

Clinical evaluation and treatment of chronic bowel symptoms following cancer in the colon and pelvic organs

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ABSTRACT

Background: Chronic gastrointestinal symptoms are common among patients surviving surgery and/or radio-/chemotherapy for cancer in the pelvic organs. However, little is known about the pathophysiology behind symptoms or the effect of treatment. The aim of the present study was to present the results of clinical evaluation and treatment of patients with chronic bowel symptoms after treatment for cancer in the colon or pelvic organs.

Material and methods: All patients referred to our department of gastroenterology between May 2016 and June 2018 with chronic bowel symptoms after treatment for cancer in the colon or pelvic organs were prospectively evaluated.

Results: In total, 60 patients had been referred. The patients were treated for cancer in the right colon ($n=31$), sigmoid colon ($n=1$), rectum ($n=14$), anal canal ($n=4$), cervix uteri ($n=5$), corpus uteri ($n=2$), ovary ($n=2$), and prostate ($n=1$). The median time from cancer treatment to referral was 5.5 (range 1–36) years. Symptoms mainly included frequent bowel movements (65%), loose stools (87%), urgency for defecation (57%), and fecal incontinence (50%). A specific cause of bowel dysfunction was found in 48 (80%) of the patients and 21 (35%) had more than one cause of bowel symptoms. Bile acid malabsorption was present in 35 patients and small intestinal bacterial overgrowth was detected in 32. Treatment included bile acid sequestrants ($n=36$), antibiotics ($n=33$), loperamide ($n=21$), and dietary intervention ($n=20$). Major improvement in bowel symptoms was reported by 23 (38%) patients, while another 27 (45%) reported some improvement.

Conclusion: Most patients with chronic bowel symptoms following cancer in the colon or pelvic organs will benefit from expert clinical evaluation and targeted treatment.

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Introduction

Survival after treatment for cancer in the pelvic region has improved significantly during the last decades. Consequently, late complications to treatment have attracted more attention. Gastrointestinal symptoms are common, not only after treatment for colon or rectal cancer, but also after other cancers in the pelvic region. Thus, 15–66% of patients with colorectal, urological, or gynecological cancers treated with surgery or radio-/chemotherapy suffer from chronic gastrointestinal symptoms [1]. Loose stools, soiling, and frequent bowel movements are common symptoms after surgical treatment of colon cancer, and in particular after right-sided hemicolectomy if more than 10 cm of the terminal ileum has been resected [2]. Long-term functional problems following treatment for rectal cancer have been described in detail as the Low Anterior Resection Syndrome (incontinence for flatus and liquid stools, frequent bowel movements, clustering, and urgency for defecation) [3,4]. In addition, radiotherapy for

prostate and gynecological cancer may cause bile acid malabsorption and chronic diarrhea [5,6].

The pathophysiology behind late gastrointestinal symptoms after treatment for pelvic cancers is multifactorial and still incompletely understood. Surgery, radiotherapy, and/or chemotherapy may disturb the normal function of the terminal ileum and cause bile acid diarrhea [1,7]. Resection of the ileocecal valve or small intestinal dysmotility from neuropathy or fibrosis may lead to small intestinal bacterial overgrowth [1]. Intestinal stenosis or adhesions may cause pain and weight loss, and temporary loop-stoma following rectal cancer may lead to a change in the micro flora of the gut. Identifying a specific cause of gastrointestinal symptoms allows targeted treatment of individual patients and improves functional results. Bile acid malabsorption after treatment for cancer can often be treated effectively with a bile acid sequestrant [8] and small intestinal bacterial overgrowth may respond to rifaximin [9] or other antibiotics. If no specific cause of gastrointestinal symptoms is found,

some patients may benefit from dietary intervention or loperamide [10].

Most patients with long-term gastrointestinal complications to cancer treatment are followed by specialists with little experience in evaluation and treatment of gastrointestinal symptoms. This is highly unfortunate since up to 50% of patients may have an identifiable cause of their symptoms and many of these will benefit from specific treatment [11]. Very often more than one cause of symptoms is present and some patients have underlying gastrointestinal disease unrelated to treatment of their cancer.

