Exploring the pathophysiology of LARS after low anterior resection for rectal cancer with high-resolution colon manometry

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Running title: HRCM after rectal cancer

Full name, department, institution, city and country of all authors:

Dra. Anne Asnong, PT, MSc - ORCID ID: 0000-0002-5042-5993 (first author)
Department of Rehabilitation Sciences, Faculty of Movement and Rehabilitation Sciences, KU Leuven
anne.asnong@kuleuven.be

Prof. Dr. Jan Tack, MD, PhD - ORCID ID: 0000-0002-3206-6704
Department of Chronic Diseases, Metabolism and Ageing, Faculty of Medicine, KU Leuven
Department of Translational Research in Gastrointestinal Disorders, University Hospitals Leuven
jan.tack@uzleuven.be

Prof. Dr. Nele Devoogdt, PT, PhD - ORCID ID: 0000-0002-8117-7080
Center for lymphedema, University Hospitals Leuven, Leuven, Belgium
Department of Rehabilitation Sciences, KU Leuven – University of Leuven, Leuven, Belgium
nele.devoogdt@kuleuven.be

Prof. Dr. An De Groef, PT, PhD - ORCID ID: 0000-0001-6771-2836
Department of Rehabilitation Sciences, KU Leuven – University of Leuven, Leuven, Belgium
Department of Rehabilitation Sciences, University of Antwerp, Antwerp, Belgium
International Research Group Pain in Motion
an.degroef@kuleuven.be

Prof. Dr. Inge Geraerts, PT, PhD - ORCID ID: 0000-0003-3617-6334 (shared last author)
Department of Rehabilitation Sciences, Faculty of Movement and Rehabilitation Sciences, KU Leuven
Department of Physical Medicine and Rehabilitation, University Hospitals Leuven
inge.geraerts@kuleuven.be

Prof. Dr. André D'Hoore, MD, PhD - ORCID ID: 0000-0002-6978-809X (shared last author)
Department of Oncology, Faculty of Medicine, KU Leuven
Department of Abdominal Surgery, University Hospitals Leuven
andre.dhoore@uzleuven.be

Full name and postal address of corresponding author:

Inge Geraerts
Department of Rehabilitation Sciences
Research Group Rehabilitation in Internal Disorders
Room 04.04 – Inge Geraerts
O&N IV Herestraat 49 - bus 1510
3000 Leuven

E-mail of corresponding author: inge.geraerts@kuleuven.be

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STRUCTURED ABSTRACT

Background:

A total mesorectal excision for rectal cancer - although nerve- and sphincter sparing - can give rise to significant bowel symptoms, commonly referred to as Low Anterior Resection Syndrome (LARS). The exact pathophysiology of this syndrome still remains largely unknown and the impact of radical surgery on colonic motility has only been scarcely investigated.

Methods:

High-resolution colon manometry was performed in patients, 12-24 months after restoration of transit. Patients were divided into two groups: patients with major LARS and no/minor LARS, according to the LARS-score. Colonic motor patterns were compared and the relationship of these patterns with the LARS-scores was investigated.

Key results:

Data were analyzed in 18 patients (9 no/minor LARS, 9 major LARS). Cyclic short antegrade motor patterns did occur more in patients with major LARS (total: $p=0.022$; post-bisacodyl: $p=0.004$) and were strongly correlated to LARS-scores after administering bisacodyl ($p<0.001$). High amplitude propagating contractions (HAPC's) that started in the proximal colon and ended in the mid-section of the colon occurred significantly less in patients with major LARS compared to patients with no/minor LARS ($p=0.015$).

Conclusions & Inferences:

The occurrence of more cyclic short antegrade motor patterns and less HAPC's (from the proximal to the mid-colon) is more prevalent in patients with major LARS. These findings help to understand the differences in pathophysiology in patients developing major versus no/minor bowel complaints after TME for rectal cancer.

