Colorectal surgery: optimisation of functional results and management of complications
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Neorectal irritability after short term preoperative radiotherapy and surgical resection for rectal cancer
**ABSTRACT**

**Objectives:** Preoperative radiotherapy followed by rectal resection with total mesorectal excision (TME) and coloanal anastomosis severely compromises anorectal function, which has been attributed to a decrease in neorectal capacity and neorectal compliance. However, to what extent altered motility of the neorectum is involved, is still unknown. The aim of the study was to compare the motor response to (prolonged) filling of the (neo)rectum in patients after preoperative radiotherapy and rectal resection with that in healthy volunteers (HVs).

**Methods:** Neorectal function (J-pouch or side-to-end anastomosis) was studied in 15 patients (median age 61 years, 10 males) 5 months after short term preoperative radiotherapy (5x5 Gy) and rectal resection with TME for rectal cancer and compared with that of 10 volunteers (median age 41 years, 7 males). Furthermore, patients with a colonic J-pouch anastomosis (n=6) were compared with patients with a side-to-end anastomosis (n=9). (Neo)rectal sensitivity was assessed using a stepwise isovolumetric and isobaric distension protocol. (Neo)rectal motility was determined during prolonged distension at the threshold of urge to defaecate.

**Results:** The neorectal volume of patients at the threshold of urge to defaecate (125 ± 45 ml) was significantly lower when compared with that of HVs (272 ± 87 ml, p<0.05). The pressure threshold, however, did not differ between patients (26 ± 9 mmHg) and HVs (21 ± 5 mmHg) and neither did the pressure threshold differ between patients with a J-pouch and side-to-end anastomosis. In HVs, no rectal contractions were observed during prolonged rectal distension. In contrast, in all 15 patients, prolonged isovolumetric and isobaric distension induced 3 (range 0-5) rectal contractions/10 min, which were associated with an increase in sensation in half of the patients.

**Conclusions:** Patients who underwent preoperative radiotherapy and rectal resection with TME, but not HVs, developed contractions of the neorectum in response to prolonged distension. We suggest that this neorectal ’irritability’ represents a new pathophysiological mechanism contributing to the urgency for defaecation after this multimodality treatment.

**INTRODUCTION**

Short term preoperative radiotherapy (5x5Gy) followed by rectal resection with total mesorectal excision (TME) is currently considered the treatment of choice for patients with a resectable rectal carcinoma.\(^1,2\) During surgery, a neorectum is created using the sigmoid colon or descending colon. After this multimodality treatment, anorectal function is often compromised as reflected by an increase in the frequency and urgency of defaecation and by incontinence.\(^3,4\) Recent research shows that up to 60% of patients experience some degree of incontinence.\(^5,6\) Suggested explanations for the impaired functional outcome include decreased internal and external anal sphincter function because of direct injury of the nervous supply,\(^7,15\) the low level of anastomosis,\(^14-16\) impaired neorectal capacity and decreased compliance,\(^7,9,10,17\) and the loss of rectal sensation.\(^18-20\)

Feacal continence results from the complex interplay between the rectum, the anal sphincter complex, the musculature of the pelvic floor, and the nerves innervating these structures. In addition to sphincter pressure generated by the anal sphincter, the importance of the rectum as a reservoir in warranting continence is increasingly appreciated. Arrival of feacal contents in the rectum will not only generate the sensations of urge, but will also trigger an adaptive relaxation of the musculature, thus creating a reservoir. This relaxation, together with anal sphincter contraction, is an important factor in the ability to defer defaecation.\(^21-23\) Abnormalities in rectal reservoir capacity, either because of impairment of this relaxation or decreased compliance (fibrosis because of earlier radiation therapy or inflammation), are considered as having an important function in the pathogenesis of feacal incontinence and urgency.\(^4,6\) In line with this reasoning, earlier studies have shown an increase in urgency, tenesmus and defaecation frequency because of decreased neorectal reservoir capacity and decreased neorectal compliance in patients who underwent TME surgery.\(^24,25\) Reactive rectal contractions were observed at the onset of distension of a barostat balloon, and in the neorectum these contractions were followed by one or more extra contractions during distension periods of 2 min, suggesting neorectal irritability.\(^25,26\)

