Patient-centered approach to Low Anterior Resection Syndrome

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The views presented in this thesis are that of the authors and do not necessarily reflect those of the Fonds de Recherche du Québec, the Ministry of Health and Social Services, the McGill University Department of Surgery, or the Fast family.

Thesis Format

This thesis, presented in manuscript-based format, includes four distinct manuscripts which are either being submitted for publication or have already been published. The first manuscript is a linked database study that has been submitted to *JAMA Surgery*. The second manuscript is an observational cohort study with cross-sectional follow-up that has been submitted to *Diseases of the Colon and Rectum*, and is currently in revisions. The third manuscript is a systematic review of online health information that has been published in *Colorectal Disease*. The fourth manuscript describes both the development of a Low Anterior Resection Syndrome patient-centered program and the study protocol for its future evaluation in a randomized controlled trial, and has been published in *BMJ Open*.

The thesis contains an Introduction and Discussion, and short preambles connecting one manuscript to the next. Inevitably, there will be some degree of repetition throughout. Please note that each manuscript (Chapters 2.1, 3.2, 4.2, and 5.2) has its own reference list and associated Tables, Figures, and Appendices. The master reference list at the end of the thesis (Chapter 8) pertains to the Introduction and Discussion chapters only (Chapters 1 and 6). Furthermore, for manuscripts which have already been submitted or accepted for publication, the abstract, main text, and references may be formatted according to the specific journal's requirements.

Contribution to Original Knowledge

The work presented in this thesis represents original contributions and adds to the body of knowledge on Low Anterior Resection Syndrome (LARS). The work highlights the prevalence of, and factors associated with, LARS after restorative proctectomy, and the long-term impact LARS may have on patient-reported outcomes. After systematically reviewing the Internet for online health information on LARS, a significant knowledge gap was identified, and a LARS Patient-Centered Program was developed. The study protocol for a future randomized controlled trial evaluating the impact of the LARS Patient-Centered Program was then described.

While I have received support from my supervisors and committee members, and input from co-authors for each study, the data presented in the following chapters represent my original work.

Author Contributions

I have made a substantial contribution to each of the individual manuscripts listed below, and had an active role in study design and conception, data acquisition, data analysis, and drafting of the manuscript. My contributions were performed under the guidance of my supervisors, Dr. Marylise Boutros and Dr. Sahir Bhatnagar, and in collaboration with the co-authors listed below. The contributions of individual authors within each manuscript is listed below:

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Abstract

Introduction: Bowel dysfunction after restorative proctectomy, referred to as Low Anterior Resection Syndrome (LARS), is a common late sequela of rectal cancer treatment that has a significant impact on long-term quality of life (QoL). Given that much of the conservative management for LARS requires effective troubleshooting and self-management behaviors, proper education and counseling may help motivate patients to become more engaged in their own LARS healthcare. The objectives of this thesis were (1) to evaluate the incidence of, and risk factors for, bowel dysfunction after restorative proctectomy; (2) to describe the consequences associated with LARS; and (3) to develop a LARS Patient-Centered Program for patients who underwent restorative proctectomy.

Methods: An observational cohort study using two linked administrative and clinical databases was performed. The cohort and relevant covariates were defined according to appropriate procedural and diagnostic codes, and bowel dysfunction was defined according to bowel symptoms and medication prescriptions. A Cox proportional hazards model was performed to identify independent risk factors associated with postoperative bowel dysfunction. A single-institution observational cohort study of consecutive patients who underwent restorative proctectomy for rectal cancer between 2007-2018 was then undertaken. Eligible patients completed various Patient-Reported Outcome Measures (PROM), and the association between LARS, bowel-related financial impact and global QoL was assessed using multiple logistic regression. A systematic review of online health information for LARS was then performed, and included websites were assessed for readability, quality, suitability, accuracy, and content. The top rated websites, along with their strengths and weaknesses, were further explored. A LARS Patient-Centered Program (LPCP) was then developed, and the informational resource to be used in the LPCP was vetted in a focus group and semi-structured interviews. The protocol for a future randomized controlled trial evaluating the impact of the LPCP on patient-reported outcomes was then described.

Results: In all, 2,197 patients underwent a restorative proctectomy and had available data in both databases. After a median follow-up of 51.6 (24.0-90.0) months, bowel dysfunction was identified in 620 (28.2%) patients. Risk factors for postoperative bowel dysfunction included extremes of age (<40 years-old: aHR 2.35, 95% CI 1.18-4.65; 70-79 years-old: aHR 1.25, 95% CI 1.03-1.52), radiotherapy (aHR 1.94, 95% CI 1.56-2.42), distal tumors (aHR 1.62, 95% CI 1.34-1.94), history of diverting ostomy (aHR 1.58, 95% CI 1.33-1.89) and anastomotic leak (aHR 1.48, 95% CI 1.06-2.05). A minimally-invasive surgical approach was protective for postoperative bowel dysfunction (aHR 0.68, 95% CI 0.53-0.86). For the single-institution cohort study, 154 patients underwent a restorative proctectomy for rectal cancer and completed the various PROMs (response rate: 85.6%). Patients with major LARS (n=47, 30.5%) reported a higher prevalence of bowel-related financial stress (53.2% vs. 5.6%, $p<0.001$) and strain (42.2% vs. 5.6%, $p<0.001$) compared to those with minor/no LARS. On multiple logistic regression, major LARS with bowel-related financial impact (OR: 4.48, 95% CI 1.60-13.46) was associated with low global QoL. The systematic review identified 25 websites for analysis. Median readability level was 10.4 (9.2-11.7), and using the DISCERN instrument, 4 (16.0%) websites had overall high quality. The included content was highly variable, and important information was often missing. Finally, a multidisciplinary team developed the framework for a LPCP, and a

LARS patient informational booklet was created using original text and illustrations. Data gathered through a focus group with patients and their caregivers, as well as semi-structured interviews with rectal cancer healthcare professionals, were analyzed to improve the booklet into its final format.

Conclusions: Bowel dysfunction after restorative proctectomy is common, and several patient, tumor, and treatment factors were associated with its development. Furthermore, patients with major LARS experience financial hardships and worse QoL compared to those with minor/no LARS. A LPCP was developed and validated by patients and healthcare professionals, and may fill an important knowledge gap for rectal cancer survivors.

Résumé

Introduction : La dysfonction intestinale après une résection du rectum, appelé Syndrome de résection antérieure basse (SARB), est une séquelle courante du traitement du cancer rectal qui peut avoir un impact important sur la qualité de vie. Étant donné qu'une grande partie du traitement du SARB nécessite un dépannage efficace et des comportements d'autogestion, l'éducation et des conseils appropriés peuvent aider à motiver les patients à s'engager davantage dans leurs propres soins de santé SARB. Les objectives de cette thèse étaient (1) d'évaluer l'incidence, et les indicateurs, de dysfonctionnement intestinal après une résection du rectum; (2) de décrire les conséquences associées au SARB; et (3) de développer un programme de support pour le SARB, pour aider les patients ayant subi une résection du rectum**.**

Méthodes : Une étude de cohorte utilisant deux bases de données administratives et cliniques liées a été réalisée. La cohorte et les variables ont été définies selon les codes de procédure et de diagnostic appropriés, et la dysfonction intestinale a été définie selon des symptômes intestinaux et des prescriptions de médicaments. Un modèle des risques proportionnels de Cox a été réalisé pour identifier des indicateurs associés à la dysfonction intestinale postopératoire. Suivant, une étude de cohorte des patients d'un seul établissement opérés pour un cancer du rectum entre 2007-2018 a été entreprise. Les patients admissibles ont complété plusieurs enquêtes, et l'association entre le SARB, l'effet financier lié à l'intestin, et la qualité de vie ont été évalués à l'aide de la régression logistique multivariée. Ensuite, une revue systématique des informations de santé sur l'Internet pour le SARB a été réalisée, et les sites Web ont été évalués pour leur lisibilité, leur qualité, leur pertinence, leur exactitude, et leur contenu. Les sites Web les mieux notés, ainsi que leurs force et leurs faiblesses, ont été étudiés plus en détail. Ensuite, un programme de support pour le SARB a été développé, et le livret informatif inclus dans le programme a été examinée dans une groupe de discussion et avec des entretiens semi-structurées. Finalement, le protocole pour un essai contrôlé randomisé évaluant l'effet du programme sur les résultats rapportés par les patients a été décri.

Résultats : Au total, 2,197 patients ont subi une résection du rectum et disposaient de résultats dans les deux bases de données. Après un suivi médian de 51.6 (24.0-90.0) mois, une dysfonction intestinale a été identifiée chez 620 (28,2%) patients. Les indicateurs de dysfonctionnement intestinal postopératoire comprenaient l'âge (<40 ans : aHR 2.35, 95% CI 1.18-4.65; 70-79 ans: aHR 1.25, 95% CI 1.03-1.52), la radiothérapie (aHR 1.94, 95% CI 1.56-2.42), les tumeurs distaux (aHR 1.62, 95% CI 1.34-1.94), histoire d'une stomie temporaire (aHR 1.58, 95% CI 1.33-1.89), et une fuite de l'anastomose (aHR 1.48, 95% CI 1.06-2.05). La chirurgie moins invasive était associée avec moins de risque pour le dysfonctionnement intestinal postopératoire (aHR 0.68, 95% CI 0.53-0.86). Pour l'étude de cohorte, 154 patients ont subi une résection du rectum pour le cancer et ont complété les enquêtes (taux de réponse : 85.6%). Les patients atteints le SARB majeur (n=47, 30.5%) ont signalé une prévalence plus élevée de stress financier (53.2% vs. 5.6%, $p<0.001$) et du tension financier (42.4% vs. 5.6%, $p<0.001$) lié à l'intestin, par rapport à ceux avec le SARB mineur / absent. Sur le régression logistique multivariée, le SARB majeur avec un effet financier lié à l'intestin (OR : 4.48, 95% CI 1.60-13.46) était associé avec une qualité de vie basse. La revue systématique a identifié 25 sites web pour l'analyse. Le niveau de lisibilité médian était 10.4 (9.2-11.7), et en utilisant l'instrument DISCERN, 4 (16.0%) sites Web étaient globalement de haute qualité. Le contenu inclus était très variable et des informations importantes manquaient souvent. Enfin, une équipe multidisciplinaire a développé le cadre pour un programme de support pour le SARB, et un livret instructif a été créé à l'aide de textes et d'illustrations originaux. Les données recueillies dans une groupe de discussion avec des patients et leurs soignants, ainsi que dans les entretiens semi-structurées avec des professionnels de la santé du cancer rectal, ont été analysées pour améliorer le livret dans son format final.

Conclusions : La dysfonction intestinale après une résection du rectum est courante, et plusieurs facteurs liés au patient, à la tumeur et au traitement ont été associés à son développement. En outre, les patients atteints de LARS majeur éprouvent des difficultés financières et une moins bonne qualité de vie par rapport à ceux qui ont un LARS mineur / absent. Un programme de support pour le SARB a été développé et validé par des patients et des professionnels de la santé, et peut combler une lacune importante dans les connaissances des survivants du cancer rectal**.**

Chapter 1: Introduction

The Rectum

The rectum represents the final portion of the human digestive tract. Many landmarks exist to define its proximal extent, including the sacral promontory, the anterior peritoneal reflection, and the sigmoid take-off.[1] Regardless of the definition used, the rectum typically measures 12 to 15 cm in length, and terminates in the anal canal. Though it is small in size, the rectum serves an important function beyond acting as the conduit between the colon and anus. The rectum primarily serves as a reservoir for stool, and through the anorectal inhibitory and rectocolic reflexes, contributes towards the complex mechanism of fecal continence.[2]

Rectal Cancer

There are many pathologies and diseases that affect the rectum. Among them all, none is more significant and impactful than malignancy. In Canada, colorectal cancer is the second leading cause of cancer-related mortality.[3] While precise estimates of rectal cancer are often lacking from national statistics due to its aggregation with colon cancer, it is estimated that one-third of colorectal cancer originates in the rectum,[4] which is disproportionately high when comparing its length to that of the colon. The annual incidence of rectal cancer has increased over the previous two decades in most developed countries,[4] in part due to the implementation of systematic screening. However, other factors are likely at play (e.g., diet and microbiome), as the increased incidence is largely driven by a spike in disease among young adults (<50 years-old) who do not meet current screening criteria.[5,6]

Since its earliest description at the turn of the nineteenth century, the management of rectal cancer has vastly evolved and transitioned into the multidisciplinary care that is offered to patients today. Sir William Ernest Miles pioneered the first curative rectal cancer resection in

1907, an operation that is now known as the abdominoperineal resection (APR).[7] This operation, which involved the resection of the entire rectum, anus, and sphincter complex, and the formation of a permanent colostomy (Figure 1a), remained the gold standard for rectal cancer surgery throughout the first half of the twentieth century. The restorative anterior resection, which involved the resection of the rectum and an anastomosis from the colon above to the lower rectum or anus below (Figure 1b), was first described in 1930. Although this operation preserved the anal sphincters and obviated the need for a permanent colostomy, it was largely dismissed and thought to be an inferior oncologic operation. It was only in 1948, when Claude Dixon reported a 64% five-year survival rate in over 400 patients who underwent an anterior resection,[8] that restorative sphincter-sparing procedures were accepted. In 1982, Professor Bill Heald further revolutionized rectal cancer surgery technique by introducing the Total Mesorectal Excision (TME),[9,10] which mandated that the entire mesorectum and its lymph nodes be removed along with the rectum. The widespread adoption of the TME resulted in decreased rates of local recurrence, from a startling 25% to a more acceptable 10%.[11,12] Finally, at the end of the century, large multicentered randomized controlled trials demonstrated the added benefit of neoadjuvant radiation therapy, which lead to an additional 50% reduction in local relapse.[13,14]

Today, the TME technique is considered the gold standard for rectal cancer surgery, and neoadjuvant radiation therapy is indicated for locally-advanced tumors.[15,16] The decision to perform an APR or a restorative proctectomy depends largely on tumor location and patient wishes. When oncologically feasible (i.e., an adequate distal margin is present), a sphincter-sparing procedure is typically the preferred option, and the restorative proctectomy is currently the most commonly performed operation for rectal cancer.[17,18]

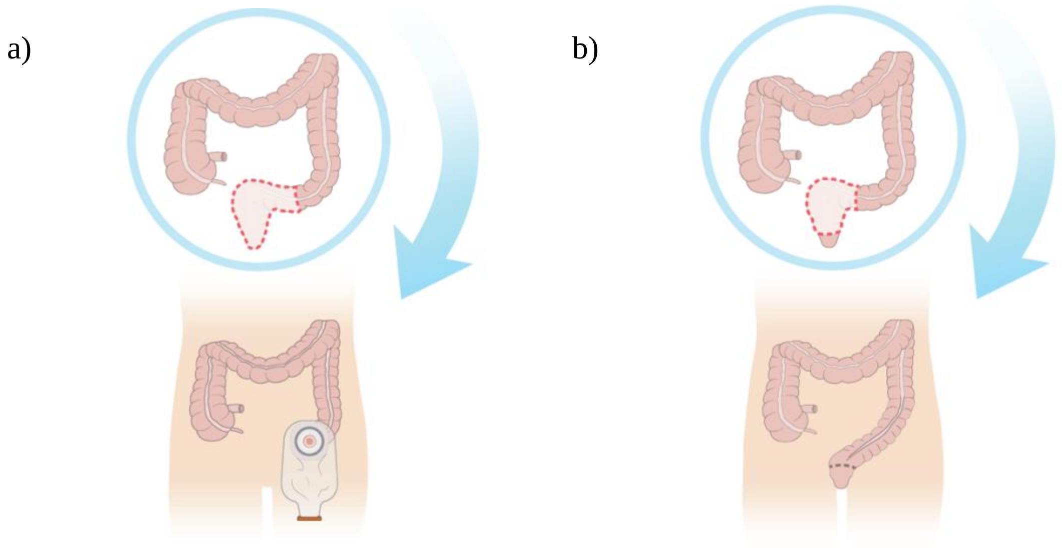

Figure 1 – Illustrations depicting two operations for rectal cancer: a) abdominoperineal resection; b) restorative proctectomy. Illustrations taken for our original LARS informational booklet (discussed in Chapter 5). © 2019, McGill University Health Center, Patient Education Office.

Low Anterior Resection Syndrome

The combination of good-quality surgery and neoadjuvant therapy has dramatically improved the long-term prognosis of patients with rectal cancer.[4] This improved survival, coupled with the rising incidence of rectal cancer, has resulted in more patients than ever before living in the survivorship phase of their cancer journey. As such, the long-term adverse effects of cancer treatment have garnered increased attention and interest. Rectal cancer survivors are at risk for several adverse effects, including emotional, psychological, financial, and physical burdens.[19,20] Among them all, postoperative bowel dysfunction is perhaps the most prevalent and significant, earning the name "Low Anterior Resection Syndrome" (LARS) at the turn of the century.

LARS is defined as disordered bowel function that develops following rectal resection, leading to a detriment in quality of life.[21] While little was known about LARS for many years, the introduction of the LARS Score in 2012 provided researchers with a common outcome measure to better study the condition.[22] Based mostly on single-center institutional reports, the epidemiology of LARS is slowly being uncovered. LARS is prevalent following restorative proctectomy, and can affect up to 70 to 90% of individuals.[21,23] Patients with LARS experience a constellation of symptoms, including fecal urgency and frequency, incontinence to liquid and stools, and evacuatory disorders, such as clustering (or fragmentation) of bowel movements.[22] Although LARS tends to somewhat improve throughout the first year, symptoms past this point are thought to be permanent and stable, with patients reporting significant bowel dysfunction up to 15 years after surgery.[24] Importantly, major LARS – defined as a LARS score ≥30 – is observed in up to 50% of patients after the first year, and has a significant impact on long-term overall quality of life (QoL).[23,25]

The pathophysiology of LARS is poorly understood, and its underlying cause is likely multifactorial.[21] From an anatomical perspective, the most evident explanation for LARS is loss of the rectum. Reduced neorectal reservoir volume is thought to explain many of the symptoms of LARS, including urgency and incontinence. In addition to reduced rectal capacity, rectal compliance is thought to change after surgery,[26,27] particularly in the setting of preoperative radiation therapy which may cause fibrosis in the pelvis. A hypocompliant rectum results in decreased distensibility of the reservoir with attendant changes in bowel function. Colonic motility may also increase after restorative proctectomy. In animal studies, rectal resection was associated with increased number and duration of colonic migrating motor complexes, which in humans are responsible for the propagation of stool to the rectum.[28] Finally, numerous iatrogenic insults may predispose to LARS: radiation therapy may cause toxicity to surrounding structures;[29] pelvic surgery may inadvertently result in denervation of the residual rectum;[30] and the introduction of endoanal stapling devices may cause structural damage to the sphincter muscles.[31] In accordance with the above, the most consistently identified risk factors associated with the development of LARS include low-lying rectal tumors (requiring a low anastomosis and resection of the entire rectum) and neoadjuvant radiation therapy.[32]

Management of Low Anterior Resection Syndrome

There is no well-established treatment algorithm for patients with LARS, and management largely draws upon the existing treatment strategies for primary fecal incontinence and other motility and evacuatory disorders.[33] Most patients are managed with a variety a conservative measures, including the use of medications (e.g., antimotility agents, bile acid sequestrants, 5-HT3 antagonists), dietary modifications, and pelvic floor exercises. If symptoms remain poorly controlled, enemas and/or transanal irrigation can be helpful and patients can be offered pelvic floor rehabilitation (e.g., biofeedback, balloon training), all of which have proven benefits in several small studies.[34-36] In cases of severe LARS causing significant impairment in QoL that persist after the first year postoperatively, sacral neuromodulation can be attempted.[37] Finally, permanent colostomy can provide a definitive resolution for intractable symptoms.

Due to the variable manifestation of LARS, management is very much empirical and symptom-based. Much of the conservative treatment strategies require a great degree of troubleshooting and effective self-management behaviors to improve bowel symptoms and achieve satisfactory QoL. For patients with LARS, these behaviors include understanding one's own symptoms, knowing how to use and dose stool bulking agents and anti-diarrheal medications, performing pelvic floor exercises, adhering to dietary restrictions and proper perianal skin management, and preparing for different social environments. As such, patients need to be educated, motivated and engaged in their own LARS healthcare in order to achieve the best possible outcome.

Among individuals undergoing rectal resection with a permanent colostomy (i.e., APR), supportive and informational interventions have demonstrated numerous benefits for patients. Two systematic reviews of supportive interventions for new ostomates identified potential benefits in QoL, emotional distress, and ostomy proficiency, self-efficacy and knowledge.[38,39] Similar benefits were observed when a chronic care self-management program was delivered to ostomy patients, while also improving patient activation scores.[40] However, evidence regarding the impact of such interventions in patients who undergo restorative procedures is lacking, despite this latter operation being far more frequently performed than APRs.[17,18] When patients are provided with the means to better understand and control important aspects of their bowel function, they may be more likely to experience positive improvements in patient-reported outcomes. In a recent review comparing long-term patient-reported outcomes after permanent ostomy or restorative procedures for rectal cancer, the authors concluded that interventions geared towards patients *without* ostomies warrant further attention.[41]

Thesis Objectives

The objectives of this doctoral thesis were fourfold:

1) To evaluate the incidence of, and factors associated with, bowel dysfunction after restorative proctectomy in a population-based cohort, and to evaluate the association between bowel dysfunction and postoperative sexual and urinary dysfunction;
2) To evaluate the financial and occupational consequences of bowel dysfunction after restorative proctectomy;

3) To evaluate online patient informational and educational materials for LARS, as part of the development of a LARS Patient-Centered Program for patients who underwent restorative proctectomy for rectal cancer; and
4) To plan for the systematic evaluation of the LARS Patient-Centered Program regarding its impact on patient-reported outcomes.

To accomplish these objectives:

1) I performed an observational population-based cohort study using two linked United Kingdom-based databases to report the incidence of, and factors associated with, bowel dysfunction after restorative proctectomy. I also studied the association between bowel dysfunction and new-onset postoperative sexual and urinary symptoms;
2) I performed an observational cohort study with cross-sectional follow-up using an institutional database of patients who underwent restorative proctectomy for rectal cancer. The study described the perceived financial and occupational hardships associated with LARS, and estimated their impact on global quality of life;
3) I performed a systematic review of online health information for patients with LARS, and conducted a focus group and semi-structured interviews with patients, caregivers, and healthcare professionals. This information provided an understanding of the educational needs of rectal cancer survivors experiencing LARS, and informed the development of a novel LARS Patient-Centered Program; and
4) I described a protocol for a multicenter randomized controlled trial evaluating the impact of a LARS Patient-Centered Program on patient-reported outcomes following restorative proctectomy for rectal cancer.

Chapter 2.1: Assessment of Long-Term Bowel Dysfunction in Rectal Cancer Survivors: A Population-Based Cohort Study

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Abstract

Introduction: The purpose of this study was to describe postoperative bowel dysfunction after restorative proctectomy, and to identify factors associated with its development.

Methods: Patients who underwent restorative proctectomy for rectal cancer between April 1998 and November 2018 were identified from the Hospital Episode Statistics database, and were linked to the Clinical Practice Research Datalink for postoperative follow-up. Bowel dysfunction was defined according to relevant symptom-based read-codes and medication prescription product-codes. A Cox proportional hazards model was performed to identify factors associated with postoperative bowel dysfunction, adjusting for relevant covariates.

Results: In total, 2,197 patients were included. The median age was 70.0 (IQR: 62.0-77.0) years-old, and the majority (59.2%) of patients were male. After a median follow-up of 51.6 (24.0-90.0) months, bowel dysfunction was identified in 620 (28.2%) patients. Risk factors for postoperative bowel dysfunction included extremes of age (<40 years-old: aHR 2.35, 95% CI 1.18-4.65; 70-79 years-old: aHR 1.25, 95% CI 1.03-1.52), radiotherapy (aHR 1.94, 95% CI 1.56-2.42), distal tumors (aHR 1.62, 95% CI 1.34-1.94), history of diverting ostomy (aHR 1.58, 95% CI 1.33-1.89) and anastomotic leak (aHR 1.48, 95% CI 1.06-2.05). A minimally-invasive surgical approach was protective for postoperative bowel dysfunction (aHR 0.68, 95% CI 0.53-0.86).

Conclusions: Bowel dysfunction was common following restorative proctectomy, and several patient, disease, and treatment-level factors were associated with its development.

Introduction

Advancements in the multidisciplinary care of rectal cancer have greatly improved its long-term prognosis.[1] This increased survival, coupled with the rising incidence of rectal cancer – particularly among young individuals[2,3] – has raised awareness regarding the long-term sequelae of treatment. Rectal cancer survivors are at risk for several adverse effects, including emotional, psychological, financial, and physical symptom burden.[4] Among them all, bowel dysfunction is perhaps the most prevalent and significant.

Bowel dysfunction after restorative proctectomy, commonly referred to as Low Anterior Resection Syndrome (LARS), is a common adverse effect of surgery that can affect over 50% of patients.[5] Despite the significance of bowel dysfunction in rectal cancer survivorship, the availability of robust and high-quality data on the disorder is lacking, largely due to challenges in its definition and measurement.[6,7] The development of the LARS score in 2012 provided a more commonly accepted outcome measure to better study the disorder;[8] however, a number of limitations have emerged with the LARS score, calling into question its reliability for the measurement of postoperative bowel dysfunction.[9] These challenges have been compounded by small sample sizes and limited statistical power, as studies using Patient-Reported Outcome Measure (PROM) data are often restricted to single-institution cohorts with variable response rates.

Real-world data on postoperative bowel dysfunction from large clinical databases may complement existing PROM data and offer some unique advantages. The use of "big data" has become increasingly popular in observational research; in addition to large sample sizes – and the associated precise estimates and narrow confidence intervals – large databases can provide a longitudinal assessment of a diverse patient population across a wide variety of healthcare settings.[10] To date, no real-world data exist on long-term bowel dysfunction after restorative proctectomy, which could provide surgeons with a better understanding of this long-term morbidity.

Thus, the goal of our study was to describe long-term bowel dysfunction in patients who underwent restorative proctectomy for neoplastic disease of the rectum and to identify risk factors for bowel dysfunction using population-level data. We also evaluated the association between bowel dysfunction and new-onset postoperative sexual and urinary symptoms.

Methods

Data Sources

This was an observational cohort study using two linked United Kingdom (UK)-based administrative databases. The Hospital Episode Statistics (HES) is a discharge database containing details of all admissions at National Health Service (NHS) hospitals in England. Each HES record contains a wide range of information, including clinical, patient, administrative, and geographic characteristics. Hospital visits can be linked longitudinally, and thus the database captures the full spectrum of a patient's operative, in-patient, and ambulatory history.

The Clinical Practice Research Datalink (CPRD) collects de-identified patient data from a network of primary care practices across the UK, and the data may be linked to other health related information to provide a longitudinal follow-up of a representative UK population. The database comprises over 11.3 million patients across 674 primary care practices, with approximately 25% of patients contributing over 20 years of follow-up data. Over 98% of the UK population is registered with a primary care practitioner, who acts as the first point of contact for non-urgent health issues and a gatekeeper to more specialized care.[11] After the specialist's role is complete, patient care is typically returned to the general practitioner. All physicians use a standardized data dictionary and coding system when recording symptoms, prescriptions, and tests. CPRD also undertakes various levels of validation and quality assurance to ensure the integrity, structure, and format of the data, and provides a patient-level data quality metric to signify "acceptability" for research.[11]

This study was approved by the Independent Scientific Advisory Committee and the Research Ethics Committee at the Jewish General Hospital. The scientific protocol (CPRD 19_106) was approved May 22, 2019, and amended on June 10, 2020 (CPRD 19_106A).[12]

Cohort Definition

All adult patients (≥18 years-old) who underwent a restorative proctectomy (OPCS procedure codes, **Appendix 1**) for a rectal neoplasm (ICD-10 codes, **Appendix 1**) between April 1, 1998 and November 1, 2018 were identified from the HES database. Patients who underwent a concomitant diverting ostomy (OPCS procedure codes, **Appendix 1**) at the time of proctectomy, or 365 days prior or 60 days following proctectomy, were screened for an ostomy closure procedure (OPCS procedure codes, **Appendix 1**) during their follow-up; patients who remained diverted were excluded. Eligible patients were then linked to the CPRD database. Patients were excluded if the primary practice was not contributing "acceptable" research-quality data, if they had less than 365 days of follow-up in CPRD prior to their proctectomy, or if their surgery followed the cessation of their practice's contribution to CPRD. Cohort entry was considered 60 days after the date of proctectomy, or 60 days after ostomy closure in cases that included proximal diversion. Cohort exit was considered at the date of transfer out of a CPRD practice, death, or if an ostomy procedure – temporary or permanent (OPCS procedure codes, **Appendix 1**) – was identified during follow-up.

Variables

Patient, disease, and treatment characteristics were collected from both HES and/or CPRD, where appropriate. Age, in years, was taken from the time of proctectomy. Medical comorbidities were taken from CPRD data in the 365 days prior to proctectomy. A Charlson Comorbidity Index (CCI) score was calculated for each patient based on the recorded comorbidities. Smoking status and body mass index were assessed using the most recent information in the 5 years prior to cohort entry. Tumor height was categorized as proximal or distal rectum, according to ICD-10 diagnosis for tumor location. The use of radiotherapy was ascertained up to 20 weeks prior to proctectomy. Postoperative radiotherapy was assessed as well to account for the practice of both strategies during the study period. The use of chemotherapy was ascertained in the 16 weeks postoperatively; this threshold has previously been used to identify curative-intent chemotherapy after rectal cancer surgery.[13,14] Operative approach was categorized as minimally invasive surgery (MIS) (laparoscopic or robotic) or open surgery (including conversions from MIS) (OPCS procedure codes, **Appendix 1**). Anastomotic leak was defined based on relevant diagnostic and procedural codes in the 90-days following proctectomy (OPCS procedure codes and ICD-10 codes, **Appendix 1**).[15,16]

Outcomes

Bowel dysfunction was defined according to bowel symptoms and bowel medication prescriptions. Symptom-based read-codes recorded in CPRD, defined as relevant symptoms reported by the patient at a clinical encounter, were used to identify bowel symptoms. The eight symptom complexes reported in the new LARS consensus definition were used to broadly identify relevant read-codes: altered bowel function, diarrhea / altered stool consistency, frequency, painful defecation, evacuatory difficulties, urgency, incontinence, and soiling.[9] Using the read-code hierarchy and key-word system, the code list was then expanded to include all possible relevant read-codes. Medication prescriptions for bowel dysfunction included loperamide, diphenoxylate hydrochloride, and bile acid sequestrants, and the prescription code list was expanded using a similar method. The final list of symptoms and medications with their corresponding read-codes and product-codes were reviewed and approved by an expert group consisting of colorectal surgeons and epidemiologists (**Appendix 2**). Two or more bowel events on discrete dates were required for the outcome definition in an attempt to capture chronic, long-term bowel dysfunction rather than isolated, short-term presentations. Thus, a patient was considered to have bowel dysfunction on the date of the second recorded bowel event (either a symptom or medication prescription) throughout follow-up.

Secondary outcomes included clinical encounters for new-onset symptoms of postoperative sexual and urinary dysfunction. Patients with pre-existing urinary and/or sexual symptoms recorded in the 365 days prior to proctectomy were excluded from each analysis, respectively. Both outcomes were operationally defined using a similar method to bowel dysfunction. The recently published recommendations by the Pelvic Floor Disorders Consortium on the use of patient-reported instruments to assess pelvic floor disorders were consulted to identify the best-suited symptoms on which to base each outcome.[17] Symptoms for male sexual dysfunction were identified from the International Index of Erectile Function diagnostic tool: erectile function, orgasmic / ejaculatory function, sexual desire, and satisfaction.[18] Relevant symptoms for female sexual dysfunction were based on the Female Sexual Function Index diagnostic tool: lubrication, pain, orgasmic function, sexual desire, and satisfaction.[19] Symptoms of urinary dysfunction in both males and females were identified from the International Prostate Symptom Score and the International Consultation on Incontinence Questionnaire – Female

Lower Urinary Tract Symptoms module: incontinence, urinary retention / difficulties emptying, frequency, urgency, and nocturia.[20,21] Based on these categories of symptoms, relevant read-codes recorded in CPRD were identified to define each outcome. All symptoms were reviewed and approved by the same expert group (**Appendix 2**). Contrary to bowel dysfunction, only one symptom-based read-code was required to define an event.

Data Analysis

Patient demographics, medical comorbidities, and tumor, treatment, and operative characteristics were presented as means with standard deviations, medians with interquartile ranges (Q1 – Q3), or frequencies with proportions, where appropriate. Chi-squared tests were used for crude analysis of categorical data. The frequency of clinical encounters for bowel symptoms and bowel medication prescriptions was reported, and the median time between cohort entry, first bowel event, and subsequent bowel events was calculated. A Cox proportional hazards regression model was performed to identify factors associated with bowel dysfunction, and included clinically relevant patient-, tumor-, and treatment-level factors. As an exploratory secondary outcome, the associations between bowel dysfunction and clinical encounters for new-onset sexual and urinary symptoms were modeled in separate multiple logistic regression models, adjusted for age, sex, smoking status, CCI score, and obesity. Adjusted hazards ratios (aHR) and odds ratios (aOR) with 95% confidence intervals (CI) were reported, respectively. An alpha=0.05 was used for statistical significance. All statistical analyses were performed using SAS version 9.4 (Cary, NC: SAS Institute Inc; 2014).

Results

In total, 5,378 adult patients underwent a restorative proctectomy during the study period while registered in an “acceptable” research-quality CPRD practice. Among them, 2,806 procedures were performed for a primary diagnosis of rectal neoplasm. Three-hundred (10.7%) patients had a diverting ostomy performed as part of their proctectomy but never underwent ostomy closure. Another 309 patients were excluded for insufficient follow-up time before and after proctectomy, leaving 2,197 eligible patients for analysis **(Figure 1)**.

