JOURNAL OF DRUG ASSESSMENT
2018, VOL. 7, NO. 1, 28–33
https://doi.org/10.1080/21556660.2018.1467916
Article 0004/1467916

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Lanreotide in the prevention and management of high-output ileostomy after colorectal cancer surgery

Pieter-Jan Cuyle[a], Anke Engelen[a], Veerle Moons[a], Tim Tollens[b] and Saskia Carton[a]

[a]Department of Gastroenterology/Digestive Oncology, Imelda General Hospital, Bonheiden, Belgium; [b]Department of Abdominal Surgery, Imelda General Hospital, Bonheiden, Belgium

ABSTRACT

Objective: Patients with stage III and high-risk stage II colorectal cancer (CRC) are advised to initiate adjuvant treatment as soon as feasible and certainly before 8 to 12 weeks after resection of the tumor. A protective ileostomy is often constructed during surgery to protect a primary anastomosis "at risk", especially in rectal cancer surgery. However, up to 17% of patients with a stoma suffer from high output, a major complication that can prevent adjuvant treatment implementation or completion. To avoid delay or cancellation of adjuvant therapy after CRC resection, effective strategies must be implemented to successfully treat and/or prevent high-output stoma (HOS).

Methods: We report two clinical case reports clearly demonstrating the impact and management of HOS in this setting. A review of the available literature and ongoing clinical studies is provided.

Results: The clinical cases describe patients with advanced stage CRC and focus on the different strategies for HOS management, presenting their outcome and how each strategy affects the implementation of adjuvant treatment. The patient population with the highest risk of developing HOS is described, along with the rationale for using somatostatin analogs, such as lanreotide, to treat and prevent high output.

Conclusion: In patients with CRC and protective ileostomies after primary resection, HOS could be treated with somatostatin analogs in combination with dietary recommendations and Saint Mark's solution. The role of this therapeutic approach as a preventive strategy in patients at high risk of developing HOS, deserves further exploration in a prospective randomized clinical trial.

ARTICLE HISTORY
Received 12 February 2018
Accepted 22 March 2018

KEYWORDS
Somatostatin analogs; lanreotide; ileostomy; high-output stoma; colorectal cancer

Introduction

Colorectal cancer (CRC) is the third most common tumor in man, and the second most common in women, in the European population, accounting for 13.2% of all new cancer cases in men and 12.7% in women [1]. In 2012, the number of new cases of CRC was 46.3 per 100,000 person-years, and the number of deaths was 18.4 per 100,000 person-years [1]. The treatment options for CRC are largely based on the type and stage of cancer. They include surgery, chemotherapy, radiotherapy, and targeted therapies, alone or in combination [2,3].

Adjuvant treatment with systemic chemotherapy aims at a reduction of relapse risk and death in CRC. Administration of adjuvant treatment is recommended in stage III and high-risk stage II CRC patients [4]. Adjuvant treatment is to be administered after primary tumor resection; its timely initiation and completion determine its effectiveness and the prognosis of the disease [5]. According to the European Society for Medical Oncology (ESMO) guidelines, adjuvant treatment should start as early as possible from the fourth week (in rectal cancer) or third week (in colon cancer) after primary resection, and not later than 8–12 weeks after the surgery [6]. However, adjuvant treatment should not be initiated in case of an inadequate postoperative recovery or pelvic septic complications [6].

Surgery is a common treatment option for CRC without distant metastases. In patients with CRC, a segmental colorectal resection and anastomosis may be performed to remove the area containing the primary tumor. In particular, during a low anterior resection and/or total mesorectal excision, it is customary to create a temporary diverting stoma (i.e. a surgically created opening in the abdomen for the discharge of fecal contents). Stomas promote anastomotic healing and prevent complications such as pelvic sepsis, caused by anastomotic leakage, which is more frequent in cases of low pelvic anastomosis [7,8]. A Cochrane review of randomized trials involving patients with rectal cancer concluded that using a diverting stoma after a low anterior resection decreases the leak ratio from 19.6% to 6.3% [9].