KEYWORDS

colon motility, colonic motor patterns, high-resolution manometry, low anterior resection syndrome, rectal cancer

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INTRODUCTION

Survival rates after rectal cancer and oncological outcomes have improved significantly over the years.[1] Improved imaging, neoadjuvant therapy and standardized surgery all add to an improved oncological outcome.[2,3] Radical surgery - a total mesorectal excision (TME) - remains the gold standard treatment. Because of the excision of the rectum, the rectal reservoir as such is lost.[4-6] As a consequence, a low anterior resection - although nerve- and sphincter sparing - may result in debilitating functional consequences concerning bowel function.[7-9] These bowel symptoms are commonly referred to as the Low Anterior Resection Syndrome (LARS); a complex syndrome consisting of a multitude of possible bowel symptoms, with consequences for the patient's quality of life.[10]

Notwithstanding the overwhelming use of 'LARS' as a term to describe these bowel symptoms (such as: incontinence for flatus or feces, frequent bowel movements, urgency and clustering of defecation), the exact pathophysiological mechanisms still remain poorly understood. It is hypothesized that the etiology of LARS is multifactorial, and relates to neo-rectal capacity and compliance[11], sphincter function[12], pelvic floor function[11], colonic motility[13] and postprandial response[14]. Based on these hypotheses, first it was explored if the creation of a rectal neo-reservoir would prevent LARS. However, evidence shows that a rectal neo-reservoir does not contribute to long term differences concerning bowel complaints, questioning its contribution to LARS/postoperative bowel function.[15,16] However, the creation of a neo-rectum has been suggested to delay motility patterns; i.e. when stool reached the rectum, a delay of defecation was observed.[17] Second, it has been demonstrated that, along with TME, a high ligation of the inferior mesenteric artery and the inferior mesenteric vein at the inferior border of the pancreas, could result in altered colonic motility and consequently affect postoperative function (LARS) due to autonomic denervation.[18-21] To our knowledge, the impact of the mechanisms associated with radical surgery on colonic motility has only been scarcely investigated.[22,23] Therefore, the innovative technique of high-resolution colon manometry (HRCM) can provide valuable insights into colonic motility patterns.[24,25] Recently, a consensus statement on terminology and definitions of these patterns was published, giving an overview of the current knowledge.[24] A recent study of Keane et al.[26] using HRCM, demonstrated that in patients who underwent distal colorectal resection (on average 6.8 years before), LARS was associated with altered colonic motility. However, as LARS has been demonstrated to be present in a general population as well,[27] the rationale of our study was to investigate the alteration of colonic motor patterns in the early postoperative stage and between patients with no or minor LARS-symptoms (LARS-score < 30) compared to patients experiencing major LARS complaints (LARS-score ≥ 30). Thus, the aim of this study was to investigate colonic motor patterns with HRCM and to assess the effect of hindgut denervation on the presence of coordinated proximal to distal contractions in rectal cancer patients suffering from varying degrees of LARS after TME.

MATERIALS AND METHODS

Patients

Approval for this trial was granted by the local Ethical Committee of the University Hospitals Leuven (main Ethical Committee, S61398) and this study was registered at Netherlands Trial Register (NTR NL7737). The following inclusion criteria were used: (i) patients who had a TME for rectal cancer and had restoration of transit for at least 12 months (TME or closure of the ileostomy occurred maximally 24 months before inclusion), (ii) patients had to be disease-free at one year after surgery (iii) patients who were able to come to UH Leuven for one complete day. Patients were excluded if they: (i) had a Hartmann procedure, abdominoperineal excision, transanal endoscopic microsurgical resection, or sigmoid resection, (ii) were incontinent for feces before surgery, and (iii) already had previous pelvic surgery, pelvic radiation or low anterior resection for non-cancer reasons. Patients were recruited between February 2019 and September 2020. This period was prolonged due to COVID-19 disruptions resulting in a break in colonoscopy/HRCM planning between March 2020 and August 2020. Based on their bowel symptoms, using the LARS-score questionnaire[28,29], patients were allocated into two different groups: (i) patients with severe or major LARS-symptoms (LARS-score ≥30) or (ii) clinically 'good' patients, with minor bowel symptoms, scoring minor or no LARS on the LARS-score questionnaire (LARS-score <30).