In this study, we want to further explore the phenomenon of neorectal contractions and hypothesise that the neorectum lacks the capacity to adapt to distension. Rectal filling with feacal content would lead to prolonged distension of the neorectum inducing neorectal contractions, subsequently contributing to the feeling of urgency. To test this hypothesis, the motor response to prolonged filling of the neorectum in patients after short term radiotherapy followed by rectal resection with TME was compared with the motor response to prolonged filling of the rectum in healthy volunteers.
During pouch formation, the circular muscle layer is transected and the propulsive direction of the distal part of the colon forming the pouch is reversed in relation to the propulsive direction of the proximal part of the colon forming the pouch, which might reduce contractility. Therefore, the motor response to rectal filling was also compared between patients with a J-pouch colorectal anastomosis and patients with a side-to-end colorectal anastomosis.

MATERIALS AND METHODS

Subjects

Fifteen patients (10 males) with a median age of 61 years (range 33-76 years) treated for rectal carcinoma located in the lower two-thirds of the rectum were evaluated. All patients had stage II disease and treatment consisted of short-term preoperative radiotherapy (5x5 Gy) followed by rectal resection with TME and colorectal anastomosis. In six patients a pouch colorectal anastomosis and in nine patients a side-to-end colorectal anastomosis was created.

None of the patients received chemotherapy and/or postoperative radiotherapy. Five months (range 4-6 months) after surgery, the patients were invited to undergo an anorectal function study. Protective loop ileostomies were closed at least 6 weeks before measurements to ensure bowel function.

In addition, ten healthy volunteers (HVs, 7 males) with a median age of 41 years (19-70 years) served as controls. None of the volunteers had either defaecation problems, as tested by the COREFO questionnaire, or a history of abdominal surgery and/or previous radio- or chemotherapy possibly compromising bowel function.

Rectal barostat and anorectal manometry

A noncompliant polyethylene bag (Figure 1) was hermetically fixed to one of two specially designed triple-lumen polyvinyl tubes and connected to the barostat. The maximum capacity of this bag was 450 ml and it had a length of 10 cm when used for patients. The maximum capacity of the bag was 600 ml and it had a length of 15 cm when used in the HVs. This balloon was connected to an electronic barostat (Synetics Medical, Stockholm, Sweden) to measure rectal compliance and rectal sensory motor function. The barostat balloons were inflated up to 10 mmHg before and after completion of the experiment to rule out any leakage of air.

A compliant latex balloon (Figure 1) was hermetically fixed onto the catheter 5 cm above the barostat balloon to allow distension of the bowel proximal to the (neo)rectum. This balloon was inflated with up to 150 ml of air before and after the completion of the experiment to rule out any leakage of air.

Figure 1 Barostat catheter with barostat balloon and latex balloon

Sphincter pressure was measured by anorectal manometry using a multi-lumen, water-perfused sleeve catheter assembly containing a 4.5 cm long sleeve and four radially distributed side holes (Dentsleeve Pty Ltd, Parkside, Australia). Each side hole was perfused with degassed water at a rate of 0.3 ml/min and intraluminal pressures were sensed by external transducers connected to a polygraph (Synetics Medical, Stockholm, Sweden).

Anorectal manometry and rectal barostat were performed simultaneously. The results were monitored and analysed with commercially available software (Polygram for Windows, version 1.11, Synetics Medical).

Positioning of the catheters

Participants received a water enema to clean the bowel and to avoid interference of stool during the measurements (Figure 2). Thereafter, the catheter with the latex balloon and barostat balloon attached was endoscopically inserted and placed in the right position with the lower edge of the barostat balloon just above the anal verge. The tip of the catheter was attached to the bowel wall using a disposable vascular clip to maintain its position. The endoscope was removed whereas the catheter was left behind in the (neo)rectum. The barostat balloon was inflated with up to 150 ml of air to allow adequate unfolding.

The anorectal manometry catheter was inserted ventrally into the barostat catheter in the anal canal. All measurements were carried out with the subjects in the left lateral position.

After the insertion of the two catheters, a recovery period of 15 min was introduced after which the minimal distending pressure (MDP) of the barostat balloon was determined. MDP is defined as the minimum pressure at which the intrabag volume is >30 ml.
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Anorectal manometry

Anorectal manometry was performed with the barostat balloon set to MDP + 2 mmHg. The mean value of the resting pressure was measured for 2 min. Thereafter, the subjects were instructed to squeeze maximally on three occasions.