Even though ostomies are low-risk surgical procedures from a technical point of view, they carry peri- and postoperative risks that need to be accurately assessed, mainly depending on the type of stoma constructed. The decision between ileostomy or colostomy construction is currently a matter of debate and sometimes reflects a personal choice of the gastrointestinal surgery team rather than being based on established guidelines. However, results from a Cochrane review and a meta-analysis provided evidence that ileostomy may be preferable to colostomy, as ileostomy is associated

CONTACT Pieter-Jan Cuyle Pieter-Jan.Cuyle@imelda.be Imeldalaan 9, 2820 Bonheiden, Belgium

Table 1. Risk factors for developing high-output stoma[17–20].

Age >65 years
Hypertension
Intraabdominal sepsis
Enteric infection
Partial or intermittent bowel obstruction
Low intestine absorptive surface (due to bowel resection, Crohn's disease, etc.)
Administration of prokinetics or metformin
Withdrawal of steroids or opiates
Conditions associated to electrolyte and fluid imbalances (e.g. thyroid/parathyroid disorders, renal disease, alcohol abuse, cirrhosis)
Chemotherapy treatment with known risk of diarrhea and intestinal mucositis

with a lower risk of stoma prolapse and fewer complications upon stoma reversal compared to colostomy [10,11]. As a result, most colorectal surgeons currently prefer ileostomy.

Nevertheless, ileostomies are associated with additional morbidities. High-output stoma (HOS) is one of the most clinically relevant complications. The normal output of a stoma can vary from 500 to 2000 mL per day, depending on the amount of liquids and food ingested and the volume of gastrointestinal secretions [12,13]. Although there is no consensus definition of HOS in the literature, HOS becomes clinically relevant when it causes significant morbidity, such as dehydration, electrolyte imbalance, renal failure, and malnutrition. These alterations are more likely to occur when the daily stoma output exceeds 2000 mL, but complications can also occur with a lower stoma output. As the stoma effluent is rich in fluids and sodium, dehydration and hyponatremia are the first symptoms. Further complications include hypomagnesemia, hypokalemia, renal failure, and malnutrition. Depending on the time of onset, HOS can be classified as early (<3 weeks after initial ostomy surgery) or late HOS (≥3 weeks after surgery) [14]. In the literature, the reported incidence ranges between 0.8% and 16.7%, which may reflect the lack of consensus definition [14–16]. Some patients are at a higher baseline risk of developing HOS due to the presence of certain risk factors (Table 1) [17–20]. In the setting of cancer treatment, chemotherapy-induced diarrhea and intestinal mucositis are frequent triggers for HOS development and/or worsening [20].

Even though no consensus guidelines exist on the management of HOS, the most commonly used strategies for HOS treatment focus on identifying its etiology and treating both the causes and the symptoms (Table 2). In most cases, a combination of dietary recommendations, use of an oral rehydration solution with sodium content ≥90 mmol/L (Saint Mark's solution) [21], and reduction of gastrointestinal secretions with somatostatin analogs (SSAs) may prove an effective strategy for managing HOS. This combinatorial strategy could also be considered to prevent the development of HOS in patients at high risk, especially if the occurrence of HOS would be life-threatening or would compromise the delivery of any concomitant treatment needed.

In this regard, patients with stage III and high-risk stage II CRC are advised to start adjuvant treatment not later than 8–12 weeks after primary resection of the tumor [6]. However, the occurrence of HOS before or during adjuvant chemotherapy will likely result in treatment delay, incomplete delivery, or cancellation. This might result in a reduced efficiency of the chemotherapy and a worse prognosis of the tumor. Therefore, a correct prevention and management of HOS would be expected to result in better oncological outcomes.

Table 2. Management of high-output ileostomy.

Identify potential causes and treat them, if any
Intraabdominal sepsis
Partial/intermittent bowel obstruction
Recurrent bowel disease (e.g. Crohn's disease)
Medication/drugs (e.g. prokinetics, metformin, withdrawal of steroids, cytotoxic agents)
Enteric infection (e.g. Clostridium, Salmonella)
Monitor and reduce fluid and electrolyte[a] losses
Restrict oral intake of hypo- and hypertonic fluids to 0.5–1 L
Implement an oral glucose/electrolyte solution containing >90 mmol/L sodium (e.g. Saint Mark's solution: 20 g glucose, 3.5 g sodium chloride, and 2.5 g sodium bicarbonate in 1 L water; ≥1 L solution per 24 h)
Implement drug therapy
○ Antimotility drugs (e.g. loperamide, codeine phosphate)
○ Drugs that inhibit gastric acid secretion (e.g. omeprazole, cimetidine)
○ Drugs that inhibit broad gastrointestinal secretions (e.g. lanreotide, octreotide)
Implement parenteral/intravenous therapy to maintain hydration and electrolyte balance
Monitor renal function and treat any alteration
Monitor nutritional status and support it, if needed

[a]Magnesium, calcium, phosphorus, potassium, and sodium should be closely monitored.

