁸ Therefore, in the context of rectal cancer, physicians should do their best to provide patients with information about anticipated outcomes such as symptoms like bowel dysfunction and their subsequent impact on daily life in the form of HRQOL in order to respect ideal SDM practices.

Bowel Dysfunction in Rectal Cancer

In our first study "Predictors of pre- and post-treatment bowel dysfunction severity in patients with rectal cancer" we found that over half of patients with rectal cancer had symptoms consistent with LARS at the time of referral to a colorectal surgeon (Table 2). Although technically not LARS 'per se' given these patients have not yet undergone a low anterior resection, pretreatment symptoms can be thought of as rectal cancer related bowel dysfunction. Pretreatment symptoms were measured with the LARS score to ease translation of pretreatment symptoms to post-treatment symptoms given post-treatment symptoms are most commonly evaluated using the LARS score.²⁶

Furthermore, in our first study, using normative data from a reference population we were able to generate predicted pretreatment LARS scores based off demographic data for each individual patient.¹¹ Importantly, when compared to predicted categories, observed pretreatment LARS categories tended to be worse (Table 2). Specifically, we found that rectal cancer patients with lower and larger tumours were more likely to have an increased mean difference between predicted and observed pretreatment LARS scores. Ultimately, supporting previous literature describing the common symptoms of rectal cancer.^{9,10} The mechanism by which this occurs is likely the result of rectal tumours causing a disruption in the normal anatomic and physiologic function of the rectum similar to how RP involves a change in rectal anatomy and physiology through surgical resection. This observation not only provides insight into our understanding of the clinical presentation of rectal cancer as most patients will have experienced some degree of bowel dysfunction prior to their treatment but the identification that this bowel dysfunction is compatible with LARS may provide patients with a realistic reference point into what LARS may be like after treatment. Being able to provide this type of information to patients is a key tenet of the SDM process as it can provide a framework in which to interpret expected outcomes.^{76,78}

In patients undergoing RP for rectal cancer we found that 82% of patients remained within the same LARS category or got worse following treatment with patients who underwent a diverting stoma at highest risk for a deterioration in their LARS category. This information may help patients decide during their pretreatment consultation whether their current bowel function is compatible with their lifestyle considering that few patients actually have an improvement in LARS following treatment. Several other studies have identified factors associated with worse LARS however, many of these studies evaluated a change in LARS score rather than a change in LARS category.⁶⁵ This is particularly important because LARS categories were defined based on the direct impact of LARS symptoms on HRQOL such that patients with no LARS had no impact, minor LARS had little impact and major LARS had some/major impact on HRQOL.²⁶ Therefore, our study was powered to detect changes in LARS categories as a change in category appears to be associated with a clinically important difference for patients.

The complexity in predicting LARS outcomes may be largely due to its development being multifactorial as tumour height, radiotherapy, total mesorectal excision and fecal diversion in addition to other patient factors have all been associated with its development.⁶⁵ However, many of these treatment related factors are associated with tumour factors such as tumor height. Specifically, lower tumours and tumours more closely related to the mesorectal fascia tend to be more strongly associated with treatment factors that increase the risk of LARS such as radiotherapy or diverting stoma.⁶⁵ Ultimately, many of these factors are interconnected and for patients, may be difficult to synthesize into something meaningful to them. Therefore, using a symptom based prediction model like the LARS score may provide patients with information that can be evaluated in the context of their daily life.

Although using pretreatment LARS symptoms may be relevant to patients who intend to undergo RP, data are limited on how HRQOL can be impacted by worsening bowel dysfunction or how patients with RP compare to those with PC in terms of HRQOL.

