Enteric physiology, neuropathology, and bowel function following colorectal resections in adults and children

Verkuijl, Sanne

DOI:
10.33612/diss.518565993

Chapter 16

Summary and conclusions

Summary

Given the improved survival rates of both colorectal cancer and congenital colorectal disorders, optimal long-term functional outcomes following colorectal resections become important to an increasing number of people. In this thesis, we assessed the long-term functional outcomes following colorectal surgery in adults and children. However, these outcomes can only be understood after in-depth studying of the underlying physiological function and neuropathological characteristics of the colon, rectum, and anal canal.

In the five parts of this thesis, we subsequently presented clinical and fundamental studies regarding anorectal physiology (Part I), the presence of bowel function problems in the adults and children of the general population (Part II), long-term functional outcomes following oncological colorectal resections in adults (Part III), long-term functional outcomes following colorectal resections because of Hirschsprung's disease in children (Part IV), and neuropathological characteristics of the colon of patients with Hirschsprung's disease (Part V). Based on the newly obtained knowledge from the studies within this thesis, we aimed to provide the clinician with evidence-based recommendations to improve functional outcomes following colorectal resections in adults and children.

Part I – Anorectal physiology

Anorectal physiology is mainly studied by anorectal manometry, but this technique remains difficult to interpret as the results are influenced by many biomechanical factors. As an example of this, we present the study in **Chapter 2**, which shows that rectal volume thresholds, using conventional volume-based anorectal manometry, may lead to a false interpretation of rectal sensibility. We conclude that rectal pressure thresholds rather than rectal volume thresholds must be used to diagnose rectal hyposensitivity.

Studies using anorectal manometry clarified the physiological process of defecation. Following the traditional concept of the process of defecation, expelling stool relies on mechanoreceptors within the rectal wall, which react upon increasing rectal pressure. However, neuropathological studies did not show mechanoreceptors in the rectum, while an abundance of sensory afferent neurons was found in the proximal anal mucosa. **Chapter 3** comprises a prospective intervention study among healthy individuals who underwent two identical anorectal manometry test sessions: one baseline session and one session with anal anesthesia or a placebo. All study participants showed an involuntary and reproducible rectal contraction, which decreased or disappeared after applying anal anesthesia. Our conclusion is that there exists a communicative reflex pathway between the anal canal and the rectum, which appears to play a role in defecation. We, therefore, referred to the newly

investigated reflex as the anorectal defecation reflex. The amplitude of the rectal contraction correlated with the electrosensitivity in the most proximal centimeter of the individual anal canal. This may indicate that the afferent nerves of the anorectal defecation reflex are located in the proximal anal canal.

Part II – Bowel function in the general Dutch population

Functional outcomes following colorectal resections cannot be interpreted without knowledge on the prevalence of bowel function problems in the general population.

In **Chapter 4** we present our findings regarding the influence of certain demographic characteristics on constipation symptoms in the general Dutch population. We observed that sex and age influenced the likelihood of constipation. Furthermore, this study shows that there are several constipation symptoms that are not included in the well-known Rome IV criteria for functional constipation, which give an equally good impression of the presence of constipation, such as straining duration and failure to defecate after experiencing urge. Therefore, we recommend to adopt a more comprehensive, individual diagnostic approach to constipation, instead of only enquiring information about stool consistency and stool frequency.

Although there are excellent, validated tools to measure bowel function in specific settings, there is no tool available that can capture bowel function in young children as well as in adults. In **Chapter 5** we present the development and validation of the Early Pediatric Defecation and Fecal Continence (DeFeC) questionnaire for children from one month to seven years of age. When used in combination with the Pediatric DeFeC (8-17 years) and adult DeFeC (18 years and over), bowel function, coexisting disorders, and/or risk factors can now be captured from infancy to adulthood. The use of the three DeFeC questionnaires benefits clinical follow-up of patients with bowel disorders as well as longitudinal studies.

In **Chapter 6** we present the results of the application of the Early Pediatric DeFeC in a representative sample of the general Dutch population. This population-based study among 791 Dutch children between one month and seven years of age shows the physiological development of bowel and urinary function during the first years of life. We found that most children are fully toilet-trained at the age of five years, although fecal incontinence remains present in 12% of the toilet-trained children. The prevalence of constipation was 14%, with an equally high prevalence in infancy and older childhood. Fecal incontinence and constipation often coexisted and were frequently accompanied by urinary incontinence. Remarkably, treatment of bowel function problems was lacking in a considerable amount of the affected children. These findings warrant clinical attention when diagnosing each of these three conditions in young children, as early treatment may prevent chronic bowel function problems.