The objective of this article is to discuss the potential clinical impact of HOS on adjuvant treatment in CRC patients, and how SSAs, such as lanreotide, can provide benefits in the management of HOS. First, two clinical cases are described, illustrating different strategies for HOS management in patients with advanced-stage CRC: dietary recommendations and efforts to reduce fluid and electrolyte losses were similar in both cases, but one of the patients received lanreotide and the other patient did not. The impact of each treatment strategy on the initiation of adjuvant treatment, along with the outcome of the disease, is reported. Finally, we discuss the rationale and available evidence for using SSAs in the management and prevention of HOS in patients at high risk.

Case description

Case A

An 80-year-old Caucasian man presented in November 2012 with an invasive, moderately differentiated adenocarcinoma of the proximal rectum, diagnosed as cT2N0M0 by CT scan, pelvic magnetic resonance imaging (MRI), and transrectal ultrasonography. At primary resection surgery, the tumor was re-assessed as pT4aN2a with vascular and perineural invasion, and an R0 resection was performed together with a protective ileostomy. Several poor prognostic risk factors were identified in this stage III tumor and 6 months of adjuvant chemotherapy with mFOLFOX-6 were recommended by the multidisciplinary team, to be started as soon as feasible.

However, after the primary surgery, the patient developed a HOS episode for which he was treated with dietary recommendations, adjustment of fluid and salt intake, and parenteral administration of fluids and electrolytes. Nonetheless, persistent clinically relevant HOS was diagnosed at the day of planned adjuvant treatment start (9 weeks post-surgery), inevitably leading to readmission and postponement of the adjuvant treatment. An advanced ileostomy reversal surgery was performed 1 week later. At 12 weeks post-resection, the

patient still presented a slow recovery from the reversal surgery, and the decision was made to cancel adjuvant therapy because of the delay outside the recommended postoperative window.

One year later, in December 2013, small lung metastases were detected but no treatment was implemented due to age, low tumor burden, slow progression rate, and asymptomatic status of the patient. In March 2015, a local recurrence causing urge incontinence was diagnosed, for which the patient underwent palliative radiotherapy (12×3 Gy) and modified de Gramont chemotherapy in the following 3 months. However, both treatments had to be interrupted because of multiple physical complaints. In January 2016, the patient had a colostomy surgery to treat his invalidating fecal incontinence, and supportive care was implemented at that moment. At the last contact with the patient, in September 2016, an adenocarcinoma was detected in the stomach, for which the patient refused any further exploration or treatment.

Case B

A 68-year-old Caucasian woman presented in May 2016 with symptoms of a colouterine fistula and was diagnosed with a cT4N2M0, moderately-to-poorly differentiated sigmoid adenocarcinoma. The tumor expanded into the uterus and presented with multiple locoregional adenopathies, but without arguments for distant metastases. Due to relatively young age and excellent performance status, the patient underwent an aggressive surgical approach with cytoreductive surgery (omentectomy, cholecystectomy, appendectomy, en bloc hysterectomy, rectosigmoidectomy, and bilateral adnexectomy) and hyperthermic intraperitoneal chemotherapy (HIPEC) procedure with oxaliplatin and 5-fluorouracil/leucovorin to prevent peritoneal recurrence in the future. Final pathology showed a pT3N0 tumor with prominent perforation but surprisingly no direct malignant invasion of the uterus. A protective ileostoma was placed during the surgery.

Six weeks after the primary resection, the patient presented with HOS, vomiting, and acute renal insufficiency. Upon treatment with a combination of dietary recommendations, Saint Mark's solution, and the SSA lanreotide (Somatuline® Autogel® 120 mg every 4 weeks, Ipsen), the patient showed a fast, favorable evolution and was able to start adjuvant treatment (mFOLFOX-6) approximately 7 weeks after the primary tumor resection.

