Functional outcome and quality of life after rectal resection
van Duijvendijk, P.

Citation for published version (APA):
Chapter 3

ANORECTAL FUNCTION AFTER RESECTION OF THE RECTUM FOR CARCINOMA BY TOTAL MESORECTAL EXCISION WITH OR WITHOUT PREOPERATIVE RADIOThERAPY. A PROSPECTIVELY COMPARATIVE EVALUATION.


From the Departments of Surgery, Radiotherapy† and Gastro-enterology‡
Academic Medical Center, Amsterdam, The Netherlands
CHAPTER 3

Abstract

Background/Aims: Rectum resection with Total Mesorectal Excision (TME) and radiotherapy (RT) are the only two treatment modalities for rectal carcinoma that have been reported to improve local control and survival although anorectal function is often comprised. Data of the effect on anorectal function are however sparse. Therefore, a prospective study was designed to evaluate the effect of RT and surgery on anorectal function and clinical outcome of patients with a rectal carcinoma.

Methods: Anorectal function was studied in 34 patients, before surgery, 4 and 12 months postoperatively of which 13 were lost to follow-up. Fourteen patients were treated by surgery alone (TME) and 7 patients also received radiotherapy (RT+TME). Ano-(neo-)rectal function was examined by a symptom questionnaire, anal manometry, anal and rectal mucosal electrosensitivity, rectal compliance and sensation.

Results: Defaecation frequency increased postoperatively in both patient groups, but significantly more in RT+TME than in the TME group. Urgency and the need to wear a pad increased in RT+TME patients to 80% respectively 100% 4 months postoperatively, whereas it increased to 39% respectively 69% in TME patients. Blood loss was still reported by 33% of the RT+TME group 12 months postoperatively. Anal mucosal electrosensitivity, resting anal pressure or squeeze pressure were not affected by either treatment. Anal manometry showed short bursts of slow waves in 57% of RT+TME group, but only in 7% of the TME group. Recto-anal inhibition reflex testing provoked significantly higher neo-rectal contractions 12 months postoperatively in RT+TME patients than in TME patients. Rectal compliance was significantly lower in the RT+TME group at both 4 months postoperatively and 12 months. Pressure thresholds for first sensation and desire to defaecate did not differ, however at 30 mmHg above minimal distention pressure, 29% of the RT+TME group reached the sensation discomfort in comparison to 50% in the TME group. Rectal mucosal electrosensitivity was higher in RT+TME patients 12 months postoperatively.

Conclusions: This study showed that RT increases urgency, defaecation frequency, usage of pads and rectal blood loss, most likely due to decreased neo-rectal reservoir capacity (compliance) and increased neo-rectal contractility (distention induced contractions). In addition sensation to distention and to electrical stimuli was reduced by RT suggesting afferent nerve injury. It remains questionable whether increased survival after RT can compensate for the substantial inferior clinical outcome in this group.
Introduction

Rectal carcinoma is one of the most common forms of cancer in the Western world. Even when a resection is considered curative, the 5-year survival is only about 50%. This figure has not improved during the last decades. Disseminated disease is the most common cause of death and many patients suffer from locoregional recurrences. In 1995, 7993 new cases of colorectal cancer were registered in the Netherlands, of whom about 25% had rectal carcinoma. The basic principle in colorectal cancer treatment is wide en-bloc resection of the tumor containing bowel segment with its mesentery, vascular supply and lymph draining structures. For a long time postoperative radiotherapy after curative resection of rectum cancer has been the standard adjuvant treatment, to try to reduce the percentage of locoregional recurrences. Over the last few years two forms of treatment have been reported to improve local control. These are respectively total mesorectal excision (T.M.E.) developed separately by Heald and Enker, and pre-operative radiotherapy. Surgery and radiotherapy can be seen as synergetic modalities, because surgery fails at the margin whereas radiotherapy fails at the center of the tumor. However, in the early postoperative period after rectal resection, bowel function is often compromised, with frequent bowel movements and faecal incontinence whereas pelvic irradiation is associated with a variable degree of injury to the anus, rectum and other pelvic organs.