Part III – Long-term bowel function following colorectal resections in adults

Together with an increased survival rate of colorectal cancer, the long-term functional outcome following oncological colorectal resections becomes important to a growing number of people.

In **Chapter 7** we present a multicenter, cross-sectional study, including 630 patients who underwent a low anterior resection for rectal or rectosigmoid cancer between 2009 and 2015 in seven hospitals in the north of the Netherlands. This study revealed the predictive role of anastomotic height for the long-term functional outcomes following low anterior resection. We showed that fecal incontinence was especially common in patients with an anastomosis below 4.5 cm, while patients with an anastomosis above 9.5 cm suffered mainly from constipation. Patients with an anastomosis between 4.5 and 9.5 cm equally suffered from constipation and fecal incontinence. The results of this study can be used as a guide to effectively screen and treat bowel dysfunction during clinical follow-up. Furthermore, we also conclude that especially radiotherapy has a detrimental effect on the long-term continence of these patients. Despite the high prevalence of bowel dysfunction following low anterior resection, this study showed an exceptionally low treatment rate of both constipation and fecal incontinence. This highlights the current undertreatment of bowel function problems following low anterior resection.

One of the most commonly used bowel function scores after low anterior resection is the low anterior resection syndrome (LARS) score. In **Chapter 8** we present a critical analysis of the LARS score in a cohort of 1259 Dutch inhabitants without any medical disorder or previous abdominal surgery. The results show that minor or major LARS is already present in more than one-third of the general population. This warrants careful interpretation of the LARS score after surgery.

In **Chapter 9** we present a systematic review and meta-analysis regarding the outcomes of oncological colon resections. Although the long-term bowel function outcomes following colon resections seemed better than the outcomes following rectal resections, significant prevalences of fecal incontinence and constipation were found. Years after surgery for colon cancer, liquid and/or solid fecal incontinence were more than four times more common compared to the general population of the same age. Constipation-associated symptoms were prevalent in twice as many patients who underwent surgery for colon cancer when compared to the general population. Due to the heterogeneity of study designs, we were unable to study the influence of time to follow-up and type of colectomy on the functional outcomes.

In **Chapter 10** we present a study in which we compared the long-term functional outcomes of 1124 patients who underwent hemicolectomy right, hemicolectomy left, or sigmoid colon resection. Like chapter 6, this was a multicenter, cross-sectional study including patients who underwent their surgical procedures between 2009 and

2015. Interestingly, sigmoid colon resection was found to be associated with constipation, which was rarely treated. In contrast, right hemicolectomy was shown to be associated with liquid incontinence and fecal urgency, which was accompanied by a worse physical and mental quality of life. Hopefully, these results contribute to a more individual screening and treatment of bowel dysfunction following surgery for colon cancer.

Part IV – Long-term bowel function following colorectal resections in children

Colorectal resections are also performed in young children, especially in children affected by Hirschsprung's disease. The affected, aganglionic bowel segment is usually removed at a very young age with an excellent survival rate. This implies that optimal long-term functional outcomes following surgery for Hirschsprung's disease are important.

In **Chapter 11** we present the results of a nationwide, cross-sectional study, including 334 patients between 8 and 45 years old who underwent surgery for Hirschsprung's disease. In contrast to the popular belief that a longer aganglionic segment leads to worse long-term functional outcomes, this study shows that fecal incontinence was comparable between patients with different lengths of the resected colon segment. On the other side, patients with aganglionosis limited to the rectosigmoid were more prone to constipation, compared to patients with a longer aganglionic segment. This finding may be related to the higher prevalence of a liquid stool consistency after removing a longer length of the water-reabsorbing colon. Although others suggested a worse quality of life in patients with a longer aganglionic segment, we did not find a significant difference in the quality of life upon reaching adulthood. The results of this study can be used for individualized follow-up after surgery for Hirschsprung's disease.