The median age was 70.0 (62.0-77.0) years-old, and the majority (59.2%) of patients were male. Almost half (45.2%) of patients had a CCI score ≥3 and most were non-obese. The underlying pathology was malignant in most cases (96.2%), and 60.1% of tumors were located in the mid-low rectum. The minority of patients received either radiotherapy (11.3%) or chemotherapy (27.4%) in the neoadjuvant / adjuvant setting. In all, 20.8% of cases were completed with an MIS approach, 24.5% of patients had a diverting ostomy which was subsequently closed, and 4.6% of patients suffered an anastomotic leak. Amongst patients with an ostomy, median time-to-closure was 233 (124-351) days (**Table 1**).

After a median follow-up of 51.6 (24.0-90.0) months, 592 (26.9%) patients had a clinical encounter for a bowel symptom, with a median time to first presentation of 475.5 (119.0-1,223.5) days. Among them, 252 (42.6%; or 11.5% of entire cohort) patients had at least two encounters for bowel symptoms (median time between first and second bowel symptoms = 249.5 (50.0-683.6) days) and 135 (22.8%; or 6.1% of entire cohort) had at least three **(Figure 2)**. Six-hundred and ninety (31.4%) patients received a bowel medication prescription, with a median time to first prescription of 104.5 (29.0-459.0) days. The majority of medicated patients received a second prescription (n=504, 73.0%; or 22.9% of entire cohort) at a median time between first and second prescription of 44.0 (23.0-127.0) days. Four-hundred and twenty-seven (61.9%; or

19.4% of entire cohort) patients received three or more prescriptions, 371 (53.8%; or 16.9% of entire cohort) received four or more prescriptions, and so forth; 217 (31.4%; or 9.9% of entire cohort) patients received 10 or more prescriptions (**Figure 3)**. Loperamide was the most commonly prescribed bowel medication (97.8% of medicated patients), with diphenoxylate (7.5%) and bile acid sequestrants (2.2%) less commonly prescribed. Bowel medication prescriptions were more commonly observed in patients with recorded bowel symptoms (57.1% vs. 21.9%, $p<0.001$).

In total, 620 (28.2%) patients met the definition for bowel dysfunction with two or more bowel events on discrete dates. On crude analysis, extremes of age (<40 years-old: HR 2.08, 95% CI 1.07-4.07; 70-79 years-old: HR 1.25, 95% CI 1.03-1.51), smoking status (HR 1.23, 95% CI 1.03-1.47), radiotherapy (HR 2.22, 95% CI 1.80-2.74), distal tumors (HR 1.85, 95% CI 1.55-2.21), history of a diverting ostomy (HR 1.89, 95% CI 1.60-2.24) and anastomotic leak (HR 1.74, 95% CI 1.25-2.40) were associated with bowel dysfunction; an MIS approach was protective for bowel dysfunction (HR 0.64, 95% CI 0.51-0.82) (**Table 2**). On Cox regression analysis, extremes of age (<40 years-old: aHR 2.35, 95% CI 1.18-4.65; 70-79 years-old: aHR 1.25, 95% CI 1.03-1.52), radiotherapy (aHR 1.94, 95% CI 1.56-2.42), distal tumors (aHR 1.62, 95% CI 1.34-1.94), history of a diverting ostomy (aHR 1.58, 95% CI 1.33-1.89) and anastomotic leak (aHR 1.48, 95% CI 1.06-2.05) remained independently associated with bowel dysfunction; an MIS approach remained protective for bowel dysfunction (aHR 0.68, 95% CI 0.53-0.86) (**Table 2**).

Using the 365 days of CPRD data prior to proctectomy, 30 (1.4%) patients had pre-existing sexual symptoms and 66 (3.0%) had pre-existing urinary symptoms. After excluding patients with pre-operative sexual and urinary symptoms, respectively, 137 (6.3%) patients reported new-onset sexual symptoms during follow-up and 304 (14.3%) reported urinary symptoms. Male sexual symptoms were reported more commonly than female sexual symptoms (163 patients with symptoms in 1,271 males vs. 4 patients with symptoms in 896 females, $p<0.001$). On regression analysis, bowel dysfunction was associated with both new-onset postoperative sexual (aOR 2.56, 95% CI 1.79-3.66) and urinary (aOR 1.97, 95% CI 1.55-2.51) symptoms.

Discussion

To our knowledge, this is the first study to use a "big data" approach for the evaluation of bowel dysfunction after restorative proctectomy. We queried two large administrative and clinical databases to report on the incidence, and risk factors, of bowel dysfunction, using a pragmatic definition based on clinical encounters and medication prescriptions for bowel symptoms. In addition to previously established disease and treatment factors, we identified several novel factors associated with postoperative bowel dysfunction, further advancing our knowledge on this critical patient-centric outcome of rectal cancer care.

Postoperative bowel dysfunction, like other functional disorders, is typically reported with the use of PROMs, and the LARS score has become the most widely accepted and utilized bowel function tool in rectal cancer patients. However, researchers have observed several limitations with the LARS score; in addition to disregarding certain important symptoms (e.g., evacuatory difficulties), the LARS score may be overly sensitive, as major LARS (score of ≥30) was observed in a significant proportion of the normative population without any previous surgery.[22,23] The LARS score is also restricted to a cross-sectional assessment of bowel dysfunction, and was not designed for repeated measurement in longitudinal follow-up. These limitations have motivated the development of a new LARS consensus PROM, which has yet to be created and tested.[9]

The present study used a combination of clinical encounters and medication prescriptions for bowel symptoms (≥2 bowel events) to define postoperative bowel dysfunction. While this definition has not previously been validated, it is a clinically-meaningful method of identifying cases of bowel dysfunction that has been similarly used to define other surgical disorders using claims-based data.[24] Bowel symptoms reported at a clinical encounter represent the ultimate form of patient-reported dysfunction, as it is information volunteered by the patient (rather than solicited through a screening questionnaire) for which he/she is actively seeking medical assistance. Bowel prescriptions further emphasize the clinical relevance of the patient's symptoms, and suggest an impact on the patient's quality of life. In an attempt to capture chronic, long-term bowel dysfunction – which best epitomizes LARS – we required two or more bowel events on discrete dates throughout follow-up. We reported an incidence of bowel dysfunction of 28.2%, which is within the range of major LARS reported in previous studies and should help substantiate our study definition.[25]

A unique aspect of this study is the longitudinal overview of bowel dysfunction provided by the data, as all events recorded within a CPRD practice are linked together. While many patients with bowel dysfunction had only one clinical encounter for bowel symptoms, over 40% had a second symptom-related visit approximately two years after proctectomy, highlighting the long-term nature of this disorder. Perhaps more interesting was the frequent use of bowel medications throughout follow-up, which consisted mainly of loperamide. The majority of patients with bowel dysfunction had multiple bowel prescriptions, with approximately one-third of patients receiving 10 or more. Despite anti-motility agents being considered by most surgeons as the mainstay of conservative management for postoperative bowel dysfunction,[26] there is a paucity of data assessing the extent of bowel medication usage in rectal cancer survivors. Our findings suggest that a significant number of patients may have some degree of medication reliance and/or dependence following restorative proctectomy, which stresses the magnitude of this disorder.

In addition to providing a detailed description of postoperative bowel dysfunction, we identified several factors associated with bowel dysfunction, which can be informative to both the surgeon and patient when discussing long-term outcomes. Radiotherapy, distal tumors, and a history of diverting ostomy are some of the most commonly identified factors associated with bowel dysfunction,[25] and are all present in the validated POLARS (Pre-Operative LARS) risk score.[27] Our data affirmed their associations with bowel dysfunction, but also identified more novel risk factors, including postoperative anastomotic leak, extremes of age, and an MIS approach. Postoperative anastomotic leak is an intuitive risk factor for bowel dysfunction, as pelvic sepsis may result in fibrosis and reduced neorectal compliance; however, given the relative infrequency of this variable, it has seldom been reported as a significant predictor.[28] Our study featured the largest sample size to date on the subject, and was thus afforded the power to study more rare exposures. Age has had variable associations with bowel dysfunction in the literature; some studies have reported older age as a risk factor for major LARS,[29] while others have reported younger age as being prognostic.[30] Our data demonstrated that both extremes of age were predictive, suggesting that age may have a non-linear relationship with postoperative bowel dysfunction. Younger patients may have high colonic motility, which could aggravate their LARS symptoms,[27,30] while elder patients may have worse baseline sphincter function predisposing them to postoperative dysfunction. Finally, MIS was protective for postoperative bowel dysfunction. This could be explained by the improved visualization afforded during deep pelvic dissection associated with an MIS approach, or bias associated with case selection.

Patients with bowel dysfunction were also at significantly higher odds of experiencing new-onset postoperative sexual and urinary symptoms, which is an important observation. Sexual and urinary dysfunction are common late sequelae of rectal cancer treatment,[31,32] yet are often under-reported and consequently under-treated. In the current study, the incidence of sexual and urinary symptoms reported by patients to their physicians was far less than that observed in studies using screening PROMs,[33,34] particularly sexual symptoms among female patients. Therefore, it behooves all physicians to probe for these symptoms in rectal cancer survivors, especially among those patients with bowel dysfunction who appear to be at higher risk.

This study has several important limitations that must be considered when interpreting its results. Like all observational studies, residual confounding by unobserved or poorly-controlled covariates may bias the estimates of association. Several variables were also unavailable in the two linked databases, such as tumor stage and provider (surgeon) characteristics, which may have been interesting to study. Importantly, patients could not be linked from one CPRD-registered practice to another, and thus patients were censored if they changed primary care physicians. Our case definition has also never been previously validated. While it is a pragmatic definition for bowel dysfunction, future work should aim at validating such a study definition with patient-level PROM-based data. Finally, outcome assessment was limited to the data recorded in CPRD, a primary care database. Given that patients often report these symptoms to their consultant surgeon as well – particularly in the early postoperative period – this could have resulted in an underestimation in the frequency of bowel dysfunction. However, the UK healthcare system has a very strong primary care presence, with 98% of the population having a general practitioner,[11] and patient care is usually returned to the general practitioner after the specialist's role is complete. Since bowel dysfunction is a long-term consequence of surgery experienced during the survivorship phase, we did not consider this to be a major limitation.

Conclusions

Bowel dysfunction is a common long-term sequela of rectal cancer surgery, and was described through a combination of clinical encounters and medication prescriptions for bowel symptoms. A significant number of patients were prescribed long-term anti-motility agents, which emphasizes the clinical relevance of this syndrome. Several patient, disease, and treatment-level factors were associated with bowel dysfunction, the knowledge of which can be informative when discussing long-term outcomes with rectal cancer patients.

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Table 1 – Description of cohort

Characteristic	**n=2,197**
Age, years, median (IQR)	70.0 (62.0-77.0)
Sex, male, n (%)	1,300 (59.2)
Body mass index (kg/m2), n (%)	-
<30	1,153 (52.5)
≥30	371 (16.9)
Missing	673 (30.6)
Smoking status, n (%)	-
Current smoker	362 (16.5)
Ex-smoker	592 (26.9)
Non-smoker	802 (36.5)
Missing	441 (20.1)
Charlson Comorbidity Index score, n (%)	-
0-2	1,202 (54.7)
3-6	871 (39.6)
≥6	124 (5.6)
Rectal neoplasm, n (%)	-
Malignancy	2,113 (96.2)
Benign	84 (3.8)
Tumor height, n (%)	-
Proximal	876 (39.9)
Distal	1,321 (60.1)
Radiotherapy, n (%)	249 (11.3)
Chemotherapy, n (%)	603 (27.4)
Operative approach, n (%)	-
Open surgery	1,739 (79.2)
MIS	458 (20.8)
Diverting ostomy, n (%)	539 (24.5)
Time to ostomy closure, days, median (Q1-Q3)	233.0 (124.0-351.0)
Anastomotic leak, n (%)	100 (4.6)

MIS = minimally invasive surgery

Table 2 – Crude and adjusted associations between patient-, tumor-, and treatment-level factors and bowel dysfunction after restorative proctectomy

Characteristic	**Number of events**	**Person-years**	**Crude HR**	**95% CI**	***Adjusted HR**	**95% CI**
Age (reference = 60-<70)	-	-	-	-	-	-
<40	9	60	2.08	1.07-4.07	2.35	1.18-4.65
40-<50	21	432	0.76	0.49-1.20	0.72	0.46-1.14
50-<60	84	1374	0.99	0.76-1.28	0.96	0.74-1.25
70-<80	238	2807	1.25	1.03-1.51	1.25	1.03-1.52
≥80	89	1121	1.05	0.81-1.35	1.11	0.85-1.44
Male sex	378	4952	1.13	0.96-1.33	1.06	0.90-1.25
†Obese (BMI ≥30)	106	1304	0.97	0.78-1.21	0.98	0.79-1.22
‡Current / ex-smoker	288	3461	1.23	1.03-1.47	1.18	0.99-1.42
Charlson Comorbidity Index score (reference = 0-2)	-	-	-	-	-	-
3-6	242	2981	1.09	0.93-1.29	1.06	0.89-1.25
≥6	32	319	1.17	0.81-1.68	1.13	0.78-1.63
Distal tumor	450	5006	1.85	1.55-2.21	1.62	1.34-1.94
Radiotherapy	106	720	2.22	1.80-2.74	1.94	1.56-2.42
Chemotherapy	175	2147	1.13	0.95-1.34	1.09	0.90-1.31
MIS operative approach	79	1252	0.64	0.51-0.82	0.68	0.53-0.86
Diverting ostomy	204	1568	1.89	1.60-2.24	1.58	1.33-1.89
Anastomotic leak	39	253	1.74	1.25-2.40	1.48	1.06-2.05

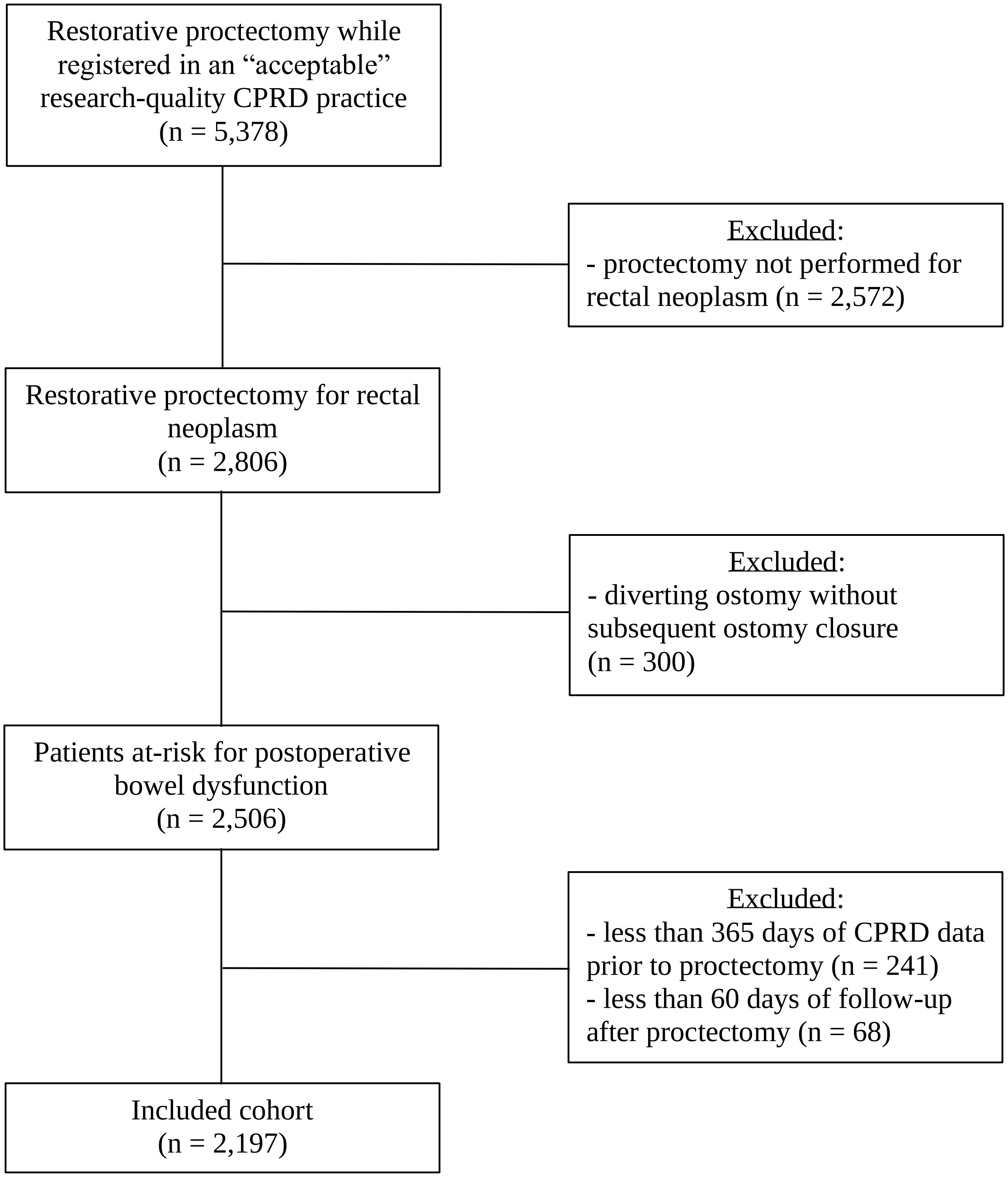
MIS = minimally invasive surgery; BMI = body mass index

*adjusted for variables included in this table

†reference = non-obese (BMI <30); data missing in 30.6% (n=673) of cohort

‡reference = non-smoker; data missing in 20.1% (n=441) of cohort

Figure 1 – Flow of included patients according to cohort inclusion criteria



CPRD = Clinical Practice Research Datalink

Figure 2 – Frequency of clinical encounters for bowel symptoms after restorative proctectomy

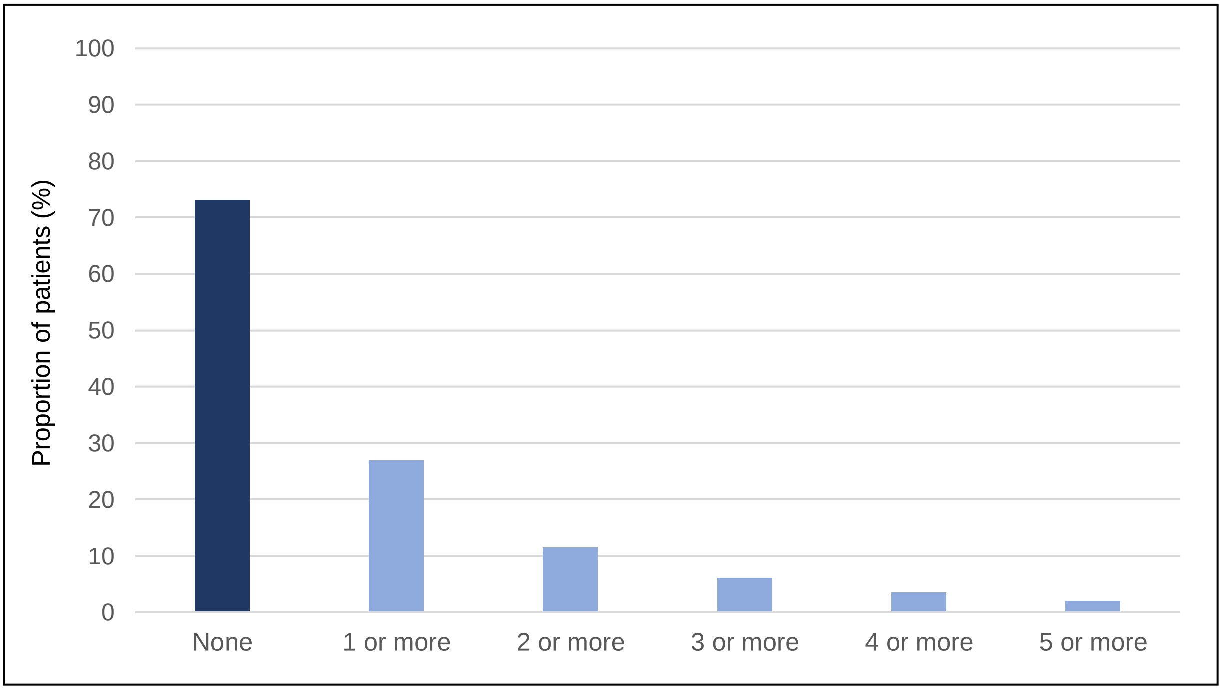
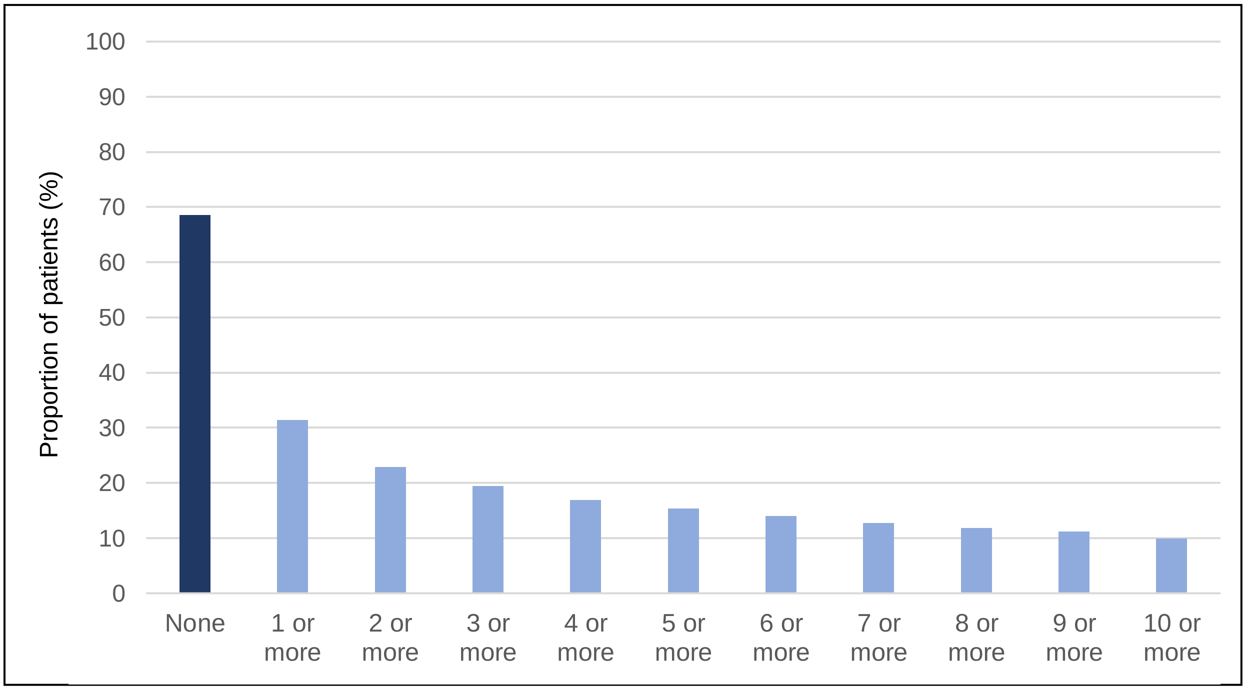


Figure 3 – Frequency of bowel medication prescriptions after restorative proctectomy



Appendix 1 – OPCS procedure codes and ICD-10 diagnostic codes used for cohort definition and variable definitions

Restorative proctectomy

OPCS
H29.1 Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus
H29.2 Subtotal excision of colon and rectum and creation of colonic pouch NEC
H33.2 Proctectomy and anastomosis of colon to anus H29.2 Subtotal excision of colon and rectum and creation of colonic pouch NEC
H33.3 Anterior resection of rectum and anastomosis of colon to rectum using staples
H33.4 Anterior resection of rectum and anastomosis NEC (not elsewhere classified)

Rectal Neoplasm

ICD-10
C19 malignant neoplasm of rectosigmoid junction
C20 malignant neoplasm of rectum
C21 malignant neoplasm of anal canal
C78.5 malignant neoplasm of large intestine and rectum
D01.1 carcinoma in situ of rectosigmoid junction
D01.2 carcinoma in situ of rectum
D12.8 benign neoplasm of rectum
D12.9 benign neoplasm of anus and anal canal
D37.5 neoplasm of uncertain behavior rectum
K62.0 anal polyp
K62.1 rectal polyp

Diverting Ostomy

Loop Ileostomy

OPCS
G74.2 Creation of temporary ileostomy
G74.3 Creation of defunctioning ileostomy

Loop Colostomy

OPCS
H15.1 Loop colostomy
H15.8 Other specified other exteriorization of colon

Ostomy Closure

Ileostomy Closure

OPCS
G69.3 Ileectomy and anastomosis of ileum to ileus
G69.8 Other specified excision of ileum
G69.9 Unspecified excision of ileum
G73.2 Closure of anastomosis of ileus
G73.3 Resection of ileostomy
G75.3 Closure of ileostomy

Colostomy Closure

OPCS
H08.1 Transverse colectomy and end to end anastomosis
H08.3 Transverse colectomy and anastomosis NEC
H08.8 Other specified excision of transverse colon
H08.9 Unspecified excision of transverse colon
H09.1 Left hemicolectomy and end to end anastomosis of colon to colon
H09.3 Left hemicolectomy and anastomosis NEC
H09.8 Other specified excision of left hemicolon
H09.9 Unspecified excision of left hemicolon
H11.1 Colectomy and end to end anastomosis of colon to colon
H11.3 Colectomy and anastomosis NEC
H11.8 Other specified excision of colon
H11.9 Unspecified excision of colon
H15.4 Closure of colostomy

Permanent Ostomy

OPCS
G74.1 Creation of continent ileostomy
H15.2 End colostomy

Operative approach

Minimally-invasive surgery:

OPCS
Y75.1 Laparoscopically assisted approach to abdominal cavity
Y75.2 Laparoscopic approach to abdominal cavity
Y75.3 Robotic minimal access approach to abdominal cavity
Y75.4 Hand assisted minimal access approach to abdominal cavity
Y75.5 Laparoscopic ultrasonic approach to abdominal cavity
Y75.8 Other specified minimal access to abdominal cavity
Y75.9 Unspecified minimal access to abdominal cavity

Conversion from minimally-invasive to open surgery:

OPCS
Y71.4 Failed minimal access approach converted to open

Anastomotic Leak

OPCS
T34.1 Open drainage of subphrenic abscess
T34.2 Open drainage of pelvic abscess
T34.3 Open drainage of abdominal abscess NEC
T34.8 Other specified open drainage of peritoneum
T34.9 Unspecified open drainage of peritoneum
T45.1 Image controlled percutaneous drainage of subphrenic abscess
T45.2 Image controlled percutaneous drainage of pelvic abscess
T45.3 Image controlled percutaneous drainage of abdominal abscess NEC
T45.4 Image controlled percutaneous drainage of lesion of abdominal cavity NEC
T45.8 Other specified image controlled operations on abdominal cavity
T45.9 Unspecified image controlled operations on abdominal cavity
H58.8 Other specified drainage through perineal region
H58.9 Unspecified drainage through perineal region
G74.2 Creation of temporary ileostomy *(on separate admission within 90 days of proctectomy)*
G74.3 Creation of defunctioning ileostomy *(on separate admission within 90 days of proctectomy)*
H15.1 Loop colostomy *(on separate admission within 90 days of proctectomy)*
H15.8 Other specified other exteriorization of colon
H21.4 Fibreoptic endoscopic insertion of expanding metal stent into colon
H24.4 Endoscopic insertion of expanding metal stent into lower bowel using fibreoptic sigmoidoscope
H27.4 Endoscopic insertion of expanding metal stent into sigmoid colon using rigid sigmoidoscope
H31.4 Image guided insertion of colorectal stent

ICD-10
K67 Disorders or peritoneum in infectious diseases classified elsewhere
K65.0 Generalized (acute) peritonitis
K65.8 Other peritonitis
K65.9 Peritonitis, unspecified
K65.1 Peritoneal abscess
K63.0 Abscess of intestine
K63.2 Fistula of intestine

Appendix 2 – Symptom-based read codes and medical prescription product-codes used for outcome definitions

Bowel symptom and medications codes were reviewed and approved by the following authors: RG, SD, NM, CAV, PB, MB

Bowel Symptoms

Read Code	**Definition**	**Symptom Complex**
J52z.11	Bowel dysfunction	Altered bowel function
19EA.00	Change in bowel habit	Altered bowel function
R078.00	Change in bowel habit	Altered bowel function
393..00	Bowels - assessment	Altered bowel function
19E..11	Faeces symptom	Altered bowel function
19EA.11	Altered bowel habit	Altered bowel function
19EZ.00	Faeces symptom NOS	Altered bowel function
19F2.00	Diarrhoea	Diarrhea / altered stool consistency
19F..11	Diarrhoea	Diarrhea / altered stool consistency
J524000	Diarrhoea after gastrointestinal tract surgery	Diarrhea / altered stool consistency
19F..00	Diarrhoea symptoms	Diarrhea / altered stool consistency
19F..00	Diarrhoea symptoms	Diarrhea / altered stool consistency
J4zz.11	Diarrhoea presumed non-infectious	Diarrhea / altered stool consistency
19EB.00	Frequency of defaecation	Frequency
19EE.00	Increased frequency of defaecation	Frequency
19EC.00	Painful defaecation	Painful defecation
19EF.00	Urgent desire for stool	Urgency
19E..00	Faeces/motions - symptoms	Urgency
19E..12	Motions - symptoms	Urgency
R076.00	Incontinence of faeces	Incontinence
R076z00	Incontinence of faeces NOS	Incontinence
R076100	Sphincter ani incontinence	Incontinence
393..11	Bowels - continence	Incontinence
3930	Bowels: incontinent	Incontinence
19E3.00	Incontinent of faeces	Incontinence
19E3.11	Incontinent of faeces symptom	Incontinence
3931	Bowels: occasional accident	Incontinence
19B5.00	Excessive flatus	Incontinence
393..12	Bowels-incontinence assessment	Incontinence
19EJ.00	Able to distinguish stool and flatus	Incontinence
19E2.00	Soiling - encopresis	Soiling
19E2.12	Soiling symptom	Soiling

19E2.11	Encopresis symptom	Soiling
19E2000	Functional encopresis	Soiling

Bowel Medications

Product Code	**Drug Substance Name**	**Medication**
9221	Loperamide hydrochloride	Loperamide
55092	Loperamide hydrochloride	Loperamide
6332	Loperamide hydrochloride	Loperamide
71213	Loperamide hydrochloride	Loperamide
16023	Loperamide hydrochloride	Loperamide
28126	Loperamide hydrochloride	Loperamide
34395	Loperamide hydrochloride	Loperamide
64402	Loperamide hydrochloride	Loperamide
17607	Loperamide Hydrochloride/Simeticone	Loperamide
9586	Loperamide hydrochloride/Simeticone	Loperamide
62465	Loperamide hydrochloride	Loperamide
28663	Loperamide hydrochloride	Loperamide
39557	Loperamide hydrochloride	Loperamide
2054	Loperamide hydrochloride	Loperamide
6951	Loperamide hydrochloride	Loperamide
21822	Loperamide hydrochloride	Loperamide
54154	Loperamide hydrochloride	Loperamide
5061	Loperamide hydrochloride	Loperamide
30664	Loperamide hydrochloride	Loperamide
62290	Loperamide hydrochloride	Loperamide
2785	Loperamide hydrochloride	Loperamide
44737	Loperamide hydrochloride	Loperamide
57215	Loperamide hydrochloride	Loperamide
75240	Loperamide hydrochloride	Loperamide
59169	Loperamide hydrochloride	Loperamide
44030	Loperamide hydrochloride	Loperamide
9971	Loperamide hydrochloride/Simeticone	Loperamide
2825	Loperamide hydrochloride	Loperamide
34427	Loperamide hydrochloride	Loperamide
62791	Loperamide hydrochloride	Loperamide
60306	Loperamide hydrochloride	Loperamide
9848	Loperamide hydrochloride/Simeticone	Loperamide
9311	Loperamide hydrochloride	Loperamide

70033	Loperamide hydrochloride	Loperamide
44345	Loperamide hydrochloride	Loperamide
10078	Loperamide hydrochloride/Simeticone	Loperamide
67905	Loperamide hydrochloride	Loperamide
58553	Loperamide hydrochloride	Loperamide
29863	Loperamide hydrochloride	Loperamide
20937	Loperamide hydrochloride	Loperamide
29678	Loperamide hydrochloride	Loperamide
62125	Loperamide hydrochloride	Loperamide
1101	Loperamide hydrochloride	Loperamide
347	Loperamide hydrochloride	Loperamide
18434	Loperamide hydrochloride	Loperamide
57341	Loperamide hydrochloride/Simeticone	Loperamide
63709	Loperamide hydrochloride	Loperamide
74371	Loperamide hydrochloride	Loperamide
62170	Loperamide hydrochloride	Loperamide
9204	Loperamide hydrochloride	Loperamide
61716	Loperamide hydrochloride	Loperamide
61357	Loperamide hydrochloride	Loperamide
33443	Loperamide hydrochloride	Loperamide
47005	Loperamide hydrochloride	Loperamide
27238	Loperamide hydrochloride	Loperamide
4086	Loperamide hydrochloride	Loperamide
62186	Loperamide hydrochloride	Loperamide
13683	Loperamide hydrochloride	Loperamide
30787	Diphenoxylate Hydrochloride/Atropine Sulphate	Diphenoxylate Hydrochloride
74031	Diphenoxylate hydrochloride/Atropine sulfate	Diphenoxylate Hydrochloride
31298	Diphenoxylate hydrochloride/Atropine sulfate	Diphenoxylate Hydrochloride
1516	Diphenoxylate Hydrochloride/Atropine Sulphate	Diphenoxylate Hydrochloride
5019	Diphenoxylate hydrochloride/Atropine sulfate	Diphenoxylate Hydrochloride
3307	Diphenoxylate Hydrochloride/Atropine Sulphate	Diphenoxylate Hydrochloride
867	Diphenoxylate Hydrochloride/Atropine Sulphate	Diphenoxylate Hydrochloride
68074	Diphenoxylate hydrochloride/Atropine sulfate	Diphenoxylate Hydrochloride