The first clinic with a specialized function dedicated to chronic bowel dysfunction after treatment for cancer was established at the Royal Marsden Hospital, London in 2000 and recently others have followed. For several years, the nurse-lead Anal Physiology Clinic at Aarhus University Hospital has treated patients with cancer sequelae such as constipation and incontinence. In May 2016, a close co-operation was established with the Department of Hepatology and Gastroenterology, Aarhus University Hospital in order to ensure specialist evaluation of the subgroup of patients with chronic diarrhea. Hence, the aim of the present paper is to report the results of clinical evaluation and treatment of a prospective cohort of patients referred to evaluation by a gastroenterologist because of chronic bowel symptoms after treatment for cancer in the colon or pelvic organs.

Material and methods

All patients referred to the Department of Hepatology and Gastroenterology at Aarhus University Hospital, Aarhus, Denmark, between May 2016 and June 2018 because of chronic bowel symptoms after treatment for cancer in the pelvic region were prospectively included in the present study. Patients were survivors of a cancer in the large bowel or in the pelvic organs and all had been treated with surgery and/or radio-/chemotherapy. The patients were evaluated with focus on symptoms at referral, results of clinical tests and response to treatment.

Clinical evaluation

All patients were seen by an experienced clinician with special interest in the field. The following chronic bowel symptoms were registered: daily number of bowel movements, where >3 movements per day were defined as frequent. Stool consistency defined by the Bristol Stool Chart with type 6 and 7 defining loose stools [12]. Additionally, urgency for defecation, fecal incontinence, nocturnal defecation, abdominal pain, and bloating were registered. The patients' symptoms were evaluated at first visit in our clinic, two to four weeks after any change in treatment and, if applicable, at termination of the course of treatment at our department.

Basic clinical evaluation included standard blood samples for inflammatory bowel disease, celiac disease, primary lactose intolerance, thyroid disease, and malabsorption. Endoscopy with biopsies was performed if the patients had not undergone endoscopy within the last three years as part of normal control or diagnostic workup.

Before September 2017, further diagnostic testing depended on the patients' symptoms. If main symptoms were loose stools and bloating, patients were offered a breath test for hydrogen and methane to determine the presence of small intestinal bacterial overgrowth. If watery diarrhea was the main symptom, a Selenium-75 homocholic acid taurine (SeHCAT) scan was performed to detect bile acid malabsorption (BAM). Retention levels <10% at day 7 defined severe to moderate BAM, while retention levels of 10–15% defined mild BAM [13,14].

In September 2017, this practice was changed because data from elsewhere indicated that symptoms poorly predict the pathophysiology of bowel dysfunction after treatment for cancer in the pelvic region [15]. Thus, all patients seen after that date had a breath test and SeHCAT scan performed.

Treatment of bowel symptoms

Patients with small intestinal bacterial overgrowth were treated with ciprofloxacin or rifaximin, while patients with BAM were treated with the bile acid sequestrants cholestyramine or colesevelam. Patients without a specific diagnosis of bowel dysfunction and those not responding to targeted treatment of a specific diagnosis were treated with loperamide or dietary intervention.

Our main endpoint was the patients' own assessment of overall effect of treatment evaluated 2–4 weeks after last change in treatment or later at termination of the course of treatment at our department, if applicable. Effect of treatment was categorized as 'no improvement' (no difference in symptoms before and after treatment), 'some improvement' (normalization of at least one symptom) and 'major improvement' (no bowel dysfunction after treatment or the patient's indication of a substantial improvement in bowel function and no remaining impairment in quality of life).

The study was approved by the Danish Data Protection Agency (Journal no. 1-16-02-972-17).

Statistics

Descriptive statistics were applied.

Results

Patient characteristics

In total, 60 patients were seen in our clinic. The majority were survivors after colorectal cancer ($n=46$). The demographics are shown in Table 1.

Symptoms at referral

Main symptoms reported at first visit are shown in Table 2. In addition, a few patients suffered from nausea, blood in the stools, clustering of bowel movements, or malodorous flatus.

Table 1. Patient characteristics.

Patient characteristics	
Patients, <i>n</i>	60
Age years, median (range)	67 (34–88)
Gender female/male	36/24
Cancer localization <i>n</i> (%)	
Right colon	31 (52)
Sigmoid colon	1 (2)
Rectum	14 (23)
Anal canal	4 (7)
Cervix uteri	5 (8)
Corpus uteri	2 (3)
Ovary	2 (3)
Prostate	1 (2)
Time from treatment to referral years, median (range)	5.5 (1–36)
Surgery, <i>n</i> (%)	55 (92)
Chemotherapy, <i>n</i> (%)	19 (32)
Radiotherapy, <i>n</i> (%)	20 (33)

Pathophysiology

Basic clinical evaluation revealed that two patients had primary lactose intolerance, one patient had ulcerative colitis, and one had a stenosis of her ileo-colonic anastomosis.