Procedure

The morning after an overnight fast of no less than twelve hours, subjects were expected at the endoscopy unit of the University Hospital of Leuven. Loperamide hydrochloride was discontinued for one day. Bowel preparation consisted of one-liter of water enemas (Moviprep) at two timepoints the day before the HRCM. The colonoscopy was performed under conscious sedation (up to 5 mg midazolam). A high-resolution manometry (HRM) catheter (10-F solid state catheter containing 40 pressure sensors spaced 2.5 cm apart, Unisensor AG, Switzerland) was clipped into the mucosa of the caecum. Two hours later, subjects were positioned in a semi-recumbent pose on a bed and colonic pressure recordings started for three hours. The subject subsequently received a standardized meal, based on the habitual Belgian lunch, and the recording of colonic pressures continued for two more hours. At this point, bisacodyl (10 mg) was administered intraluminally, thereafter pressure recording continued for a maximum of one hour. When the measurement was finished, the HRM was removed with a gentle pull.

High-resolution manometry analysis

The PlotHRM program was used to visually analyze the manometric recordings. For this study, the outcome of interest was the number of occurrences of six different motor patterns[24,25]: (1) + (2) short single propagating motor pattern (antegrade/retrograde), (3)+(4) long single propagating motor pattern (antegrade/retrograde), (5) simultaneous pressure wave and (6) high amplitude propagating contraction (HAPC). For the interpretation of the HAPC's, subdivisions were made for the start- and end-point of each HAPC, i.e. the number of channels used was divided by three, to be able to estimate whether the pattern started/ended in the proximal-, mid- or distal colon (Figure 1). Furthermore, cyclic patterns were categorized as well. Measurements were analyzed from the point the patients received their meal. The total amount of patterns as well as the number of patterns after administration of bisacodyl were analyzed.

Statistical analysis

Statistical analysis for comparison between groups was performed using the non-parametric two-tailed Mann-Whitney U test. Furthermore, Spearman correlation coefficients were used to analyze the relationship between the continuous LARS-score and the occurrence of different colonic motor patterns. Statistical analyses were performed using the Statistical Package for Social Sciences software for Windows, version 28 (SPSS, Inc. Chicago, IL). The correlation coefficients were interpreted as weak (below 0.40), moderate (0.40 - 0.74), strong (0.75 - 0.90) and very strong (above 0.90).[30] The 0.05 level of significance was applied. Considering the small sample size, the results in this study were interpreted in an exploratory way.

RESULTS

Study conduct

Between 12-24 months after TME/stoma closure, 19 patients were included: nine patients with a LARS-score below 30 (no/minor LARS, range = 11-29) and ten patients with a LARS-score higher or equal to 30 (major LARS, range = 31-41). Of all contacted patients (n = 26), 21% declined/were not able to come to the hospital for a full day, 7% could not be reached and in 4% there was a language barrier. Other than the LARS-scores, patient characteristics did not differ between the groups (Table 1). One patient with major LARS experienced a serious adverse event (SAE; acute fever, nausea, vomiting; not-related to the measurement) and could not complete the measurement (no bisacodyl was administered). This patient was excluded from the analyses because the SAE interfered with the interpretation of the measurement.

Differences between groups

Most types of motor patterns did not differ in number between both groups (no/minor LARS versus major LARS) (Table 2 + Table 3). However, the incidence of cyclic short antegrade motor patterns was significantly higher in the major LARS-group compared to the no/minor LARS group ($p = 0.022$). This was also the case when comparing this type of pattern, after administering bisacodyl ($p = 0.004$). In all patients, HAPC's were only observed after the administration of bisacodyl. Furthermore, the number of

HAPC's starting in the proximal colon and ending in the mid-section of the colon was significantly lower in the major LARS-group ($p = 0.015$). No other differences were found between the groups, an overview is provided in Table 3.

Relationship of LARS-scores to number of motor patterns

The occurrence of most of the motor patterns was not correlated to the LARS scores. A strong correlation was found between LARS-scores and the incidence of cyclic short antegrade motor patterns (post-bisacodyl), with major LARS-patients showing significantly more of this type of contraction ($r = 0.75$; $p < 0.001$). No other significant correlations were found, an overview is provided in Table 3.

DISCUSSION

This study showed that patients with major LARS exhibited significantly more cyclic short antegrade motor patterns compared to patients with no/minor LARS. Secondly, HAPC's that started in the proximal colon and ended in the mid-section of the colon occurred significantly less in patients with major LARS. In line with this, cyclic short antegrade motor patterns were strongly correlated to the LARS-scores. No other significant differences were found between patients with major versus no/minor LARS.