There is an ongoing debate about the pathophysiology of this disturbed functional outcome. Explanations for impaired anorectal function include decreased internal and external anal sphincter function due to direct damage or injury of the nervous supply, the level of the colo-anal anastomosis, impaired neo-rectal capacity and or compliance, and the loss of rectal sensation. The substantial number of studies on anal sphincter function, however, give no absolute clarification for the impaired anorectal function. Therefore more emphasis must be put on the impact of impaired neo-rectal capacity, compliance, and the change in rectal sensation. At present, few studies have prospectively evaluated rectal function, before and up to one year after rectal surgery and only two studies have compared operated patients with or without radiotherapy. Only one of them had a prospective setup. Although manometry and neo-rectal compliance measurements were performed in all studies, they only correlated the outcome to bowel frequency or to an overall score of clinical bowel function. A comparison of neo-rectal compliance and sensation between patients who underwent both radiotherapy and surgery and those who underwent surgery
alone, has not been performed. Moreover, a combination of early and late postoperative assessment to evaluate changes in anorectal motor and sensory function in time has not been carried out. Therefore, a prospectively study was designed to evaluate the effects of TME and radiotherapy on anal sphincter and ‘rectal’ function and to study the degree of adaptation in time. In addition, changes in functional outcome at different time points were evaluated in relation to the clinical outcome in order to gain more insight in the underlying pathophysiological mechanisms in these patients.

Material and methods

Subjects
Between August 1996 and June 1999, thirty-four patients who were treated for a rectal carcinoma by surgery alone, i.e., total mesorectal excision and a colo-anal anastomosis (TME group) or with additional radiotherapy (RT+TME group) were studied. Only patients with a resectable rectal carcinoma below the level of S1/S2 were included, provided that the distal border of the tumor is within 15 cm of the anal verge.

Study protocol
Patients answered a questionnaire regarding their anorectal function and were examined by means of anorectal manometry, rectal and anal mucosal electrosensory testing, pudendal nerve terminal motor latency (PNTML) time and (neo-)rectal compliance and visceral sensation measurements. This was assessed one week before surgery or radiotherapy and 4 and 12 months postoperatively. All subjects underwent bowel preparation by means of a sodium-phosphate enema either at home or at least one and a half hour before onset of the anorectal function measurements.

The questionnaire assessed defaecation frequency during day and or night-time, stool consistency, blood loss per anum, the ability to differentiate between flatus and stools, soiling during day and night-time, anal incontinence score, urgency to defaecate, episodes with passive incontinence, loss of a large quantity, urinary incontinence, the need to wear pads, sensation of incomplete evacuation, and tenesmus. The answers were characterized as never, occasional (less than once a week), frequent (at least once a week) or every day occurrence. The anal incontinence score as described by Pescatori gives an indication of the type of incontinence, i.e., incontinent for flatus, liquid and or solid stools, and the frequency, ranging from never to every day.
Subjects were placed in left lateral position for anorectal manometry. After insertion of the catheter the recordings were allowed to stabilize for 15 min, after which the mean value of the resting pressure was measured for 2 min. From this period the frequency and amplitude of slow waves as well as the organization of the wave patterns were assessed. Slow waves are generated by sinusoidal waves of electrical activity of the internal anal sphincter. Hereafter the subjects were instructed to maximally squeeze on three occasions. The terminal inflatable balloon was inflated with increasing volumes (10 to 50 ml) in order to assess a (neo)rectal-anal inhibitory reflex (RAIR). RAIR was defined as an reduction of internal anal sphincter pressure from baseline of at least 10 mmHg of 5 seconds’ duration. After removal of the manometric assembly, a ring-electrode was inserted into the (neo-)rectum approximately 10 cm above the anal verge to measure rectal mucosal electrosensitivity. A small pulsed electric current generated by a computer controlled stimulator (Dantec Keypoint, Skovlunde, Denmark) and increased until subjects reported some rectal/abdominal sensation. The amperage of first sensation was recorded on three occasions. The electrode was then positioned into the mid-anal canal and the same measurements were done to estimate the anal mucosal sensation threshold. Following these measurements the barostat-bag was inserted into the (neo-)rectum. To prevent curling-up of the bag and kinking of the catheter, the folded bag was into a non-flexible tube. After insertion of approximately 20 cm, the ‘over’ tube was withdrawn. The bag was slowly inflated with 80-125 ml to allow adequate unfolding and was then drawn back against the pelvic floor or in postoperative patients just above the anastomosis. The catheter was secured with tape to maintain its position. A recovery period of 15 min was allowed after which minimal distension pressure (MDP) was determined. Thereafter, an intermittent isobaric pressure controlled distention protocol, (pressure steps of 3 mmHg lasting 2 minutes) was started. Subjects were asked at the onset of the distension, at 30s and at 60s to score their sensation on a scale varying from (a) nothing, (b) first sensation, (c) a light desire to defaecate, (d) desire to defaecate, (e) urgent desire to defaecate, (f) intolerable discomfort. The experiment was stopped when subjects experienced intolerable discomfort or when 50 mmHg was reached. After the barostat study, three reproducible PNTML recordings were taken from each side. The protocol was approved by the Hospital Ethics Committee and informed consent was obtained from all patients.
CHAPTER 3