Proximal colonic distension

To evaluate the response of the (neo)rectum to proximal colonic distension, the barostat balloon was set to MDP + 2 mmHg and the latex balloon was distended during 30 s in different volume steps (50 ml, 75 ml, 100 ml, 125 ml, 150 ml or until discomfort was reported).

Stepwise isovolumetric distension protocol

Isovolumetric distensions were performed beginning with volume steps of 25 ml in patients and 50 ml in HVs. Each distension lasted 1 min after which the volume was increased further until the participant reported discomfort or pain. Sensations were scored 30 s after each distension step using a 6-point scale with verbal descriptors (0 = no sensation, 1 = first sensation, 2 = first sense of urge, 3 = normal urge to defaecate, 4 = severe urge to defaecate, 5 = discomfort/pain). Sensations were logged onto the data file at each score point. If the participant reported discomfort or pain, the barostat balloon was instantly deflated.

Prolonged isovolumetric distension

To evaluate the motor response of the (neo)rectum to rectal filling, a prolonged isovolumetric distension (10 min) was performed with the volume fixed at the level of urge to defaecate (sensation 3) as scored during the preceding stepwise isovolumetric distension protocol. During the period of prolonged distension, sensations were scored every minute or when the participant indicated an increase or decrease in sensation.

Stepwise isobaric distension protocol

The stepwise isobaric distension protocol was performed beginning with fixed pressure steps of 3 mmHg above MDP with a maximum absolute pressure of 55 mmHg. Each distension lasted 1 min and sensation was scored 30 s after each distension. The barostat balloon was deflated if the participant indicated discomfort or pain (sensation 5).

Prolonged isobaric distension

A prolonged isobaric distension (10 min) was also performed to obtain information about the motor response of the (neo)rectum to rectal filling. The pressure was fixed at the level of the urge to defaecate (sensation 3) as scored during the preceding stepwise isobaric distension protocol. Sensations were scored every minute or when the participant indicated an increase or decrease in sensation.

Questionnaire

All participating patients were asked to complete a validated questionnaire preoperatively and 4 months postoperatively. This COREFO questionnaire was developed to evaluate postoperative problems thoroughly in a comprehensive manner for patients. The COREFO questionnaire consists of five multi-item scales: incontinence (9 questions), social impact (9 questions), frequency (2 questions), stool related aspects (3 questions) and need for medication (3 questions). The questionnaires were assessed in combination with objectively measured results to look for a potential correlation.

Data analysis

All data are given as mean ± s.d., unless stated otherwise. Continuous data were compared using Student’s t-test, whereas a non-parametric test (Mann-Whitney) was used in case of ordinal data. Differences were considered significant at the 5% level. The reported values for the maximum squeeze pressure are the mean of three efforts. The response during sigmoidal distension is presented as the absolute volume decrease (in ml) in the barostat balloon and as the percentage volume decrease of the barostat balloon. The barostat volume, measured just before each sigmoidal distension, was subsequently set as 100%.
A temporary increase of >10 mmHg in the barostat balloon during prolonged isovolumetric distension was considered a contraction (Figure 3). A temporary decrease of >15% of the barostat balloon volume during prolonged isobaric distension was considered a contraction (Figure 4). All tracings in Figures 3 and 4 represent a period of 10 min. (Neo)rectal capacity was determined at the end of the isobaric distension protocol. The pressure volume curves were constructed using the mean volume of the last 30 s (when equilibration of the volume was reached) at each of the consecutive pressure steps during the stepwise isobaric distension protocol. The volume-pressure curves were described with the following equation: \[ V = A(1-e^{-kp}) \], where \( V \) is the volume, \( A \) is the maximum volume, \( k \) is an expansion constant and \( p \) is pressure. Compliance is defined as \( dV/dp \) and computed at \( V/2 \) which is halfway the maximum volume. The (neo)rectal compliance was calculated using a nonlinear mixed-effect model for fitting the pressure volume curves of each individual. This analysis was performed as reported earlier by our group. Statistical evaluations were performed using commercially available software (SPSS 11.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Sphincter function

There was a significant difference in resting pressure between patients (40 mmHg, SD 15) and HVs (71 mmHg, SD 25; \( p<0.05 \)). Although the maximum squeeze pressure was lower in patients (107 mmHg, SD 47) than in HVs (153 mmHg, SD 66; \( p=0.15 \)), this difference was not statistically significant.