This study investigated colonic motor patterns between patients with different degrees of LARS complaints after TME for rectal cancer. The LARS-score - which was used to represent the extent of bowel complaints - has been proven to be highly sensitive to detect LARS.[28,31] However, recent studies showed that symptoms comprising the LARS-score are common in the general population as well.[7,32] Therefore, group comparisons were made between patients with no/minor LARS and patients with major LARS, in order to capture possible differences in patterns related to the degree of bowel complaints. Previous research investigating the relationship between LARS and colonic motor patterns, showed an association between LARS and altered colonic motility.[26] Keane et al.[26] showed that a low anterior resection was associated with diminished distal colonic retrograde motor patterns, which have been suggested to function as a rectosigmoid brake.[33,34] They also found significantly diminished numbers of antegrade propagating contractions in patients suffering from LARS (LARS-score > 20), compared to a healthy control group. Yet, the results of the current study could not confirm these findings. In particular, Keane et al. indicated less cyclic retrograde motor patterns in the LARS group compared to the control group, as opposed to our study, where more cyclic short antegrade motor patterns could be observed in patients with major LARS. Regardless of the contrasting results, a clear-cut comparison is difficult due to a few differences between the studies. First and most importantly, different groups were compared. In the study of Keane et al.[26] patients suffering from LARS were categorized as patients with a score above 20 (minor/major LARS). Comparisons were made with rectal cancer patients without LARS (score ≤20) and healthy controls. As mentioned before, in the current study, patients with no/minor LARS were compared with patients with major LARS complaints. Secondly, the catheter was clipped to the mucosa of the splenic flexure in the study of Keane et al. (demonstrating only the results of the colon descendens)[26], as opposed to the mucosa of the caecum in the current study. Consequently, in the current study patterns occurring over the total colon were investigated as opposed to patterns detected in the 20 sensors proximal of the anastomosis (patients)/the rectosigmoid junction (healthy controls).[26] Lastly, Keane et al.[26] used an automated interpretation of patterns, in contrast with the visual inspection that was used in this study. The combination of all of the factors mentioned above, probably contributed to the contrasting conclusions regarding the colonic motor patterns. After all, the incidence of only two types of patterns was significantly different between groups in the current study and neither of them was a retrograde pattern.

As mentioned before, in this study patients with major LARS did present with more cyclic antegrade motor patterns in total, as well as after administering bisacodyl. In previous research in healthy humans, cyclic propagating motor patterns were mainly found to be retrograde and were suggested to function as a sigmoid brake.[33,34] To date, the clinical relevance of cyclic antegrade motor patterns is not clear, hence the clinical relevance of the significant result found between no/minor LARS patients and major LARS patients also remains unclear.[24] However, Ng et al.[35] showed that patients with major LARS had accelerated colonic transit. Therefore, it could be argued that the manifestation of more severe bowel complaints - as represented by higher LARS-scores - could be related to a higher incidence of cyclic antegrade motor patterns which could thus also underlie the accelerated colonic transit. Nevertheless, as the link between colonic motor patterns and colonic transit has not been studied in detail, these underlying mechanisms need to be further investigated.

Bowel preparation is part of the standard procedure preceding HRCM, but could result in low numbers of HAPC's.[24] Because bisacodyl has prokinetic effects[36], it was administered intraluminally, which resulted in all of the observed HAPC's in this study. Although the total amount of HAPC's did not differ, by specifying the origin and endpoint of these contractions, a difference was found in the number of HAPC's starting in the proximal colon and ending in the mid-section of the colon. The fact that the incidence of this type of HAPC's was found to be significantly lower in the major LARS-group, could mean that more patients in the no/minor LARS group were better equipped to stop the HAPC from reaching the rectum. In other words, since less HAPC's started in the proximal colon and ended in the mid-section in patients with major LARS, this might point to a lack of breaking mechanisms. This could translate in more functional complaints in daily living. To the best of our knowledge, no previous research investigated the link between origin and endpoint of HAPC's in relation to LARS.