After one cycle (2 weeks), mFOLFOX-6 was replaced by modified de Gramont chemotherapy due to postoperative general weakness of the patient. Under this intensified supportive therapy for HOS, the patient was able to complete 6 months of adjuvant treatment. No disease recurrence was detected at the last follow-up, in April 2017.

Discussion

We present two clinical cases illustrating the impact of different management strategies for HOS on the implementation of adjuvant treatment after CRC surgery. Both patients had high-risk tumors that were surgically treated with curative intention and presented a clear indication for additional adjuvant chemotherapy. In both patients, the protective ileostomy was complicated by clinically significant HOS, requiring hospital admission. Despite supportive treatment and preventive measures in case A, the HOS episode was poorly controlled and mandated an early ileostomy reversal. As often seen in clinical practice, the two consecutive surgical interventions in a short time interval prevented sufficient patient recovery to allow for adjuvant treatment initiation within the meaningful window of 12 weeks. Whether or not related to the lack of adjuvant treatment, this patient suffered an early disease relapse.

In case B, the supportive and preventive measures taken (including administration of lanreotide) were effective enough to allow completion of adjuvant treatment and, up to present, no disease recurrence has occurred.

These cases clearly highlight the clinical impact of HOS in patients with advanced-stage CRC who require adjuvant treatment after tumor resection. An adequate management of HOS is crucial for a timely initiation and completion of the adjuvant treatment. The authors recognize that several factors might have influenced the outcome in these patients, and that the cases reported cannot be used to determine the efficacy of the different treatment strategies described.

Adjuvant treatment is indicated in patients with stage III and high-risk stage II CRC, and should be initiated as soon as possible after primary resection [4]. The effectiveness of adjuvant treatment decreases with increasing time between surgery and treatment initiation. A >8-week delay in adjuvant treatment in resected stage III colon cancer is associated with higher mortality [5]. A meta-analysis showed that, in patients with resected CRC, a 4-week increase in the time to adjuvant treatment start was associated with lower overall survival (hazard ratio [HR]: 1.14; 95% confidence interval [CI]: 1.10–1.17) and disease-free survival (HR: 1.14; 95% CI: 1.10–1.18) [22]. A retrospective study in patients with rectal cancer showed that readmission within 60 days of primary resection, most commonly HOS-related, was associated with a delay in adjuvant chemotherapy initiation (odds ratio [OR]: 3.01; 95% CI: 1.42–6.38) [23].

A loop ileostomy is usually preserved for at least 6 weeks to allow anastomotic healing, after which it can be reversed providing that no anastomotic leakage has occurred. In the clinical practice, chemotherapy should be postponed an additional 4-week period after the reversal surgery to allow for wound healing and restoration of natural transit. However, considering that adjuvant treatment should not be initiated later than 8–12 weeks after the primary resection surgery [6], the aim is usually to start and complete adjuvant treatment with the stoma in place. As illustrated in the clinical cases presented here, early recognition and aggressive treatment of clinically relevant HOS are mandatory to preserve correct adjuvant treatment delivery.

Ideally, preventive strategies should be implemented in selected patient populations at risk. Several risk factors associated with HOS development have been identified in the literature (Table 1). The loss of intestinal absorptive surface, typical of patients with a previous bowel resection or with inflammatory conditions such as Crohn's disease, leads to an

increase in stoma output, a failure in maintaining the balance of certain electrolytes, and a reduction in nutrient absorption [18]. In addition, patients with an ileal resection have the fat stimulation of their ileal brake removed, which increases their gastric emptying rate and decreases their small intestine transit time [24].

HOS can also be caused by enteric infections. HOS-related enteritis is mostly caused by *Clostridium difficile*, but other bacteria (such as *Salmonella spp*) or viruses can be involved [19]. An early identification of the causal agent with specific laboratory tests is crucial to implement the correct treatment and prevent the mortality associated with this condition, which is remarkably high in patients with total colectomy [25]. Presence of intraabdominal sepsis (at first presentation, for example with gastrointestinal perforation, or at a later phase, secondary to anastomotic leakage) can also cause HOS. In these cases, the treatment is based on a rapid, appropriate surgical intervention and on parenterally administered antibiotics.