1358	Diphenoxylate hydrochloride/Atropine sulfate	Diphenoxylate Hydrochloride
34982	Diphenoxylate hydrochloride/Atropine sulfate	Diphenoxylate Hydrochloride
10973	Diphenoxylate Hydrochloride/Atropine Sulphate	Diphenoxylate Hydrochloride
17857	Diphenoxylate hydrochloride/Atropine sulfate	Diphenoxylate Hydrochloride
24084	Colestyramine anhydrous	Bile acid sequestrant
6365	Colestipol hydrochloride	Bile acid sequestrant
34201	Colestyramine anhydrous	Bile acid sequestrant
1212	Colestipol hydrochloride	Bile acid sequestrant
18081	Colestipol hydrochloride	Bile acid sequestrant
11785	Colestyramine anhydrous	Bile acid sequestrant
61087	Colestyramine anhydrous	Bile acid sequestrant
644	Colestyramine anhydrous	Bile acid sequestrant
60101	Colestyramine anhydrous	Bile acid sequestrant
1764	Colestyramine anhydrous	Bile acid sequestrant
75806	Colestyramine anhydrous	Bile acid sequestrant
68386	Colestyramine anhydrous	Bile acid sequestrant
19938	Colestipol Hydrochloride	Bile acid sequestrant
37266	Colesevelam hydrochloride	Bile acid sequestrant
72988	Colestyramine anhydrous	Bile acid sequestrant
1716	Colestyramine anhydrous	Bile acid sequestrant
5564	Colestipol Hydrochloride	Bile acid sequestrant
73910	Colestipol hydrochloride	Bile acid sequestrant
37953	Colesevelam hydrochloride	Bile acid sequestrant
32110	Colestyramine anhydrous	Bile acid sequestrant
6155	Colestyramine Anhydrous	Bile acid sequestrant

Sexual symptom codes were reviewed and approved by the following authors and consultants: RG, SD, NM, CAV, PB, MB

Male Sexual Function Symptoms

Read Code	Definition	Symptom Complex
E227311	Erectile dysfunction	Erectile function
K273.11	Erection painful	Erectile function
E227300	Impotence	Erectile function
K27y100	Impotence of organic origin	Erectile function
67IA.00	Advice about impotence	Erectile function

8HTj.00	Referral to erectile dysfunction clinic	Erectile function
1ABC.00	Cannot sustain an erection	Erectile function
Eu52212	Male erectile disorder	Erectile function
7C25F00	Operations on penis for erectile dysfunction NEC	Erectile function
1ABB.00	Cannot get an erection	Erectile function
7C25E00	Treatment of erectile dysfunction NEC	Erectile function
1ABD.00	Painful erection	Erectile function
1D1B.00	C/O erectile dysfunction	Erectile function
8IE8.00	Referral to erectile dysfunction clinic declined	Erectile function
Eu52213	Psychogenic impotence	Erectile function
E227500	Inhibited male orgasm	Orgasmic / ejaculatory
E227600	Premature ejaculation	Orgasmic / ejaculatory
Eu52400	Premature ejaculation	Orgasmic / ejaculatory
Eu52311	Inhibited orgasm	Orgasmic / ejaculatory
E227.11	Lack of libido	Sexual desire
E227100	Inhibited sexual desire	Sexual desire
Eu52012	Hypoactive sexual desire disorder	Sexual desire
Eu54000	Lack or loss of sexual desire	Sexual desire
Eu52013	Lack of libido	Sexual desire
E227.00	Psychosexual dysfunction	General sexual dysfunction / satisfaction
E227z11	Fear of ejaculation	General sexual dysfunction / satisfaction
E227z00	Psychosexual dysfunction NOS	General sexual dysfunction / satisfaction
E227000	Unspecified psychosexual dysfunction	General sexual dysfunction / satisfaction
Eu52300	Orgasmic dysfunction	General sexual dysfunction / satisfaction
38G2.11	International index of erectile function - 5 items	General sexual dysfunction / satisfaction
Z4Q..00	Sexual dysfunction counseling	General sexual dysfunction / satisfaction
1598	Sexual dysfunction problem	General sexual dysfunction / satisfaction
ZV41700	Problem with sexual function	General sexual dysfunction / satisfaction

Female Sexual Function Symptoms

Read Code	Definition	Symptom Complex
1595	Dyspareunia	Pain
K580	Dyspareunia due to non psychogenic cause in the female	Pain
15D..00	Dyspareunia	Pain
Eu52300	Orgasmic dysfunction	Orgasmic
E227400	Inhibited female orgasm	Orgasmic
Eu52311	Inhibited orgasm	Orgasmic

E227.11	Lack of libido	Sexual desire
E227100	Inhibited sexual desire	Sexual desire
Eu52012	Hypoactive sexual desire disorder	Sexual desire
Eu54000	Lack or loss of sexual desire	Sexual desire
Eu52013	Lack of libido	Sexual desire
E227.00	Psychosexual dysfunction	General sexual dysfunction / satisfaction
E227z00	Psychosexual dysfunction NOS	General sexual dysfunction / satisfaction
E227000	Unspecified psychosexual dysfunction	General sexual dysfunction / satisfaction
Z4Q..00	Sexual dysfunction counseling	General sexual dysfunction / satisfaction
1598	Sexual dysfunction problem	General sexual dysfunction / satisfaction
14E3.00	Sexual function problem	General sexual dysfunction / satisfaction
ZV41700	Problem with sexual function	General sexual dysfunction / satisfaction

Urinary symptom codes were reviewed and approved by the following authors and consultants:
RG, SD, NM, CAV, PB, MB

Urinary Function Symptoms

Read Code	**Definition**	**Symptom Complex**
1A23000	Functional urinary incontinence	Incontinence
R083200	Urge incontinence	Incontinence
16F..00	Double incontinence	Incontinence
8D7..12	Incontinence control	Incontinence
3940	Bladder: incontinent	Incontinence
R083.00	Incontinence of urine	Incontinence
R083100	Urethral sphincter incontinence	Incontinence
Kyu5A00	Other specified urinary incontinence	Incontinence
394..11	Bladder-incontinence assessment	Incontinence
R083z00	Incontinence of urine NOS	Incontinence
1593	Stress incontinence	Incontinence
1A26.00	Urge incontinence of urine	Incontinence
1A24.00	Stress incontinence	Incontinence
8HTX.00	Referral to incontinence clinic	Incontinence
K586.00	Stress incontinence - female	Incontinence
K198.00	Stress incontinence	Incontinence
1A23.00	Incontinence of urine	Incontinence
8D71.00	Incontinence control	Incontinence
R086000	Slowing of urinary stream	Urinary retention / difficulties emptying
R082400	Retention of urine unspecified	Urinary retention / difficulties emptying
1A32.11	Retention - symptom	Urinary retention / difficulties emptying
1A32.00	Cannot pass urine - retention	Urinary retention / difficulties emptying

R082.00	Retention of urine	Urinary retention / difficulties emptying
1A1..13	Urinary frequency	Frequency
1A27.00	Urge to pass urine again shortly after finishing voiding	Frequency
R084000	Frequency of micturition, unspecified	Frequency
1A1Z.00	Micturition frequency NOS	Frequency
R084z00	Frequency of micturition or polyuria NOS	Frequency
R084.00	Micturition frequency and polyuria	Frequency
1A1..00	Micturition frequency	Frequency
1A12.00	Frequency of micturition	Frequency
1A1..11	Frequency of micturition	Frequency
1A22000	Nocturnal enuresis	Nocturia
R084200	Nocturia	Nocturia
1A13.00	Nocturia	Nocturia
K1...00	Other urinary system diseases	General urinary dysfunction
R08..00	Urinary system symptoms	General urinary dysfunction
1A...12	Urinary symptoms	General urinary dysfunction
Kyu5.00	Other diseases of urinary system	General urinary dysfunction
16F0.00	Functional urinary and faecal incontinence	General urinary dysfunction
1AZZ.00	Genitourinary symptom NOS	General urinary dysfunction
8HTa.00	Referral to genitourinary clinic	General urinary dysfunction
1AZ6100	Moderate lower urinary tract symptoms	General urinary dysfunction
1AZ6.00	Lower urinary tract symptoms	General urinary dysfunction

Chapter 3.1: Consequences of Low Anterior Resection Syndrome – Preamble

In the previous chapter, I performed a population-based cohort study using two linked United Kingdom-based databases to demonstrate the high incidence of bowel dysfunction after restorative proctectomy. According to our study definition, roughly 30% of patients experienced long-term postoperative bowel dysfunction, which is well within the range of major Low Anterior Resection Syndrome (LARS) reported in single-institution studies using Patient-Reported Outcome Measure data. Furthermore, I performed a multivariate Cox regression analysis to identify the association between numerous patient-, tumor-, and treatment-level factors and the development of bowel dysfunction. While many of these factors have been well described in the literature (e.g., radiotherapy and distal tumors), several more novel predictors of bowel dysfunction, such as young age, anastomotic leak, and open surgery, were reported. Bowel dysfunction was also associated with new-onset postoperative sexual and urinary symptoms, suggesting that patients with dysfunction in one domain may be more likely to experience other pelvic dysfunctions as well.

While the previous chapter offered a broad overview of this long-term sequela of rectal cancer surgery, the downstream consequences of bowel dysfunction could not be elucidated. Furthermore, the prevalence of LARS, and its consequences, in our *own* patient population in Montreal, Quebec, have never been described; knowledge of which would be important when considering the development of a patient-centered intervention. In this next chapter, I developed an institutional database of patients who underwent restorative proctectomy at the Jewish General Hospital, and performed a cross-sectional assessment of numerous patient-reported outcomes. In addition to reporting the prevalence of major LARS in this cohort, I sought to evaluate the occupational and financial hardships experienced by patients secondary to their altered bowel function. The association between LARS, bowel-related financial hardships and global quality of life was then assessed in a multiple logistic regression model.

Chapter 3.2: Financial and Occupational Impact of Low Anterior Resection Syndrome in Rectal Cancer Survivors

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Abstract

Background: The financial impact of cancer has been well described in many patient populations. However, rectal cancer survivors may face the added burden of Low Anterior Resection Syndrome (LARS), a long-term sequala of treatment which may uniquely impact their financial well-being.

Objective: To assess bowel-related financial stress and strain and to evaluate its association with global quality of life (QoL).

Design: Retrospective cohort study with cross-sectional follow-up.

Settings: Single university-affiliated hospital in Montreal, Quebec, Canada.

Patients: All patients who underwent restorative proctectomy for neoplastic disease of the rectum.

Intervention(s): LARS severity.

Main Outcome Measures: Bowel-related financial stress and strain, occupational impact, and global QoL.

Results: Of 180 eligible rectal cancer survivors who were contacted, 154 completed the questionnaires (response rate: 85.6%) at a median follow-up of 57.5 months (IQR: 34.1-98.1) after proctectomy. Major LARS was reported in 30.5% of individuals, while 69.5% reported minor/no LARS. Individuals with major LARS reported a higher prevalence of bowel-related financial stress (53.2% vs. 5.6%, $p<0.001$) and strain (42.2% vs. 5.6%, $p<0.001$) compared to those with minor/no LARS. Among those who were working preoperatively (n=100), the majority of participants with major LARS reported an impact of their new bowel function on ability to work (70.6%), including delayed return to work (44.1%), the need to change schedules (35.3%) or roles (20.6%), and complete long-term medical absence from work (14.7%). Global QoL was worse in participants with major LARS (58.3 vs. 75.0, $p<0.001$). On multiple logistic regression, major LARS with financial impact (OR: 4.48, 95% CI 1.60-13.46) was associated with low global QoL compared to minor/no LARS.

Limitations: Missing covariates, non-response bias and recall bias.

Conclusions: LARS was associated with considerable financial stress and strain and difficulties returning to work.

Introduction

The financial impact of cancer has been well-described in many patient populations.[1-3] Large national cohort studies have demonstrated that early cancer survivors incur an annual excess economic burden of over $15,000 USD, due to a combination of direct (e.g., medical costs) and indirect (e.g., missed work days and lost household productivity) healthcare costs.[4] While highest amongst *recently* diagnosed cancer survivors, the economic burden may extend far into the survivorship phase.[4,5] This has been demonstrated in long-term colorectal cancer survivors, where a recent study estimated that approximately 40% of patients experienced cancer-related financial stress or strain, and that an adverse financial impact of cancer was associated with worse quality of life (QoL).[6] Coupled with the rising incidence of colorectal cancer in young, working individuals and the improved long-term survival of this disease,[7-9] the financial impact of colorectal cancer during survivorship is of growing importance.

The financial burden among rectal cancer survivors warrants particular attention due to specific disease and treatment issues. In addition to major abdominal surgery, the risk for a temporary or permanent ostomy, and the need for radiation therapy and/or chemotherapy, rectal cancer survivors may face the added burden of Low Anterior Resection Syndrome (LARS), a long-term sequela of treatment.[10] LARS is observed in 70 to 90% of patients following restorative proctectomy,[11] and although symptoms may improve somewhat in the first year or two after surgery, long-term major bowel dysfunction can remain in over 50%.[12-14]. Accordingly, LARS may pose unique financial stresses to rectal cancer survivors; in addition to out-of-pocket expenses related to the management of LARS (e.g., chronic medication use, enema and transanal irrigation systems, biofeedback, and pelvic physiotherapy)[15], patients may encounter difficulties returning to work at the same capacity. To date, the financial and occupational impact of LARS has not been well described.

The purpose of this study was to estimate the financial impact of LARS in long-term rectal cancer survivors, and to evaluate its association with global QoL.

Methods

Healthcare Setting

This was an Institutional Review Board–approved retrospective cohort study with cross-sectional follow-up that took place in Montreal, Quebec, Canada, between July and October of 2019. As with the rest of Canada, the majority of healthcare in the province of Quebec is publicly funded (~70%), with the remaining covered by private insurance (~11%) or borne out-of-pocket (~16%).[16] Patients do not pay for cancer-related treatment, such as surgery, hospital admissions, and radiation therapy and/or chemotherapy. Out-of-pocket expenses and/or private insurance coverage are usually required for parking and transport to and from the hospital, medications, healthcare supplies (e.g., ostomy, enemas, transanal irrigation systems), and allied healthcare professionals' services (e.g., pelvic physiotherapy). It is estimated that 65% of Canadians have some form of private health insurance, most commonly through their employer.[16] Compensation while on medical leave is similarly variable; without private insurance, patients must apply for federal unemployment insurance beyond eight weeks.

Patient Population

This study included individuals who underwent restorative proctectomy for rectal cancer (0 to 15 cm from the anal verge) at a single university-affiliated tertiary-care hospital from July 2007 to January 2018. Potentially eligible participants were first identified from the Operating

Room database, and only individuals with primary, non-metastatic disease were further considered for inclusion. Individuals with a current ostomy or those undergoing treatment with chemotherapy or radiation therapy for any active malignancy were excluded. All remaining eligible individuals were contacted by phone for participation.

Covariates

A retrospective chart review was undertaken to collect data on relevant patient, disease, and treatment variables. Patients characteristics included age, sex, and American Society of Anesthesiologists score (taken from the proctectomy operation); disease characteristics included the pathologic stage of the cancer and tumor height from the anal verge (based on pre-treatment pelvic MRI); and treatment characteristics included the use of neoadjuvant radiation therapy, type of mesorectal excision (total vs. partial), height of anastomosis (colorectal vs. coloanal), type of reconstruction (straight vs. side-to-end or colonic J-pouch), use of diverting ileostomy, and anastomotic leak requiring treatment (International Study Group of Rectal Cancer grade B or C).[17]

Patient-Reported Outcomes

Long-term bowel function among rectal cancer survivors was assessed using the LARS score.[18] The LARS Score is a 5-item, self-administered tool aimed at assessing symptoms of bowel dysfunction, with each question scored according to the perceived importance to patients. The scores of the 5 questions sum to 42 points, and the tool allows for the categorization of patients as having major (30-42 points), minor (21-29 points), or no LARS (0-20 points). Commonly, individuals with major LARS are compared to individuals with minor / no LARS, given the significantly higher impact on QoL observed with major LARS.[12,13]

The financial impact of LARS was assessed using a modified version of a validated questionnaire aimed at measuring financial hardship amongst cancer survivors.[6,19,20] The questionnaire includes two questions; one measures objective cancer-related financial stress, while the other measures subjective cancer-related financial strain. For the current study, the term "cancer" was replaced with the term "bowel", to assess the impact of LARS specifically, rather than the diagnosis of rectal cancer as a whole. *Objective* bowel-related financial stress was assessed as the impact of the individual's bowel function on the household's ability to make ends meet, and *subjective* bowel-related financial strain as the impact on the individual (i.e., how the individual *feels* about the household's ability to make ends meet because of his/her bowel function). The overall interpretation of financial impact was performed similar to previous studies.[6] Both questions were scored using a scale from 1 (less difficult/concerned) to 7 (more difficult/concerned), and responses were categorized as more difficult/concerned (5-7), no impact (4), or less difficult/concerned (1-3). For analysis purposes, individuals who reported having increased difficulties/concerns (5-7) with financial stress or strain were considered as having bowel-related financial impact.

QoL was assessed using the European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ-C30), a 30-item self-administered questionnaire aimed at various domains of QoL. The final two questions, both scored using a scale from 1 to 7, ask about the individual's perceived overall health and quality of life during the past week. Both scores are transformed into a final score out of 100, and together, make up the global QoL scale.[21] The EORTC-QLQ-C30 has been well validated in individuals with rectal cancer, and is commonly used in research on LARS.[11-13]

Lastly, individuals who reported to be working prior to their rectal cancer operation were directed to answer a short, investigator-generated questionnaire regarding any potential impact their new bowel function has (or had) on their ability to work. Specifically, individuals were asked whether or not their new bowel function caused delayed returns to work (>3 months after treatment completion), changes in work schedule, changes in role at work, or the complete inability to return to work (i.e., forced retirement or long-term medical absence).

Data Analysis

Data were presented as medians with interquartile ranges (Q1 – Q3) or frequencies with proportions, where appropriate. Wilcoxon rank-sum tests and chi-squared tests were used to compare continuous non-normal and categorical data, respectively. Bowel-related financial stress and strain and occupational impact were compared between individuals with and without major LARS. In order to assess the added burden of bowel-related financial impact, a three-category composite exposure was created: major LARS with financial impact, major LARS without financial impact, and minor / no LARS with or without financial impact. Global QoL was compared between the three groups. Given that there is no existing cut-off for global QoL as per the EORTC scoring manual, individuals within the lowest quartile of global QoL were considered to have "low QoL", as has been performed previously.[6] The association between LARS with bowel-related financial impact and low QoL was then assessed in a multiple logistic regression model, adjusting for patient and disease characteristics. Covariates for the model were selected based on prior subject knowledge and clinical significance as potential confounders in the relationship between LARS severity, bowel-related financial impact, and QoL. An alpha=0.05 was set for statistical significance. All statistical analyses were performed with R v3.5.1.[22]

Results

Of 327 eligible individuals who underwent restorative proctectomy for rectal cancer, 180 could be contacted by telephone. Twenty-six individuals declined participation, which left 154 who received and completed the questionnaires (response rate: 85.6% among those who could be contacted, or 47.1% of all eligible individuals) at a median follow-up of 57.5 (34.1-98.1) months after surgery. Individuals who declined participation were older than those who were included; however, non-participants were otherwise similar to those who participated with regards to patient and disease characteristics **(Table 1)**.

Among those included, 47 (30.5%) reported major LARS, 33 (21.4%) minor LARS, and 74 (48.1%) no LARS. The median age was 64.0 (57.0-72.0) years, and the majority were female (54.5%). Roughly one-third of the cohort had a coloanal anastomosis (34.4%) and 46.1% received neoadjuvant radiation therapy (23.4% endorectal brachytherapy; 22.7% external beam radiotherapy). Compared to individuals with minor / no LARS, individuals with major LARS had a lower median age (60.0 vs. 65.0 years, p=0.009) and were more likely to be female (61.7% vs. 38.3%, p=0.012). Patient, tumor, and treatment characteristics, as well as duration of follow-up, were otherwise similar between the two groups of patients **(Table 2)**.

Bowel-related financial stress and strain were reported in 20.1% and 16.2% of the cohort, respectively. Individuals with major LARS reported a higher prevalence of bowel-related financial stress (53.2% vs. 5.6%, p<0.001) and strain (42.2% vs. 5.6%, p<0.001) compared to those with minor / no LARS **(Figure 1)**. One-hundred individuals reported working prior to their rectal cancer operation. Among them, 34 (34.0%) reported major LARS and 66 (66.0%) minor / no LARS. A higher proportion of individuals with major LARS reported an impact of their new bowel function on their ability to work (70.6% vs. 21.2%, $p<0.001$). Furthermore, individuals with major LARS reported higher proportions of delayed return to work (44.1% vs. 10.6%, $p<0.001$), changes in work schedule (35.3% vs. 9.1%, $p<0.001$) and role at work (20.5% vs. 1.5%, $p=0.007$), and sustained medical absence from work (14.7% vs. 0%, $p=0.008$) **(Figure 2)**.

Median global QoL in the entire cohort was 66.7 (60.4-83.3) out of 100, and was significantly lower among individuals with major LARS compared to those with minor / no LARS (66.7 vs. 83.3, $p<0.001$). When individuals with major LARS were further distinguished as those with and without bowel-related financial impact, median global QoL scores were as follows: major LARS with financial impact, 58.3 (41.7-66.7); major LARS without financial impact, 66.7 (50.0-66.7); and minor / no LARS, 83.3 (66.7-91.7). Using a cut-off in global QoL as ≤60 (first quartile = 60.4), 26.0% (40/154) of individuals had low QoL. Individuals with major LARS were more likely to report low QoL compared to those with minor / no LARS (36.2% vs. 21.5%, $p=0.020$). On multiple logistic regression, adjusting for age, sex, American Society of Anesthesiologists score, neoadjuvant radiation therapy, locally-advanced pathologic tumor stage (pT3 or pN+), and anastomotic leak, major LARS with bowel-related financial impact was independently associated with low QoL (adjusted OR: 4.23, 95% CI 1.38-14.84). However, major LARS without bowel-related financial impact did not demonstrate an association with low QoL (adjusted OR: 2.22, 95% CI 0.64-8.92) **(Table 3)**.

Discussion

This is the first study to evaluate the financial hardships experienced by individuals suffering from LARS after rectal cancer surgery. The principal finding is that approximately 20% of all long-term rectal cancer survivors who underwent a restorative proctectomy reported a significant financial impact that they attributed to their new bowel function. Furthermore, LARS severity discriminated well between those with and without financial hardships. Individuals with major LARS were significantly more likely to experience financial impact, with nearly half reporting bowel-related financial stress and strain. Finally, among individuals with major LARS, bowel-related financial impact further contributed to their already diminished global QoL, and represents an added source of suffering in this patient population.

Since the description of the LARS score in 2012, a large body of research has emerged on the association between LARS and QoL; however, the financial impact of LARS has not been adequately explored. Emmertsen et al. prospectively studied 260 Danish rectal cancer survivors, and reported lower global QoL at 3 and 12 months after surgery in patients with major LARS.[11] While symptoms of LARS tend to improve after the first year, the impairment in QoL observed in individuals with LARS often persists. A recent study of 282 individuals demonstrated sustained impairments in long-term QoL for as long as five years between measurements in the same individuals.[23] Furthermore, subdomains of QoL are likewise impacted by LARS. Juul et al. studied 796 individuals from four European countries ranging anywhere from 1.4 to 10.5 years after surgery. Individuals with major LARS reported worse global QoL as per the EORTC-QLQ-C30, as well as worse physical, role, emotional, and social functioning. Interestingly, although "financial difficulties" is a single-item scale on the EORTC questionnaire, the authors did not thoroughly evaluate that outcome, instead choosing *a priori* to focus their analysis on the eight scales that they deemed more relevant to rectal cancer survivors.[13] They stated that there was no evidence – nor was it their clinical experience – that bowel dysfunction had an effect on financial well-being, which underscores the importance of this work.

In our patient population, approximately 30% of individuals reported major LARS, which is comparable to institutional data from recent publications.[12,13,24] Of these, roughly 50% reported bowel-related financial impact, compared to only 5% of patients with minor / no LARS. Even in a public healthcare system, there are numerous costs associated with the management of LARS which may contribute to its financial impact. Loperamide, for instance, is the mainstay of therapy, and many individuals are dependent on taking several tablets each day. In addition to loperamide, other medications have been proposed (e.g., diphenoxylate, codeine, amitriptyline), all of which may incur some degree of personal cost. Also important are the non-pharmacological costs, which are increasingly borne out-of-pocket.[19] Patients may be managed with enemas, transanal irrigation, and biofeedback,[25,26] which at most, are only partially covered with private insurance. While there is no good data available to quantify the direct cost of LARS therapy, data from the literature on primary fecal incontinence can be extrapolated to provide an approximation. In an analysis of 332 patients, Xu et al. estimated mean annual direct medical and non-medical costs for the treatment of fecal incontinence to be $2,353 USD and $209 USD, respectively.[27]

Perhaps more significant to individuals suffering from LARS is the indirect cost generated from loss of productivity. Due to their abnormal and unpredictable bowel function, individuals with LARS may find it challenging to return to work at the same capacity. They may have to make certain compromises in work schedule or job description to accommodate toileting needs and to protect against physically demanding labor. The psychological and financial impact that ensues is particularly problematic given that rectal cancer is increasingly affecting younger individuals who are still of working age.[7,8] Our study demonstrated that the majority of individuals with major LARS experienced an impact of their new bowel function on their ability to work. Perhaps most troubling, roughly 15% of individuals with major LARS were still on sick leave solely due to their bowel dysfunction. A recent study developed a prediction model for return to work among patients with colorectal cancer, but unfortunately did not study colon and rectal cancer separately; thus, the impact of bowel dysfunction could not be appreciated.[28] However, our findings echo the sentiments previously shared in qualitative studies exploring the experiences of patients after sphincter-sparing surgery, where several interviewed patients described their inability to return to their former employment due to unpredictable bowel symptoms.[29]

The results of this study have a number of implications for clinicians caring for patients with rectal cancer. First and foremost, all clinicians should be aware of the financial hardships associated with LARS to identify those who are struggling most. While there is growing evidence for the financial impact of colorectal cancer as a whole,[6] clinicians must recognize that LARS carries its own set of consequences beyond the initial diagnosis and management of rectal cancer. In most cases, LARS will persist long after the patient is cured from their disease.[23] Patients should also be conditioned to the potential life-altering effects of LARS, and preferably early on in the decision-making process. Presently available decision aids for rectal cancer surgery provide basic statistics for LARS but may underemphasize the long-term impact it can have on the individual.[30] If fully informed about the implications of bowel dysfunction on their ability to return to work and financial future, it is plausible that some patients may actually prefer a permanent ostomy. Finally, from a hospital and government standpoint, the findings of this study further stress the need for a dedicated LARS support allied health professional team in high-volume rectal cancer centers, which is not routinely available.

This study provides novel data and information on the lived experiences of individuals with LARS. Additional strengths of the study include the relatively high response rate and the use of several validated patient-reported outcomes measures. However, there are important limitations to the work that must be considered. As with all questionnaire-based studies, there is a risk for non-response bias, as it is possible that non-responders were not missing at random. However, we showed that non-participants were similar to included individuals. With respect to the assessment of occupational impact, there is also the potential for recall bias, as many patients reported past difficulties they encountered when returning to work after surgery. There are also important socioeconomic variables missing from this analysis, such as household income and insurance status. Finally, the findings of this study may not be generalizable to rectal cancer patients from other countries, particularly those with considerably different healthcare systems.

Conclusions

Among individuals who underwent a restorative proctectomy, LARS was associated with considerable financial stress and strain, and difficulties returning to work. Patients should be counseled about the potential long-term consequences of LARS, and healthcare teams should be prepared to readily identify those who are struggling most. Future research is required to better quantify the direct and indirect costs of LARS.

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Table 1 – Comparison of individuals included and those excluded

Characteristic	**Included n=154**	**Non Response n=147**	**Declined n=26**	***p***
Age, years, median (IQR)	64.0 (57.0-72.0)	64.0 (54.0-73.0)	71.0 (65.0-81.0)	0.009
Sex, female, n (%)	70 (45.5)	68 (46.3)	12 (46.2)	0.98
ASA score, n (%)	-	-	-	0.80
I/II	120 (77.9)	116 (78.9)	19 (73.1)	-
III/IV	34 (22.1)	31 (21.1)	7 (26.9)	-
Pathologic T-stage, n (%)	-	-	-	0.98
0/1/2	83 (53.9)	81 (55.1)	14 (53.8)	-
3/4	71 (46.1)	66 (44.9)	12 (46.2)	-
Pathologic N-stage, n (%)	-	-	-	0.92
0	102 (66.2)	100 (68.0)	18 (69.2)	-
1/2	52 (33.8)	47 (32.0)	8 (30.8)	-
Neoadjuvant radiation, n (%)	71 (46.1)	70 (47.6)	10 (38.5)	0.69
Tumor height, cm, median (IQR)	10.0 (7.0-13.0)	9.0 (7.0-11.8)	10.0 (8.0-13.0)	0.27
TME (vs. PME), n (%)	76 (49.4)	81 (55.1)	13 (50.0)	0.59
Coloanal anastomosis, n (%)	53 (34.4)	55 (37.4)	8 (30.8)	0.75
Straight anastomosis (vs. colonic J-pouch or end-to-side), n (%)	131 (85.1)	133 (90.5)	24 (92.3)	0.28
Anastomotic leak, n (%)	17 (11.0)	13 (8.8)	4 (15.4)	0.57
Diverting ileostomy, n (%)	83 (53.9)	72 (49.0)	12 (46.2)	0.61
Duration of ileostomy, days, median (IQR)	270.0 (161.0-333.0)	278.0 (155.0-342.0)	284 (174.0-355.0)	0.68

LARS = Low Anterior Resection Syndrome; IQR = interquartile range; ASA = American Society of Anesthesiologists; TME = total mesorectal excision; PME = partial mesorectal excision

Table 2 – Comparison of individuals with major LARS and minor / no LARS

Characteristic	**Major LARS n=47**	**Minor / No LARS n=107**	***p***
Age, years, median (IQR)	60.0 (52.0-66.5)	65.0 (58.5-73.0)	0.009
Sex, female, n (%)	29 (61.7)	41 (38.3)	0.012
ASA score, n (%)	-	-	0.10
I/II	41 (87.2)	79 (73.8)	-
III/IV	6 (12.8)	28 (26.2)	-
Pathologic T-stage, n (%)	-	-	0.45
0/1/2	28 (59.6)	55 (51.4)	-
3/4	19 (40.4)	52 (48.6)	-
Pathologic N-stage, n (%)	-	-	0.11
0	36 (76.6)	66 (61.7)	-
1/2	11 (23.4)	41 (38.3)	-
Neoadjuvant radiation, n (%)	22 (45.8)	49 (46.8)	0.96
Tumor height, cm, median (IQR)	9.4 (7.0-12.0)	10.4 (7.2-14.0)	0.13
TME (vs. PME), n (%)	28 (62.2)	48 (47.1)	0.090
Coloanal anastomosis, n (%)	20 (44.4)	33 (32.4)	0.16
Straight anastomosis (vs. colonic J-pouch or end-to-side), n (%)	41 (91.1)	90 (88.2)	0.44
Anastomotic leak, n (%)	8 (17.0)	9 (8.4)	0.20
Diverting ileostomy, n (%)	28 (59.6)	55 (51.4)	0.45
Duration of ileostomy, days, median (IQR)	256.5 (161.8-304.5)	280.0 (161.0-347.0)	0.67
Follow-up, months, median (IQR)	52.0 (28.5-83.8)	60.4 (34.6-99.0)	0.39

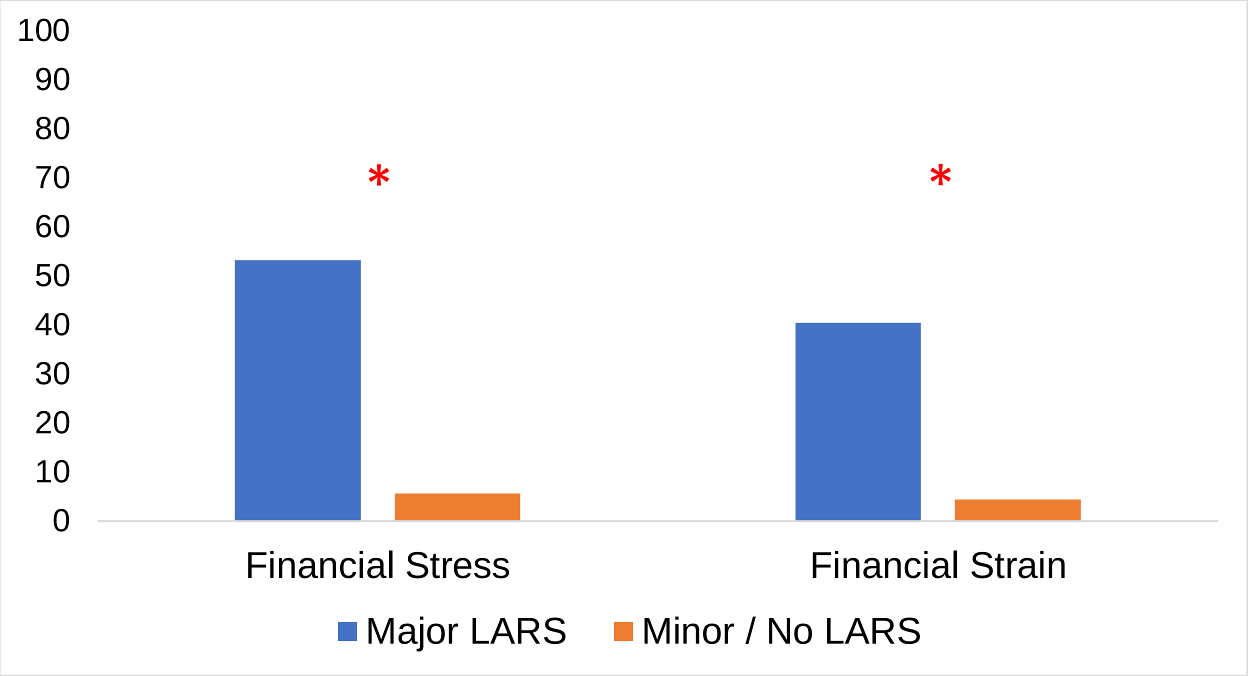
LARS = Low Anterior Resection Syndrome; IQR = interquartile range; ASA = American Society of Anesthesiologists; TME = total mesorectal excision; PME = partial mesorectal excision