A limitation of the current study is the sample size. Larger studies are necessary to generalize the results, but due to the extent of the (preparation for the) HRCM-procedure, patient recruitment was not without its struggles. In the current study, there might have been a selection bias based on willingness of the patient to participate. Lastly, groups were predefined based on LARS-scores, since patients suffering from major LARS experience a worse quality of life.[7] However, basing groups on these scores could also possibly have influenced results, since major LARS does occur in a general population as well.[7,32]

To conclude, this study has shown that in general, the colonic motor patterns in patients with LARS after low anterior resection did not differ between patients with varying degrees of bowel complaints. However, cyclic short antegrade motor patterns did occur more in patients with major LARS. HAPC's that started in the proximal colon and ended in the mid-section of the colon occurred significantly less in patients with major LARS, compared to patients with no/minor LARS. These findings help to fill in some of the gaps in understanding the pathophysiology of the enigma that is LARS.

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DISCLOSURES

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

AA: acquisition/analysis/interpretation of data, drafting of the work, final approval, agreement to be accountable, project management; JT: conception/design of the work, analysis/interpretation of data, drafting of the work, critically revising of the work, final approval, agreement to be accountable, consultation/supervision; ND: analysis/interpretation of data, drafting of the work, critically revising of the work, final approval, agreement to be accountable; ADG: analysis/interpretation of data, drafting of the work, critically revising of the work, final approval, agreement to be accountable; ADH: conception/design of the work, analysis/interpretation of data, drafting of the work, critically revising of the work, final approval, agreement to be accountable, project management, fund procurement, consultation/supervision; IG: conception/design of the work, analysis/interpretation of data, drafting of the work, critically revising of the work, final approval, agreement to be accountable, project management, fund procurement, consultation/supervision

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TABLES

Table 1: Baseline characteristics.

	No/minor LARS (n = 9)		Major LARS (n = 10)	
	Median (IQR)		Median (IQR)	
LARS-score (continuous, 0-42)	25.0 (12)		37.0 (5.8)	
Age (years)	55.0 (21.3)		55.4 (11.7)	
	n	%	n	%
Gender				
Male	8	88.9	9	90.0
Female	1	11.1	1	10.0
Tumor height (from anal verge)				
Low (0-5 cm)	6	66.7	8	80.0
Mid (6-10 cm)	2	22.2	2	20.0
High (11-15 cm)	1	11.1	0	0.0
Type of reconstruction				
Straight coloanal anastomosis	5	55.6	7	70.0
Side-to-end coloanal anastomosis	3	33.3	2	20.0
Colon pouch-anal anastomosis/J-pouch	1	11.1	1	10.0
Anastomosis				
Manual	3	33.3	5	50.0
Stapled	6	66.7	5	50.0
Neoadjuvant therapy				
No	6	66.7	3	33.3
Chemo- and/or radiotherapy	3	33.3	7	77.8
Adjuvant therapy				
No	6	66.7	7	70.0
Chemotherapy	3	33.3	3	30.0
Stoma				
Yes	5	55.6	9	90.0
No	4	44.4	1	10.0

Table 2: Overview of pattern frequencies.

	No/minor LARS (n = 9)		Major LARS (n = 9)	
	Median	IQR	Median	IQR
Short single propagating motor pattern - antegrade	16,0	41,0	43,0	37,0
Short single propagating motor pattern - retrograde	55,0	66,5	78,0	119,5
Long single propagating motor pattern - antegrade	8,0	11,0	4,0	14,0
Long single propagating motor pattern - retrograde	9,0	24,0	16,0	33,5
Simultaneous pressure wave	51,0	113,5	113,0	93,5
Cyclic short antegrade motor pattern	0,0	5,0	5,0	3,0
Cyclic short retrograde motor pattern	4,0	6,5	10,0	17,5
Cyclic long antegrade motor pattern	0,0	0,0	0,0	0,0
Cyclic long retrograde motor pattern	0,0	2,5	0,0	3,5
Cyclic simultaneous pressure wave	30,0	48,5	32,0	29,0
High amplitude propagating contraction (total)	9,0	8,5	7,0	3,5
HAPC proximal	3,0	3,5	2,0	2,5
HAPC proximal-mid	4,0	1,5	1,0	2,0
HAPC proximal-distal	0,0	2,5	1,0	3,5
HAPC mid	0,0	0,0	0,0	0,5
HAPC mid-distal	0,0	1,0	0,0	1,0
HAPC distal	0,0	3,0	0,0	0,0

Median = median number of motor patterns, IQR = interquartile range

Table 3: Overview of results.