Health-Related Quality of Life in the Treatment of Rectal Cancer

The use of patient-reported outcome measures, such as HRQOL, have become the mainstay in evaluating healthcare outcomes and providing value-based care.⁷⁹ Furthermore, most patients value patient-oriented evaluation of outcomes and measurement using individualized tools may provide patients with more relevant information to prioritize their values than more generic instruments.^{56,58,59,80} However, in the context of rectal cancer, HRQOL outcomes have been largely measured using tools that may lack sensitivity to assess individual patient values. ^{56–60} In our second study, patients treated for rectal cancer with either RP or PC underwent evaluation of HRQOL using the PGI, a patient-reported outcome measure that uses a patient-centric approach to the evaluation of HRQOL.^{56,59} Evaluating HRQOL using the PGI allows patients the freedom to identify HRQOL domains that have been affected and weigh their importance in the context of the patient's own individual values and expectations.^{56,59} In addition, the PGI provides overall HRQOL scores and identifies important HRQOL domains that can, in turn, provide patients with meaningful information on how their life may change following treatment. Therefore, the use of the PGI to evaluate individualized HRQOL outcomes may provide patients with valuable information in the SDM process given previous studies using generic HRQOL instruments have failed to meaningfully differentiate HRQOL outcomes between RP and PC.⁴⁶

In our second study, we found that overall patients treated with RP had better HRQOL scores than those treated with PC. However, despite the equivocal findings of previous literature, we found that by using the PGI to measure HRQOL there was significant heterogeneity in overall HRQOL within the RP group that appears to be related to LARS severity.⁵⁸ Specifically, in a subset of patients treated with RP that had major LARS there was no difference in overall HRQOL when compared to PC whereas, those with no/minor LARS had significantly better HRQOL than those with PC. Detection of a clear distinction between LARS categories and overall HRQOL is likely the result of the increased sensitivity of the PGI when compared to previously used HRQOL instruments, many of which have been criticized for their lack of relevance to patients.^{56,58} Furthermore, the PGI has the added benefit of allowing patients to self report HRQOL domains that are affected and therefore, although patients with major LARS and patients with PC had similar overall HRQOL scores important differences in HRQOL domains were identified.⁵⁹ Specifically, patients with PC had more issues with body image, sexual function and involvement in sports whereas patients with RP had worse ability to sleep, travel, remunerative employment and take care of ones self. Therefore, our findings build on previous literature that have identified potential differences in affected HRQOL domains between RP and PC and when accounting for heterogeneity of RP patients, contrast with previous findings that overall HRQOL may be similar between these treatment strategies.^{58,81–85} Ultimately, these findings improve the clarity of the current literature on what patients can expect following the treatment for rectal cancer which, in turn, is necessary for patients to accurately weigh the risks and benefits of alternative treatments.78

Clinical Relevance

In order to adequately inform patients in the SDM process reasonable estimates of anticipated LARS severity and associated HRQOL outcomes as well as HRQOL outcomes for PC should

be provided.^{76,78} The impact of bowel dysfunction on HRQOL appears to be highly specific to each patient and knowledge of expected HRQOL outcomes may allow patients to opt for RP or PC based on their own values and wishes.^{18,86} For example, if prior to treatment a patient had already been experiencing symptoms consistent with major LARS then based on the findings of our first study we would anticipate this patient would most likely continue to have LARS following treatment. With this information, the patient and provider could then discuss anticipated HRQOL outcomes between someone with RP and major LARS versus someone with PC. With further discussion, patients may reveal certain values such as a love for travel, or concerns about remunerative employment and therefore, based off the findings of our second study, patients who undergo RP and have major LARS are more likely to report issues with these HRQOL domains and maybe this patient would benefit more from a PC. By contrast, should a patient report values such as preservation of sexual function or involvement in sports then RP may be the better choice for that individual. Furthermore, if a different patient initially presented prior to treatment with no symptoms consistent with LARS then based on our first study, their odds of developing major LARS would be significantly lower and therefore based on our findings from our second study, may have an overall HRQOL benefit by avoiding PC altogether. Ultimately, patients with a new diagnosis of rectal cancer should be screened prior to treatment with the LARS score in order to provide an expected trajectory of symptoms and then patients should be informed of not only overall HRQOL outcomes but of which HRQOL domains are likely to be affected by either treatment strategy.