Table 3 – Multiple logistic regression model for low global quality of life

Characteristic	**OR**	**95% CI**
LARS and bowel-related financial impact (reference = Minor / No LARS)	-	-
Major LARS with financial impact	4.23	1.38-14.84
Major LARS without financial impact	2.22	0.64-8.92
Age, years	1.03	0.99-1.07
Sex, male	1.19	0.56-2.58
ASA score III/IV	1.31	0.58-2.34
Neoadjuvant radiation	1.02	0.48-2.56
Locally-advanced pathologic stage	0.65	0.30-1.40
Anastomotic leak	1.22	0.29-3.22

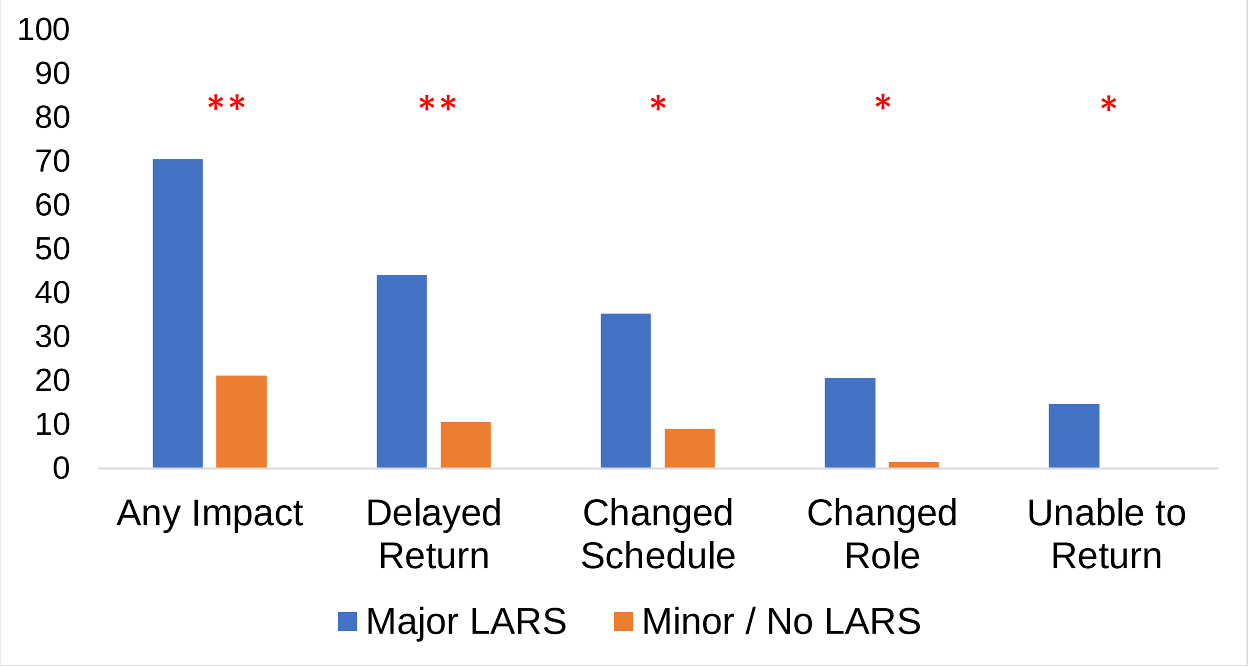
OR = odds ratio; CI = confidence interval; LARS = Low Anterior Resection Syndrome; ASA = American Society of Anesthesiologists

Figure 1 – Proportion of individuals with bowel-related financial stress and strain, stratified by severity of LARS



* = *p*<0.001
LARS = Low Anterior Resection Syndrome

Figure 2 – Proportion of individuals with occupational impact, stratified by severity of LARS (denominator = individuals who reported as working prior to rectal cancer surgery)



** = *p*<0.001; * = *p*<0.01
LARS = Low Anterior Resection Syndrome

Chapter 4.1: Systematic Review of Online Health Information – Preamble

In the previous two chapters, I have demonstrated the burden of Low Anterior Resection Syndrome (LARS) among individuals who underwent restorative proctectomy. I have shown that LARS is a common late sequela of rectal cancer treatment that continues to affect patients long after they are cured of their disease. Several factors were associated with long-term bowel dysfunction, including distal tumors, radiation therapy, and postoperative anastomotic leaks. LARS also had a direct impact on the individual's perceived sense of well-being. Major LARS was associated with worse global quality of life, as well as financial hardships and difficulties returning to work.

Given the high prevalence of LARS and its wide-ranging and lasting impact, supportive interventions geared towards individuals with bowel dysfunction are warranted. The management of LARS is very much empirical and requires a great deal of individual engagement; therefore, a large component of helping individuals with LARS involves support, education and counseling. Our goal is to create a LARS Patient-Centered Program, aimed at helping patients navigate through their new life with LARS. Prior to developing the informational component of the Program, I performed a systematic review of the Internet for online health information available to individuals with LARS. The strengths, weaknesses, and gaps in knowledge identified through this review helped guide the development of a novel informational resource, which will form the foundation of our supportive LARS Patient-Centered Program.

Chapter 4.2: Assessing the Readability, Quality, and Accuracy of Online Health Information for Rectal Cancer Survivors with Low Anterior Resection Syndrome

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Abstract

Introduction: Management of Low Anterior Resection Syndrome (LARS) requires a high degree of patient engagement. This process may be facilitated by online health-related information and education. The objective of this study was to systematically review current online health information on LARS.

Methods: An online search of Google, Yahoo and Bing using the search terms “low anterior/anterior resection syndrome” and “bowel function/movements after rectal cancer surgery” was performed. Websites were assessed for readability (8 standardized tests), suitability (Suitability Assessment of Materials instrument), quality (DISCERN instrument), accuracy, and content (using a LARS-specific content checklist). Websites were categorized as academic, governmental, non-profit, or private.

Results: Of 117 unique websites, 25 met inclusion criteria. Median readability level was 10.4 (9.2-11.7) and 11 (44.0%) websites were highly suitable. Using the DISCERN instrument, 7 (28.0%) websites had clear aims, 2 (8.0%) divulged the sources used, and 4 (16.0%) had overall high quality. Only 8 (32.0%) websites defined LARS and 10 (40.0%) listed all five major symptoms associated with the LARS score. The number of websites varied in their discussion of diet modifications (80.0%), self-help strategies (72.0%), medication (68.0%), pelvic floor rehabilitation (60.0%), and neuromodulation (8.0%). Median accuracy of websites was 93.8% (88.2%-96.7%). Governmental websites scored highest in overall suitability (p=0.0079) and quality (p<0.001).

Conclusions: Current online information for LARS is suboptimal. Websites are highly variable, important content is often lacking, and material is too complex for patients.

Introduction

Restorative proctectomy is being increasingly performed for rectal cancer as surgeons continue to push the limits of sphincter preservation.[1,2] However, despite avoiding a permanent ostomy, many patients are left with significant bowel dysfunction. Low Anterior Resection Syndrome (LARS) encompasses a collection of bowel symptoms, such as frequency, urgency, incontinence, and clustering of bowel movements,[3] that can affect up to 70-90% of patients.[4,5] While symptoms may improve in the first 1-2 years after surgery, long-term bowel dysfunction can persist in over 70% of patients and major dysfunction in over 50%.[6-8] LARS remains a significant concern for survivors of rectal cancer surgery as increased severity correlates with worse perceived global health status and quality of life (QoL).[5,8,9]

Symptoms of LARS are unpredictable and variable, and as such, management is empirical and symptom-based.[4] Much of the care requires effective troubleshooting and self-management behaviors, and appropriate education could help motivate patients to better engage in their own care. Given that LARS is a fairly complex disorder, patients may turn to the Internet for information. The Internet has rapidly become one of the greatest sources of medical information for patients, given how easy, affordable, and efficient it is to access.[10,11] Research suggests that over 80% of Internet users look for health information online,[12] and that most patients are interested in using the Internet to answer their medical questions.[13] Patients searching the Internet also feel more empowered about their healthcare,[14,15] and report that satisfaction with health-related educational information reduces emotional distress.[16] However, the quality of online medical information for patients can be quite variable. Reading materials are rarely written at the American Medical Association recommended sixth-grade reading level,[17-19] are often lacking important content,[20] may not be conducive to learning, or may be inaccurate.[21]

The purpose of this study was to assess the readability, quality, suitability, accuracy and content of online health information for patients with LARS, in order to identify the best available materials for patients and to understand the most common strengths and deficiencies among websites. Secondarily, we aimed to identify any differences in these assessments by website affiliation.

Methods

Search Strategy

The search terms "low anterior / anterior resection syndrome" and "bowel function / movements after rectal cancer surgery" were both used in Google, Yahoo and Bing to yield six sets of search results. Identical searches were performed in two cities – Montreal, Canada and Toronto, Canada – in the months of July and August 2017. Each of the six searches was limited to the first six web pages (60 websites), as it has been demonstrated that 99% of Internet users do not search beyond the first 50 websites for health information.[22] Two independent reviewers (R.G. and N.W.C.) screened each unique website for inclusion, based on the following criteria: 1) English-language only; 2) free of charge; 3) explicitly designed for patients to read alone, without the support of a healthcare professional; and 4) the website featured, at a minimum, a dedicated section on postoperative bowel function. After compiling a final list of websites for inclusion, each website was presented to a third reviewer (senior author M.B.) who agreed on its inclusion. Websites were excluded if they were intended for healthcare professionals or required a healthcare professional's support when reading. Websites were also excluded if they were password-protected, support groups/blogs, the wrong type of website (advertisement, news article, book, video-only), or irrelevant to LARS. The need for internal review board approval was waived at our institution as the information being studied was already in the public domain.

Website Affiliation

Websites were classified into four mutually exclusive categories: (1) academic, if the website had a ".edu" domain or was clearly part of a university's webpage; (2) governmental, if the website had a ".gov" domain; (3) non-profit, if the website had a ".org" domain; or (4) private, if the website did not fit into any of the categories above and belonged to a private holder. Website domains were confirmed using the WHOis.net database.[23]

Readability

Eight standardized tests were used to compute the median readability score for each website, as the use of multiple tests has been shown to improve reliability and accuracy of readability scores.[24] The following tests were used: the Coleman-Liau index, the Flesch-Kincaid Grade level, the FORCAST Readability formula, the Fry Readability graph, the Gunning Fog index, the New Fog Count, the Raygor Readability estimate, and the SMOG (Simple Measure of Gobbledygook) Readability formula. Median readability levels were then compared to educational equivalences. Readability was assessed using the Readability Studio Professional Edition version 2015.1 software (Oleander Software Ltd).

Suitability

The Suitability Assessment of Materials (SAM) is a validated instrument to objectively assess the suitability of health information materials for a particular audience. The SAM rates six domains: content, literacy demand, graphics, layout and type, learning stimulation and motivation, and cultural appropriateness. Each area contributes 3-4 SAM factors to give a total of

22 items in the instrument. Each item is given a score a 0 (not suitable), 1 (adequate), or 2 (superior), depending on objective criteria described in the instrument. The maximum number of points per website is 44. If a particular item is not relevant to the website, it can be subtracted from the denominator. The final assessment depends on the total score: superior (70-100%), adequate (40-69%), or not suitable (0-39%). Mean SAM scores for each item, from all three reviewers, were also calculated to identify global areas of weakness across all websites.

Quality

The DISCERN instrument is a validated tool designed to help health information consumers judge the quality of written information about treatment choices. It includes 15 questions, eight of which relate to the reliability of the publication and seven of which focus on specific details of the information. The 16th question relates to the overall quality of the material, and takes into account responses from questions 1-15. Each question is rated from 1-5 (1-poor quality, 5-excellent quality).[25]

Accuracy

Accuracy was determined by an expert panel of three experienced colorectal surgeons (P.S, S.D.W, M.B.). Each material was read independently, and inaccurate statements were identified. A fourth individual (R.G.) identified *a priori* the total number of statements for each website, to ensure a consistent denominator for each expert. The proportion of accurate statements was then calculated for each website, based on an average of the three experts' evaluations. Median accuracy was reported for all websites.

Content

The same panel of three colorectal surgeons (P.S, S.D.W, M.B.) created a LARS-specific content checklist to assess the content of each website. The checklist was created through an iterative process with the following question in mind: if you were designing a LARS website for patients, what information would you want included? Each website was then assessed using the checklist by three separate reviewers (R.G., N.W.C., A.P.), and items were reported as either being present or absent (binary outcome). The proportion of websites that included information on each item was reported.

Statistical Analysis

Suitability, quality, and content of included websites were assessed independently by three trained reviewers (R.G., senior General Surgery resident; N.W.C., Colorectal Surgery fellow; A.P., Colorectal Surgery attending), and accuracy was assessed independently by three senior Colorectal Surgery attendings (P.S., S.D.W., M.B.). Interrater reliability (IRR) was calculated for each assessment with either intracluster correlation (ICC) or Light's Kappa (κ) coefficients, where appropriate. Scores for readability, overall suitability, overall quality and accuracy from each reviewer were compared by website affiliation; content was not analyzed by affiliation, as there was no summative "content completeness" score and the assessment was exploratory in nature. Data were treated as non-parametric. Median scores were compared in all four affiliation groups by use of the Kruskal-Wallis test with an $\alpha=0.05$. All statistical analyses were performed using R v3.4.1 (R Development Core Team. 2017. *R: A Language and Environment for Statistical Computing*. Vienna, Austria).

Results

Three-hundred sixty websites were identified from the six searches. The majority were duplicates owing to the overlap in search terms and search engines. Twenty-five of the 117 unique websites met inclusion criteria and were further analyzed **(Figure 1)**. The affiliation of included websites was as follows: 6 (24.0%) academic, 4 (16.0%) governmental, 11 (44.0%) non-profit, and 4 (16.0%) private **(Appendix 1)**. Only 9 (36.0%) websites had been updated in the past 2 years. The authors of the information were not clearly stated in 14 (56.0%) websites, and were variable in the 11 others: 3 (12.0%) were written by physicians alone, 3 (12.0%) by nurses alone, and 5 (20.0%) by a multidisciplinary team consisting of physicians and nurses. Only one of those websites explicitly mentioned patient involvement in the development of the information. Assessment of readability demonstrated a median website score of 10.4 (9.2-11.7), which corresponds to a 10th-grade reading level. No website was written at the American Medical Association recommended 6th-grade reading level, and there were no differences by website affiliation (*p*=0.16) **(Table 1)**.

In applying the SAM instrument, 11 (44.0%) websites were highly suitable, 13 (52.0%) were adequate, and 1 (4.0%) was not suitable (median ICC=0.53 ("fair agreement"), Q1-Q3 0.43-0.59). Overall suitability was higher among government-affiliated websites than academic, non-profit, or private (*p*=0.0079) **(Table 1)**. **Figure 2** presents the mean scores from each reviewer for each SAM item. Typography and layout were generally strong (mean suitability scores of 1.92 and 1.55, respectively) while the use of summaries (0.68), graphics (0.43), illustrations (0.62), and interaction (0.47) were poor **(Figure 2)**.

In applying the DISCERN instrument to measure website quality, only 7 (28.0%) websites had clear aims (explicitly stating what is the material meant to cover and who might find it useful), 2 (8.0%) reported what sources of information were used, and 8 (32.0%) offered additional sources of material (median ICC=0.65 ("good agreement"), Q1-Q3 0.53-0.78) **(Figure 3)**. Websites seldom went into detail to explain the various treatment options; 11 (44.0%) explained how each treatment worked, and no website consistently explained the risks associated with treatment. In total, only 4 (16.0%) websites were rated as good/excellent in overall quality **(Figure 3)**, and overall quality was highest among government-affiliated websites (*p*<0.001) **(Table 1)**. Accuracy of websites was generally high. The median accuracy of all websites was 93.8% (88.2%-96.7%) (median ICC=-0.54 ("fair agreement"), *p*=0.83) and was similar across website affiliations (*p*=0.57) (**Table 1)**. Examples of inaccurate statements identified by the experts included: "increased flatus as a symptom of LARS"; "most symptoms of LARS tend to improve over a period of months"; "LARS is always treatable/temporary"; "incontinence is not a common problem of LARS".

Important content was often missing from websites (median κ=0.66 ("good agreement"), Q1-Q3 0.43-0.83). Most websites described some of the major LARS symptoms, but only 10 (40.0%) described all five symptoms included in the LARS score **(Table 2)**. Frequency (92.0%) and urgency (88.0%) were the most commonly listed, while incontinence to flatus (60.0%) and clustering of bowel movements (64.0%) were less commonly discussed. Websites were poor at discussing incidence of LARS (24.0%) or any risk factors for LARS (40.0%). For treatment, the majority discussed medication (e.g. loperamide) (68.0%), stool bulking agents (64.0%), dietary changes (80.0%), perianal skin management (60.0%) and pelvic floor exercises (60.0%). More aggressive treatment modalities were infrequently mentioned, such as enemas/rectal irrigation (16.0%), neuromodulation (sacral neuromodulation (SNM) / percutaneous tibial nerve stimulation) (8.0%), or colostomy (4.0%) **(Table 2)**.

Taking into account all assessments, three of the highest rated websites based on the assessments and expert opinion are presented in **Table 3**.

Discussion

This study systematically reviewed the Internet for online health information for patients with LARS, with the purpose of identifying the highest quality websites for this audience and highlighting major strengths and deficiencies in what is currently available. LARS is a common and often chronic condition facing survivors of rectal cancer surgery and given the difficulties in managing symptoms, patients are often left troubleshooting for solutions. While the Internet has become a powerful tool for medical information,[26] its ability to help patients become better informed and more involved in their personal healthcare is very much contingent on the individual website's comprehension, content, and accuracy. Suboptimal online health information can have a negative impact on patient care and outcomes.[21,27]

Given that 99% of the U.S. population has graduated from the 6th-grade, the American Medical Association recommends that health-related educational materials be written at that level.[28] The current review, which employed eight standardized readability tests in order to improve the accuracy of the analysis, did not report a single website that is written at the recommended 6th grade readability level. The reported median readability of 10.4 (10th grade reading level) suggests that 5-7% of the U.S. population above 18 years-old would not be able to read the materials, based on 2017 census data.[29] Unfortunately, this a common problem with patient education materials in colorectal surgery and other fields.[17-19] Furthermore, only 32% of websites consistently avoided medical jargon, which can pose a large barrier to patient education.[30] There was also a marked shortage in the use of summaries or reviews, both of which have been associated with better retention of knowledge[31] and greater patient engagement in making good healthcare choices.[32]

The quality of websites was assessed using the DISCERN instrument. Only 16% of websites were rated as good/excellent overall, and exploring the results of the individual items within the questionnaire revealed many opportunities for improvement. Qualitative research has shown that reliability is a significant patient concern with regards to using the Internet for health-related purposes.[33] In this review, only 8% of websites provided references, and 44% were considered to be balanced and unbiased. Providing readers with details regarding the sources of information may reassure them that they are not being misguided. Only 28% of websites offered an introductory statement about the intended target audience and what sort of information will be covered, which can help patients decide whether the information is right for their educational needs. Studies using the DISCERN instrument to assess online health information for other colorectal conditions, such as colorectal cancer, familial adenomatous polyposis, and diverticular disease, have highlighted similar important gaps.[20,34,35]

Content assessment of health-related websites is debatable,[15] given that websites may not be designed to address an entire health condition but rather highlight particular topics within it. For this reason, we did not report the proportion of "content completeness" for each website, as this incorrectly assumes that each website was designed to be a comprehensive review of the condition. Nonetheless, we wanted to provide a descriptive overview of aspects of the condition which are poorly represented in the current body of online health information, as has been done in similar recent analyses.[20] For instance, the term "Low Anterior Resection Syndrome" was only described in 32% of websites, while the rest gave no specific name to the entity of impaired bowel function after rectal cancer surgery. While this term was only recently popularized in 2012,[3] it points to the outdated nature of most websites. The ability for patients to name their condition may allow them to better identify and communicate with others experiencing similar difficulties. Websites usually listed urgency (88%), frequency (92%), and incontinence to stools (76%) as potential symptoms, but less frequently described incontinence to flatus (60%) and clustering of bowel movements (64%). This is important, as studies exploring both physicians' and patients' perspectives on LARS have shown that physicians grossly overestimate the impact of frequency and liquid stool incontinence on quality of life, and markedly underestimate the impact of clustering and incontinence to flatus.[36] Websites also often lacked important information, such as the frequency of LARS and major risk factors for this syndrome; data that can be obtained from recent multicenter studies with long-term follow-up.[4,7,9] Furthermore, interventional treatment strategies, such as neuromodulation and colostomy, were seldom listed. Although both are considered last resort options,[37] they are within the scope of knowledge that a patient may expect from an informational page on LARS.

When comparing websites by affiliation, governmental websites scored highest in overall suitability and quality. One can hypothesize that governmental organizations have more designated funding and infrastructure to construct a website that is well suited for patients than do academic or private institutions. However, readability remained an issue irrespective of website affiliation, and should be an area of focus in future patient-oriented materials on LARS. In a similar analysis performed on online health information for pancreatic cancer treatment, readability of government-owned websites was found to be easier than academic and media-affiliated websites, but harder than those owned by non-profit organizations.[19]

The strengths of this study are that it used a systematic search strategy to identify all potentially relevant websites on LARS, that three reviewers independently performed each assessment, and that multiple validated assessment tools were used to evaluate all important aspects of what makes a successful health information website for patients. However, there are several limitations to this study. Our search was limited to English-language, publicly-accessible websites that were identified by searching the Internet in two Canadian cities on two discrete dates. The results from any search engine such a Google may vary depending on the search terms and the geographic location of the search, and despite evaluating the first 60 hits from each search, it is possible that some important websites were missed. We also did not systematically search through social media platforms. While Twitter and others have become prominent sources of medical information,[38] we felt that we would not be able to submit these posts to our assessments. There was also a varying degree of disagreement between reviewers using each instrument. This can be expected in these kinds of analyses,[20] and is inherent to the subjective nature of many of these assessments, despite the instruments' attempts to base evaluations on objective criteria. Lastly, we did not assess for information on other functional outcomes after rectal cancer surgery, such as sexual or genitourinary dysfunction. Although likely less pervasive than bowel dysfunction, both of these outcomes can greatly impact QoL and should be part of postoperative rectal cancer patient materials.

Conclusion

The Internet can be a very powerful tool to help patients become better informed and more involved in their healthcare. For patients with LARS, where self-management is crucial for successful control of symptoms, availability of good quality information is important. Based on this review, the current body of online information for patients with LARS is suboptimal. Websites are highly variable, important content is often lacking, and the material is written at too complex a reading level for patients. The creation of a comprehensive but easy to comprehend LARS website might fill an important gap for rectal cancer survivors.

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Table 1 – Assessment of readability, suitability, quality, and accuracy by website affiliation

Affiliation	**Median Readability level (Q1-Q3)**	**p^***
Academic n=6	10.3 (8.8-11.5)	0.16
Government n=4	10.7 (9.7-12.5)	
Non-profit n=11	10.0 (8.6-11.5)	
Private n=4	10.7 (10.0-12.0)	
Affiliation	**Median Suitability level (Q1-Q3)**	**p^***
Academic n=6	67.7% (61.5-71.9%)	0.0079
Government n=4	81.9% (78.1-84.5%)	
Non-profit n=11	63.6% (55.3-74.6%)	
Private n=4	63.0% (49.8-80.5%)	
Affiliation	**Median Quality level (Q1-Q3)**	**p^***
Academic n=6	3.0 (1.0-3.0)	<0.001
Government n=4	5.0 (4.5-5.0)	
Non-profit n=11	3.0 (3.0-3.0)	
Private n=4	3.0 (2.5-3.0)	
Affiliation	**Median Accuracy level (Q1-Q3)**	**p^***
Academic n=6	90.8% (87.5-97.4%)	0.57
Government n=4	95.2% (92.6-97.0%)	
Non-profit n=11	95.7% (84.6-96.3%)	
Private n=4	95.0% (91.8-96.3%)	

* = *p*-value assessing difference in distribution among all four groups

Table 2 – Content of websites (displayed as number (proportion) of websites that provided information)

Does the website provide information regarding:	**Yes, n (%):**
Definition of “LARS”	8 (32%)
Relevant anatomy	17 (68%)
Incontinence to flatus	15 (60%)
Incontinence to liquid stool	19 (76%)
Frequency of bowel movements	23 (92%)
Clustering of bowel movements	16 (64%)
Urgency	22 (88%)
Incidence of LARS	6 (24%)
Possible mechanisms of pathophysiology	17 (68%)
Any risk factors*	10 (40%)
Prognosis / natural history of LARS	21 (84%)
Rx: medication	17 (68%)
Rx: bulking agents	16 (64%)
Rx: dietary restrictions	20 (80%)
Rx: self-help strategies	18 (72%)
Rx: perianal skin care	15 (60%)
Rx: enemas / rectal irrigation	4 (16%)
Rx: pelvic floor exercises	15 (60%)
Rx: neuromodulation (SNM/PTNS)	2 (8%)
Rx: colostomy	1 (4%)
Reference to other materials / support groups	17 (68%)

*any one of the following: radiotherapy, tumor height, age, type of anastomosis, type of reconstruction, baseline incontinence

LARS = Low Anterior Resection Syndrome; Rx = treatment; SNM = sacral neuromodulation; PTNS = percutaneous tibial nerve stimulation

Table 3 – Three of the highest rated websites

Name	URL
Beating Bowel Cancer	www.beatingbowelcancer.org/understanding-bowel-cancer/living-with-bowel-cancer/long-term-changes-bowel-habit/
National Health Services	www.eastcheshire.nhs.uk/Patient%20Information%20Leaflets/On%20the A-Z/Managing%20bowel%20after%20Anterior%20Resection%2011453.pdf
Bladder Bowel	www.bladderbowel.gov.au/assets/doc/ImproveBowelAfterSurgery.html

Figure 1 – PRISMA diagram for website inclusion

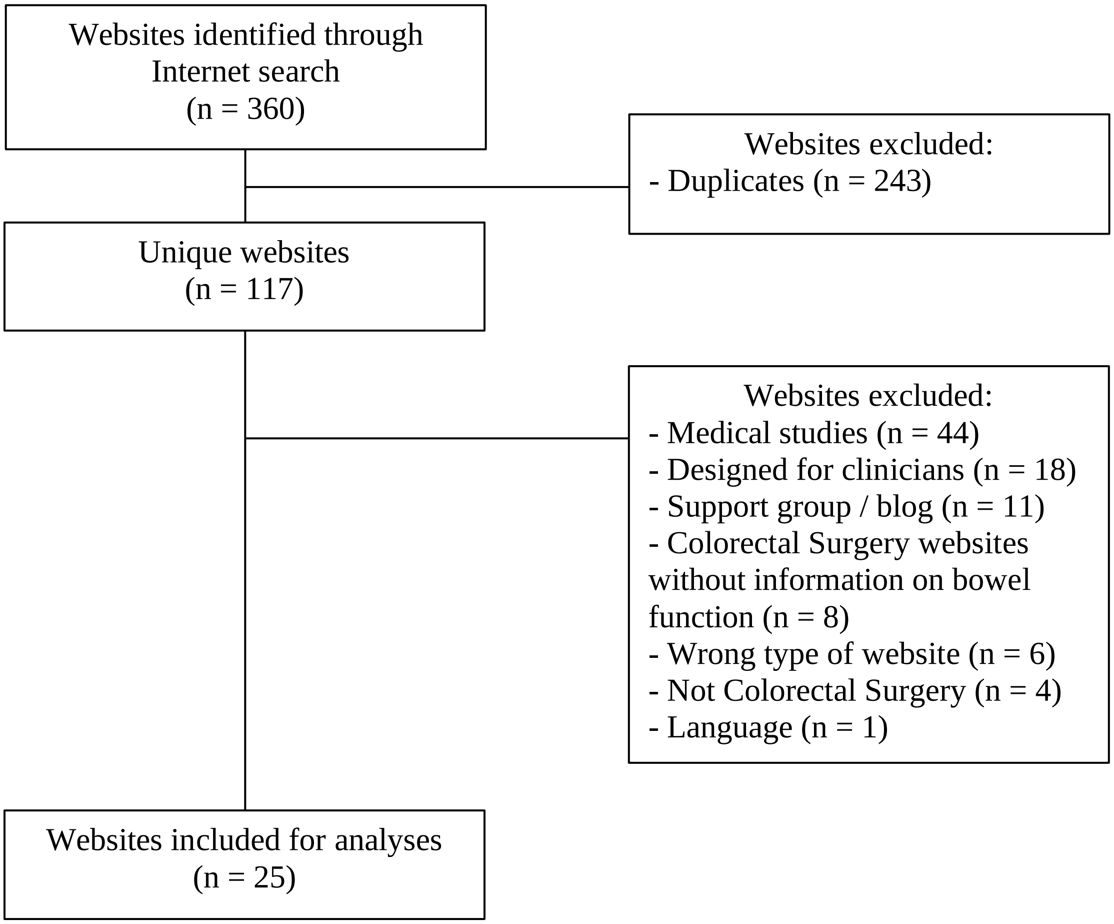
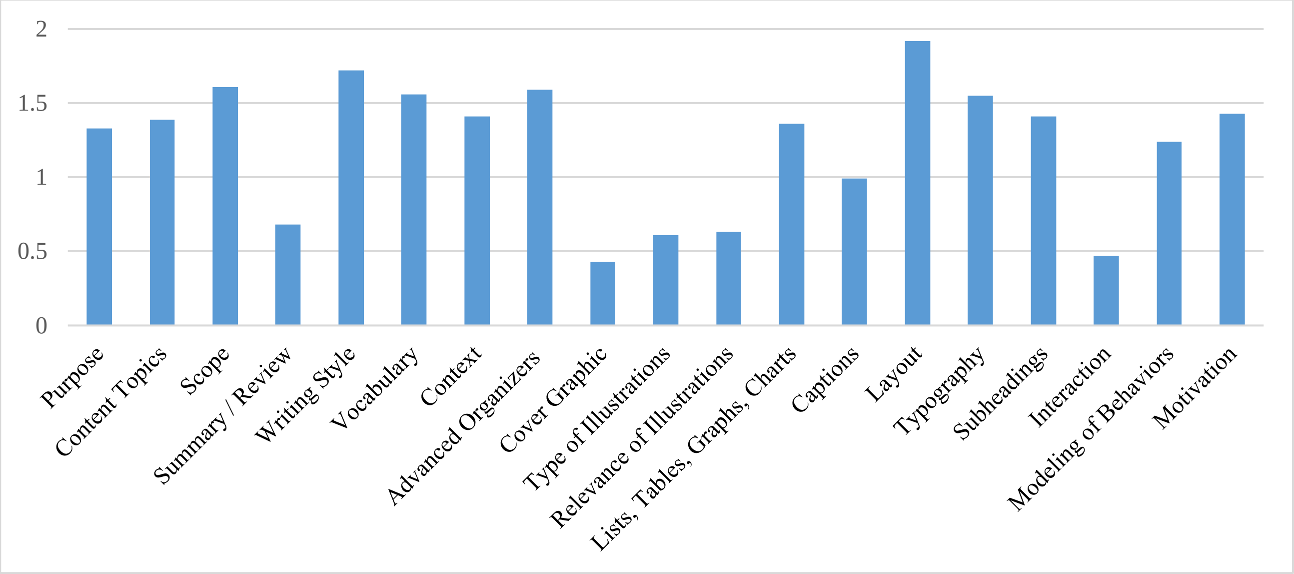
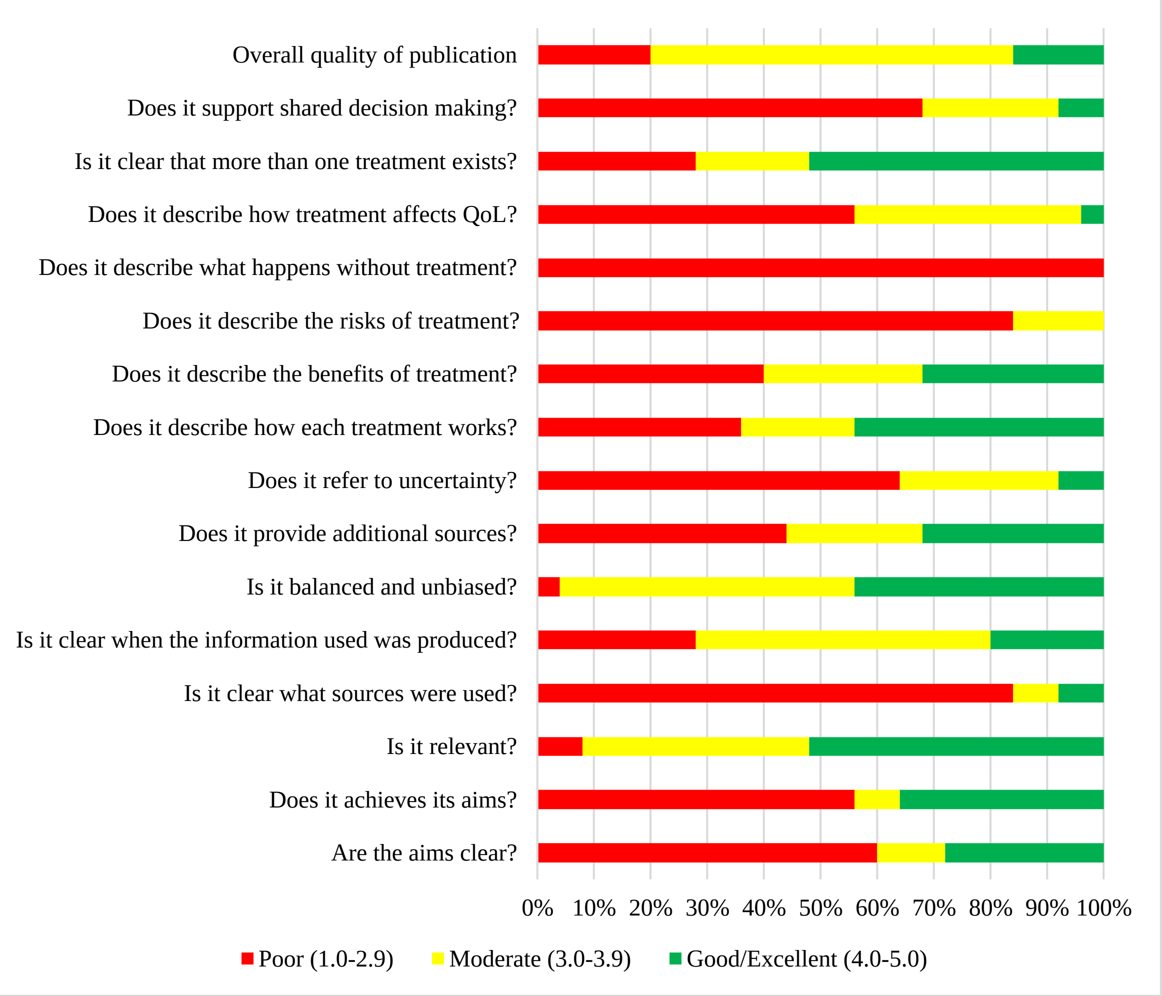