Equipment

Anorectal manometry
Anorectal manometry was recorded using a multi-lumen 14.5 cm long, waterperfused sleeve catheter assembly, with a 4 cm long sleeve and 5 radially distributed side holes, positioned at 1, 2, 3, 4 and 6.5 cm and a terminal inflatable balloon at 8.5 cm from the anal verge (Dentsleeve Pty Ltd, Parkside, Australia). Each sidehole 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 (Synectics Medical, Stockholm, Sweden) and monitored and analyzed with commercially available software (Polygram for Windows, Synectics Medical).

Mucosal electrosensitivity / Pudendal nerve terminal motor latency
A 1-cm long bipolar ring-electrode (Dantec 21L10, Skovlunde, Denmark) mounted on a Foley-urine catheter was used to measure the rectal and anal mucosal electrosensitivity. For measuring the PNTML time, a St. Mark’s pudendal electrode (Dantec Medical, Denmark) was used.

Rectal barostat study
To measure compliance and rectal sensitivity, an electronic barostat (Synetics Medical, Stockholm, Sweden) was used. There was a fixed pressure limit that automatically triggered balloon deflation for pressures above 55 mmHg. A non-compliant polyethylene bag was hermetically fastened to a double-lumen 12F Salem polyvinyl tube (Sherwood medical, St. Louis, USA) and connected to the barostat. The maximum capacity of the bag was 350 ml and had a maximal diameter of 11 cm and a length of 14 cm. The balloon was inflated up to 20 mmHg, prior to and following completion of the experiment to rule out any leakage of air.

Data analysis
Two way analyses of variance were used for comparison of pre- and post operative data as well as for comparison between the TME and RT+TME groups. The values reported for maximum squeeze pressure and mucosal electrosensitivity thresholds are the mean of three efforts. Non-parametric tests were used in case of ordinal data and proportions of events were compared by means of chi-square tests, values < 0.05 were considered statistically significant. Phasic volume-pressure curves for compliance calculation were obtained from mean volume values reached during each 120-second pressure step. 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 $V_{\frac{V}{2}}$, which is halfway the maximum volume. A mixed non-linear model was used to estimate the mean compliance curves for patients (pre- and postoperatively) in the TME and RT+TME groups by means of the restricted maximum likelihood method. In addition comparisons of the fixed effects estimations of the fitted compliance curves in time, and between patients the TME and RT+TME groups were performed using a Wald test on fixed effects. Overall goodness of fit was assessed by the Bayesian Information Criterion.

Results

Thirty-four patients were enrolled in the study protocol, the TME group consisted of 20 patients, and the RT+TME group contained 14 patients. Characteristics of the patient groups and details of radiation treatment are shown in Table 1.

Six patients in the TME group were lost to follow-up for various reason. Three patients withdrew themselves from the study because the investigations were regarded too strenuous. In one patient it was decided intraoperatively to perform an abdomino-perineal resection, in another patient it was intraoperatively decided to perform a Hartmann’s procedure because of peritoneal metastases, whereas the sixth patient died from septic complications.

Table 1: Details of patients treated with Total Mesorectal Excision (TME) with or without radiotherapy (RT).