Among the 47 patients who underwent hydrogen and methane breath test, 32 (68% [54.8–81.4%]) had small intestinal bacterial overgrowth (Table 3).

Among the 43 patients who had a SeHCAT scan performed, 29 (67% [53.4–81.4%]) had severe to moderate BAM (retention level <10%), while 6 (14% [3.6–24.3%]) patients had mild BAM (a retention level of 10–15%) (Table 3). In total, a specific cause of bowel dysfunction was found in 48 (80% [69.9–90.1%]) of the patients. In 21 (35% [22.9–47.1%]) patients, more than one cause was found.

Treatment

The use of different treatment modalities is summarized in Table 4. Thus, small intestinal bacterial overgrowth was first treated with ciprofloxacin or rifaximin (*n* = 33). Patients who had no or only minor response to treatment had another cycle with the other antibiotic (*n* = 15).

Bile acid malabsorption was treated with cholestyramine. If this was without effect or poorly tolerated, colesevelam was given. One patient not responding to cholestyramine and colesevelam was treated with colestipol. A few of the first patients seen in our clinic (*n* = 6) were treated with bile acid sequestrants empirically without a prior SeHCAT scan.

Dietary intervention was offered motivated patients with no specific underlying pathophysiology (*n* = 2) or without sufficient response to specific treatment (*n* = 18). Intervention included low-fat diet for patients with BAM (*n* = 14), a dietary restriction of the fiber content in the diet (*n* = 2), a change in consistency of food and fiber (like mashed potato) (*n* = 2), lactose free diet (*n* = 2), and a low content of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) (*n* = 4). The low FODMAP diet was not first option but chosen if the normal dietary intake was with a very high content of FODMAPs (e.g., ryebread, onion) or if the low-fat diet had a less satisfactory effect.

Table 2. Symptoms at referral to our clinic.

Symptoms at referral	>3 bowel movements per day						
	Urgency for defecation	Fecal incontinence	Nocturnal defecation	Abdominal pain	Bloating	Loose stools	Urgency for defecation
All cancers, <i>n</i> = 60	34 (57%) [44.1–69.2%]	30 (50%) [37.3–62.7%]	8 (13%) [4.7–21.9%]	15 (25%) [14.0–36.0%]	14 (23%) [12.6–34.0%]	52 (87%) [78.1–95.3%]	34 (57%) [44.1–69.2%]
Right colon, <i>n</i> = 31	18 (58%) [40.7–75.4%]	12 (39%) [21.6–55.9%]	4 (13%) [1.1–24.7%]	10 (32%) [15.8–48.7%]	9 (29%) [13.1–45.0%]	30 (97%) [90.6–100%]	18 (58%) [40.7–75.4%]
Sigmoid colon, <i>n</i> = 1	1 (100%)	1 (100%)	–	–	–	1 (100%)	1 (100%)
Rectum, <i>n</i> = 14	9 (64%) [39.2–89.4%]	6 (43%) [16.9–68.8%]	3 (21%) [0–42.9%]	–	4 (29%) [4.9–52.2%]	9 (64%) [39.2–89.4%]	9 (64%) [39.2–89.4%]
Anal canal, <i>n</i> = 4	1 (25%) [0–67.4%]	4 (100%)	–	1 (25%) [0–67.4%]	–	3 (75%) [32.6–100%]	1 (25%) [0–67.4%]
Cervix uteri, <i>n</i> = 5	3 (60%) [17.1–100%]	3 (60%) [17.1–100%]	–	2 (40%) [0–82.9%]	–	5 (100%)	3 (60%) [17.1–100%]
Corpus uteri, <i>n</i> = 2	1 (50%) [0–100%]	2 (100%)	–	1 (50%) [0–100%]	–	2 (100%)	1 (50%) [0–100%]
Ovary, <i>n</i> = 2	1 (50%) [0–100%]	1 (50%) [0–100%]	–	1 (50%) [0–100%]	–	1 (50%) [0–100%]	1 (50%) [0–100%]
Prostate, <i>n</i> = 1	–	1 (100%)	1 (100%)	–	–	1 (100%)	–

Data are presented as number (% [95%-CI]). Loose stools defined by type 6 and 7 on the Bristol Stool Chart [12].

Table 3. Results of diagnostic tests.