Future Directions

The chapters presented in this thesis represent early work in the understanding of which patients are expected to develop LARS and how the treatment of rectal cancer is anticipated to

impact HRQOL. The prediction of LARS has proven to be complex and difficult to achieve with high accuracy.^{42,43,65} This is likely due to multifactorial development of LARS with patient, tumor and treatment variables all playing a role in symptom onset and patient experience.^{58,65} Therefore, our approach to predicting LARS using pre-treatment LARS may serve as a basis on which to build more accurate prediction models that account for the multifactorial nature of LARS development. Specifically, it may be beneficial to include additional variables such as sphincter function prior to treatment, tumor height or neoadjuvant radiotherapy to the pre-treatment prediction model in order to augment our model. Future studies will aim to do so. Similarly, HRQOL and how it is affected by bowel dysfunction is highly specific to each individual patient.⁸⁶ Future studies could evaluate potential inherent differences in underlying HRQOL between patients that end up with one treatment strategy as opposed to another. Therefore, measurements of baseline values of HRQOL may be important prior to an individual's journey through the treatment and recovery processes as some studies have found little change in HRQOL before and after surgery for colorectal cancer.⁸⁷ Furthermore, few studies have evaluated the role of patient activation, the concept of a patient's own involvement in their care and its impact on HRQOL in this context.⁸⁸ Interestingly, decreased patient activation has been associated with increased complications and utilization of healthcare resources.⁷⁵ As a result, screening for degree of baseline patient activation or promoting involvement in one's own care may play a significant role in future studies to better understand or improve outcomes following surgery for rectal cancer.

Limitations:

The studies included in this thesis were performed at a single high-volume university-affiliated colorectal tertiary referral center that specializes in complex cases of colon and rectal cancer. As a result, these results may lack generalizability to centers with different experience and/or

patient demographics. Included patients were voluntary participants in our institution's rectal cancer registry and a subset of patients were recruited at follow-up (Chapter 3). Therefore, there is potential for volunteer bias. However, given the participation rate in our studies our results are likely representative of our population as a whole. Furthermore, there was some heterogeneity in follow-up time within groups and therefore patients with increased follow-up time may have more time to adapt to lifestyle changes and therefore there may be a response shift in HRQOL. In order to adjust for this we included follow-up time in our regression models.

Bowel dysfunction was measured using the LARS score which although encompasses the majority of the constellation of bowel-related symptoms following rectal cancer treatment, it neglects constipation which in turn can be disruptive to HRQOL.³¹ Furthermore, previous studies evaluating bowel-related quality of life have found that the LARS score may lack sensitivity in predicting HRQOL outcomes.⁸⁶ Despite the well reported relationship between LARS and impaired HRQOL, some techniques such as trans-anal irrigation or pelvic floor rehabilitation exist to help minimize LARS symptoms and could potentially mitigate the negative impact of LARS on HRQOL.^{89,90} Therefore, further understanding of these interventions and more widespread application could contribute to further benefit of RP over PC.

Lastly, there may be inherent differences between patients that were selected for RP versus those that underwent PC that were not measured or controlled for. Factors such as cultural differences could weigh heavily in the decision making process and this was not accounted for in our analyses. In addition, some patients who underwent PC may not have been candidates for RP given the extent of local invasion - this may have affected their HRQOL.

Conclusion:

The treatment of rectal cancer is a complex and evolving process and HRQOL outcomes appear to be affected by patient, tumor and treatment factors. Understanding the odds of developing LARS following RP and the impacts of LARS severity or PC on HRQOL serves as a critical component of the SDM process regarding the treatment of rectal cancer. Overall, when feasible, patients diagnosed with rectal cancer appear to have a significant HRQOL benefit when treated with RP over those treated with PC unless major LARS is anticipated. If patients are likely to develop major LARS following treatment with RP, a thorough discussion of individual goals, values and wishes should be discussed as patients who undergo RP and develop major LARS have similar overall HRQOL outcomes with distinct differences in the affected HRQOL domains.
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