<table>
<thead>
<tr>
<th>Patients</th>
<th>TME</th>
<th>RT + TME</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Mean age (years (range))</td>
<td>65 (38-83)</td>
<td>69 (38-85)</td>
</tr>
<tr>
<td>Gender (Male / Female)</td>
<td>16/4</td>
<td>9/5</td>
</tr>
<tr>
<td>Tumor stage (Astler Coller classification A,B1,BII,CI,CII,D)</td>
<td>1,7,9,0,3,0</td>
<td>0,2,5,1,6,0</td>
</tr>
<tr>
<td>Preoperative radiation dose 25 Gy in 5 fractions</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Preoperative radiation dose 60 Gy in 28 fractions</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Postoperative radiation dose 50 Gy in 25 fractions</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Median tumor height above anal verge (cm (range))</td>
<td>8 (3-15)</td>
<td>6.5 (2.5-11)</td>
</tr>
<tr>
<td>Median anastomotic height above anal verge (cm (range))</td>
<td>4 (2-7)</td>
<td>3.5 (2-8)</td>
</tr>
</tbody>
</table>

In the RT+TME group seven patients were lost to follow-up. Three patients developed liver metastases postoperatively, two out of these three received postoperative radiotherapy and one of them died within the first year after surgery. In one patient the bowel continuity was not restored because the pre-
and postoperative manometry results were considered not sufficient enough to maintain continence. Three other patients died during the first follow-up year, two patients due to postoperative complications and one because of a pancreatic cancer diagnosed 6 months postoperatively. The latter received postoperative radiotherapy. Therefore 7 patients who received preoperative radiotherapy followed by surgery and 14 patients who underwent surgery alone were re-evaluated at four and twelve months after surgery. The biological effect of the two radiotherapy schedules is according to the linear quadratic formula 37.5 in the 5 x 5 Gy in 1 week schedule and 54.8 in the 28 x 2.1 Gy schedule.\textsuperscript{33} No complications were encountered in any of the measurements. In none of the subjects, the duration of the experiments exceeded four hours.