	Breath test		SeHCAT retention		
	Positive	Negative	<10%	10–15%	Normal (>15%)
All cancers, <i>n</i> =60	32	15	29	6	8
Right colon, <i>n</i> =31	20	6	14	4	3
Sigmoid colon, <i>n</i> =1	–	–	1	–	–
Rectum, <i>n</i> =14	7	4	6	–	5
Anal canal, <i>n</i> =4	1	2	3	1	–
Cervix uteri, <i>n</i> =5	2	1	3	–	–
Corpus uteri, <i>n</i> =2	1	1	1	1	–
Ovary, <i>n</i> =2	1	–	1	–	–
Prostate, <i>n</i> =1	–	1	–	–	–

Data are presented as numbers. SeHCAT: Selenium-75 homocholesterol acid taurine.

Table 4. Treatment modalities used in our clinic.

Treatment modalities	<i>n</i> (%)
Antibiotics	
Ciprofloxacin	28 (47)
Rifaximin	13 (22)
Other ^a	7 (12)
Bile acid sequestrants	
Cholestyramine	31 (52)
Colesevelam	19 (32)
Both	14 (23)
Loperamide	21 (35)
Laxative	9 (15)
Dietary intervention ^b	20 (33)
Stoma	2 (3)

^aAmoxicillin (*n* = 4), metronidazole (*n* = 3).

^bFat and/or fiber reducing regimen.

Loperamide was given to 21 patients, either as sole treatment (*n* = 5) or to enhance the effect of other treatment (*n* = 16).

Effect of treatment

The patients were followed for a median (range) time of 56 (14–433) days. The number of patients with frequent bowel movements and loose stools after treatment in our clinic is shown in Table 5. In total, 38% [26.0–50.6%] (*n* = 23) of the patients reported a major improvement in bowel function, while 45% [32.4–57.6%] (*n* = 27) experienced some improvement. Ten patients (17% [7.2–26.1%]) had no improvement.

Discussion

In a prospective cohort of 60 cancer survivors referred to our clinic because of chronic bowel symptoms, a specific cause of symptoms was found in 80% and 35% had more than one cause diagnosed. More than two-thirds experienced some (45%) or major (38%) improvement in their bowel function after treatment. At referral, the most common symptoms were frequent bowel movements (65%) and loose stools (87%). After treatment, 54% [38.2–69.5%] of the patients with frequent bowel movements had at least 50% reduction in number of daily bowel movements, while 50% [36.4–63.6%] of patients with loose stools had improved consistency. Our results are much in line with previous data from the Royal Marsden Hospital in London [11], which showed that 70% of patients experienced a significant improvement after

Table 5. Symptoms after treatment in our clinic.

Symptoms after treatment	>3 bowel movements per day		Loose stools
All cancers, <i>n</i> =60	12	14	
Right colon, <i>n</i> =31	3	8	
Sigmoid colon, <i>n</i> =1	–	–	
Rectum, <i>n</i> =14	5	3	
Anal canal, <i>n</i> =4	1	–	
Cervix uteri, <i>n</i> =5	1	2	
Corpus uteri, <i>n</i> =2	1	1	
Ovary, <i>n</i> =2	1	–	
Prostate, <i>n</i> =1	–	–	

Data are presented as numbers. Loose stools defined by type 6 and 7 on the Bristol Stool Chart [12].

treatment for gastrointestinal symptoms following cancer treatment.

Bowel symptoms after radiation therapy for gynecological cancer have previously been divided into five syndromes (urgency syndrome, leakage syndrome, excessive gas discharge, excessive mucus discharge, and blood discharge) [16,17]. However, our patient group was much more heterogeneous and only one third had received radiotherapy. Thus, we did not divide the symptoms into the five syndromes but merely described frequencies of specific symptoms.

During the last decade, functional results of treatment for cancer in the pelvic organs have received increasing attention. Radiotherapy of the pelvic region and abdominal surgery may cause bacterial overgrowth and bile acid malabsorption [8,18,19]. This is consistent with the present results, where almost 70% of the tested patients had small intestinal bacterial overgrowth. The use of breath tests to identify bacterial overgrowth has been questioned. Sensitivity ranges but can be improved by combining tests for both hydrogen and methane [20]. Some clinicians favor endoscopy with duodenal aspirate as the diagnostic test for small intestinal bacterial overgrowth. One advantage of this approach is that the type of bacteria and their sensitivity to antibiotics can be identified. The main limitations are the necessity of endoscopy and that only aspiration from the duodenum can be used. In our cohort, several patients responded to antibiotics. Unfortunately, the dysmotility or structural abnormalities predisposing to bacterial overgrowth in the small intestine are chronic and symptoms returned in four of our patients. Hence, some patients may need repeated treatments of antibiotics, and in some patients the bacterial overgrowth is untreatable [19].