Figure 2 – Mean suitability score from three reviewers for each item in the Suitability Assessment of Materials instrument



Score of 0 = not suitable; score of 1 = adequate; score of 2 = superior
Item on Reading Grade Level was omitted due to formal readability assessment
Items on Cultural Appropriateness were omitted (not applicable)

Figure 3 – Pooled assessment of websites using the DISCERN instrument to measure website quality



Appendix 1 – Characteristics of the 25 websites included in the analysis

	Website Hyperlink	Country	Affiliation	Last Updated*
1	http://colonrectalsurg.wustl.edu/en/Patient-Care/Low-Anterior-Resection-Syndrome	USA	Academic	2011
2	http://www.nshealth.ca/sites/nshealth.ca/files/patientinformation/nsccp0027.pdf	Canada	Government	2014
3	http://www.med.umich.edu/1libr/Surgery/GenSurgery/ColorectalSurgery/LARSyndrome.pdf	USA	Academic	2016
4	http://surgery.ucsf.edu/media/7777795/After-Rectal-Cancer-Surgery.pdf	USA	Academic	2011
5	http://www.cornwallcolorectalsurgeon.com/wp-content/uploads/2010/02/Anterior-Resection-Syndrome-leaflet-no-2.pdf	UK	Private	N/A
6	https://www.beatingbowelcancer.org/understanding-bowel-cancer/living-with-bowel-cancer/long-term-changes-bowel-habit/	UK	Non-Profit	2017
7	http://www.eastcheshire.nhs.uk/Patient%20Information%20Leaflets/On%20the%20A-Z/Managing%20bowel%20after%20Anterior%20Resection%2011453.pdf	UK	Government	2015
8	https://www.mskcc.org/cancer-care/patient-education/about-your-low-anterior-resection-surgery	USA	Non-Profit	2017
9	http://www.bladderbowel.gov.au/assets/doc/ImproveBowelAfterSurgery.html	Australia	Government	2013
10	https://www.coloplast.co.uk/Global/UK/Continence/Peristeen/Managing-your-bowel-function-Patient-Booklet.pdf	UK	Private	2015
11	https://www.fairfaxcolorectal.com/docs/Bowel%20Management%20after%20Colorectal%20Surgery.pdf	USA	Private	N/A
12	http://www.macmillan.org.uk/information-and-support/bowel-cancer/colon/treating/surgery/surgery-explained/bowel-function-after-surgery.html#192808	UK	Non-Profit	2014
13	http://www.colidoscope.com/patients/life_after_surg.html	USA	Academic	2012
14	http://www.aboutincontinence.org/causes-of-incontinence/colorectal-cancer.html https://cancernz.org.nz/assets/Uploads/BowelCancerBowelFunction-LINKS.pdf	USA	Non-Profit	2016

15	https://www.bowelcanceraustralia.org/recipe-for-recovery	Australia	Non-Profit	2014
16	https://en.wikipedia.org/wiki/Lower_anterior_resection#Low_Anterior_Resection_Syndrome	USA	Non-Profit	2018
17	https://www.bowelcanceruk.org.uk/about-bowel-cancer/living-with-bowel-cancer/long-term-and-late-side-effects/	UK	Non-Profit	2016
18	http://about-cancer.cancerresearchuk.org/about-cancer/bowel-cancer/living-bowel-cancer/eating	UK	Non-Profit	2015
19	http://www.canadianpharmacymeds.com/blog/how-to-adapt-to-bowel-changes-after-colorectal-cancer/	Canada	Non-Profit	N/A
20	http://www.uhn.ca/PrincessMargaret/PatientsFamilies/Specialized_Program_Services/Getting_Back_On_Track/Colorectal/Ongoing_Late_Side_Effects/Pages/bowel_function.aspx	Canada	Academic	2015
21	http://myhealth.ucsd.edu/Conditions/Cancer/34,BColT5	USA	Academic	2015
22	https://www.slhd.nsw.gov.au/concord/cancer/pdfs/Bowel_Function_Forum.pdf	Australia	Government	N/A
23	http://www.cancervic.org.au/about-cancer/cancer_types/bowel_cancer/diet-bowel-changes.html	Australia	Non-Profit	2015
24	http://jjs.me.uk/patientinfo/advicebowelsurgery.html	UK	Private	2015
25	https://cancernz.org.nz/assets/Uploads/BowelCancerBowelFunction-LINKS.pdf	New Zealand	Non-Profit	2010

*if year of last update not provided, the year of initial website development was used
USA = United States of America; UK = United Kingdom; N/A = not available

Chapter 5.1: Towards a Patient-Centered Approach – Preamble

In the previous chapter, I performed a systematic review of online health information for patients with Low Anterior Resection Syndrome (LARS), assessing relevant websites for readability, suitability, quality, accuracy, and content. Our review demonstrated multiple deficiencies in the available online resources: most websites were written at too complex a reading level, important content was typically lacking, and the overall quality was highly variable. Furthermore, several key educational features were missing from almost all websites, including the use of summary statements to help with the retention of information and illustrations and graphics to better explain why and how LARS develops. Given the potential significance of LARS education and counseling in improving quality of life and long-term bowel function in rectal cancer survivors, the creation of a comprehensive patient resource might fill an important gap in knowledge.

In 2018, I formed a LARS education working group, consisting of colorectal surgeons, a colorectal cancer pivot nurse, a pelvic physiotherapist, and motivated rectal cancer patients. In collaboration with the McGill University Patient Education Office, we developed an original LARS informational booklet. This booklet, which can also be accessed online, will be part of a LARS Patient-Centered Program, aimed at supporting rectal cancer survivors with their bowel function in the first year following ileostomy closure. In the next chapter, I described the development of our LARS informational booklet, which included gathering original qualitative data through focus group and semi-structured interviews. The data included constructive feedback for the booklet, as well as guidance on how to best implement the booklet into a LARS Patient-Centered Program, and ultimately into clinical practice. I then designed a multicenter randomized controlled trial assessing the impact of the LARS Patient-Centered program on patient-reported outcomes, including bowel function and quality of life. The trial, which was generously funded by the Canadian Society of Colon and Rectal Surgeons and the McGill University Rossy Cancer Network, was launched at the lead site in Montreal, Quebec in November 2019 and at two collaborating sites in August 2020. This next chapter also described the study protocol for the ongoing trial.

Chapter 5.2: Development and Evaluation of a Patient-Centered Program for Low Anterior Resection Syndrome: Protocol for a Randomized Controlled Trial

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Presentations: None.

Abstract

Introduction: Low Anterior Resection Syndrome (LARS) is described as disordered bowel function after rectal resection that leads to a detriment in quality of life, and affects the majority of individuals following restorative proctectomy for rectal cancer. The management of LARS includes personalized troubleshooting and effective self-management behaviors. Thus, affected individuals need to be well informed and appropriately engaged in their own LARS management. This manuscript describes the development of a LARS Patient-Centered Program (LPCP) and the study protocol for its evaluation in a randomized controlled trial.

Methods and Analysis: This will be a multicenter, randomized, assessor-blind, parallel-groups, pragmatic trial evaluating the impact of a LPCP, consisting of an informational booklet, patient diaries, and nurse support, on patient-reported outcomes after restorative proctectomy for rectal cancer. The informational booklet was developed by a multidisciplinary LARS team, and was vetted in a focus group and semi-structured interviews involving patients, caregivers, and healthcare professionals. The primary outcome will be global quality of life (QoL), as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (QLQ-C30), at 6 months after surgery. The treatment effect on global QOL will be modeled using generalized estimating equations. Secondary outcomes include patient activation, bowel function measures, emotional distress, knowledge about LARS, and satisfaction with the LPCP.

Ethics and Dissemination: The Research Ethics Committee (REC) at the Integrated Health and Social Services Network (CIUSSS) for West-Central Montreal (health network responsible for the Jewish General Hospital) is the overseeing REC for all Quebec sites. They have granted ethical approval (MP-05-2019-1628) for all Quebec hospitals (Jewish General Hospital, McGill University Health Center, CHU de Quebec) and have granted full authorization to begin research at the Jewish General Hospital. Patient recruitment will not begin at the other Quebec sites until inter-institutional contracts are finalized and feasibility / authorization for research is granted by their respective REC. The results of this study will be presented at national and international conferences, and a manuscript with results will be submitted for publication in a high-impact peer-reviewed journal.

Registration: This trial was registered on clinicaltrials.gov on February 4, 2019 (no: NCT03828318).

Strengths and Limitations of the Study

- This will be the first randomized controlled trial evaluating a supportive intervention for patients with Low Anterior Resection Syndrome
- This study will collect longitudinal data on patient-reported outcomes following restorative proctectomy, and will report on the natural evolution of several important outcome measures over the first postoperative year
- The informational booklet used in the trial underwent a rigorous pre-trial assessment and was revised into its final format based on feedback obtained in focus groups involving patients, caregivers, and healthcare professionals
- As with any longitudinal study, there is a risk for attrition throughout the study period, which could be a source of bias in the final results
- Management in the standard care group will vary by institution; however, none of the participating institutions have a formal LARS program for rectal cancer survivors

Introduction

Restorative proctectomy is increasingly performed for rectal cancer as surgeons continue to push the limits of sphincter preservation.[1,2] However, despite avoiding a permanent ostomy, many individuals are left with significant bowel dysfunction after sphincter-sparing surgery. Low Anterior Resection Syndrome (LARS) encompasses a series of negative bowel symptoms, such as frequency, urgency, incontinence, and clustering of bowel movements,[3] that can affect 70 to 90% of patients following restorative proctectomy.[4,5] Although symptoms may improve somewhat in the first year or two after surgery, long-term bowel dysfunction often remains in more than 70% of patients and major dysfunction in over 50%.[6-8] As such, LARS remains a significant concern for rectal cancer survivors and their significant others, as increased severity correlates with worse perceived global health status and quality of life (QoL).[5,8,9]

Currently, there is no well-established treatment strategy for LARS, and management is both empirical and symptom-based.[4] LARS is usually managed with a combination of lifestyle, pharmacological, and at times, interventional strategies, with mixed success. Due to the individual nature of each patient's cluster of symptoms, much of the care requires personalized troubleshooting and self-management behaviors to improve bowel symptoms and QoL.[4] These behaviors include understanding one's own symptoms, knowing how to use and dose stool bulking agents and anti-diarrheal medications, performing pelvic floor exercises, adhering to dietary recommendations, proper perianal skin management, and preparing ahead of social engagements. Thus, individuals need to be well informed, motivated and engaged in their own LARS management to take more control over their bowel function and achieve optimal outcomes.

Among individuals undergoing rectal resection with a permanent ostomy (e.g., abdominoperineal resection), there is evidence that supportive and informational interventions improve QoL, ostomy proficiency, self-efficacy and knowledge.[10-12] However, evidence regarding the impact of such interventions in patients who undergo restorative proctectomy is lacking, despite the latter operation being far more frequently performed.[1] When provided with the means to better understand and control important aspects of their bowel function, patients may be more likely to experience positive improvements in self-reported outcomes. In a recent review comparing long-term patient-reported outcomes after ostomy or sphincter-sparing surgery for low rectal cancer, the authors concluded that interventions geared towards patients without ostomies warrant further attention.[13]

This paper describes a study protocol for a randomized controlled trial (RCT) investigating the impact of a LARS Patient-Centered Program (LPCP) on patient-reported outcomes after restorative proctectomy for rectal cancer. Furthermore, qualitative data are presented that were gathered through a focus group assembling individuals with LARS and their caregivers, and through semi-structured interviews with rectal cancer healthcare professionals, as a joint effort to develop the LPCP.

Methods and Analysis

Phase 1: Study Protocol for Proposed RCT

The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[14]

Objectives

The overall objective of this study is to evaluate the effects of a LPCP on patient-reported outcome measures (PROMs) after restorative proctectomy for rectal cancer. Specifically, our primary objective is to evaluate the extent to which a LPCP improves global QoL, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30), at 6 months after surgery in comparison to standard care. Secondary objectives include the effects of a LPCP on symptom change, patient activation, bowel function, emotional distress, patient knowledge, and satisfaction with LARS care.

Participants and Setting

This multicenter RCT involves participants from multiple institutions across North America with high-volume Colorectal Surgery or Surgical Oncology practices. Patients who have undergone restorative proctectomy for neoplastic disease (benign or malignant) located in the rectum (0-15cm from the anal verge) with a diverting ostomy and who are scheduled for ostomy closure are eligible for inclusion. Patients will be recruited approximately one month prior to ostomy closure by their individual surgeon, who will go through the informed consent process with them. Exclusion criteria include: 1) active chemotherapy or radiotherapy treatment at the time of consent; 2) major colonic resection in addition to proctectomy; 3) inability to be contacted by telephone; 4) inability to read and comprehend English or French; and 5) inability to provide clear and informed consent. The study is estimated to be open from November 2019 to November 2022.

Randomization

Consecutive participants will be randomized in a 1:1 ratio into one of two groups: 1) LARS Patient-Centered Program; or 2) Standard Care. Block randomization with randomly varying block sizes will be performed to ensure an equal number of participants in each group.

Randomization will also be stratified by participating institution. An online centralized computer-generated randomization sequence will be used to ensure allocation concealment.

LARS Patient-Centered Program

The LPCP consists of an informational booklet, patient diaries, and nursing support made available only to patients randomized to the intervention group.

1. Informational Booklet and Patient Diaries:

The goals of the booklet are to inform individuals with rectal cancer about postoperative bowel dysfunction, manage expectations, and review the different treatment strategies. Prior to developing the booklet, our team conducted a systematic review of online health information for LARS to assess the readability, suitability, quality, accuracy and content of materials currently available to patients.[15] We concluded that the current body of health information for patients with LARS is suboptimal. In particular, no patient material was written at the American Medical Association-recommended 6th grade reading level, there was little use of headings, summaries and illustrations to accompany the text, and important content was missing. We then set out to develop our own informational booklet, drawing on the important elements emphasized in each assessment tool used in the systematic review. After developing the first draft of the booklet, patients, caregivers, and healthcare professionals provided feedback to improve the booklet into its current format. The booklet was then translated into French and underwent a similar evaluation process. A more thorough description of the booklet's development process can be found below (see Phase 2 below).

The booklet will be introduced to patients at the time of study recruitment (before ostomy closure). Participants will be instructed to read through the booklet at least once prior to their ostomy closure operation and will be encouraged to consult it as much as needed thereafter. In addition to the informational booklet, participants will receive Bowel Symptom, Diet, and Loperamide diaries and will be instructed to use them whenever experiencing any symptoms of bowel dysfunction, and for 2 weeks prior to each scheduled nurse phone call (please see the next section below). The goal of these diaries is to assist participants in recognizing the underlying patterns related to their symptoms so that they can optimize their self-management.

2. Nursing Support:

Nursing support will be centralized from one institution and made available to participants in the intervention group, by telephone and email. The study nurse (bilingual in English and French) has expertise in rectal cancer management and postoperative bowel dysfunction. She will briefly review the booklet content with participants by telephone at the beginning of the study (prior to ostomy closure) and answer related questions. Postoperatively, the nurse will have scheduled telephone calls with participants at 1-, 3-, 6-, 9-, and 12-months, to provide support and periodically review their completed diaries for troubleshooting. Lastly, she will be available to speak with participants in between scheduled calls, either by phone or by email.

Standard Care Group

Participants randomized to the standard care group will not have access to either the informational booklet nor nursing support. Instead, they will only receive a paper copy (and/or instructions for online access) of the Colorectal Cancer Association of Canada (CCAC) module on “Living with Colorectal Cancer”. The standard care group will also receive the usual care for LARS information and counseling that is routinely made available at their hospital, with participating hospitals asked to provide a description of what constitutes “standard care” for LARS. Due to the expected heterogeneity in institutional LARS practices, participating institutions will be accounted for in the final statistical model in addition to stratified randomization by institution. Participants in the standard care group will be told that they can have access to the informational booklet when the study is complete.

Data Collection

Baseline demographics, medical comorbidities, and disease and treatment characteristics will be obtained from chart review, including known predictors of bowel dysfunction (e.g., tumor height, neoadjuvant radiotherapy, type of proctectomy [total vs. partial mesorectal excision], reconstruction technique [straight anastomosis vs. neorectal reservoir], and anastomotic leak after proctectomy). The remaining data will be gathered from self-reported questionnaires at study time-points throughout the 12-month study period.

Outcomes

Outcomes will be measured with the use of various PROMs and recorded into an online registry (REDCap) by a blinded assessor. PROMs captured at the same time-point will be completed as a single package. The schedule for all PROMs can be found in **Table 1**. The PROM package for each time-point (available in both English and French) will either be mailed to participants, disseminated via email, or completed over the phone, depending on participants' preferences. Participants will receive email and telephone reminders for incomplete questionnaires. The study timeline for both groups can be found in **Figures 1 and 2**. The following outcomes and PROMs will be collected:

1. Quality of Life:

QoL will be measured using the EORTC-QLQ-C30, a self-report questionnaire developed to assess QoL for patients living with or beyond cancer. It consists of 30 items, which aggregate into 1 global QoL scale, 5 functional scales, 3 symptom scales, and 6 single items. The

EORTC-QLQ-C30 has been well validated in individuals with rectal cancer and correlates significantly with LARS severity.[5,8,9]

2. Symptom Changes:

The Measure Your Medical Outcome Profile (MYMOP2) is a patient-centered measure that assesses changes over time in a specific symptom identified as most bothersome to the patient.[16,17] The patient also identifies a daily activity that is being restricted or prevented by the symptom. Both the symptom and the activity are scored using a 6-point Likert-type scale in the last week.

3. Patient Activation:

Patient activation measures the degree of knowledge, skills, and confidence for self-management of healthcare.[18] In patients with chronic medical conditions, patient activation is associated with increased adherence to medication and decreased healthcare resource utilization.[19] We believe that the LPCP may increase patient activation, which may ultimately translate into increased patient engagement in their LARS healthcare.

The Patient Activation Measure-13 (PAM-13) is a 13-item questionnaire. Responses are based on a Likert scale ranging from “disagree strongly” to “agree strongly”, and the final score is a transformation ranging from 0 to 100 according to a conversion formula provided by the developers. Activation is then categorized into 1 of 4 groups based on their transformed score: Level 1, “overwhelmed and not ready to take an active role” (≤47.0); Level 2, “realize they have a role to play, but lack the knowledge and confidence” (47.1-55.1); Level 3, “beginning to take action, but still lack confidence” (55.2-72.4); Level 4, “can manage their healthcare, but may struggle to maintain the behaviors” (≥72.5).

4. Bowel Function:

Bowel function will be measured postoperatively using three validated tools/questions. The LARS Score is a 5-item tool aimed at symptoms of bowel dysfunction, with each question weighted differently according to the perceived importance by patients. The scores of the 5 questions sum to 42 points. The LARS Score allows the categorization of patients as having major (30-42 points), minor (21-29 points), or no LARS (0-20 points). The Cleveland Clinic Florida / Wexner Fecal Incontinence Score (WFIS) is a 5-item tool aimed at measuring the frequency of incontinence to gas and liquid or solid stools, and its consequences (pad wearing and lifestyle alterations). Each question ranges from 0 (never) to 4 (always) and the total score is measured out of 20. Lastly, each participant will be asked a single, validated, bowel-related QoL question: "Overall, how much does your bowel function affect your quality of life?" Responses categorize respondents into 1 of 3 grades: "not at all" (no impairment); "very little" (minor impairment); "somewhat" or "a lot" (major impairment). Bowel-related QoL is significantly correlated with both the LARS Score and general QoL as per previous studies.[9]

5. Emotional Distress:

Many patients with LARS describe emotional distress, anxiety, and isolation (see Phase 2 below). The LPCP is designed to alleviate some of the distress associated with LARS, and may provide hope that symptoms can be optimally managed.

Emotional distress will be measured using the Hospital Anxiety and Depression Scale (HADS), which has been validated in colorectal cancer survivors.[20,21] It includes 7 items aimed at assessing depression and 7 items for anxiety. Each item is scored 0-3, and is based on frequency of symptoms. The total score is out of 21, and individuals can be categorized as "normal" (0-7), "borderline abnormal" (8-10), or "abnormal" i.e., depressed or anxious (11-21).

6. Knowledge:

Given that the LPCP is partly an informational intervention, knowledge related to LARS will be measured using a short, investigator-generated, multiple-choice questionnaire. The items reflect key concepts in etiology/risk factors and management of LARS. We believe that improving LARS knowledge will further improve patient activation and engagement in LARS healthcare, which may lead to improvements in QoL and possibly bowel function.

7. Satisfaction:

Satisfaction related to LARS care received throughout the study period (information and support) will be assessed in both groups using a short, investigator-generated, 2-item questionnaire. Responses will be recorded using a 5-point Likert scale, ranging from “not satisfied” (1) to “very satisfied” (5).

Statistical Analysis

Descriptive analyses will include means with standard deviations, medians with ranges, or frequencies with proportions, where appropriate. Continuous outcomes will be compared using a t-test or Wilcoxon rank-sum test and categorical outcomes using χ^2 tests. The treatment effect on global QoL and bowel function will be modeled using generalized estimating equations (GEE).[22] This method accounts for 1) the within-subject correlation between responses at different time-points, and 2) possible clustering of responses among patients from the same hospital. GEE models also make use of all the available data, so that patients can contribute to the model if they have data available for any single time-point. An appropriate correlation structure will be chosen using the quasi-likelihood information criterion. The effect size, standard error, and 95% confidence interval for the estimate of the treatment effect at 6 months will be reported. For the remaining secondary outcomes, pairwise comparisons will be performed at various time-points.

Power Analysis and Sample Size Calculations

The primary outcome of the study is global QoL at 6 months, as measured by the EORTC QLQ-C30. Based on the largest available cohort of patients with QoL data who have undergone restorative proctectomy for rectal cancer and who are ostomy-free, mean global QoL score is assumed to be 77 (maximum possible score is 100) with a standard deviation of 19.[9] According to the consensus guidelines on the use of the EORTC QLQ-C30 to power a randomized controlled trial, a mean difference in global QoL of 10 points (small-medium treatment effect) is the most appropriate expected effect-size for interventions aimed to improve QoL in cancer patients.[23] Thus, with an alpha=0.05 and power=0.80, we estimate that 45 participants are required in each arm of our study. Given the risk for attrition over the 6-month study period, the adjusted final sample size accounting for a 30% attrition rate is 64 participants in each arm (128 patients in total).

Registration

This trial was registered on clinicaltrials.gov on February 4, 2019 (no: NCT03828318).

Phase 2: Development of Informational Booklet

The first draft of the informational booklet was developed by a multidisciplinary team of healthcare professionals who care for patients with rectal cancer. The initiative was co-led by a General Surgery resident (R.G.) and a Colorectal Surgery attending (M.B.), and included a senior colorectal cancer oncology pivot nurse, pelvic physiotherapist, and members of the McGill University Patient Education Office. The booklet was designed to review important information regarding the epidemiology, symptomatology, and management of LARS. The booklet was written at a 6th-grade reading level, which is recommended by the American Medical Association for any patient material,[24] and included original illustrations designed by our team.

An Institutional Review Board-approved qualitative study was subsequently undertaken to evaluate the booklet. A single focus group with rectal cancer patients and their caregivers, as well as individual semi-structured telephone interviews with healthcare professionals, were conducted.

Participants for the focus group were recruited from individual Colorectal Surgeons practicing at a single institution. The focus group included 12 participants (six patients and their caregivers/partners) and followed a semi-structured interview guide (**Supplementary File 1**). Each patient was a minimum of 6-months removed from ileostomy closure (if diverted) or proctectomy. Participants' characteristics are reported in **Table 2**. Each participant/caregiver was given two copies of the informational booklet and allowed three weeks to review the booklet and generate their own thoughts. The purpose of the focus group was to obtain feedback regarding the first draft of the booklet, to better understand participants' current/past experiences with LARS, and to incorporate changes into the booklet to meet the informational needs of rectal cancer survivors. The focus group was audio-recorded and transcribed, and data were analyzed using the grounded theory.[25,26] The constant comparative method was applied; data from participants were coded based on emerging patterns, concepts, and themes to generate theory, which was then analyzed and categorized accordingly so that descriptive statements could be formed.[27] The principal findings from the thematic analysis of the focus group are displayed in **Table 3**. Patients and their caregivers described the emotional difficulties of living with LARS and the general lack of support and preparation they received from their healthcare team. They unanimously supported the development and dissemination of the booklet, reporting that it would have had a major impact on their outlook and knowledge regarding LARS in their first year after surgery. Some of the feedback included more emphasis to be placed on expectation management and emotional support, and they asked for more detail regarding enema use. They also requested a list of healthcare providers who could support them in their LARS care, and more examples for foods which may activate their LARS.

Healthcare professionals from multiple institutions across North America were invited to review the booklet as well. In total, 10 healthcare professionals comprised of seven Colorectal Surgeons and three nurses in Gastrointestinal Oncology, and each was interviewed using a semi-structured interview guide (**Supplementary File 2**). Characteristics of the healthcare professionals are reported in **Table 4**. Similar to patient participants, each healthcare professional was given one copy of the informational booklet and allowed three weeks to review the booklet and generate their own thoughts. The focus of these interviews was largely on content and management strategies; to ensure that our booklet would be as comprehensive and inclusive as possible. Furthermore, healthcare professionals were asked about the layout and structure, clinical applicability, and other means of improving the booklet. Similar to the focus group, the interviews were recorded, and the same methods were used for data analysis. The principal findings from the interviews are displayed in **Table 5**. Healthcare professionals felt that the booklet was accurate and comprehensive, and that it would complement the role of a clinician/nurse in supporting patients with LARS. Several interviewees recommended additional medications and illustrations, but did not feel the layout or structure needed to be further revised. Small changes in language were recommended as well (e.g., “stoma” instead of “bag” – most healthcare professionals felt that patients understand the meaning of stoma).

Based on the results of this qualitative study, the informational booklet was modified into its final format (**Supplementary File 3**). The booklet was then professionally translated into French language, and underwent a similar evaluation process with French-speaking patient volunteers.

Patient and Public Involvement

Patients were involved in the development of the informational booklet to be used as part of the LPCP. Patients and the public were not involved in the design of the study; however, the outcomes proposed in this study are specifically designed to assess participants' experience with LARS and the LPCP. The authors would also like to thank Dr.'s Steven D. Wexner, Patricia Sylla, Mitchell Bernstein, as well as Holly Bonnette and Tracy Chornopyski, for their contributions.

Ethics and Dissemination

The Research Ethics Committee (REC) at the Integrated Health and Social Services Network (CIUSSS) for West-Central Montreal (health network responsible for the Jewish General Hospital) is the overseeing REC for all Quebec sites. They have granted ethical approval (MP-05-2019-1628) for all Quebec hospitals (Jewish General Hospital, McGill University Health Center, CHU de Quebec) and have granted full authorization to begin research at the Jewish General Hospital. Patient recruitment will not begin at the other Quebec sites until inter-institutional contracts are finalized and feasibility / authorization for research is granted by their respective REC. The English-language patient consent is presented as **Supplementary File 4**.

The results of this study will be presented at national and international meetings, and a manuscript will be submitted for publication in a high-impact peer-reviewed journal. We anticipate that the findings will inform the development of future rectal cancer survivorship programs with a focus on bowel dysfunction, in an effort to improve the long-term QoL of individuals with rectal cancer.

Data Sharing Statement

Individual patient data from this trial will not be shared.