Clinical characteristics
All patients, but one in the TME group, presented with persistent blood loss per anum as principal symptom (Table 2). The percentage of patients with blood loss decreased postoperatively in both groups, although after 12 months, 33% of patients in the RT+TME group still had regular episodes with blood loss. The percentage of patients that had soiling during daytime was comparable between the two groups before treatment, but showed after 4 and 12 months a significant increase as compared to before surgery in the TME group, in contrast to the RT+TME group where this was not observed. Four months after treatment, patients in the RT+TME group had a significantly increased defaecation frequency during the day (10 versus 4 times), and showed a tendency to more often needing to wear a pad (100 versus 69%) and to suffer more from urgency (80 versus 39 %), as compared to patients from the TME group. Twelve months after treatment these differences were less pronounced in the former two parameters and disappeared for urgency. Moreover, 4 months after treatment only the RT+TME group showed a significant increase in urgency as compared to preoperative values. Tenesmus, although significantly more present preoperatively in the TME group, decreased after 4 months and even further 12 months postoperatively in the TME group, while there was a increasing tendency in the RT+TME group. For soiling during the night, the anal incontinence score, episodes with passive incontinence, sensation of incomplete defaecation and urinary incontinence both treatment groups showed an increase or increasing tendency in percentage of patients with these symptoms or an increasing tendency in the score both after 4 and 12 months as compared to the preoperative status.
<table>
<thead>
<tr>
<th></th>
<th>TME Pre-OP</th>
<th>RT+TME Pre-OP</th>
<th>TME 4 months Post-OP</th>
<th>RT+TME 4 months Post-OP</th>
<th>TME 12 months Post-OP</th>
<th>RT+TME 12 months Post-OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss per anum</td>
<td>% Pts (% every day)</td>
<td>93 (43)</td>
<td>100 (29)</td>
<td>15* (0)</td>
<td>20* (0)</td>
<td>7* (0)</td>
</tr>
<tr>
<td>Soiling during day-time</td>
<td>% Pts (% every day)</td>
<td>50 (7)</td>
<td>57 (14)</td>
<td>85* (15)</td>
<td>67 (0)</td>
<td>71* (21)</td>
</tr>
<tr>
<td>Soiling during night-time</td>
<td>% Pts (% every day)</td>
<td>7 (0)</td>
<td>0</td>
<td>38* (7)</td>
<td>20 (0)</td>
<td>50* (21)</td>
</tr>
<tr>
<td>Defaecation frequency / day</td>
<td>mean (SD)</td>
<td>3 (3)</td>
<td>4 (2)</td>
<td>5 (3)</td>
<td>10* (6)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Defaecation frequency / night</td>
<td>mean (SD)</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Need to wear a pad</td>
<td>% Pts (% day &amp; night)</td>
<td>29 (0)</td>
<td>14 (14)</td>
<td>69* (54)</td>
<td>100* (60)</td>
<td>64* (29)</td>
</tr>
<tr>
<td>Urgency of defaecation</td>
<td>% Pts (% every day)</td>
<td>21 (7)</td>
<td>14 (0)</td>
<td>39 (8)</td>
<td>80* (0)</td>
<td>29 (0)</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>% Pts (% every day)</td>
<td>71 (21)</td>
<td>28* (0)</td>
<td>54 (0)</td>
<td>40 (0)</td>
<td>36* (0)</td>
</tr>
<tr>
<td>Anal incontinence score²⁵</td>
<td>median (range)</td>
<td>2 (0-5)</td>
<td>2 (0-4)</td>
<td>3 (0-5)</td>
<td>4 (0-4)</td>
<td>4 (0-5)</td>
</tr>
<tr>
<td>Episodes with passive incontinence</td>
<td>% Pts (% every day)</td>
<td>7 (0)</td>
<td>0</td>
<td>31 (0)</td>
<td>40 (0)</td>
<td>36* (0)</td>
</tr>
<tr>
<td>Sensation of incomplete defaecation</td>
<td>% Pts (% every day)</td>
<td>50 (21)</td>
<td>33 (0)</td>
<td>54 (23)</td>
<td>60 (20)</td>
<td>57 (14)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>% Pts (% every day)</td>
<td>21 (0)</td>
<td>0</td>
<td>33 (0)</td>
<td>50 (0)</td>
<td>50 (7)</td>
</tr>
<tr>
<td>Loss of large quantities of stools</td>
<td>% Pts (% every day)</td>
<td>0</td>
<td>0</td>
<td>8 (0)</td>
<td>20 (0)</td>
<td>14 (0)</td>
</tr>
</tbody>
</table>

Pre-OP = preoperative; Post-OP = postoperative; * significantly different (p < 0.05) from preoperative values. † significantly different (p < 0.05) from TME patients; ‡ significantly different (p < 0.05) from 4 months postoperatively.
Finally, both forms of treatment did not lead to considerable changes in defaecation frequency during the night, stool consistency, or the ability to differentiate between flatus and faeces.

**Manometry, mucosal sensitivity and PNMLT outcome**

The results of the anal manometry, mucosal sensitivity and pudendal nerve latencies are shown in Table 3. Preoperative resting pressures, squeezing pressures and RAIR data were not different between the two treatment groups. Postoperatively, there was a decrease in resting pressure in both treatment groups although this was only significant 4 months postoperatively in the TME group. The maximum squeezing pressure showed no significant decrease in comparison to preoperative values. Both treatment groups showed postoperatively a tendency for an increase in slow wave amplitude although there was no significant difference between the two treatment groups as well as there were no differences in the slow wave frequencies. However an obvious change in anal motility was seen 12 months after treatment in the patients in group RT+TME, where short bursts of pressure waves were observed in a significantly higher percentage (57%) of the patients as compared to that of the patients in the TME group (7%) (Figure 1).

The RAIR preoperatively was present in all patients in both groups. The presence of RAIR was significantly decreased 4 months postoperatively to 43% and 29% in respectively the TME group and the RT+TME group, but recovered to respectively 79% and 72% after 12 months.

Remarkably, during the RAIR assessment strong neo-rectal contractions (Figure 2), with pressures up to 321 mmHg (mean $84 \pm 31$ mmHg, RAIR induced with 40 ml), were seen 4 months postoperatively in both treatment groups, while preoperatively these contractions have not been observed in any patient. One year postoperatively, these contractions decreased to preoperative values in the TME group, but they remained in 72 percent of the patients in the RT+TME group. In addition to RAIR induced contractions, spontaneous contractions of the neo-rectum leading to a positive RAIR were sometimes observed (Figure 2).