The risk of having bile acid diarrhea after resection of the terminal ileum depends on the length of the resected segment [21]. During right-sided hemicolectomy for cancer, only a minor resection of the terminal ileum is performed. Despite this, 18 of our 31 patients treated for cancer in the right colon had BAM. Whether this is due to the ileal resection alone, or the loss of the ileocecal valve contributes, remains obscure. Small intestinal bacterial overgrowth may cause deconjugation of bile acids in the ileum and thereby BAM. Hence, all of our patients were treated with antibiotics first if both bacterial overgrowth and BAM were detected.

The golden standard for diagnosis of BAM is analysis of bile acids in stools collected during 24 h, but the test is

cumbersome. However, SeHCAT scan is a safe alternative with high sensitivity and specificity [22,23]. In our cohort, 29 patients had severe to moderate BAM based on SeHCAT. Future studies are necessary to establish whether BAM is so common after right-sided hemicolectomy that patients should be treated empirically with bile acid sequestrants. It is, however, clinically important that BAM is not restricted to patients in whom ileal resection has been performed. Thus, 59% [40.7–76.5%] of our patients treated for cancer outside the right colon had BAM.

Once identified, BAM is usually treatable with the bile acid sequestrants cholestyramine or colesevelam. In our cohort, 32 out of 36 treated patients responded to bile acid sequestrants. However, time is needed to find the individual dose necessary to alleviate symptoms without having significant side effects [24,25]. Long-term follow-up of a large cohort of patients with bile acid diarrhea of various etiologies showed that only half of the patients had sufficient symptom relief from the bile acid sequestrants [26]. Strict attention to find the correct dose of sequestrants combined with dietary intervention with a low-fat diet may improve this number.

It is noteworthy that in three patients (5%), we found a specific cause of bowel dysfunction unrelated to treatment for cancer. This is in accordance with a previous report [19] and underlines the need for general evaluation of gastrointestinal symptoms.

A group of patients was seen by our dietician either because no underlying specific cause was found or because targeted treatment of bowel symptoms was insufficient. Patients with BAM were instructed in a low-fat diet, while patients with bloating and loose stools were instructed to reduce dietary fibers and four patients were instructed in a low FODMAP diet. However, the effect of the low FODMAP diet is controversial and the risk of inadequate nutrition has been discussed [27]. All patients reported improvement in bowel function after dietary adjustments. This is in accordance with Gupta et al. [11], who treated patients with BAM with low-fat diet. However, long-term compliance might be a challenge and future studies should clarify the role of dietary intervention in patients with chronic bowel dysfunction following treatment for cancer in the pelvic region.

The time from cancer treatment to referral to our clinic varied from 1 to 36 years. This probably reflects clinical practice and referral patterns and illuminates the unfulfilled need for regular follow-up and referral of patients with bowel dysfunction. Some patients ($n=5$), who had symptom relief by simple measures, had suffered unnecessarily for more than 20 years.

There are several limitations to the present study. Most prominent is the lack of a standardized evaluation program for the first patients seen in our clinic. Tests were made based on the patients' most prominent symptoms. This practice changed as data from the United Kingdom showed that the presence of symptoms poorly predict the underlying pathophysiology [15]. Hence, we may have underestimated the proportion of patients with more than one cause of bowel dysfunction. Some patients might have changed their

diet without seeing our dietician. Similarly, some patients might themselves have taken loperamide, psyllium fibers, or other medication, while they were treated in the clinic. Therefore, some of the improvements might be a result of the combined treatment. Moreover, our clinical service to this patient group is new and the follow-up period is short. Results from long-term follow-up will be available in the future.

In conclusion, many survivors of cancer in the pelvic region suffer from chronic bowel symptoms due to bile acid malabsorption or small intestinal bacterial overgrowth. A substantial proportion of the patients benefit from targeted treatment with bile acid sequestrants and antibiotics or from simple dietary intervention and loperamide. We recommend that all survivors of cancer in the colon or pelvic organs, who have chronic bowel dysfunction, should be referred to a specialist with the aims of identifying an underlying cause and initiate relevant treatment.

Disclosure statement

The authors report no conflicts of interest.

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