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Table 1 – Schedule of Patient-Reported Outcome Measures

	Preoperatively	1 month	3 months	6 months	12 months
EORTC-QLQ-C30	X	X	X	X	X
MYMOP2		X		X	X
PAM-13	X	X		X	X
LARS Score, WFIS, BQoL		X	X	X	X
HADS	X	X		X	X
Knowledge	X	X		X	
Satisfaction				X	

EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
MYMOP2 = Measure Your Medical Outcome Profile
PAM-13 = Patient Activation Measure
LARS Score = Low Anterior Resection Syndrome Score
WFIS = Wexner Fecal Incontinence Score
BQoL = Bowel-Related Quality of Life
HADS = Hospital Anxiety and Depression Scale

Table 2 – Characteristics of patient participants in focus group (caregivers not included)

Characteristics	**n = 6**
Age, years, median (range)	61 (32-71)
Gender, n	-
Male	4
Female	2
Neoadjuvant radiotherapy, n	5
Diverting loop ileostomy, n	5
Extent of mesorectal excision, n	-
Partial mesorectal excision	0
Total mesorectal excision	6
Anastomotic height, n	-
Colo-Rectal Anastomosis	3
Colo-Anal Anastomosis	3
Anastomotic leak, n	1
Months since proctectomy, median (range)	15 (7-22)
LARS Score, median (range)	28 (12-39)
LARS Score severity, n	-
Major	3
Minor	2
None	1
Overall, how much does your bowel function affect your QoL?	-
Not at all / very little	2
Somewhat	2
A lot	2
EORTC global quality of life, median (range)	83 (50-100)

QoL = quality of life; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30

Table 3 – Principal findings from thematic analysis of focus group with patients and caregivers

LARS is as much a psychological disorder as it is a physical condition	Participants felt underprepared for their new bowel function, which greatly contributed to their anxiety
	Participants felt alone and isolated, as if they were the only patients experiencing these symptoms
	Participants were never explained that symptoms may improve; most felt extremely hopeless in the first few months postoperatively
The booklet was easy to read and follow	Participants found that the booklet was written at an appropriate level for patients
	Participants found the images extremely helpful in understanding how, and why, LARS occurs
	Participants felt that the booklet was complete, and was a perfect length
Information was lacking in certain keys areas	Participants wanted more emphasis to be placed on emotional wellbeing in the booklet
	Participants wanted more examples of foods that could trigger their LARS, as well as more detail on how to use and find an enema
	Participants agreed that it is vital to have a dedicated nurse to review the booklet and provide additional support
The booklet is an excellent resource that would have made a big difference in their first year	The booklet's greatest impact is in terms of expectation management and psychological reassurance
	Participants agreed that they would have consulted the booklet frequently in the first year after surgery

LARS: Low Anterior Resection Syndrome

Table 4 – Characteristics of interviewed healthcare professionals

Characteristics	**n = 10**
Gender, n	-
Male	5
Female	5
Practice, n	-
Colorectal Surgeon	7
Nurse	3
Experience, years, median (range)	-
Colorectal Surgeon	16 (9-21)
Nurse	19 (4-22)
Annual rectal cancer volume, patients, median (range)	-
Colorectal Surgeon	30 (20-50)
Nurse	50 (50-75)
Time spent per visit discussing LARS, minutes, median (range)	-
Colorectal Surgeon	8 (5-20)
Nurse	23 (30-45)

Table 5 – Principal findings from thematic analysis of semi-structured interviews with healthcare professionals

Barriers to effectively educating patients on LARS	All HCPs felt that "insufficient time in their schedules" was the most significant barrier to adequately discussing LARS with their patients
	Most HCPs felt that information provided to patients in clinic is often not retained
	Most HCPs did not have a consistent resource on LARS to offer to patients
The booklet is accurate, comprehensive, and easy to read	All HCPs felt that the major points on LARS were covered
	Most HCPs felt that less information on rectal cancer was needed in the booklet
	All HCPs felt that the illustrations were accurate and helpful in explaining LARS
	Several additional medications were recommended (e.g., codeine, amitriptyline)
The booklet is a clinically relevant resource for patients	All HCPs would give this booklet to their patients, and believe that it would a helpful supportive resource
	All HCPs would give it just prior to surgery (or ileostomy closure, if a stoma was performed)

LARS = Low Anterior Resection Syndrome; HCP = healthcare professional

Figure 1 – Study timeline for patients in the LARS Patient-Centered Program

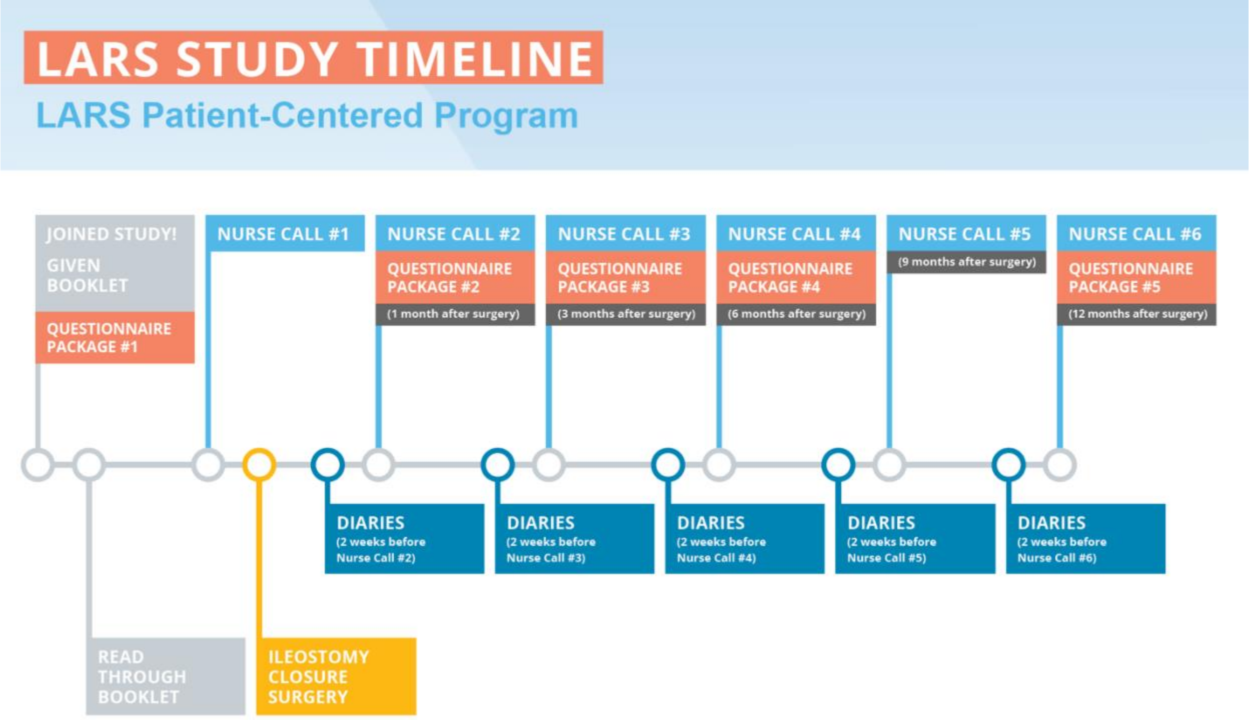
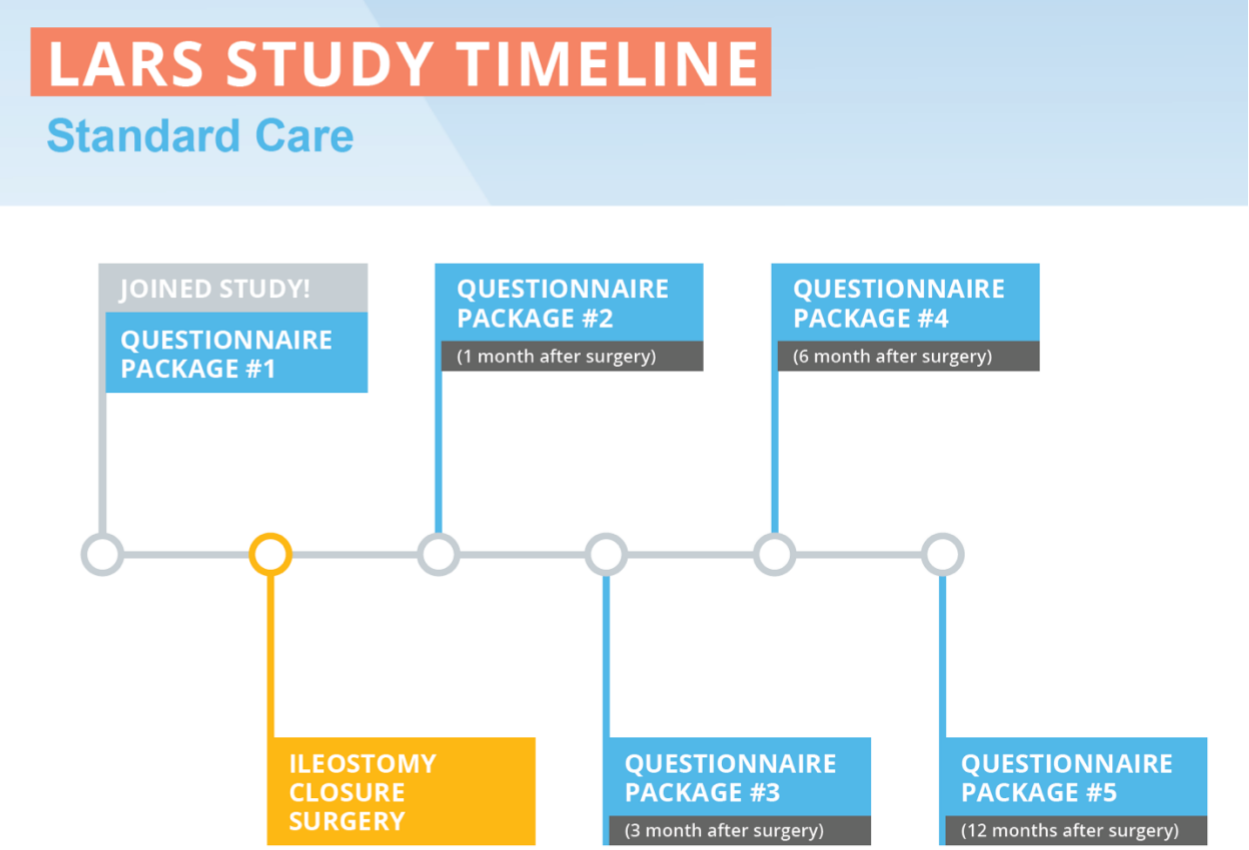


Figure 2 – Study timeline for patients in the Standard Care Group



Supplementary File 1 – Semi-structured interview guide for focus group with patients and caregivers

Introduction

Good afternoon everybody and welcome! Thank you for being here today and for helping us in the creation of our educational booklet on Low Anterior Resection Syndrome, also know as LARS.

Today I will be asking you about your impressions and feedback of the booklet.

My name is Richard Garfinkle – I am a senior resident in General Surgery and have been conducting research with the Colorectal Surgery group for many years.

You were all invited because you’ve all undergone surgery for rectal cancer and have been identified by your doctors as having experience with bowel dysfunction since your operation. Your doctors also thought you’d be great participants for this focus group, and we appreciate your input.

There are no wrong answers but rather differing points of view.

Please feel free to share your point of view even if it differs from what others have said. Keep in mind that we're just as interested in negative comments as positive comments, and at times the negative comments are the most helpful.

You've probably noticed the microphone. We're tape recording the session because we don't want to miss any of your comments. People often say very helpful things in these discussions and we can't write fast enough to get them all down. We will be on a first name basis today but we won't use any names in our reports. You may be assured of complete confidentiality.

To respect each other’s confidentiality, what has been said here will stay here. Is everyone comfortable with that?

In respect of everyone’s time, we will try to wrap this up in under an hour. We may go a little over, but not more than 15 minutes. Is everyone okay with that? If you have to leave at any point, not a problem, just let me know when.

Well, let's begin. We've placed name cards on the table in front of you to help us remember each other's names. Let's find out some more about each other by going around the table. Everyone can introduce themselves by name, and in one or two sentences, describe your story with rectal cancer and your treatment.

> *Given everyone a chance to speak.*
> *Then proceed with the following:*

Now that everyone has been introduced, we can go on with discussing the LARS booklet.

General overview

Overall what is your impression of the booklet?
Who had heard about LARS before reading this booklet, and how / from where?
Was LARS or bowel function after surgery discussed with your surgeon?
What did you like about the booklet?
What did you not like about the booklet?
Have you read or found similar booklets like this one in the past, and where did you find them?

Content

Did you like the information that was chosen for the booklet?
Was there any topic about LARS that was discussed in too much detail?
Was there any topic about LARS that was discussed in too little detail, or not discussed at all?
How was the overall length of the booklet?
In your experience dealing with LARS, have you learnt any tips and tricks that should be added to the booklet?
Are there important abdominal or bowel symptoms that you've had to deal with that are missing from this booklet?
What new information did you learn from this booklet?
For the caregivers in the room: how can the booklet be made better for caregivers to learn about LARS?

Clinical relevance

Would you have liked to receive a booklet like this before your rectal cancer operation?
How would this booklet have better prepared you for life after surgery?
Would you like an Internet (online) or mobile-application version of the booklet?
Do you see yourself reading over this booklet only before surgery, or would you use it again after surgery?

LARS diaries

Have you used bowel or food diaries before? And who suggested you use one?
How did using a diary help you?
What are your thoughts about the diaries that we've included in the booklet?
Would you use these diaries? And how often?
Would you prefer the diary as an online diary or as an app?
How would you improve the diaries?

Final comments

Do you have any final comments?

We’ve come to the end. Thank you everyone for your time and feedback! It is really appreciated and the past hour or so has been very productive. If anyone has any concerns or anything they want taken out of the recording, let me know, it’s not a problem. I’ll stick around after to talk if you have anything to say.

Supplementary File 2 – Semi-structured interview guide for healthcare professionals

Introduction

Thank you for agreeing to be part of this study exploring the educational needs of rectal cancer survivors with Low Anterior Resection Syndrome (or LARS). You’ve been given our educational booklet that we created for patients to use as part of an intervention in a randomized controlled trial, and have agreed to participate in a brief phone interview.

The phone interview will take about 20 minutes. Is now a good time?

Thank you for reading through our first draft of the educational booklet. To ensure that the booklet is relevant and that the content is both accurate and helpful, we appreciate your feedback. This will allow us to improve the booklet prior to giving it to patients.

Participant demographics

What is your full name, role, and institution of work?
How many years have you been in your role?
What volume of rectal cancer patients do you treat a year?
How much time do you currently spend per rectal cancer patient discussing LARS?
What are the barriers to spending more time with patients on this subject?

General overview

What was your overall impression of the booklet?
What are your thoughts regarding the layout and structure of the booklet?
Does the order of topics make sense?
What are your thoughts regarding the images and illustrations selected?
What was your favorite part / least favorite part of the booklet?

Content

Did you notice any inaccurate statements in the booklet?
Is there any important aspect of LARS that is missing from the booklet?
Are there any topics that are explored in too much / too little detail?
Do you have any additional tips and tricks regarding LARS treatment that are not included in the booklet?
Did you learn anything new?

Clinical relevance

Do you think this booklet would be useful for patients?
Would you recommend this booklet to patients and to colleagues?
How can the booklet be made more relevant for patients to use?
Do you think patients would like an online or mobile-application platform for the booklet?

If this booklet is found to be beneficial for patients, how would you incorporate this booklet into clinical practice in the future?

LARS diaries

Do you find the diaries useful for patients?
Have you ever instructed patients to use a bowel or food diary, and what has been their compliance?
What important information is missing from the diaries that might be helpful for patients to better reflect on their bowel symptoms?

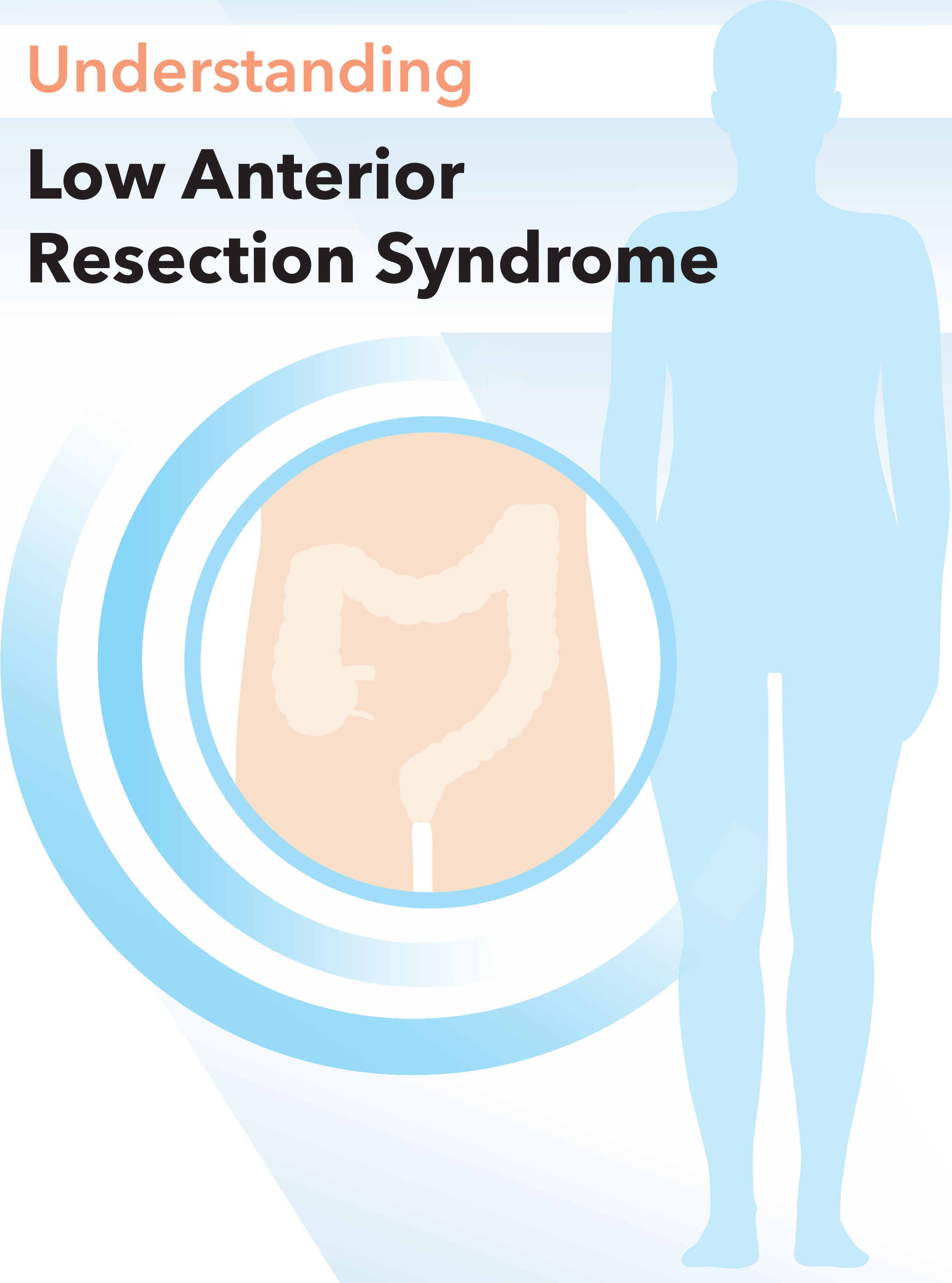
Final comments

Do you have any final comments?

We thank you very much for your participation in this interview. Your feedback is greatly appreciated and will help us refine this booklet for the betterment of patient education.

Supplementary File 3 – Original LARS informational booklet (beginning on the next page)

Understanding
Low Anterior Resection Syndrome



A special message for you and your family

This booklet will explain what Low Anterior Resection Syndrome (LARS) is. The more you understand, the more you can get involved with your own treatment. We want to help you have more control over your LARS. This should make daily life less stressful and more comfortable for you.

Share this booklet with family members and caregivers. It is important for them to understand what to expect and how to help you manage your symptoms.

Your LARS treatment team

Welcome to this educational booklet on Low Anterior Resection Syndrome (LARS).

We have designed this booklet for you because you have had surgery for rectal cancer. How you go to the bathroom now has probably changed a lot. The symptoms that you might be feeling after this surgery are called LARS.

We want to help you learn how to control your LARS symptoms. This booklet was written by Colorectal Surgeons, Nurses and Physiotherapists who specialize in rectal cancer. We also asked patients who have had rectal cancer surgery to review this guide. They have shared their experiences with us to help improve this booklet for you.

We will review rectal cancer surgery, what LARS is, why LARS happens, and most importantly, how to best manage your LARS. Check out the chapters below for a full overview of LARS, or skip ahead to the chapters that directly answer your questions.

We have included a list of some of the references we used so that you can understand where our up-to-date knowledge comes from. We also included a link to online health resources just for patients, so that you can read what other people are saying about how they manage their LARS.

It is important to remember that you may, or may not, have the symptoms listed in this booklet. But it is better to know how to manage them. This way, if they do happen, it is less stressful and anxiety-provoking.

This booklet is not a prescription! It does not replace a doctor, nurse, or physiotherapist! This should complement discussions you have with your colorectal specialist. Speak to us if you have questions or concerns.

We will be there each step of the way.

Table of content

INTRODUCTION

What is LARS?

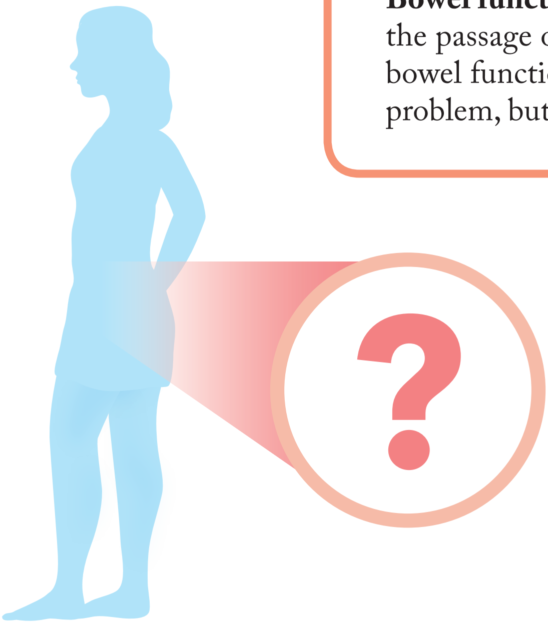
If you have had surgery for rectal cancer, how you go to the bathroom now has probably changed a lot. The symptoms that you might be feeling after the bowel surgery are called **LARS**.

LARS stands for **Low Anterior Resection Syndrome**.

It refers to changes in bowel function after Low Anterior Resection surgery.

What do we mean by bowel function?

Bowel function is how the body controls the passage of stool and gas. We often take bowel function for granted until there is a problem, but it is a complex process.



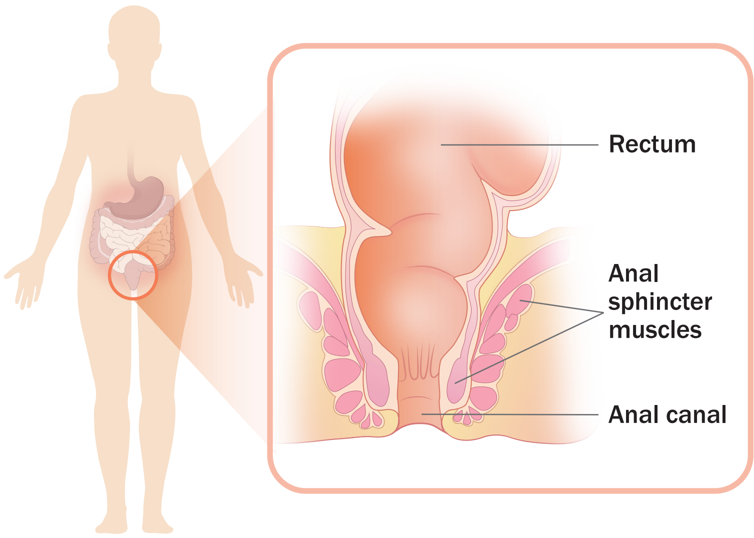
Let's begin by reviewing the changes in your body that occurred with surgery before we talk more about LARS.

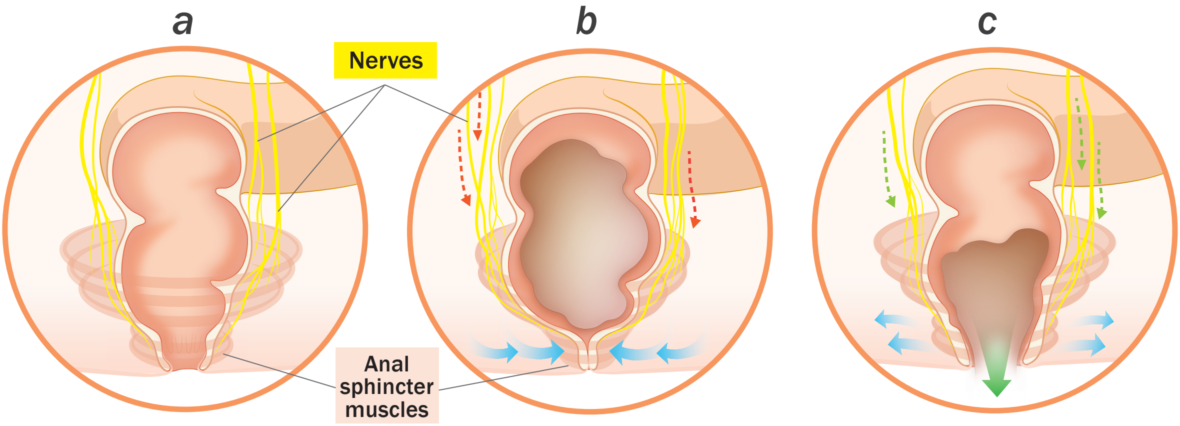
SURGERY FOR RECTAL CANCER

What is the rectum?

The rectum is the last part of the digestive tract that ends at the anus, the opening where stool exits the body. Its main role is to store stools.

The rectum is surrounded by the **anal sphincter muscles**. These muscles tighten up to help us hold our stool in (*b*) and relax when we empty our bowels (*c*). This allows us to have control over our **bowel movements**.





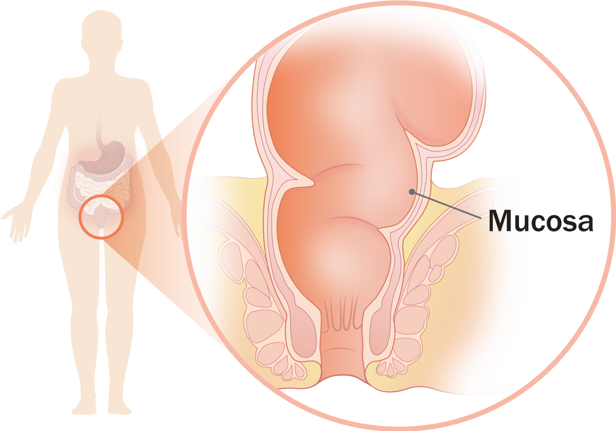
There are also special **nerves** that control the rectum's ability to stretch, and which control our anal sphincter muscles. These nerves play an important role in controlling how the rectum works.

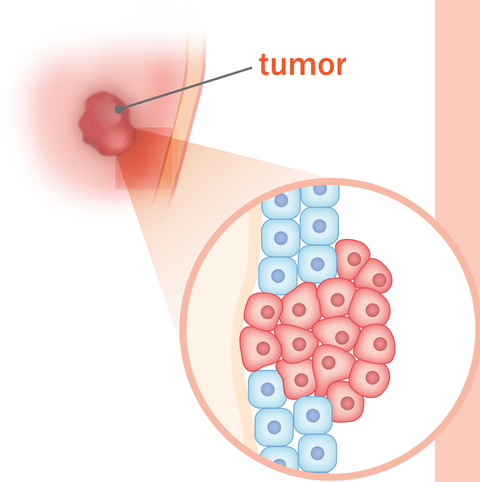
The rectum is also very stretchy, which allows it to store a lot of stool before we decide to empty.

What is rectal cancer?

Cells are the building blocks that make up the tissues and organs of your body.

When a cell gets old or damaged, your body either repairs the cell or gets rid of it, and a new cell grows in its place. This process of cell repair and growth is very regulated and controlled.





Sometimes, this process ***is not*** regulated and controlled. If this happens, the damaged cells in the rectum stick together to form a polyp. This is a benign (non-cancerous) growth in the rectum.

Over time, the cells in the polyp can become abnormal. These cells are now considered malignant (cancerous).

When the cells are cancerous, the growth is no longer called a polyp, and instead is called a **cancer**.

How is rectal cancer treated?

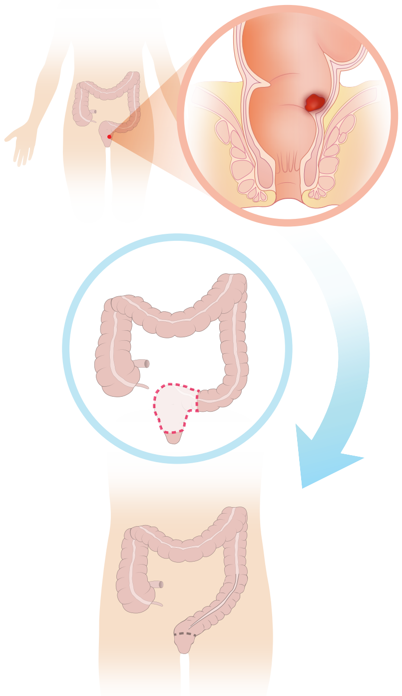
Rectal cancer is usually treated by surgery. The operation involves removing part of, or all of, the rectum. Before surgery, **radiotherapy** is sometimes used to try and shrink the tumor and make it less likely to come back after surgery.

There are two different types of surgery:

1. LAR surgery

If the cancer does not touch the anal sphincter muscles, these muscles stay, and the colon above can be connected to the lower rectum or anus. This way, you will be able to empty your bowels through your anus.

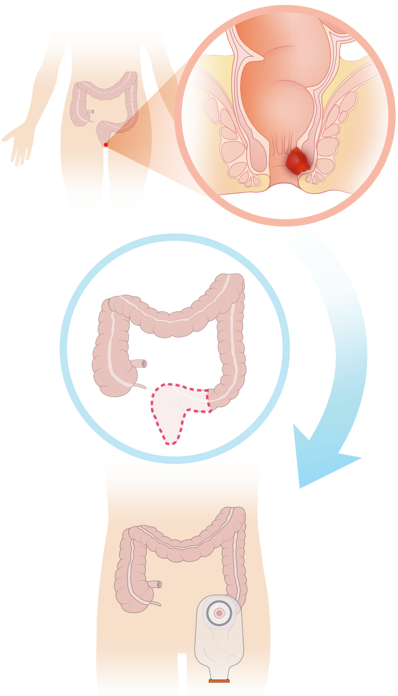
This is called a **Low Anterior Resection (LAR) surgery**. Some patients might get a temporary stoma ("bag"), usually known as an 'ileostomy'. But this is usually removed later.



2. APR surgery

If the cancer touches the anal sphincter muscles, then these muscles are removed with the rectum. Without sphincter muscles, we don't have control over when we empty stool. The solution is to create a permanent stoma, known as a 'colostomy'.

This is called an **Abdominoperineal Resection (APR) surgery**.



Summary

- The rectum is the last part of the digestive tract before the anus.
- Rectal cancer is treated with surgery, and sometimes radiotherapy.
- There are two types of surgery:
  1. Abdominoperineal Resection (APR): Patients will have a permanent stoma after.
  2. Low Anterior Resection (LAR): Patients will have a new connection made so that stool exits through the anus.
- The rest of this booklet will focus on patients who have Low Anterior Resection surgery. The next chapter will explain what LARS is and what sort of symptoms it can lead to.

WHAT IS LARS?

LARS stands for Low Anterior Resection Syndrome. Remember what a Low Anterior Resection surgery is from the previous chapter?

After you have Low Anterior Resection surgery, how you go to the bathroom will change. LARS refers to some of these changes.

Symptoms of LARS

Frequency

This means emptying your bowels often. Since everyone is different, when we say "frequent", we mean more than what is normal for you.

Urgency

This means that when you feel the need to go, you *really* need to go. There is little to no warning time to give you a chance to get to the bathroom.

Incontinence to liquid stools

This is accidental leaking of liquid stool.

Symptoms of LARS

Incontinence to flatus

This is accidental passing of gas.

Clustering

This means having to go to the bathroom many times because there is still more stool that has to come out.

For example, as you leave the bathroom thinking that you are done, you need to go back to the bathroom to empty your bowels again. It is often called "fragmentation" of bowel movements as well.

You may also have **OTHER** bowel-related symptoms because of your surgery (e.g. bloating, belly cramps, difficulty emptying your bowels, constipation, increased gas), and these symptoms may also trouble you.

It is important to understand that every patient experiences LARS differently. You may experience some symptoms associated with LARS, while another patient may experience more or fewer symptoms.

Also, some symptoms may bother you more than others. You may find that frequency is the most bothersome symptom that interferes with your day-to-day life, while the next patient may feel that clustering of bowel movements is the most bothersome. Everyone is different.

How can you figure out which symptoms are bothering you?

Use our **BOWEL TROUBLE diary** at the end of this booklet.

The goal of this diary is to understand what symptoms you are having, how severe they are, and what time of day they are happening, to give you and your doctor or nurse specialist the best idea of how to intervene.

Summary

- LARS refers to changes in bowel function after Low Anterior Resection surgery.
- There are 5 major symptoms associated with Low Anterior Resection surgery.
- Your may have a few or more of these symptoms.
- Use our **BOWEL TROUBLE diary** to explore which symptoms are affecting you most.
- The next chapter gives more background information on LARS to understand why it develops.

COMMON QUESTIONS ABOUT LARS

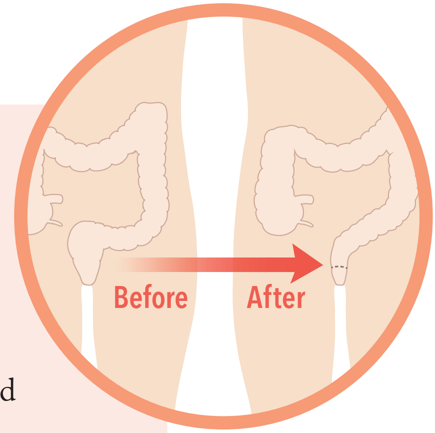
Why does LARS happen?

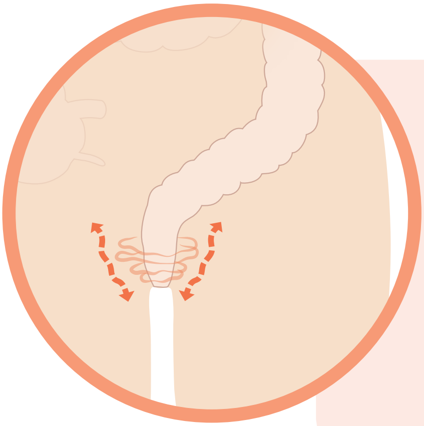
There is no single cause for LARS. For most patients, it is probably a combination of things. Here we list some of the common causes that we think about, but others may exist too.

Loss of storage

After surgery on the rectum, the rectum is removed. Unfortunately, the colon is not a good replacement for the rectum. The colon simply cannot store as much stool as the rectum. Plus, the colon's normal job is to absorb water and and move stool downward.

When the colon is used to replace the rectum, it can lead to feeling the need to empty your bowels often.

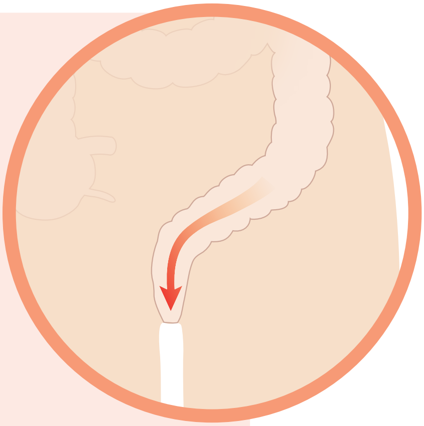




Weak sphincter muscles

If your sphincter muscles were weak to begin with (even without you knowing!), this weakness will start to show once the rectum is removed. The sphincters can also get weak with radiotherapy.

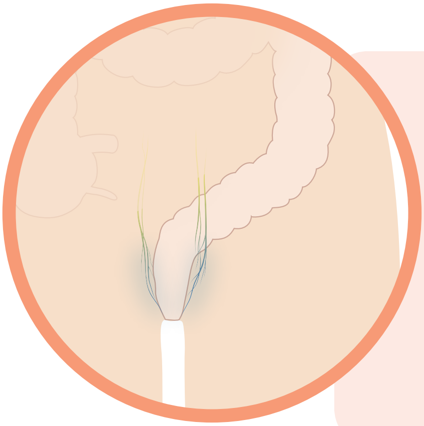
Faster colonic transit



The movement of stool from the beginning of the colon to the anus is called "colonic transit."

After rectal cancer surgery, because the stool is moving through the colon faster, the colon has less time to absorb fluid. This means that the stool comes out soft, or is liquid. It can also leak accidentally and make you want to *go* often.

Also, with things moving faster, more stool is being delivered than can be stored, which makes you have to empty your bowels more often.



Nerve damage

Both surgery and radiotherapy can irritate the nerves that control your sphincter muscles. When this happens, it can lead to accidental leakage, the urge to go often, and not emptying your bowels completely.