Preoperative anal- and rectal mucosal sensitivity and PNTML data of patients did not differ between both treatment groups. There were also no postoperative changes in anal mucosal sensitivity and PNTML data. There was, however, a significant postoperative increase in rectal mucosal electrosensitivity in the RT+TME group. No data are given for PNTML data 4 months postoperatively, since this examination was experienced as too strenuous by eight patients.
Figure 1: Changed anal slow wave pattern, 12 months after treatment in patients who underwent surgery alone (TME) and surgery and radiotherapy (RT+TME). Channels 1-5 represent ports situated at 1, 2, 3, 4 and 6.5 cm from the anal verge. Channel 6, represents the pressure in the sleeve ranging from 0 to 4 cm from the anal verge. Short bursts of pressure waves were observed in the channel at the top that represents the pressure in the neo-rectum as well as in the lower five channels representing the pressures in the anal canal. The slow wave pattern in the TME group was unaltered.

Figure 2: Typical tracing showing pressure recordings of a neo-rectal contraction during rectal-anal inhibition reflex (RAIR) measurement. Channels 1-5 represent ports situated at 1, 2, 3, 4 and 6.5 cm from the anal verge. Channel 6, represents the pressure in the sleeve. Channel 1, represents the pressure in the neo-rectum where the pressure rises to 300 mmHg (grey area). Simultaneously a positive RAIR is seen in the lower five channels positioned in the anal canal. The RAIR is followed by a spontaneous contraction of the neo-rectum.
<table>
<thead>
<tr>
<th></th>
<th>TME Pre-OP</th>
<th>RT+TME Pre-OP</th>
<th>TME 4 months Post-OP</th>
<th>RT+TME 4 months Post-OP</th>
<th>TME 12 months Post-OP</th>
<th>RT+TME 12 months Post-OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting pressure (mmHg)</td>
<td>58 (24)</td>
<td>63 (23)</td>
<td>38 * (20)</td>
<td>40 (16)</td>
<td>43 (20)</td>
<td>31 (23)</td>
</tr>
<tr>
<td>Maximum squeezing pressure (mmHg)</td>
<td>147 (51)</td>
<td>192 (124)</td>
<td>122 (59)</td>
<td>138 (49)</td>
<td>132 (52)</td>
<td>142 (73)</td>
</tr>
<tr>
<td>Slow waves amplitude (mmHg)</td>
<td>12 (5)</td>
<td>8 (4)</td>
<td>16 (9)</td>
<td>23 (15)</td>
<td>19 (12)</td>
<td>22 (15)</td>
</tr>
<tr>
<td>Slow waves frequency (mmHg)</td>
<td>11 (4)</td>
<td>10 (3)</td>
<td>9 (2)</td>
<td>8 (2)</td>
<td>10 (3)</td>
<td>8 (1)</td>
</tr>
<tr>
<td>(neo)Rectal-Anal Inhibitory Reflex (RAIR)</td>
<td>100%</td>
<td>100%</td>
<td>43% *</td>
<td>29% *</td>
<td>79%</td>
<td>72%</td>
</tr>
<tr>
<td>(Neo-)Rectal Contractions during RAIR (mmHg)</td>
<td>18 (16)</td>
<td>19 (15)</td>
<td>76* (96)</td>
<td>58 (72)</td>
<td>16 † (15)</td>
<td>72 † (46)</td>
</tr>
<tr>
<td>Anal mucosal electrosensitivity (mAmp)</td>
<td>7.7 (3.5)</td>
<td>7.1 (2.6)</td>
<td>6.7 (2.3)</td>
<td>8.4 (1.3)</td>
<td>6.5 (1.7)</td>
<td>6.7 (2.0)</td>
</tr>
<tr>
<td>Rectal mucosal electrosensitivity (mAmp)</td>
<td>26 (10)</td>
<td>29 (10)</td>
<td>33 (20)</td>
<td>47 † (17)</td>
<td>29 (11)</td>
<td>53 ‡ (30)</td>
</tr>
<tr>
<td>PNTML (Left (ms))</td>
<td>2.4 (0.4)</td>
<td>2.0 (0.4)</td>
<td>2.2 (0.4)</td>
<td>2.5 (1.1)</td>
<td>2.2 (0.2)</td>
<td>2.4 (0.5)</td>
</tr>
<tr>
<td>PNTML (Right (ms))</td>
<td>2.1 (0.2)</td>
<td>2.0 (0.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pre-OP = preoperative; Post-OP = postoperative; * significantly different (p < 0.05) from patients preoperatively and 12 months Post-OP; † significantly different from patients 4 months Post-OP; ‡ significantly different from TME patients; SD between brackets.
Mean compliance curves for patients (pre- and postoperatively) in both treatment groups are shown in Figure 3. The preoperative rectal compliance was not different between the patients from the two treatment groups (9.3 vs. 9.1 ml/mmHg, respectively (Table 4)). In both treatment groups 4 months postoperatively, compliance significantly decreased in comparison to preoperative values (4 months TME alone: 3.6 ml/mmHg, 4 months RT+TME: 2.6 ml/mmHg). The compliance of the patients in the RT+TME group was significantly lower than that of the patients in the TME group, both at 4 and 12 months postoperatively.