Proximal colonic distension-induced (neo)rectal contractions

Distension proximal of the (neo)rectum resulted in a volume decrease of the rectal barostat balloon in all patients except one. Volume decrease occurred immediately after minimal distension (50-75 ml) of the proximally located balloon. The percentage volume decrease (Figure 5) after proximal colonic distension was larger in patients than in HVs, but did not reach statistical significance. There was no difference in volume decrease between StE patients and JP patients (results not shown). Similarly, distension of the sigmoid induced a transient relaxation of the anal sphincter in all but 2 HVs. In contrast, in only one of 15 patients, did we observe a reduction in anal sphincter pressure in response to proximal colonic distension.

(Neo)rectal sensitivity

Volume controlled distension

Thresholds for 'first sensation' and 'urge to defaecate' and 'discomfort' during the stepwise isovolumetric distension protocol were smaller in patients than in HVs (Figure 6). Thresholds for 'first sensation', 'urge to defaecate' and 'discomfort' during the stepwise isovolumetric distension protocol were not different between StE and JP. In all ten HVs, 'discomfort' was reached during this protocol at a mean volume of 360 ± 97 ml. In 12 of 15 patients, the threshold of discomfort was not reached. In these patients, maximum (safety) pressure (55mmHg) was reached before the sensation of discomfort could be reported.
Pressure-controlled distension

Thresholds for 'sensation', 'urge to defaecate' and 'discomfort' during isobaric distension were not different between StE and JP patients. There was a significant difference in the threshold for 'first sensation' between patients and HVs (Table 1). Rectal capacity was significantly higher in HVs (308 ± 77 ml) than the neorectal capacity in patients (164 ± 47 ml; p=0.000). Compliance of the rectum in HVs (26 ± 8 ml/mmHg) was significantly higher than compliance of the neorectum in patients (12 ± 7 ml/mmHg; p=0.000). The compliance curves are shown in Figure 7. Compliance of the neorectum in StE patients (13 ± 9ml/mmHg) was comparable to that in JP patients (11 ± 4ml/mmHg; p=0.5).

(Neo)rectal irritability

In HVs, the mean threshold for urge was 272 ± 87 ml during isovolumetric distension and 21 ± 5 mmHg during isobaric distension. No rectal contractions were observed during either prolonged isovolumetric distension (Figure 3) or prolonged isobaric distension (Figure 4) at the threshold of urge to defaecate. The mean threshold for urge in patients was 125 ± 45 ml during isovolumetric distension and 26 ± 9 mmHg during isobaric distension. In patients, prolonged isovolumetric distension (Figure 3) at the threshold of urge to defaecate induced a median of two contractions (range 0-5) per patient with a mean increase in pressure of 21 ± 9 mmHg per contraction. During prolonged isobaric distension (Figure 4) at the threshold of urge to defaecate, a median of three contractions (range 0-5) per patient was seen with a mean volume decrease of 31 ± 16 % of the barostat balloon.

When comparing the results in the StE and JP patients, no significant differences were identified (Table 2).

In seven of 15 patients, the onset of a neorectal contraction during either prolonged isovolumetric or prolonged isobaric distension resulted in a simultaneous increase of sensation of one level in sensation score. All sensations returned to the level prior to the neorectal contraction.

COREFO Questionnaire

The overall score of the COREFO questionnaire did not differ between JP patients (29 ±10) and StE patients (36 ±19) at the time of the barostat measurements, and neither were there any differences in the five different subscales between JP patients and StE patients.
Neorectal function is often compromised after radiotherapy and rectal resection with TME, resulting in urgency for defaecation and faecal incontinence. In this study, we show that, in contrast to HVs, patients who underwent TME developed neorectal contractions in response to prolonged distension (10 minutes) suggesting increased neorectal irritability. Between patients with a colonic J-pouch anastomosis and those with a side-to-end anastomosis, no significant differences could be detected. Neorectal contractions were associated with an increase in sensation in nearly half of the patients. This motor pattern in combination with the decreased neorectal capacity, decreased neorectal compliance and decreased anal resting pressure most likely explains the occurrence of urgency in these patients.