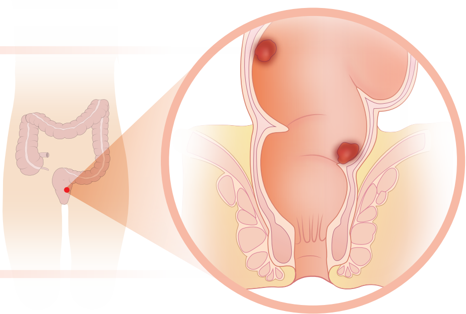
With what you just learned, can you think of some of the important factors that might *increase* or *decrease* your risk for LARS?

Who gets LARS?

Here are some of the main factors:

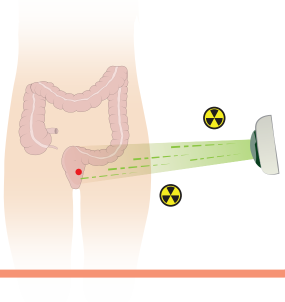
Low rectal tumors

The more rectum that is removed, the MORE likely you are to get LARS.



Radiotherapy

While radiotherapy helps to shrink the tumor, it can cause damage to the nerves and the bowel. This can affect the bowel's ability to stretch and store stool properly.

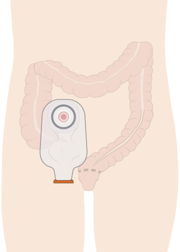


Age

We don't completely understand why, but studies show that **younger** patients tend to have more problems with LARS.

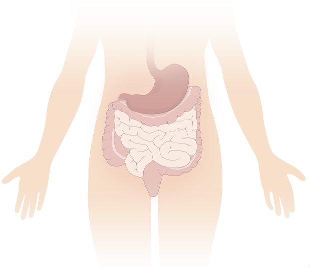
Temporary Ileostomy

When the temporary stoma is there, the colon is not being used. During this time the colon gets weaker. It does not respond in the same way to having stool pass through.



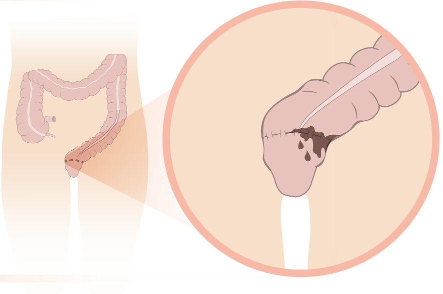
Bowel function before getting rectal cancer

Your bowel function before surgery is important. If you already had some bowel issues before surgery, you are more likely to have symptoms after surgery.



Anastomotic leak

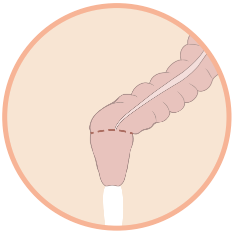
After the rectum is removed, the colon is reconnected to the lower rectum or anus. Sometimes, you can develop a “leak” of stool at this connection, which can worsen LARS.



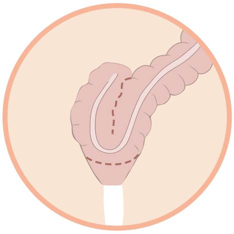
The size of the storehouse

There are different ways that the colon can be reconnected to the lower rectum or anus. Depending on the type of reconnection, you may have a bit more or less storage room.

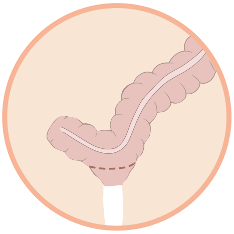
Some of these connections tend to function better than others at the start (e.g. “J-pouch” or “side-to-end” or “coloplasty” connections). However, most research shows that no matter what type of reconnection you have, they will likely all work the same after 2 years.



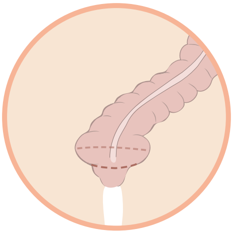
straight



J-pouch



side-to-end

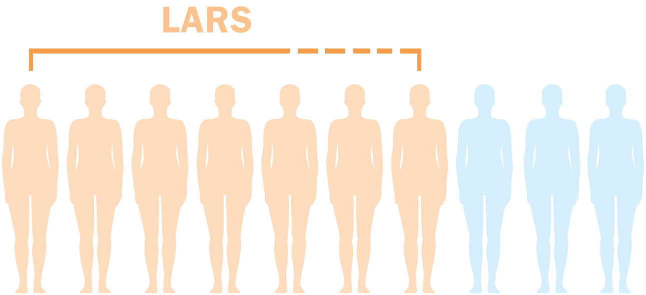


coloplasty

How common is LARS?

LARS seems to affect 5 to 7 out of every 10 patients after Low Anterior Resection surgery, with more than half of patients saying that it affects their quality of life.

Even people who DON'T have rectal cancer surgery can have these types of symptoms (e.g. accidental leakage, frequent bowel movements). So you are definitely not alone if you experience LARS.



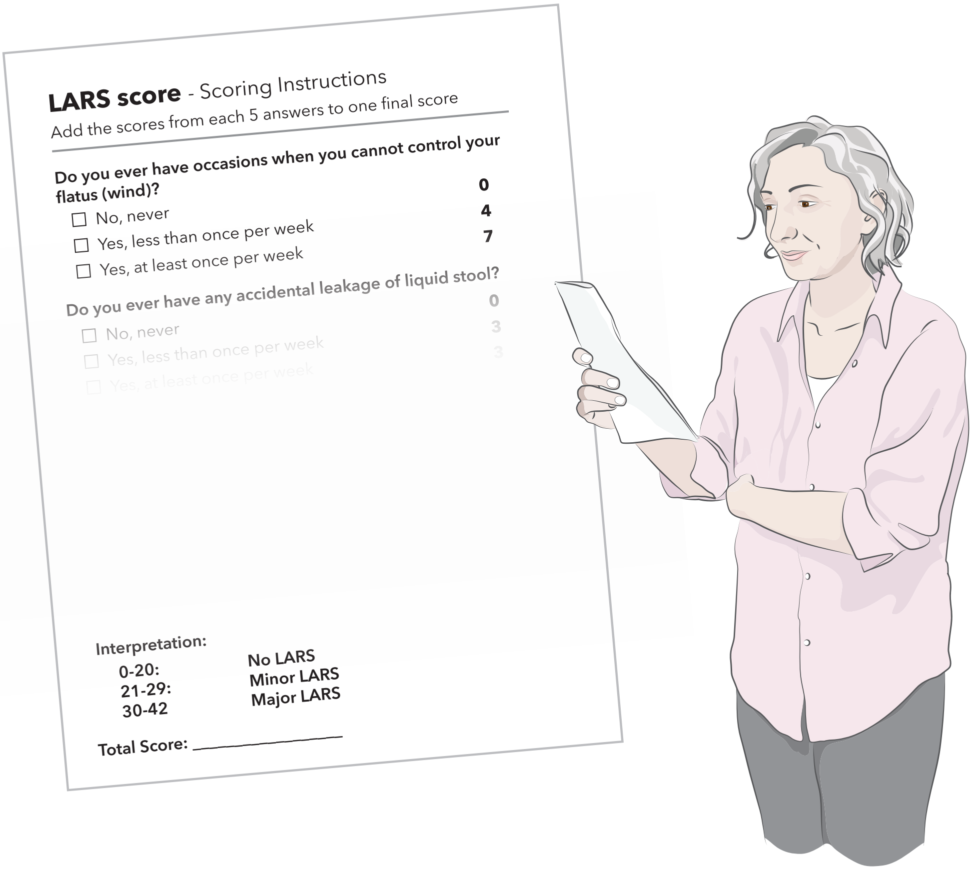
How is LARS diagnosed?

Unlike other medical problems, LARS is not diagnosed with blood tests, x-rays, or biopsies. The diagnosis of LARS is based on your symptoms.

We normally say that you have LARS if your bowel symptoms have lasted more than 1 month since your Low Anterior Resection surgery (or the removal of your temporary stoma).

Questionnaires can give us more information about your symptoms that can help to diagnose you and to follow your symptoms over time. There are a couple of questionnaires that can be used; one is called the "**LARS Score**."

Your doctor might also order tests to investigate other conditions that might be similar to LARS.



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**
☐ 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**
☐ Yes, at least once per week	**3**

Interpretation:

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

Total Score: ______________

How long will my LARS symptoms last?

For most patients, LARS symptoms are usually worse immediately after surgery, and improve slowly during the first 2 years after surgery. It is hard to know for sure what your experience will be, if your symptoms will improve and how long they might last.

Even if LARS might be long term, generally, you can expect to reach a new baseline after about 2 years.

Why do things settle down after 2 years? It is tough to tell. Some research shows that these two things can improve over time:

- The ability of the colon and anus to 'speak' with the rest of the digestive tract.
- The ability of the colon and anus to slow things down coming from above.

It could also be that your bowels (the colon from above that is reconnected to the lower rectum or anus) adapts over time to be able to accommodate more stool and act as a better storehouse.

In addition, patients learn to live with their LARS and find strategies to deal with their "new normal".

This booklet will hopefully provide you with some suggestions of how to deal with your LARS symptoms, reduce the symptoms, and manage the problems associated with LARS.

Summary

- There are several possible explanations for why LARS occurs, but it is hard to show a single cause.
- We are getting better at predicting who will get LARS. Patients with tumors lower down in the rectum and patients who received radiotherapy are at highest risk.
- LARS is diagnosed by listening to the patient's symptoms - so speak up!
- LARS usually improves over the first 2 years after surgery, but some people may continue to have symptoms long term.
- The next few chapters will focus on how to best treat and manage LARS.

OVERVIEW OF TREATMENT OPTIONS

A word on treatment of LARS

LARS is a tricky condition to treat. Every patient is different.

For this reason, the treatment of LARS sometimes requires a bit of trial and error, to find the best possible solution for you. If at first the treatment does not provide you relief in your symptoms, do not despair! Your doctor and nurse can continue working with you to find the best solution.

While LARS is not always "curable" and may be a long-term condition, our hope is to offer suggestions that can make your symptoms better.

What can you do to help manage your LARS?

Here are some strategies to control your LARS. In the next few chapters, we will go over each strategy in detail.

Remember, every patient is different! Use the methods that work best for you.

1. Slow down colonic transit

As we explained earlier, part of the reason LARS develops is because stool moves through the colon too quickly.

Some ways you can slow down colonic transit are:

- **a.** Changes in what you eat and drink (dietary changes)
- **b.** Medication
- **c.** Stool bulking agents

2. Improve your ability to "hold on"

You can train your body to deal with the urge of always having to go to the bathroom:

- **a.** Pelvic floor exercises
- **b.** Pelvic floor biofeedback

3. Improve your ability to fully empty your bowels

Some things you can do to make sure you fully empty your bowels are:

a. Proper toileting habits
b. Enemas and transanal irrigation

4. Managing the current situation

To avoid LARS from impacting your day-to-day life, it is important to know about:

a. Perianal skin care
b. Self-management strategies

5. Surgical procedures for LARS

IF you've tried the strategies mentioned, and you STILL have no relief from your LARS, there are other treatment options.
Speak to your colorectal specialist about:

a. Neuromodulation
b. Permanent stoma

Summary

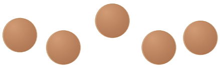
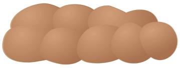
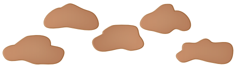
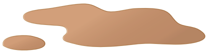
- There are different strategies to manage LARS.
- Try as many strategies as you need to give yourself the best possible chance at gaining control of your LARS.
- Need more information about the treatments?
- The next few chapters will explain more about each one!

SLOW DOWN COLONIC TRANSIT

Stool consistency

When colonic transit is fast, stool comes out too soft. Slowing down colonic transit lets the colon absorb more water, and helps to get stools more firm.

The **Bristol Stool Chart** shows what your stool consistency can be like.

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces, entirely liquid

Type 4 (smooth and soft, like a sausage or snake) is the ideal consistency.

Type 6 (fluffy, mushy stool, like oatmeal) or **Type 7** (completely liquid) happen a lot in patients with LARS. If that's the case for you, then colonic transit is certainly something that you need to work on.

Dietary changes

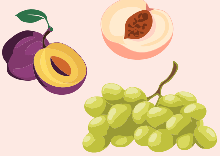
How can diet improve my LARS?

Many of the symptoms related to LARS can be made worse with certain foods or drinks.

For example, some foods might make you feel full of gas. Other foods may travel through your digestive system quickly. Others may activate your bowels to move.

You can help manage your LARS by figuring out which foods trigger your symptoms, and trying to remove them from your diet.

What are some examples of foods that might trigger my LARS?



Fruits

Grapes, peaches, plums, berries, dried fruits may activate the bowel and make your stool softer.

Vegetables

Many vegetables, such as broccoli, cauliflower, cabbage, onions and beans may activate the bowel, and can cause gas and “explosive windy stools”.

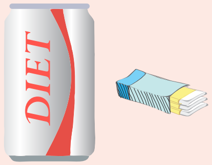
First, try eating vegetables that have no seeds, like cooked carrots, potato, puréed or canned vegetables. Later, you can try lettuce or tomatoes in small amounts. Remember, the key to finding out which foods you can manage is trying them out one at a time and making sure you always chew your foods well.

“Insoluble” dietary fibre

Nuts, seed, certain rice or bran cereals, wholegrain breads, corn, and vegetables with peel and stringy parts can all activate the bowel and make stools softer (more on fibre in the Stool Bulking Agents chapter).

Spicy foods

Many spicy foods, such as curry and chilli, can make your bowels move more and make your stools softer.



Sorbitol

A sweetener that is often found in "sugar-free" foods (example: diet drinks, sugar-free gum, some candy or snack bars) can lead to looser stools, bloating and gas.

Are there any drinks that might trigger my LARS?

Caffeine

Any drink that has caffeine, such as coffee or certain teas, can activate the bowel and make your stools softer.

Alcohol

Beer and wine are examples of alcoholic drinks that can activate the bowel.

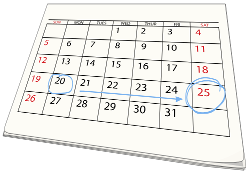
Moderate fluid intake

Drink about 8 cups of water per day. Drinking more water may make your bowel movements too loose and drinking less water may result in small pellet-like stools (Type 1 on the Bristol Stool Chart).

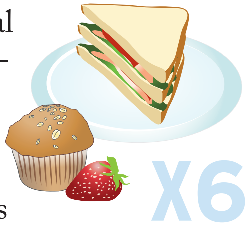
Figuring out which foods are bothersome

Use our **DIET diary** to help you figure out which foods affect your LARS (see next section for more).

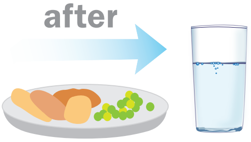
Eliminate foods one at a time. When you make a change to your diet, wait at least one week to really see the effect.



Do not reduce your total amount of food intake – that will not help! Some people find it better to have 6 small meals instead of 3 meals a day. You can try this.



We also recommend that you drink at the end of your meals or in between meals instead of during them, so as not to over-activate your bowels.



It can be tough to know for sure which foods are causing your symptoms. The food that you eat can take anywhere from a few hours to 2-3 days to come out the other end! Use the DIET diary to help you identify types of foods that affect your symptoms.

Summary

- The foods you eat can trigger symptoms of LARS.
- This list provides some common examples but is not a complete list.
- It is important for YOU to discover what bothers YOUR LARS in order to improve YOUR symptoms.
- Use our **DIET diary** to keep track of your progress!

Medication

Loperamide

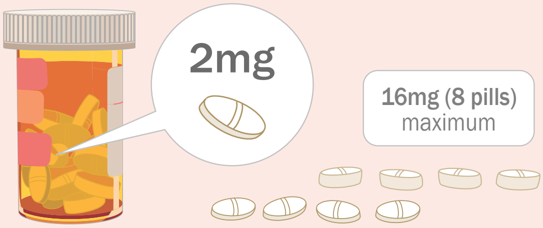
Loperamide (also known as **Imodium®**) is the first-line medication used to slow down colonic transit. You don't need a prescription to take it.

Loperamide works by slowing down how food moves through the intestine. This allows more fluid to be absorbed by the intestine along the way, so that your stool is thicker and the amount of stool is less. This can help some of the LARS symptoms you might be having, especially frequency and urgency.

The best time to take loperamide is **30 minutes before a meal**. This will help the intestine prepare for incoming food. After your meal, if you don't empty your bowels, do not take loperamide again until you have a bowel movement.

You may also find that loperamide helps you more with certain foods, and you may want to always take it before those foods.

If you wake up often at night to empty your bowels, you may also take loperamide **before you go to bed**.



Loperamide usually come in **2 mg pills**. Start by taking one pill at a time to see how it works and to make sure you don't have side-effects. If it doesn't improve your symptoms, you can take it several times during the day. **Do not take more than 8 pills in one day (total of 16mg)**.

Taking too much loperamide can lead to difficulty having a bowel movement (because your stool is hard), cramps in your stomach or feeling sick to your stomach (nausea).

Loperamide can help some people. If you are taking it to treat your LARS, it is perfectly fine to take it long-term.

Not sure how much loperamide to take? Is it ***really helping***? Are you taking it at the right times? Use our **LOPERAMIDE diary** at the back of the booklet to keep track of how you are using loperamide, and to make sure you are using it according to YOUR symptoms.

Other prescription medications

Diphenoxylate (also known as **Lomotil®**) also works by slowing down how food moves through your intestines.

Some side effects can include feeling dizzy, flushed, feeling like you have to vomit or having stomach cramps.

Cholestyramine (also known as **Questran®** or **Cholamine**) is a prescription medication that stops the stool from getting too liquid by decreasing a type of salt product from building up in your stools. This can help with frequency and urgency.

Amytriptyline (also know as **Elavil®**) is another prescription medication that is sometimes used to help with frequency and urgency. It works by slowing down contractions in the digestive tract. Side effects include constipation, dry mouth, and others if used inappropriately.

Codeine, which is usually used as a pain-killer, can be used as well, but may cause nausea and constipation. It is also a "narcotic" pain-killer. Patients can become addicted if they do not use it carefully and as prescribed by their doctor.

Summary

- Loperamide is a medication that is often used to slow down intestinal transit and harden stool.
- It might improve your LARS symptoms, especially frequency and urgency.
- Sometimes it takes a while to figure out the best dose for you. Use our **LOPERAMIDE diary** to make sure you are using it correctly.
- There are other medications you might be able to use (such as diphenoxylate, cholestyramine, amitriptyline, and others).
- Always consult with your doctor before starting any medication.

Stool bulking agents

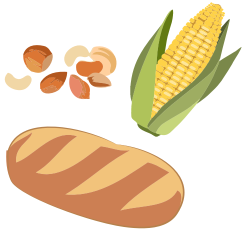
Is fiber good or bad for LARS?

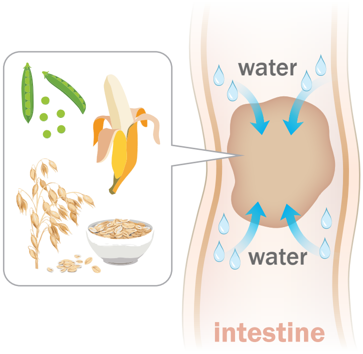
Fiber is a tricky subject to master! There are two types of dietary fiber: “insoluble” and “soluble”.

“Insoluble” fiber

speed up bowel activity and is often used to treat constipation (difficulty having a bowel movement because of hard stool). Foods with “insoluble” fiber include those listed in the Dietary Changes chapter (wholegrain breads, bran, corn, some nuts and seeds, etc.).

These insoluble fibers are usually foods that you want **to avoid** because they might worsen your LARS.





“Soluble” fibre

act more like a sponge, soaking up extra water and becoming a gel-like substance.

This in turn makes your stools bulkier (hence, the name “stool bulking” agents!), which can improve some LARS symptoms.

Foods high in “soluble” fibre include oats, barley, rye, legumes (lentils, peas), and peeled fruits.

“Soluble” fibre supplements

You can add soluble fibre to your diet by taking fibre supplements. Psyllium has “soluble” fibre. It usually comes as a powder that you can mix with water or food.

Some brands on the market are **Metamucil®**, **Benefiber®**, **Konsyl®**, etc.

These products can really help your LARS symptoms. They are usually available in a powder form, although you can also find them as pills or wafers (powders are more effective).

You might hear that you should take psyllium with lots of water. While this is not wrong, it may not be best for treating LARS symptoms. Why is that?

Psyllium and other "soluble" fibres work by attracting water like a sponge and becoming a gel-like substance. You want it to "sponge-up" the extra water already in your stools and not to add more water for it to absorb.

So, do not take psyllium with too much water. Instead, sprinkle it on your food (for example: oatmeal, peanut butter, banana, yogurt). Make this part of your morning breakfast routine.

You should start to see a change in your stool consistency in a couple of days. If not, you can increase the dose. For example, if you started with one tablespoon, try using two.

Just make sure not to take more than 10g per day (look at the labels to see how many grams are in one tablespoon or scoop). Taking too much psyllium can give you stomach cramps or constipation. Psyllium can also have the opposite effect in some people, and can worsen diarrhea. Give yourself at least 2 weeks to see if the psyllium is helping you.

Summary

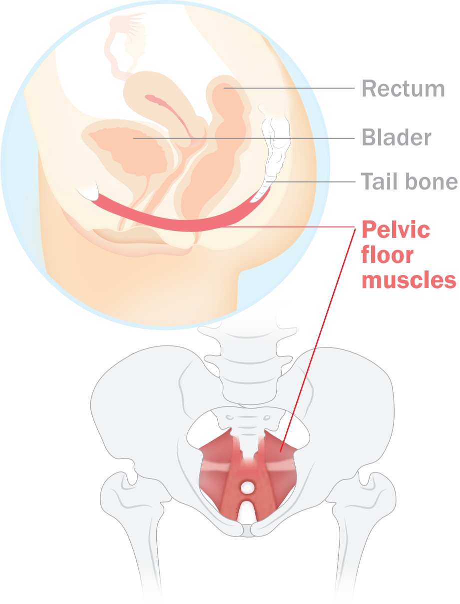
- "Soluble" fibre acts like a sponge to soak up excess water in the intestine, which makes your stool thicker.
- Fibre supplements can be added to your diet, but must be taken properly in order to work well.

IMPROVE YOUR ABILITY TO "HOLD-ON"

Pelvic floor exercises

What is the "pelvic floor"?

The **pelvic floor** is made up of muscles that stretch like a hammock from your tailbone in the back to the pubic bone in the front. In a man, the pelvic floor supports the rectum and bladder. In a female, the rectum, bladder, and uterus lie on the pelvic floor.



What do the pelvic floor muscles do?

Because the pelvic floor muscles support the rectum, they can affect how your bowels empty.

Just like any other muscle in the body, the pelvic floor needs to be worked out (trained) if you want it to be strong and well controlled.

First you need to figure out where your pelvic floor muscles are. Sit or lie down. Try to relax your thighs, buttocks, and belly muscles.

Now try to squeeze and lift the anus up into your pelvis as if you were holding in gas or stool. Then relax, allowing the anus to drop down to its normal position.

Do this a couple of times to make sure you've found the right muscles. Try NOT to squeeze your buttock muscles or belly muscles.

Each time you "squeeze and lift", try to hold that feeling for up to 8 seconds. If you can't get to 8 seconds because it is too difficult, hold it for as long as you can. With time, you will get better at this.

After 8 seconds, release the "squeeze and lift". Take a break for 10 seconds. Then repeat the same thing.

Do this 10 times, and repeat this exercise 3 times a day.

If you are not sure if you are working the right muscles, sit comfortably in bed or on the floor with your back supported and your knees bent. Use a mirror to see the anus and watch for it to tighten and move inward.

Alternately, you can place your index finger over the anus. When you squeeze you should feel the anus move inward and away from your finger.

If you see or feel the anus bulge outward, you may be pushing instead of lifting which may worsen symptoms.

If you are having trouble getting the hang of this exercise, you can ask your doctor or a pelvic health physiotherapist.

We generally recommend continuing exercising, especially if it has given you some relief.

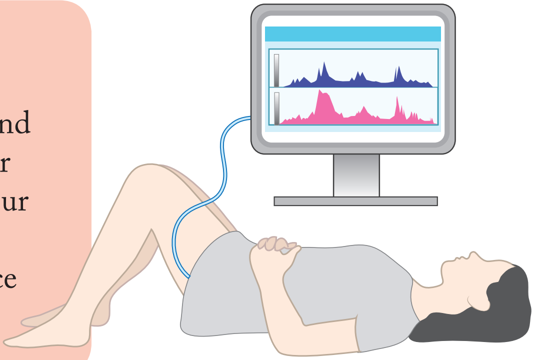
Remember, like any muscle, when you stop working out, the results may disappear.

Biofeedback

Biofeedback is another tool that can help you find and control your pelvic floor and sphincter muscles to improve how well you can hold back stool. It can only be performed with specialized pelvic health physiotherapists. There are two common types.

Pelvic floor biofeedback

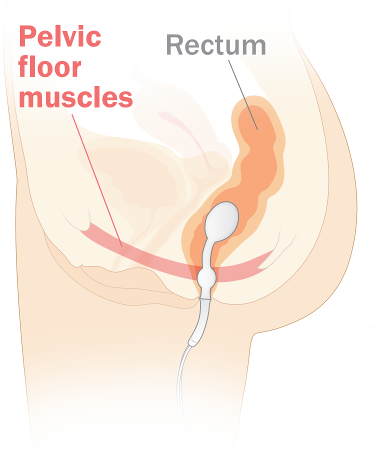
Pelvic floor biofeedback uses electrodes and sensors to measure the way your sphincter muscles contract and allows you to see your contraction on a screen. The goal is to improve isolation, strength, and endurance of the sphincter muscles.



Rectal balloon training

Rectal balloon training involves a health care professional gently inserting a small balloon into the anus which can be inflated with water or air. The balloon can be inflated until the point where you start to feel the urge to have a bowel movement.

With each session, your health care professional will gradually increase the amount it is inflated to slowly improve the amount of balloon (and hopefully, stool) that your anus can accommodate before the urge "to go" kicks in.



The goal is to improve the storage of stool and to give you more time to reach the toilet before you leak.

Summary

- The pelvic floor plays a big role in normal bowel function.
- In patients with LARS, pelvic floor exercises can be performed at home to improve symptoms.
- Pelvic floor biofeedback is a way to help train the pelvic floor. These need to be performed with a colorectal specialist, pelvic health physiotherapist or nurse.

IMPROVE YOUR ABILITY TO FULLY EMPTY YOUR BOWELS

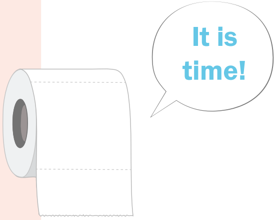
Proper toileting habits

People often take for granted the simple action of sitting on the toilet and emptying their bowels. However, for people with LARS, this can sometimes be difficult.

Here are several tips for going to the bathroom that will help you fully empty your bowels.

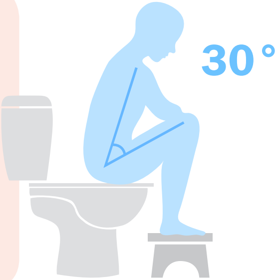
Only go to the bathroom when you really have to go!

Remember the chapter on pelvic floor exercises and training? Well, if you allow stool to build up in the anus until you absolutely need to go, you will train yourself to be able to hold-on more, which will hopefully lead to less frequent episodes of urgency.



When on the toilet, it is important to position yourself correctly to fully empty your bowels.

This includes leaning forward, resting your elbows on your thighs, and lifting up your knees above the level of your hips (putting your feet on a foot-stool might help). This should help the stool exit.



Do not sit on the toilet for a long period of time. Do not strain hard.

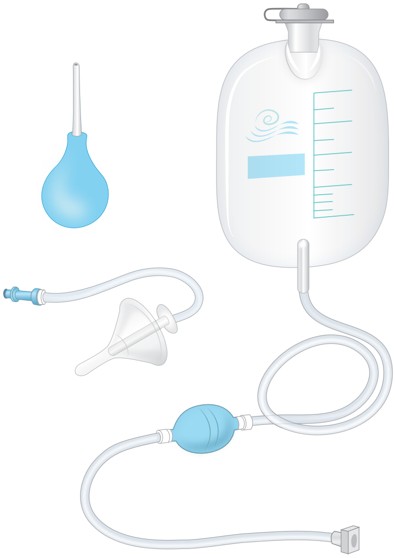
Straining on the toilet can actually weaken the pelvic floor muscles and cause swelling around the anus that bleeds easily (hemorrhoids).

Enemas and rectal irrigation

If you are still having some difficulties even after trying these methods, **enemas** and **rectal rinses** may provide extra relief.

Both of these work by flushing water up your anus to help empty your bowels.

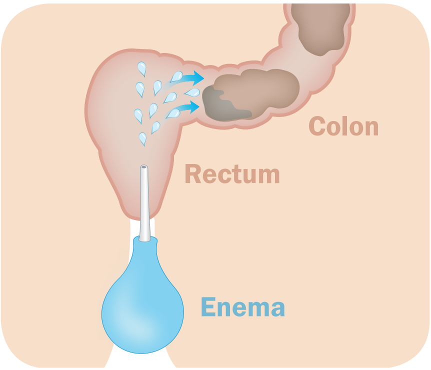
It can help with many of the symptoms of LARS, especially clustering and incontinence.



A rectal irrigation system is simple to use. You need a bag filled with lukewarm tap water, a tubing system, a pump, and small balloon catheter that is inserted into the anus.

While sitting on the toilet, you can start the pump, and the system will spray water up your anus, which flushes out the stools and activates the bowels to empty fully.

In the beginning, you can do this once or twice a day, but after a while you might not have to do it so often.



Enemas are similar to rectal irrigation systems and are simpler to use. They deliver either water or a water-like medication up the anus.

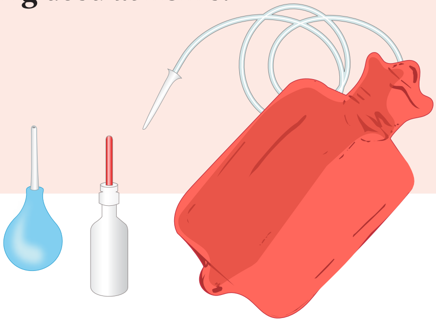
Enemas can usually be found at any local pharmacy. Rectal irrigation systems may be more difficult to find, **and you should** ask you colorectal specialist, nurse, or pharmacist for help.

While they are rare, some people can have complications with either enemas or rectal irrigation systems.

Some of these rare complications include abnormal heart rhythms due to the bowel filling up rapidly with water, injuries to the bowel, and possibly changes in the level of electrolytes (chemicals in your blood).

Before beginning enemas or rectal irrigations, it is important to speak with your colorectal specialist or nurse.

Both methods should be explained in-person by a nurse before being used at home.

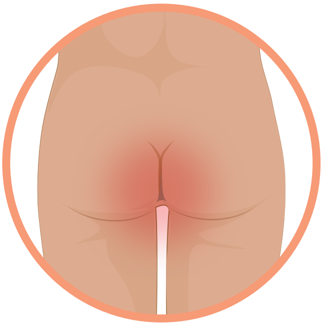


Summary

- Fully emptying your bowels is important to improve LARS symptoms.
- Proper toileting habits include only going when you really have the urge to go, getting in a good position on the toilet, and trying not to strain.
- Enemas and rectal irrigations work by flushing water up your anus to empty out the bowels.
- Discuss this with a colorectal specialist to decide if it is safe for you.

MANAGING THE CURRENT SITUATION

Perianal skin care



Why perianal skin care?

Frequent or loose bowel movements can cause the skin around your anus, genital areas and bum to become irritated. Your skin may be red, sore and itchy.

What factors cause skin irritation?

Extra moisture

from leakage of stool or if you are wearing pads that are wet.

Mechanical irritation

from constantly wiping with rough toilet paper.

Chemical irritation

caused by leakage of stool or using the wrong type of products to clean your bum.

Infection

we are all at higher risk for skin infections (fungus and bacteria) in conditions of extra moisture, chemical irritation, or mechanical irritation.

Goal 1 – Clean the skin

Use warm water to wash the area gently once or twice a day, or after each bowel movement.

You can also wash the area gently by using a hand shower, a bidet or sitzbath basin.

If you feel sore in the bum area from passing stools often, sitting in water (room temperature) can help.

If you use a product to clean the skin, it should be "pH-balanced" (not acidic or basic), and should not include alcohol, soap, or fragrances. These products can cause more harm than good.

To dry the area, pat it with a soft cloth rather than wiping. Do not use dry toilet paper or rough cloths. Try wetting the toilet paper before wiping, or using washable reusable J-cloth type of tissue or soft cotton material.

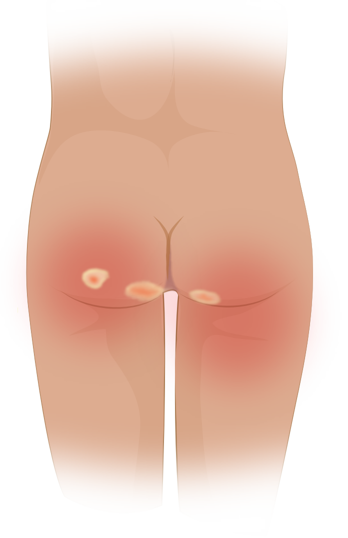
Do not use pre-moistened toilet wipes as they often contain chemicals that can irritate the skin.

If you still choose to use wipes, use non-alcoholic, fragrance-free baby ones. Make sure to check if they can be flushed down the toilet.

Goal 2 – Prevent skin breakdown

If the skin is irritated, it is at risk of "breaking down".

Skin breakdown means that the first layer of skin (or even deep layers) is destroyed, and a cut or sore develops.