Certain pharmacological treatments can increase the risk of HOS. The administration of prokinetics or metformin and the withdrawal of steroids or opiates can increase the output of a stoma [19]. Patients under these treatments should be carefully monitored for early recognition of HOS.

Age >65 years and hypertension have also been correlated with higher risk of HOS and might identify good candidates for preventive measures [17]. Older patients may have altered physiology of water absorption in the small intestine, resulting in a lower capacity to absorb water. In addition, they frequently suffer from comorbidities that decrease the ability to tolerate fluid shifts, such as altered renal function. Hypertension may worsen the clinical impact of HOS if certain antihypertensive drugs are used. Thiazide diuretics and angiotensin-converting enzyme inhibitors, both used as first-line therapy in some patients with hypertension, can contribute to dehydration, acute renal insufficiency, and electrolyte imbalances [17]. By extension, patients with conditions that are associated with electrolyte and water imbalances or with concomitant/previous renal impairment can also be considered at high risk of HOS.

We propose that CRC patients with a protective ileostomy presenting with any of these risk factors should not only be closely monitored, but also receive adequate prophylactic treatment against HOS. Such treatment could consist of the combination of dietary recommendations, Saint Mark's solution, supportive medication, and SSAs. The use of SSAs is supported by extensive clinical experience in several indications that require a reduction of gastrointestinal secretions, such as refractory diarrhea, gastrointestinal fistulas, small bowel obstruction, conservative management of gastrointestinal perforation, dumping syndrome, and perioperative management in gastrointestinal surgery [26–32].

SSAs have greater potential in reducing stoma output through their broad inhibitory action on gastrointestinal secretions compared to proton pump inhibitors, which inhibit only gastric acid secretion [33–36]. Lanreotide also increases the duodeno-cecal transit time, promoting the retention of gastrointestinal content [34]. Antimotility agents such as loperamide can be co-administered with SSAs to increase the gastrointestinal transit time.

In a study conducted in severe short bowel syndrome patients with an ileostomy, the SSA octreotide significantly reduced the daily stoma output and the loss of sodium and chloride. The patients also reported easier management of the ileostomy and a reduction in thirst [37]. Ladefoged et al. conducted a double-blind, placebo-controlled balance study and found that patients with a short bowel and a jejunostomy who were treated with octreotide showed reduced stoma output and increased sodium intestinal absorption [38]. Other studies and case reports have reported similar benefits of octreotide in HOS [39–42]. The use of lanreotide for the treatment of HOS has been less extensively studied than the use of octreotide. In a previously published case report, a patient with subtotal colectomy and ileorectal anastomosis suffering from persistent diarrhea (for more than 1 year) was successfully treated with lanreotide. One month after a single subcutaneous injection of lanreotide 120 mg the diarrhea resolved, both the patient's stool transit and quality of life were improved [27]. In an exploratory, controlled clinical trial in patients with idiopathic refractory diarrhea, 51.5% of the patients showed response to lanreotide at day 56 (120 mg lanreotide injections were given at day 0 and day 28). In patients on lanreotide treatment, the number of stools per day decreased significantly from 5.7 at baseline to 3.7 at day 56, and clinically meaningful improvements were found in disease-specific quality of life [26].

Despite the evidence above, more data from randomized clinical studies are needed to support the use of SSAs in the treatment and prevention of HOS. Currently, several clinical trials are assessing the benefits of SSAs other than octreotide in HOS. The ongoing LIFE study (EudraCT: 2013-003998-10) is investigating the use of lanreotide to reduce output in patients with high-output enterocutaneous fistula or enterostomy, compared to the standard of care. The ILEHOS study (NCT02354768) is an ongoing multicenter, randomized trial evaluating the efficacy of lanreotide combined with anti-diarrheal drugs as first-line treatment in HOS, compared to anti-diarrheal drugs alone. The SOMILEO study (NCT02713776) is an upcoming pilot, double-blind, randomized, placebo-controlled trial that will evaluate the effect of the SSA pasireotide on the effluent volume of patients with enterostomas.