Under physiological circumstances, the rectum acts as a reservoir and accommodates rectal filling, contributing to capacity to postpone defaecation. This motor pattern is most likely triggered by mechanoreceptors in the rectal wall. In the guinea pig rectum, a high density of slowly adapting low threshold mechanoreceptors with specialised intraganglionic laminar endings (rIGLEs) has been shown. This specialised class of mechanoreceptors probably detects both rectal distension and contraction and is likely to be involved in activation of recto-spinal pathways for defaecation. Lynn et al. recently showed that these mechanoreceptors adapted to maintained distension suggesting a function in the accommodation to rectal filling. In our study, prolonged distension at the threshold of urge to defaecate failed to induce rectal motor activity in healthy subjects. Similarly, Kwan et al. did not observe deviating rectal motor activity during prolonged rectal distension in healthy volunteers. In contrast to HVs, prolonged distension of the neorectum in patients at the threshold of the urge to defaecate triggered contractile activity, as illustrated by an increase of more than 10 mmHg in the barostat balloon during isovolumetric distension and a reduction of more than 15% of baseline volume of the barostat balloon during isobaric distension. These contractions were seen during the entire period of distension and were not limited to the first few minutes after distension. In half of the patients, a contraction was even associated with an increase in sensation. Corsetti et al. reported a similar response during a barostat procedure in healthy volunteers with the barostat balloon placed in the descending colon. Colonic contractions were observed in response to prolonged colonic distensions (30 min), which increased in frequency after the administration of neostigmine. These contractions were associated with an increase in sensation reported by the majority of volunteers (7 out of 10). We hypothesise that the contractions occurring in the neorectum during prolonged distension in our study are similar to the colonic contractions described by Corsetti et al. Comparable contractions to distension have also been shown in the guinea pig distal colon: maintained circumferential stretch resulted in an ongoing discharge of synchronised ascending excitatory and descending inhibitory neuronal pathways to the circular muscle, leading to propulsion of a bolus. In this respect, it is important to emphasise that the rIGLEs are absent in the guinea pig colon. Therefore, as the neorectum is reconstructed from sigmoid/colon descendens, the different motor response to distension in patients after TME may be explained by the absence of rIGLEs and the lack of this adaptive mechanism. On the basis of these findings, we hypothesise that filling of the neorectum with faecal material induces neorectal contractions, probably as an intrinsic property of the colon, contributing to the occurrence of urgency in patients after rectal resection. The influence of radiotherapy on neorectal irritability is probably limited, since radiation is not applied to the sigmoid or descending colon used to create a reservoir. In addition, as can be seen from the results of the isovolumetric distension

Table 2 Comparison of the neorectal irritability, neorectal volume, and neorectal compliance between J-pouch coloanal anastomosis and side-to-end coloanal anastomosis

<table>
<thead>
<tr>
<th>Volume contractions (median)</th>
<th>Increased pressure (mm Hg)</th>
<th>Pressure contractions (median)</th>
<th>Volume decrease (%)</th>
<th>Maximal volume (ml)</th>
<th>Compliance (m/l/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pouch</td>
<td>2 (± 2)</td>
<td>21 (± 9)</td>
<td>2 (± 2)</td>
<td>23 (± 17)</td>
<td>171 (± 53)</td>
</tr>
<tr>
<td>Side-to-end</td>
<td>3 (± 2)</td>
<td>20 (± 9)</td>
<td>3 (± 2)</td>
<td>37 (± 14)</td>
<td>159 (± 45)</td>
</tr>
<tr>
<td>p</td>
<td>0.7</td>
<td>0.8</td>
<td>0.4</td>
<td>0.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Values in mean, unless stated otherwise

DISCUSSION

Neorectal function is often compromised after radiotherapy and rectal resection with TME, resulting in urgency for defaecation and faecal incontinence. In this study, we show that, in contrast to HVs, patients who underwent TME developed neorectal contractions in response to prolonged distension (10 minutes) suggesting increased neorectal irritability. Between patients with a colonic J-pouch anastomosis and those with a side-to-end anastomosis, no significant differences could be detected. Neorectal contractions were associated with an increase in sensation in nearly half of the patients. This motor pattern in combination with the decreased neorectal capacity, decreased neorectal compliance and decreased anal resting pressure most likely explains the occurrence of urgency in these patients.
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protocol, the volumes triggering the different sensations are smaller in patients than in healthy volunteers as a result of decreased compliance. Therefore, sensations are reached sooner in patients, further leading to increased stool frequency.