	Total	Post-bisacodyl	Total		Post-bisacodyl	
	Mann-Whitney U-test		Spearman correlation			
	P-value		Coefficient	P-value	Coefficient	P-value
Short single propagating motor pattern – ant.	0.452	0.178	-0,07	0,776	0,12	0,650
Short single propagating motor pattern – ret.	0.401	0.185	-0,01	0,971	0,26	0,295
Long single propagating motor pattern – ant.	0.723	0.651	-0,18	0,466	-0,20	0,433
Long single propagating motor pattern – ret.	0.478	0.755	-0,01	0,961	-0,17	0,505
Simultaneous pressure wave	0.508	0.691	-0,07	0,797	0,11	0,670
Cyclic short antegrade motor pattern	0.022	0.004	0,45	0,059	0,75	<0,001
Cyclic short retrograde motor pattern	0.156	0.324	0,32	0,193	0,40	0,097
Cyclic long antegrade motor pattern	0.317	1.000	0,05	0,853	-	-
Cyclic long retrograde motor pattern	0.494	0.586	0,37	0,129	0,02	0,930
Cyclic simultaneous pressure wave	0.453	0.216	-0,06	0,800	-0,09	0,725
High amplitude propagating contraction (total)		0.179			-0,24	0,344
HAPC proximal		0.445			-0,29	0,240
HAPC proximal-mid		0.015			-0,45	0,059
HAPC proximal-distal		0.457			0,34	0,174
HAPC mid		0.145			0,29	0,242
HAPC mid-distal		1.000			0,23	0,350
HAPC distal		0.225			-0,36	0,147

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Figure 1: Start-/endpoints of the HAPC's.

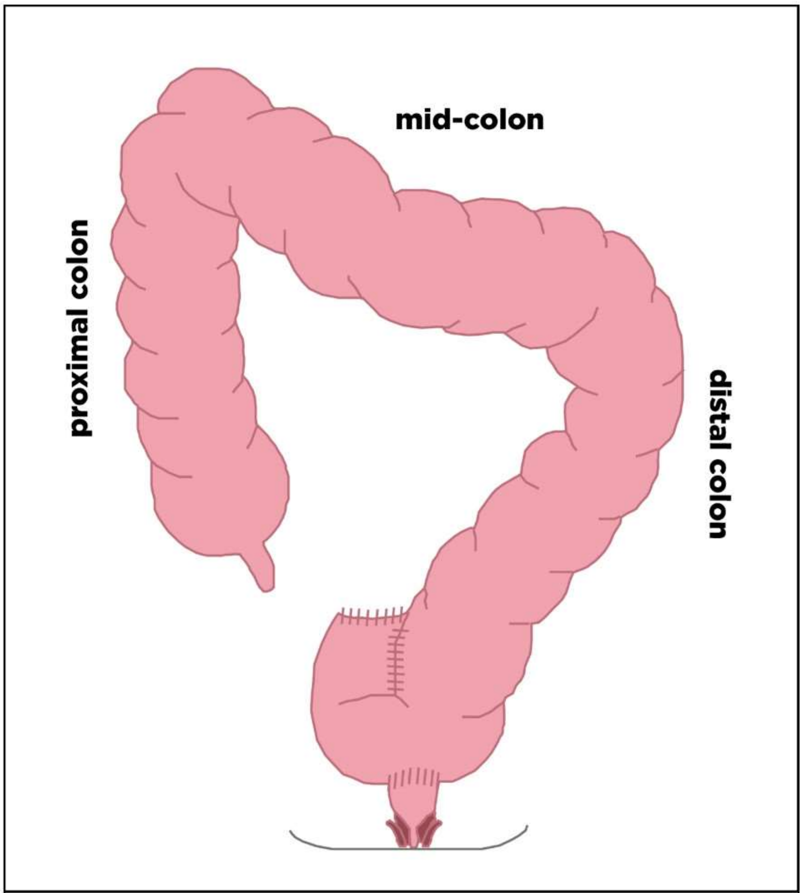

Figure 1: Start-/endpoints of the HAPC's.