In **Chapter 12** we compared patients with familial and non-familial Hirschsprung's disease. The prevalence of familial Hirschsprung's disease in our study population was 16% and the closest family member with the same disease was mostly a first-degree relative (in 56% of the cases). Remarkably, we showed a higher prevalence and severity of constipation but a better generic quality of life in adult patients with familial Hirschsprung's disease. These results suggest that familial experience with Hirschsprung's disease may improve coping with postoperative gastrointestinal problems in the long term. This emphasizes the need for a larger role of family members during the follow-up of patients with Hirschsprung's disease.

Part V – Neuropathological characteristics of the colorectum

Both **Chapters 10 and 11** show that despite successful removal of the affected, aganglionic bowel segment of patients with Hirschsprung's disease, bowel function problems are common. Therefore, it is interesting to take the neuropathological characteristics of the remaining, ganglionic colon of these patients into consideration.

Chapter 13 contains a narrative review of the current knowledge on the long-term outcomes following surgery for Hirschsprung's disease and summarizes the current guidelines for patients with bowel dysfunction after primary surgery. We found that constipation is reported in 22% to 33% of adult patients and fecal incontinence in 9% to 19% of adult patients. These numbers of persisting bowel dysfunction indicate that the remaining, ganglionic colon may not be completely healthy and functional. Interestingly, we found that the ganglionic part of the colon of individuals affected by Hirschsprung's disease deviates from the colon of unaffected individuals on different neuropathological levels. However, the relation between these neuropathological differences and clinical bowel function is still unclear. Therefore, we conclude that in-depth studies of colonic neuropathology combined with longitudinal functional outcomes following surgery for Hirschsprung's disease are needed to develop new surgical techniques, structural follow-up, or new treatment options.

Finally, in **Chapter 14** we present the preliminary results of our most recent study. In this international, cross-sectional study, analyzed the relative presence of nitrergic neurons in the ganglionic part of the colon of a large study population of children who underwent surgery for Hirschsprung's disease. Nitric oxide is one of main inhibitory neurotransmitters that causes relaxation of the bowel. The preliminary results show a relative overabundance of nitrergic neurons and a larger neuron size in the ganglionic colon of patients with Hirschsprung's disease compared to healthy controls. Remarkably, both the overabundance of nitrergic neurons and the larger neuron size correlate with severe postoperative constipation in the long term. This indicates that broadening of the routine neuropathological assessment of the surgically resected colon may possibly benefit preventive management of postoperative constipation in patients with Hirschsprung's disease.

Main conclusions

Part I

- Rectal hyposensitivity needs to be measured by rectal pressure thresholds. The use of rectal volume thresholds causes a false classification of rectal sensitivity.
- The anorectal defecation reflex is a newly investigated pathway between the proximal anal canal and the rectum, which appears to play a role in defecation.

Part II

- Bowel function can be assessed from infancy till adulthood using the Early Pediatric Defecation and Fecal Continence (DeFeC) questionnaire (1 month-7 years) in combination with the equivalent Pediatric DeFeC (P-DeFeC, 8-17 years) and the adult DeFeC (≥18 years).
- Dutch children usually become continent for stools around the age of five years.

Part III

- Anastomotic height is closely related to postoperative fecal incontinence (especially <4.5 cm) and constipation (especially >9.5 cm) following low anterior resection.
- A bad low anterior resection syndrome (LARS) score cannot immediately be interpreted as a bad postoperative outcome without an individual or population-based baseline score.
- Patients following right-sided colectomies are especially prone to liquid fecal incontinence and fecal urgency. Following sigmoid colon resections, patients suffer mainly from constipation-associated problems.
- Even though bowel function problems continue to exist years after surgery for colorectal cancer, most patients with postoperative constipation and fecal incontinence remain untreated.

Part IV

- In the long term, patients with Hirschsprung's disease with a long or total colonic aganglionic segment do not suffer from more fecal incontinence in comparison to patients with aganglionosis limited to the rectosigmoid.
- Patients with familial Hirschsprung's disease suffer from twice as much constipation compared to non-familial cases. Nevertheless, psychosocial generic quality of life of familial cases is better upon reaching adulthood, implying better coping.

Part V

- The remaining, ganglionic colon of Hirschsprung-affected animals and humans shows many neuropathological deficiencies.
- The remaining, ganglionic colon of patients with Hirschsprung's disease contains a relative overabundance of nitrergic neurons and larger neurons, compared to healthy individuals. Both the relative presence of nitrergic neurons and the larger neuron size correlate with severe postoperative constipation.