Data coming from these and new clinical studies in the next years will provide experts with more evidence to create official, consistent guidelines for HOS treatment, and to implement new strategies for the prevention of ileostomy-related complications.

Conclusions

The two cases presented here support the use of lanreotide for the effective management of high-output ileostomy. In patients with CRC and protective ileostomies after primary resection, HOS could be treated with SSAs in combination with dietary recommendations and Saint Mark's solution. The role of this therapeutic approach as a preventive strategy in patients at high risk of developing HOS, deserves further

exploration in a prospective randomized clinical trial. The correct prevention and management of HOS is crucial to avoid delays in adjuvant treatment initiation and to improve completion rates in CRC patients, which would, in turn, improve the outcomes and prognosis of the disease.

Transparency

Declaration of funding

Medical writing services were funded by Ipsen NV.

Declaration of financial/other relationships

The authors have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. JDA peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

The authors thank Sara Rubio, PhD (XPE Pharma and Science), who provided medical writing services on behalf of Ipsen NV.

Ethics: Informed consent was obtained from the patients for publication of this manuscript.

References

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer (Oxford, England: 1990). 2013;49:1374–1403.
[2] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) Rectal Cancer; 2016.
[3] National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) Colon Cancer; 2016.
[4] Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl.6):vi64–vi72.
[5] Hershman D, Hall MJ, Wang X, et al. Timing of adjuvant chemotherapy initiation after surgery for stage III colon cancer. Cancer. 2006;107:2581–2588.
[6] Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer: a personalized approach to clinical decision making. Ann Oncol. 2012;23:2479–2516.
[7] Beets GL. Is a diverting stoma always necessary for a low anterior resection of a rectal cancer? In: Valentini V, Schmoll H-J, van de Velde CJH, editors. Multidisciplinary management of rectal cancer; Berlin Heidelberg: Springer-Verlag; 2012. p. 257–259.
[8] Hanna MH, Vinci A, Pigazzi A. Diverting ileostomy in colorectal surgery: when is it necessary? Langenbecks Arch Surg. 2015;400:145–152.
[9] Montedori A, Cirocchi R, Farinella E, et al. Covering ileo- or colostomy in anterior resection for rectal carcinoma. Cochrane Database Syst Rev. 2010;12(5):CD006878.
[10] Guenaga KF, Lustosa SA, Saad SS, et al. Ileostomy or colostomy for temporary decompression of colorectal anastomosis. Cochrane Database Syst Rev. 2007;24(1):CD004647.
[11] Tilney HS, Sains PS, Lovegrove RE, et al. Comparison of outcomes following ileostomy versus colostomy for defunctioning colorectal anastomoses. World J Surg. 2007;31:1142–1151.
[12] Debongnie JC, Phillips SF. Capacity of the human colon to absorb fluid. Gastroenterology. 1978;74:698–703.
[13] Phillips SF, Giller J. The contribution of the colon to electrolyte and water conservation in man. J Lab Clin Med. 1973;81:733–746.
[14] Baker ML, Williams RN, Nightingale JM. Causes and management of a high-output stoma. Colorect Dis. 2011;13:191–197.
[15] Arenas Villafranca JJ, López-Rodríguez C, Abilés J, et al. Protocol for the detection and nutritional management of high-output stomas. Nutr J. 2015;14:45.
[16] Kwiatt M, Kawata M. Avoidance and management of stomal complications. Clin Colon Rect Surg. 2013;26:112–121.
[17] Chun LJ, Haigh PI, Tam MS, et al. Defunctioning loop ileostomy for pelvic anastomoses: predictors of morbidity and nonclosure. Dis Colon Rect. 2012;55:167–174.
[18] Peter C, Neil H. Ostomy management. In: Yeo CJ, McFadden DW, Pemberton JH, et al. editors. Shackelford's surgery of the alimentary tract. Philadelphia (PA): Elsevier Health Sciences; 2012. p. 2248–2261.
[19] Nightingale J, Woodward JM. Guidelines for management of patients with a short bowel. Gut. 2006;55:iv1–iv12.
[20] Stein A, Voigt W, Jordan K. Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol. 2010;2:51–63.
[21] Forbes A. Intestinal failure and short bowel syndrome. Medicine. 2003;31:98–100.
[22] Biagi JJ, Raphael MJ, Mackillop WJ, et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. JAMA. 2011;305:2335–2342.
[23] Phatak UR, Kao LS, You YN, et al. The impact of ileostomy-related complications on the multidisciplinary treatment of rectal cancer. Ann Surg Oncol. 2014;21:507–512.
[24] Nightingale JM, Kamm MA, van der Sijp JR, et al. Disturbed gastric emptying in the short bowel syndrome. Evidence for a 'colonic brake'. Gut. 1993;34:1171–1176.
[25] Lundeen SJ, Otterson MF, Binion DG, et al. *Clostridium difficile* enteritis: an early postoperative complication in inflammatory bowel disease patients after colectomy. J Gastrointest Surg. 2007;11:138–142.
[26] Bisschops R, De Ruyter V, Demolin G, et al. Lanreotide autogel in the treatment of idiopathic refractory diarrhea: results of an exploratory, controlled, before and after, open-label, multicenter, prospective clinical trial. Clin Ther. 2016;38:1902–1911 e1902.
[27] Schoeters P, De Pooter K. Lanreotide autogel in the treatment of persistent diarrhea following a total colectomy. Case Rep Gastrointest Med. 2015;2015:686120.
[28] Peeters M, Van den Brande J, Francque S. Diarrhea and the rationale to use Sandostatin. Acta Gastroenterol Belg. 2010;73:25–36.
[29] Gayral F, Campion JP, Regimbeau JM, et al. Randomized, placebo-controlled, double-blind study of the efficacy of lanreotide 30 mg PR in the treatment of pancreatic and enterocutaneous fistulae. Ann Surg. 2009;250:872–877.
[30] Szilagyi A, Shrier I. Systematic review: the use of somatostatin or octreotide in refractory diarrhoea. Aliment Pharmacol Ther. 2001;15:1889–1897.
[31] Nehra V, Camilleri M, Burton D, et al. An open trial of octreotide long-acting release in the management of short bowel syndrome. Am J Gastroenterol. 2001;96:1494–1498.
[32] Mulvihill SJ. Perioperative use of octreotide in gastrointestinal surgery. Digestion. 1993;54(Suppl.1):33–37.
[33] Drewe J, Sieber CC, Mottet C, et al. Dose-dependent gastrointestinal effects of the somatostatin analog lanreotide in healthy volunteers. Clin Pharmacol Ther. 1999;65:413–419.
[34] Lamrani A, Vidon N, Sogni P, et al. Effects of lanreotide, a somatostatin analogue, on postprandial gastric functions and biliopancreatic secretions in humans. Br J Clin Pharmacol. 1997;43:65–70.
[35] Sobhani I, Rene E, Ramdani A, et al. Lanreotide inhibits human jejunal secretion induced by prostaglandin E1 in healthy volunteers. Br J Clin Pharmacol. 1996;41:109–114.