The neo-rectal compliance 4 months postoperatively in both groups was significantly lower than that of 12 months postoperatively, indicating that there was some adaptation 12 months postoperatively.

As described by Akervall et al.,

reactive rectal contractions were observed at the onset of every distention of the barostat-bag. Four months and 12 months postoperatively, the mean amplitude of these contractions was significantly larger in the TME group as compared to the preoperative values. Such an increase in amplitude was not found in the RT+TME group (Table 4).

**Pressure thresholds to induce (Neo-)Rectal sensation**

The preoperative pressure threshold to induce first sensation in the rectum of patients in the TME group (6, range 0-12 mmHg) was equal to that in the rectum of patients in the RT+TME group (3, range 3-6 mmHg) (Table 4). Postoperatively both at 4 and 12 months there was no difference either. A similar result was seen for the pressure threshold to induce desire to defaecate. The preoperative pressure thresholds to induce the sensation of intolerable discomfort was not different between the groups (TME 21 mmHg, RT+TME 21 mmHg). However, postoperatively this pressure threshold was not reached by all patients at 50 mmHg. At 4 months 79% of the TME group and 86% of the RT+TME group reached the threshold at similar pressures as compared to preoperative values (respectively 23 and 24 mmHg). At 12 months the percentage of patients reaching the thresholds was 64% in the TME group and 43% in the RT+TME group. Likewise, at 30 mmHg above MDP only 29% of the patients in the RT+TME group whereas 50% of the patients in the TME group already reached the threshold. The decrease in the number of patients reaching the threshold was only significant in the RT+TME group (Figure 4).
Figure 3: Volume-pressure curves obtained during isobaric distentions in patients before and after surgery with or without radiotherapy. The compliance of the neorectum in all patients 4 and 12 months postoperatively was significantly lower than that of the rectum in preoperative patients. Patients with radiotherapy had a significant lower compliance than patients who underwent surgery alone at 4 and 12 months postoperatively.

Figure 4: Percentage of patients reaching the pressure threshold for discomfort at 50 mmHg. Pre-OP = preoperative; * significantly different from patients preoperatively and 4 months after treatment.
Volume at pressure thresholds to induce (Neo-)Rectal sensation

Preoperatively, the volume at pressure the thresholds for first sensation and intolerable discomfort were similar, although threshold to induce desire to defaecate in the rectum of patients in the TME group (150 ml, SD 50 ml) was higher than that of patients in the RT+TME group (89 ml, SD 20 ml) (Table 4). Postoperatively, the volumes at all thresholds in both treatment groups tended to be decreased, but the volumes at the thresholds desire to defaecate and intolerable discomfort decreased significantly more in the patients of the RT+TME group as compared to those of the TME group.