The best treatment to prevent skin breakdown is to reduce the contact between the skin around your bum and stool, by treating things like stool frequency and incontinence.

If you are already following some of the recommendations from the previous chapters, here are some other ways to prevent skin breakdown.

Use a skin cream like a diaper-rash type.

Zincofax® without fragrance, ihle's paste, Sudacream®, Calmoseptine®, Coloplast Citrix Acid barrier ointments are some examples.

Wear cotton underwear

instead of synthetics (nylon, polyester) so that you don't perspire in that area.

If it is hard to control when you pee or have a bowel movement, you can wear disposable pads or disposable underwear.

Just make sure to throw out the pad or underwear when it gets wet.

⚠ If you notice foul smelling odors or discharge from the skin around your bum, you might have an infection, and might need antibiotics. Consult a doctor if you are concerned about this.

Summary

- LARS can irritate the skin around your anus and bum, which can cause discomfort and skin breakdown.
- The goals of skin care are: cleaning the skin, and preventing skin breakdown.
- Creams, protective barriers, and disposable pads are just a few ways that you can keep your perianal skin healthy.

Self-management strategies

What are self-management strategies

While you are starting to use some of the treatment strategies covered in this booklet, it will take time for your LARS to improve. In some cases, even after months of treatment, your LARS will only improve slightly.

> Self-management strategies are ways to prepare for every situation and ways to regain control when dealing with LARS.

Some self-management strategies were already covered in previous chapters – for example, properly taking loperamide, avoiding certain foods, keeping a food diary, and good perianal skin care with the use of appropriate products.

Here are some other important tips that can help maintain your quality of life.

Social self-management strategies

Some patients with LARS stay at home because they worry that their symptoms can flare up at any time. **So much as possible, don't let LARS stop you from your daily activities**.

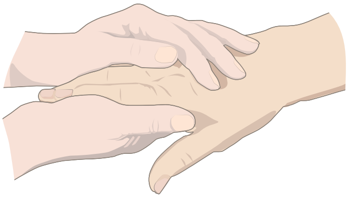
One helpful tip is to always know the location of the closest bathroom, whether inside a building or walking around outside. Some cities even have mobile-phone or Internet Apps for this.

Another is to try and arrange your activities according to your bowel habits.

For instance, if you know that your LARS is worse in the morning or after certain meals, plan your activities in the afternoon.

Also, get used to carrying a "**survival pack**" with you when you leave the house. Your pack might include non-alcoholic baby wipes, extra underwear, skin creams, and loperamide medication.

Emotional self-management strategies



Some people find that there is a link between their emotional state and their bowels.

During times of high stress, some people go to the bathroom more often and have looser stools.

While you might not be able to completely remove stress for your life, try to engage in activities that keep you relaxed.

Reading, yoga, taking a bath, and listening to music are some examples that you might find helpful.

It is also important to express your emotions related to your frustration about LARS.

Speak to your nurse, family or friends about what you are going through.

Some people find it more helpful to speak with other patients who are experiencing similar problems.

They may relate to you better, and might offer some personal solutions that they've discovered.

Online blogs and chat rooms can be easily found on the Internet, and are encouraged. You can also ask your surgeon if he/she knows a patient that you could speak with!

Remember that everyone is unique; you will learn what works best for you to cope with LARS.

Summary

- Self-management strategies give you some control over your LARS.
- It is important to plan for social situations so that you are not limited in what you can do or where you can go.
- It is also important to limit stress and express your feelings of frustration when needed.

SURGICAL OPTIONS TO TREAT LARS

When to consider these?

If you have tried all other treatment strategies for your LARS with no improvement, and your symptoms are still having a big impact on your quality of life, there are other options to consider.

These all involve **surgery**. There are risks associated with all surgical procedures, so make sure to be well informed and speak to your colorectal specialist about the risks and benefits for you.

These treatment options require a serious discussion with your colorectal specialist. This chapter will only cover the basics of these procedures.

Neuromodulation

For severe LARS, if more conservative treatment strategies have not helped, you may be considered for neuromodulation. What's neuromodulation?

Neuromodulation is a form of treatment that affects the nerves that control the bowel and muscles around the anus.

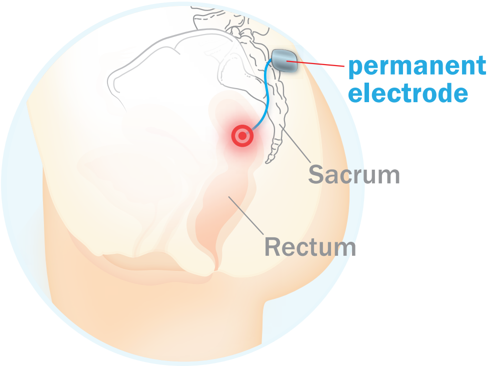
Remember at the beginning when we spoke about the nerves that control the bowel and the sphincter muscles? These nerves can be targeted as a treatment.

There are two main sets of nerves that can be targeted: 'sacral' and 'posterior tibial.'

"**Sacral neuromodulation**", or SNM, is the most widely studied form of neuromodulation used for LARS.

SNM involves placing an electrode near the spine, which can electrically stimulate the nerves that control the bowel and sphincter muscles.

The first step of SNM is to implant a temporary electrode for 2 weeks. If there is improvement, a permanent electrode can be placed.



Remember that this is a surgery, meaning that there are risks such as infection or surgical complications. Also, SNS may not be covered by insurance for LARS treatment.

If you want to learn more about SNS, speak to your colorectal specialist to see if you would qualify for this treatment.

Not everyone will improve with the temporary electrode, so SNS is not for everyone.

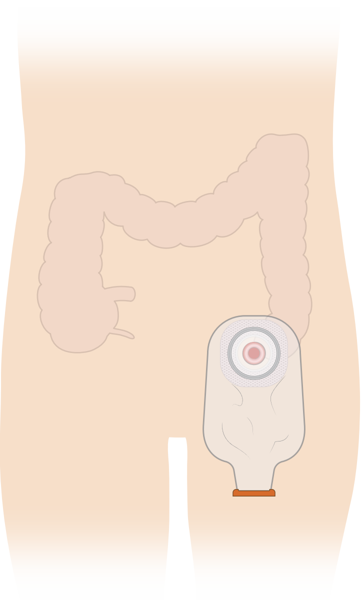
When it works, SNS has been shown in research studies to improve incontinence, urgency, and clustering of bowel movements.

Permanent Stoma (Colostomy)

If LARS is seriously affecting your quality of life, you can speak to your colorectal specialist about undergoing surgery to create a **permanent colostomy**.

You may have had a temporary stoma (an ileostomy). A permanent stoma (colostomy) involves the colon. A colostomy is usually easier to manage than an ileostsomy because the stool that empties into the bag is thicker.

We understand that passing stool from the anus is more natural and typically more convenient. Having a stoma seems like an odd thing to "choose", but it does offer you relief of your LARS and a way of emptying your bowels that you can more or less be in control of.



Remember that choosing a permanent colostomy requires another surgery. This can lead to any number of complications, such as wound infections, blood clots, serious infections in your belly, and the risks of anesthesia (being put to sleep during surgery). There are also late complications that can happen from having a colostomy, such as a hernia (bulge) around the stoma.

If a permanent colostomy seems like a better alternative to your current situation dealing with LARS, speak to your colorectal specialist to learn more about the risks and benefits.

Summary

- Neuromodulation (SNS) and surgery for a permanent colostomy are both invasive procedures that can be considered in cases of severe LARS.
- This is a brief overview of the risks and benefits of either treatment – both require a discussion with your colorectal specialist to properly review all options.

SOME FINAL THOUGHTS

LARS is a common condition facing rectal cancer survivors, and its management can be tricky. It may seem that despite your best efforts, your bowel symptoms continue to affect your daily activities.

Don't despair!

Our goal is to help you understand your LARS, reflect on your symptoms, and find some solutions that work for you.

If you can do this, you will almost certainly see some degree of improvement.

Remember, you are not alone! There are many rectal cancer patients going through the exact same experience.

We wish you success!

REFERENCES AND OTHER MATERIALS

References

Here is a list of some of the medical articles that we used to make this module. We do not expect you to be able to understand these articles, as they are written for doctors and not for patients.

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Ramage L, Qiu S, Kontovounisios C, Tekkis P, Rasheed S, Tan E. A systematic review of sacral nerve stimulation for low anterior resection syndrome. Colorectal Disease. 2015.

Landers M, McCarthy G, Livingstone V, Savage E. Patients' bowel symptoms experiences and self-care strategies following sphincter-saving surgery for rectal cancer. Journal of Clinical Nursing. 2014.

Health Professionals for LARS

There are many people that you can reach out to for questions about your LARS. Some of them are listed here. Speak to your colorectal specialist to get a referral.

- Your physician (surgeon or oncologist)
- Nurse specializing in cancer care or Colorectal Surgery
- Pelvic physiotherapist
- Dietician
- Pharmacist
- Other patients!

Patient materials

Here are some additional online patient materials on LARS that you may find helpful.

Bladder Bowel

www.bladderbowel.gov.au/assets/doc/ImproveBowelAfterSurgery.html

Beating Bowel Cancer

www.beatingbowelcancer.org/understanding-bowel-cancer/living-with-bowel-cancer/long-term-changes-bowel-habit/

National health Services

www.eastcheshire.nhs.uk/Patient%20Information%20Leaflets/On%20theA-Z/Managing%20bowel%20after%20Anterior%20Resection%2011453.pdf

Coloplast

www.coloplast.co.uk/Global/UK/Continence/Peristeen/Managing-your-bowel-function-Patient-Booklet.pdf

BOWEL TROUBLE DIARY

Date							
Number of bowel movements							
Average stool consistency (Bristol)							
Time of symptoms (please circle)	AM Noon PM	AM Noon PM	AM Noon PM	AM Noon PM	AM Noon PM	AM Noon PM	AM Noon PM
Number of incontinence episodes:	Gas	Gas	Gas	Gas	Gas	Gas	Gas
	Mild liquid	Mild liquid	Mild liquid	Mild liquid	Mild liquid	Mild liquid	Mild liquid
	Major liquid	Major liquid	Major liquid	Major liquid	Major liquid	Major liquid	Major liquid
	Stool	Stool	Stool	Stool	Stool	Stool	Stool
Did you have to rush to the toilet because of a sudden urge?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
Did you have to go to the toilet twice, or more, in the same hour?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
What other symptoms did you have? (circle all that apply)	Difficulty emptying	Difficulty emptying	Difficulty emptying	Difficulty emptying	Difficulty emptying	Difficulty emptying	Difficulty emptying
	Constipation	Constipation	Constipation	Constipation	Constipation	Constipation	Constipation
	Cramps	Cramps	Cramps	Cramps	Cramps	Cramps	Cramps
	Bloating	Bloating	Bloating	Bloating	Bloating	Bloating	Bloating

DIET DIARY

Date							
Bothersome symptom	Frequency Urgency Incontinence Clustering Constipation Bloating	Frequency Urgency Incontinence Clustering Constipation Bloating	Frequency Urgency Incontinence Clustering Constipation Bloating	Frequency Urgency Incontinence Clustering Constipation Bloating	Frequency Urgency Incontinence Clustering Constipation Bloating	Frequency Urgency Incontinence Clustering Constipation Bloating	Frequency Urgency Incontinence Clustering Constipation Bloating
Possible troublesome food today: (please circle all that apply)	Fruits Vegetables Spicy Food Sweets Nuts Other:	Fruits Vegetables Spicy Food Sweets Nuts Other:	Fruits Vegetables Spicy Food Sweets Nuts Other:	Fruits Vegetables Spicy Food Sweets Nuts Other:	Fruits Vegetables Spicy Food Sweets Nuts Other:	Fruits Vegetables Spicy Food Sweets Nuts Other:	Fruits Vegetables Spicy Food Sweets Nuts Other:
Possible troublesome beverages today: (please circle all that apply)	Coffee Tea Alcohol Other:	Coffee Tea Alcohol Other:	Coffee Tea Alcohol Other:	Coffee Tea Alcohol Other:	Coffee Tea Alcohol Other:	Coffee Tea Alcohol Other:	Coffee Tea Alcohol Other:
Foods or beverages eliminated since last diary entry							

LOPERAMIDE DIARY

Date							
How many Loperamide pills did you take today?	Morning ⓪ ① ② Noon ⓪ ① ② Evening ⓪ ① ② Before bed ⓪ ① ②	Morning ⓪ ① ② Noon ⓪ ① ② Evening ⓪ ① ② Before bed ⓪ ① ②	Morning ⓪ ① ② Noon ⓪ ① ② Evening ⓪ ① ② Before bed ⓪ ① ②	Morning ⓪ ① ② Noon ⓪ ① ② Evening ⓪ ① ② Before bed ⓪ ① ②	Morning ⓪ ① ② Noon ⓪ ① ② Evening ⓪ ① ② Before bed ⓪ ① ②	Morning ⓪ ① ② Noon ⓪ ① ② Evening ⓪ ① ② Before bed ⓪ ① ②	Morning ⓪ ① ② Noon ⓪ ① ② Evening ⓪ ① ② Before bed ⓪ ① ②
Did you take Loperamide 30 minutes before your meal?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
Do you think it helped with your symptoms?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No

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IMPORTANT

Centre universitaire
de santé McGill

McGill University
Health Centre

Office d'éducation des patients
Patient Education Office

Ce document est disponible sur le site de
l'Office d'éducation des patients du CUSM
www.educationdespatientscusm.ca

Supplementary File 4 – Patient consent form

Introduction:

You are being invited to be a research participant. This research is designed to investigate the use of a supportive intervention on patient-reported outcomes in patients who have undergone surgery for rectal cancer. You have the right to know about the purpose and procedures that are to be used in this research study, and to be informed about the potential benefits and risks of this research.

Before you agree to take part in this study, it is important that you read the information in this consent form. You should ask as many questions as you need to in order to understand what you will be asked to do. You do not have to take part in this study if you do not want to.

The Medical/Biomedical (MBM) Research Ethics Committee of the Centre intégré universitaire de santé et de services sociaux of West Central Montreal Health (CIUSSS WCMH) has approved and is responsible for the continuing ethical oversight of the study at the Jewish General Hospital.

Goals and Objectives:

After surgery for rectal cancer, many patients suffer from Low Anterior Resection Syndrome (LARS), which includes a variety of negative bowel-related symptoms as a consequence of removing the rectum. LARS can negatively impact quality of life. **The goal of this study is to evaluate the impact of a supportive intervention for LARS, with the hopes that it will improve various outcomes in patient care after surgery.** Specifically, to identify whether our supportive intervention focusing on LARS can:

- improve the quality of life among patients undergoing surgery for rectal cancer
- increase patient engagement in their own healthcare, as measured by the “Patient Activation Measure” (a questionnaire designed at evaluating the patient’s knowledge, skills, and confidence in care for their own health)
- improve bowel symptoms
- decrease emotional distress

Procedures:

- We are inviting all patients who underwent a Low Anterior Resection to remove a tumor in the rectum and who had a temporary ostomy (“bag”), and who are now scheduled to have their ostomy closure operation (the “reconnection” operation).
- As part of the study, we will access your medical chart from the hospital and collect some important information regarding your rectal cancer operation, as part of the research.
- You will then be randomly assigned to either the supportive intervention group or the control group (no supportive intervention), meaning that you will have a 50/50 chance of receiving the LARS education
- The **supportive intervention group** will receive two resources to help them manage their LARS:
  1) Educational booklet

2) Specialized nursing care

- The **control group** will **not** have access to the two resources listed above. That does not mean that control group participants shouldn't be counseled on LARS. These participants will have access to any resources that are normally available at their hospital. This may include discussions with their colorectal surgeon in the office, appointments with a nurse, and any pamphlets or online resources that your doctor might normally recommend.

Participants in the intervention group

Educational Booklet

- Participants in the intervention group will have access to an educational booklet.
- This educational booklet offers all of the essential information on LARS, including tips and tricks on how to best manage LARS at home.
- It also offers special diaries for various aspects of treatment, where participants can be expected to write down different things that did, or did not, work for their LARS. This will help reinforce positive behaviors that have helped.

Specialized nursing care

- Participants in the intervention group will have access to a specialized nurse with many years of experience caring for rectal cancer patients. The nurse will speak with participants once before their surgery and walk them through the educational booklet.
- After surgery, the nurse will call participants 5 more times during the first 12 months – at 1 month, 3 months, 6 months, 9 months, and 12 months – to answer any questions, and review the diaries.
- Lastly, the nurse will have "office hours" once a week, where she will be available by telephone or by email to answer more urgent questions.
- It is important to remember that the role of this nurse is only to help with LARS care, and she does not replace a doctor for more urgent medical issues. The nurse will use her years of experience and professional judgment to decide what sort of issues might fall outside of her role.

Participants in both groups

- Participants in both the intervention and control groups will receive several questionnaires, which will allow us to understand if the supportive intervention is helping patients with their LARS.
- **Questionnaires** will be sent out once before surgery, and then 4 more times after surgery – **at 1 month, 3 months, 6 months, and 12 months.**
- Questionnaires can either be mailed to you, sent by email, or answered over the phone – whichever you prefer. If you choose to have the questionnaires mailed to you we will include an envelope and postage so that you can send back the completed questionnaires.
- You may receive telephone calls from our research coordinator to ensure that you have received the questionnaires.

Duration

All participants, whether part of the intervention group or control group, will be followed for the first 12 months after their surgery. The first questionnaire is to be completed just prior to surgery, and the final questionnaire 12 months after surgery. After the 12 months have passed, we will not contact you for any other reasons related to the study.

Reimbursements

Participants will receive $10 for each set of completed questionnaires, and $20 once all questionnaires are completed. The 10$ gift for each completed set of questionnaires will be sent to participants as soon as the completed questionnaire is received by the research team.

Risks, Discomforts and Side-Effects:

By taking part in this study, you should be at no increased risk for unwanted side-effects or discomfort. No new medication is being recommended for the purpose of the study. All of the treatment strategies recommended in the educational booklet and by the specialized nurse are considered "standard" treatments, and are usually already discussed by the treating surgeon. If any of the questions make you uncomfortable you may choose not to answer them, or, if you become upset you may contact the PI, the nurse or any member of the research team.

Benefits:

If you are part of the supportive intervention group, we hope (and anticipate) that your knowledge regarding LARS will increase, and that you might be more active in the care of your LARS. Because of this, you may experience improvements in your quality of life and even in the severity if your LARS symptoms. If you are part of the control group, you will be less likely to get any benefit, as you are acting as a comparison group to see if our intervention is making a difference. At the end of the study, regardless of the findings, we will make our educational booklet publicly available to all participants.
That being said, we cannot guarantee that you will receive any direct benefits from this study.

Voluntary participation/withdrawal:

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from the study at any time, without giving any reason.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the doctor in charge of this research study or the clinical team.

If you withdraw or are withdrawn from the study, the information collected during the study will nonetheless be stored, analyzed or used to protect the scientific integrity of the research project.

Unexpected discoveries

Any new findings that could influence your decision to stay in the research project will be shared with you as soon as possible. If this happens, we will contact you to set up a visit with your treating surgeon or oncologist. This physician will share this information with you and plan your subsequent management.

Confidentiality:

While you take part in this research study, the researcher in charge and study staff will collect and store personal identifiable information about you in a file for the purpose of the research study. Only information necessary for the research study will be collected.

All the information collected about you during the study will remain confidential within the limits of the Law. To protect your identity, your name and identifying information will be replaced with a code number that has no identifying information. The code will be linked to your hospital ID and the link between the code and your identity will be held by the researcher in charge of the study. No information that discloses your identity will be allowed to leave the institution. Your study information will be kept in a de-identified manner for 10 years by the researcher in charge of the study, after which it will be anonymized. The data will be held in a password protected file and a password protected computer in locked offices at the Jewish General Hospital. After 10 years, the anonymized data will be kept indefinitely by the Investigator for the purposes of future research in colorectal surgery After 10 years, the consent forms will be shredded in the confidential bin provided by the CIUSSS du Centre-Ouest-de-L'ile-de-Montreal.

The study information may also be used for other reasons related to the study or to help in the development of future studies.

The study information could be printed/published in medical journals or shared with other people at scientific meetings, but your identity will not be revealed.

For monitoring, control and protection purposes, your research study file as well as your medical file could be checked by a person authorized by the Research Ethics Committee of the CIUSSS du Centre-Ouest-de-l'ile de Montreal or by persons mandated by authorized public agencies. These persons are bound by a confidentiality agreement.

For safety purposes, and in order to communicate information that is required in order to protect your well-being, the principal researcher of this study will keep separate from the research documents your personal information including your name, contact information, the date your participation in the study began and when it ended for the period of ten years after the end of the study. The data will be kept in a de-identified manner for 10 years following study completion and then it will be anonymized for use in future studies on colorectal surgery. After 10 years, the consent forms will be shredded in the confidential bin provided by the CIUSSS du Centre-Ouest-de-L'ile-de-Montreal.

You have the right to look at your study file in order to check the information gathered about you and to correct it, if necessary, as long as the study researcher or the institution keeps this information. However, you may only have access to certain information once the study has ended so that the quality of the research study is protected.

Should you suffer any harm:

By agreeing to participate in this research study, you do not give up any of your legal rights nor discharging the doctor in charge of this research study or the institution of their civil and professional responsibilities.

Investigator Compensation

The researcher in charge of this study has been awarded funding from a various professional medical societies and research granting agencies, to help cover the cost of running the study. The funds have been deposited into a research and development account.

Contact information or questions:

If you have any questions regarding the study, you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

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For all questions regarding your rights as a research participant for this study, or if you have comments or wish to make a complaint, you may contact the Local Commissioner of Complaints and Quality of Services of the CIUSSS du Centre-Ouest-de-l’ile-de-Montreal at 514-340-8222 ext. 24222.

STATEMENT OF CONSENT

Impact of a Patient-Centered Program for Low Anterior Resection Syndrome

I have reviewed the information and consent form. Both the research study and the information contained in the consent form were explained to me. All my questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.
I authorize the research study team to have access to my medical record and biopsy results for the purposes of this study. I do not give up any of my legal rights by signing this consent form.

I agree to be re-contacted by the study team in the future regarding further participation in this study or to be asked about participation in other studies. Agreeing to be re-contacted does not mean I have to participate in these other studies.

YES NO INITIALS ☐

Name of the Participant Signature
Date

Consent form administered and explained in person by:

Name of the person obtaining consent Signature
Date

I certify that this information and consent form were explained to the research participant, and that the questions the participant had were answered. I undertake, together with the research team, to respect what was agreed upon in the information and consent form, and to give a signed and dated copy of this form to the research participant.

Name of the Investigator
Signature Date

Chapter 6: Discussion

Bowel dysfunction after restorative proctectomy, commonly referred to as Low Anterior Resection Syndrome (LARS), is a common sequela of rectal cancer treatment. It has been demonstrated that up to 50% of patients experience major LARS after the first postoperative year,[23,25] and that changes in bowel function past this point are likely to be permanent.[24,42] Given the strong association between bowel function and long-term global quality of life (QoL),[23,25] LARS is a critical patient-reported outcome after rectal cancer surgery. Nonetheless, little consideration has been given to the educational and informational needs of rectal cancer survivors regarding LARS,[41] both of which may help engage patients in their own LARS healthcare. Therefore, the overarching objectives of this thesis were to describe the burden of postoperative bowel dysfunction, to systematically review online health information on LARS, and to develop a LARS Patient-Centered Program (LPCP) for rectal cancer survivors. The work emanating from this thesis will ultimately serve to better counsel patients regarding postoperative bowel dysfunction and its consequences, and to equip them with the necessary tools and knowledge to control their symptoms and improve their QoL.

I began by performing a population-based observational cohort study using two linked administrative and clinical databases to report on the incidence and risk factors of bowel dysfunction after restorative proctectomy (Chapter 2). While all of the existing data on postoperative bowel dysfunction has relied on Patient-Reported Outcomes Measures (PROMs), such as the LARS Score and others,[43,44] this study was the first to take a “big data” approach to this disorder. There are several advantages to the use of population-level databases in observational research, including large sample sizes, precise estimates, and a diverse patient population.[45] The Hospital Episode Statistics database and Clinical Research Practice Datalink are both United Kingdom-based national databases, and together, provided 2,197 eligible patients over a twenty-year study period, rendering this study the largest to date on postoperative bowel dysfunction.

Using a pragmatic case definition including clinical encounters for bowel symptoms and relevant medication prescriptions, we reported an incidence of bowel dysfunction of 28.2%. While slightly on the lower side, this incidence is well within the range of major LARS reported in systematic reviews and meta-analyses of mostly single-institution series. Furthermore, estimates of bowel dysfunction based on PROM data typically overestimate the incidence of clinically-relevant dysfunction, as the LARS Score has been criticized for being overly sensitive.[46,47] We also presented longitudinal data on bowel medication prescriptions – mostly consisting of the anti-motility agent loperamide – and demonstrated that approximately 10% of all long-term rectal cancer survivors (or 31.4% of those with bowel dysfunction) received 10 or more prescriptions throughout follow-up. This novel data highlights the high prevalence, as well as the long-term nature, of postoperative bowel dysfunction after restorative proctectomy.

Finally, we queried the data to study factors associated with postoperative bowel dysfunction. Distal tumors and the use of radiotherapy were both associated with postoperative bowel dysfunction, consistent with pre-existing subject knowledge.[48] History of a diverting ostomy was another positive risk factor, the pathophysiology of which may be related to diversion colitis and subsequent colonic and rectal atrophy.[49] However, ostomies are more preferentially performed when operating on distal rectal tumors that were preoperatively irradiated, and therefore, the association may simply be representative of these other established risk factors. Age appeared to have a non-linear relationship with bowel dysfunction, and several theories may explain this observation. Younger patients may report a higher symptom severity due to the more radical change in bowel function that ensues after surgery, as they are more likely to have had perfect preoperative function. They also typically lead more active and mobile lives; therefore, the impact of LARS on QoL may be higher. It has also been suggested that colonic motility, which is increased in younger compared to older individuals, could contribute towards the pathophysiology of LARS.[40,50] Older patients, on the other hand, may also be at higher risk of postoperative bowel dysfunction, as they may be at a worse starting point in regards to their preoperative function. Our results also demonstrated that postoperative anastomotic leak was associated with bowel dysfunction, while minimally-invasive surgery was protective. Altogether, these data contribute to the growing body of knowledge on LARS, and can be helpful in the preoperative consent process when counseling patients about postoperative expectations and long-term outcomes.

In the next chapter, I performed an observational cohort study with cross-sectional follow-up to report on the financial and occupational hardships experienced by patients with LARS (Chapter 3). While LARS has been repeatedly correlated with worse QoL,[23,25] the financial and occupational impact of the disorder was, until now, relatively unexplored. A recent study evaluated patient-reported work ability during the first two years after rectal cancer diagnosis, and demonstrated that work ability deteriorates with treatment; at 24 months, 32% of patients needed substantial adaptations in work activities.[51] However, the authors did not correlate outcomes with severity of postoperative bowel dysfunction. Therefore, we felt this was an important patient-centered aspect of the disorder that warranted proper evaluation.

After developing an institutional database of rectal cancer patients who underwent restorative proctectomy, we disseminated multiple PROMs evaluating LARS severity, bowel-related financial impact (stress and strain), global QoL, and occupational impact. We reported an incidence of major LARS of 30.5%, which was quite similar to that of postoperative bowel dysfunction reported in Chapter 2 (28.2%). The principal findings of this study were that nearly half of all patients with major LARS reported bowel-related financial stress and/or strain (i.e., felt that their ability to make ends meet was impacted by their bowel function), and that patients with major LARS were far more likely to report difficulties returning to work at the same capacity because of their new bowel function. Furthermore, major LARS with bowel-related financial impact was associated with low QoL, while major LARS without bowel-related financial impact was not. These results would suggest that financial stress and strain have an additive effect with bowel dysfunction, compounding the negative impact on global QoL. Physicians caring for patients with rectal cancer should be cognizant of the financial and occupational hardships associated with postoperative bowel dysfunction, and additional supportive resources should be targeted to such patients.

After describing the burden of postoperative bowel dysfunction in rectal cancer survivors, I turned my attention towards the development of a patient-centered intervention to improve outcomes among patients with LARS. The LPCP was conceptualized as an informational and supportive intervention, geared towards rectal cancer patients entering the survivorship phase of their cancer journey. The concept was largely driven by similar interventions successfully implemented for patients with new ostomies, where multiple benefits in patient-reported outcomes were observed.[37,38] For patients who undergo restorative procedures, the first few postoperative years tend to be the most difficult, both in terms of physical symptom control and emotional and psychological suffering; therefore, the LPCP will ultimately be offered to patients immediately after proctectomy, or ileostomy closure in cases that involved diversion.

I began by concentrating on the informational component of the LPCP, and completed a systematic review of online health information for LARS (Chapter 4). The goals of this study were to identify the top available online resources for patients, and to study their strengths and weaknesses to help guide the development of a novel LARS informational tool. We chose to study the Internet as it has become the most frequently consulted public resource for patients with healthcare questions,[52,53] and patients who seek healthcare information online report feeling empowered and motivated.[54,55] Therefore, the Internet was thought to be a potentially rich source of patient-directed information on LARS.

After analyzing all 25 included websites for readability, suitability, quality, accuracy, and content, I drew several conclusions regarding the available body of online health information for LARS. First and foremost, all websites were written at too complex a reading level (median=10.4) according to the American Medical Association-recommended 6th grade reading level,[56] which has been similarly demonstrated in other subjects.[57,58] Second, websites were lacking key educational features which could have helped in the retention of knowledge.[59] For example, summaries for each section, illustrations and graphics to complement the text, and engaging language were all seldom used. Third, important content was often missing, including treatment options for more advanced LARS and a proper description of symptoms. The assessment of content was somewhat debatable, as it unfairly assumed that all websites were intended to cover the entirety of the topic. However, we wanted to provide a broad overview of the information available to patients online, according to a novel LARS content checklist generated by collaborating Colorectal Surgeons with expertise in rectal cancer care.

With these points in mind, I set out to develop and validate the informational component of the LPCP (Chapter 5). I formed a multidisciplinary LARS working group consisting of colorectal surgeons, a colorectal cancer pivot nurse, a pelvic physiotherapist, and motivated rectal cancer patients. I wrote an original script for a LARS informational booklet, covering the epidemiology and management strategies for LARS, and created patient diaries for diet, bowel trouble, and loperamide use. In conjunction with the McGill University Patient Education Office, we designed original illustrations to complement the text, highlighting the key principles in anatomy, stool assessment, and self-management behaviors. A qualitative study was subsequently undertaken, whereby rectal cancer survivors (along with their caregivers) were invited to participate in a focus group reviewing the content and clinical applicability of the booklet. Patients provided honest feedback and constructive criticism, and all unanimously supported the development of the booklet, stating that it would have made a huge difference in their outlook and experience with LARS in the first postoperative year. Semi-structured interviews were also performed with healthcare professionals caring for patients with rectal cancer. All interviewed healthcare professionals echoed the sentiments of the patient group, and provided input as to when, and how, they would implement such a booklet and supportive program.

Finally, I described the protocol for a future multicenter randomized controlled trial evaluating the clinical effectiveness of the LPCP. The intervention, which will include the informational booklet and specialized nursing support, will be compared to standard care for LARS counseling and management offered at participating hospitals. The primary outcome will be global QoL, as measured by the European Organisation for Research and Treatment of Cancer QLQ-C30. Secondary outcomes will include bowel function scores, patient activation scores, and emotional distress, among others. Our underlying hypothesis is that patient-centered information and support for LARS will help reduce the anxiety and stress surrounding bowel dysfunction, increase patient engagement in their own LARS healthcare, and educate patients regarding optimal self-management strategies; this, in turn, will improve the experience and outlook of patients with LARS, improve global QoL, and potentially improve LARS severity through increased patient activation.

Since the initiation and completion of this thesis, a group out of the Netherlands published similar work on their screening and treatment protocol for LARS, as well as preliminary data regarding its implementation.[60] Similar to our LPCP, the Dutch “postoperative guidance protocol for LARS” was nurse-led, and included information on self-management strategies and lifestyle advices to optimize LARS. Their program included the systematic screening of patients within the first few days to weeks after discharge from hospital using the LARS Score and Bristol Stool score, and included both in-person and telehealth visits with the study nurse. Based on screening results, a basic algorithm was developed for initial conservative management (e.g., starting Psyllium fibers if Bristol Stool score was 5-7, or loperamide if frequency was 15-20 bowel movements per day). Preliminary data compared 48 patients who were managed within this protocol (19 restorative proctectomies, 29 sigmoid resections) to 195 historical controls. The authors observed positive trends in global QoL, as well as social, role, and physical functioning, and decreased rates of major LARS among patients managed within the protocol; however, the small number of patients (particularly rectal resections) precluded the achievement of statistical significance. Furthermore, the use of historical controls presents other challenges and biases. Nonetheless, this data provides early proof-of-concept that an informational and supportive intervention for LARS can improve patient-reported outcomes, and we hope to substantiate their findings in our randomized controlled trial.

Chapter 7: Conclusions

In this doctorate thesis, I reported on the incidence, risk factors, and consequences of bowel dysfunction after restorative proctectomy. In addition to its high prevalence, postoperative bowel dysfunction, commonly referred to as Low Anterior Resection Syndrome (LARS), was associated with significant financial and occupational hardships, and worse global quality of life. An informational and supportive intervention was thus conceptualized, with the goal of helping patients navigate their new postoperative bowel function and achieve the best possible outcome. After identifying a major gap in knowledge, I developed a LARS informational booklet, which was subsequently validated in a focus group and semi-structured interviews with patients and healthcare professionals. A protocol for a randomized controlled trial evaluating the impact of a novel LARS Patient-Centered Program on patient-reported outcomes was then described.

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