The rectum in HVs as well as the neorectum in patients, contracted in response to sigmoidal or proximal colonic distension, representing the peristaltic reflex. This reflex consists of a smooth muscle contraction and oral and anal relaxation to the site of the stimulus, respectively, and was first described by Bayliss and Starling. The relaxation of the anal sphincter induced by distension of the sigmoid or proximal colon was observed in all but two HVs, but in only one of 15 patients. In our opinion, the transient relaxation of the anal sphincter in response to proximal colonic distension is somewhat similar to the rectal anal inhibitory reflex, and most likely represents the inhibitory wave preceding the contractile part of the peristaltic reflex, as shown earlier in studies using a double colonic barostat balloon. In addition, relaxation of the anal sphincter as part of a peristaltic wave in the colon has also been clearly shown by Herbst et al. during mass movement. We therefore believe that this relaxation of the anal sphincter indirectly shows regeneration of the enteric nervous connection between the colon and the anal sphincter. As there is no significant difference in response to sigmoidal or proximal colonic distension between HVs and patients, the peristaltic reflex seems to be undisturbed after rectal resection and does not appear to be involved in the abnormal anorectal function. This colorectal reflex has also been described in healthy volunteers in a fasting state by Ng et al.

Clinical implications

As the neuromuscular properties of the sigmoid and colon, especially the capacity to adapt to filling, are very different from those of the rectum, it seems unlikely that, when used to create the neorectum, it will be suitable to functionally replace the rectum or function as a reservoir. In this study, we provide evidence that the exaggerated motor response of the neorectum may have an important function in the impaired anorectal function of patients who underwent rectum resection. On the basis of this observation, two major therapeutic strategies could be proposed to improve the clinical outcome after such an operation. First, the formation of a J-pouch colonoanal anastomosis could theoretically lead to a reduction in urgency. During pouch formation, the circular muscle layer is transected and the propulsive direction of the distal part of the colon forming the pouch is reversed in relation to the propulsive direction of the proximal part of the colon forming the pouch. In addition, a larger neorectal capacity is created, compared with a straight or side-to-end coloanal anastomosis, most likely also contributing to impaired urgency and/or defaecation frequency. In this study patients with a J-pouch colonic anastomosis showed fewer contractions and a slightly larger maximal volume of the neorectum than patients with a side-to-end anastomosis, although these differences were not statistically significant, most likely because of the low numbers of patients studied. Many patients did not want to participate in a barostat study, as they found the study protocol too incriminating, which might have caused a selection bias. An earlier randomised trial comparing functional results of the colonic J-pouch with the side-to-end anastomosis, however, did show a higher maximum tolerated volume and threshold volume in the colonic J-pouch group at 3 and 6 months, associated with better functional results in terms of stool frequency and urge in JP patients, especially in the early postoperative phase. Another study reported a 40% greater maximum neorectal volume in the JP group at 2 years, but could not detect an influence on the function. Therefore, the impact of the type of pouch on functional outcome remains controversial.

Apart from changing the operative technique, medication reducing gastrointestinal motility could be used to reduce the occurrence of urgency. For example, the 5-HT3 receptor antagonist granisetron has been shown to inhibit postprandial contractions in patients after low anterior resection. Therefore, one might speculate that 5-HT3 receptor antagonists such as granisetron might also inhibit neorectal irritability and thus reduce urgency in these patients.

In conclusion, in patients after short term radiotherapy and rectal resection with TME, a physiological volume of stool in the neorectum will not only lead to more pronounced sensations because of the smaller neorectal capacity, but will also lead to neorectal contractions instead of neorectal accommodation. This observation does not seem to be significantly influenced by the type of coloanal anastomosis performed. We suggest that this neorectal irritability represents a new pathophysiological mechanism which contributes to urge to defaecate.

What is current knowledge: functional outcome after radiotherapy and TME rectal resection is impaired.

What is new here: neorectal irritability represents a new pathophysiological mechanism contributing to urgency.

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REFERENCES