[36] Harris AG. Somatostatin and somatostatin analogues: pharmacokinetics and pharmacodynamic effects. Gut. 1994; 35:S1–S4.

[37] Kusuhara K, Kusunoki M, Okamoto T, et al. Reduction of the effluent volume in high-output ileostomy patients by a somatostatin analogue, SMS 201-995. Int J Colorect Dis. 1992;7:202–205.

[38] Ladefoged K, Christensen KC, Hegnhoj J, et al. Effect of a long acting somatostatin analogue SMS 201-995 on jejunostomy effluents in patients with severe short bowel syndrome. Gut. 1989;30:943–949.

[39] Neef B, Horing E, von Gaisberg U. Successful treatment of a life-threatening ileostomy diarrhea with the somatostatin analog octreotide. Deutsche Med Wochenschrift (1946). 1994;119:869–874.

[40] Nightingale JM, Walker ER, Burnham WR, et al. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. Aliment Pharmacol Ther. 1989;3:367–373.

[41] Shaffer JL, O'Hanrahan T, Rowntree S, et al. Does somatostatin analogue (201–995) reduce high output stoma effluent? A controlled trial. Gut. 1988;29:A1432–A1433.

[42] Cooper JC, Williams NS, King RF, et al. Effects of a long-acting somatostatin analogue in patients with severe ileostomy diarrhoea. Br J Surg. 1986;73:128–131.