Patients who were lost to follow-up

There were 13 patients lost to follow-up, 6 patients in the TME group and 7 patients in the RT+TME group. The mean age was 70.7 years for the TME group and 71.9 years for the RT+TME. In the TME group five patients had a Dukes B and one patient a Dukes C rectal carcinoma diagnosed, whereas in the RT+TME group three patient had a Dukes B and four a Dukes C carcinoma. Other clinical variables before treatment were also comparable between the two groups, being blood loss per anum as principal symptom present in respectively 67 and 86 % of the patients, median defaecation frequency in both groups 4 times during the day, soiling in 50 and 57 %, anal incontinence score 2 and 3, urgency in 17 and 0 % and tenesmus in 50 and 30% of the patients. Only 17 percent of the patients in the TME group needed to wear a pad as compared to 57 % in the RT+TME group. The manometry data showed no differences in mean resting pressures (respectively, 58 and 46 mmHg), mean squeezing pressures (respectively, 171 and 181 mmHg) and the presence of RAIR in all patients of both groups. Neither was there a difference in compliance (respectively, 8.6 and 9.0 mmHg/ml) nor in the volumes and pressures to induce various rectal sensations. For example the mean volumes for sensation intolerable discomfort were respectively, 192 and 212 ml and the corresponding median pressures where in both groups 27 mmHg.
Table 4: Compliance and median pressures to induce rectal sensation results in patients treated with total mesorectal surgery (TME) or radiotherapy (RT) with TME.

<table>
<thead>
<tr>
<th></th>
<th>TME Pre-OP</th>
<th>RT+TME Pre-OP</th>
<th>TME 4 months Post-OP</th>
<th>RT+TME 4 months Post-OP</th>
<th>TME 12 months Post-OP</th>
<th>RT+TME 12 months Post-OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance (ml/mmHg (SE))</td>
<td>9.3 (0.8)</td>
<td>9.1 (1.0)</td>
<td>3.6 * (0.5)</td>
<td>2.6 * (0.2)</td>
<td>5.1 * (0.7)</td>
<td>4.1 * (0.7)</td>
</tr>
<tr>
<td>(Neo-)Rectal Contractions during barostat distention (ml (SD))</td>
<td>9 (10)</td>
<td>25 (8)</td>
<td>41* (24)</td>
<td>29 (14)</td>
<td>23* (24)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Median pressures inducing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First sensation (mmHg (range))</td>
<td>6 (0-12)</td>
<td>3 (3-6)</td>
<td>3 (0-9)</td>
<td>6 (0-6)</td>
<td>3 (0-15)</td>
<td>3 (0-9)</td>
</tr>
<tr>
<td>Desire to defaecate (mmHg (range))</td>
<td>11 (3-30)</td>
<td>9 (6-18)</td>
<td>9 (3-50)</td>
<td>9 (3-15)</td>
<td>12 (3-36)</td>
<td>9 (3-50)</td>
</tr>
<tr>
<td>Mean volumes inducing:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First sensation (ml (range))</td>
<td>53 (25)</td>
<td>35 (35)</td>
<td>34 (33)</td>
<td>18 (14)</td>
<td>38 (27)</td>
<td>18 * (9)</td>
</tr>
<tr>
<td>Desire to defaecate (ml (range))</td>
<td>150 (50)</td>
<td>89 * (20)</td>
<td>60 * (37)</td>
<td>35 * (23)</td>
<td>112 (53)</td>
<td>67 * (39)</td>
</tr>
</tbody>
</table>

Pre-OP = preoperative; Post-OP = postoperative; * significantly different from patients preoperatively; † significantly different from patients 4 months Post-OP; ‡ significantly different from TME patients.
Discussion

In this study anal and rectal function in combination with clinical outcome was assessed in patients before and after radiotherapy followed by surgery for rectal cancer, and compared to that of patients that underwent surgery alone. The major finding in this study was that anorectal function, as measured by both objective functional tests and subjective clinical outcome questionnaires, was substantially inferior in patients who underwent both radiotherapy and surgery as compared to patients who underwent surgery alone. This is in contrast to the postulation that preoperative radiotherapy results in few late adverse effects because the colon that is used to construct the neo-rectum lies outside of the irradiation field, and therefore its function should be less affected.¹

All patients in this study who underwent both surgery and radiotherapy used pads postoperatively and eighty percent suffered at the same time from urgency which was accompanied with soiling in a substantial percentage during the day and during the night. In addition, the mean defaecation frequency was as high as ten times during the day. In contrast, the patients who underwent surgery alone had a significantly lower defaecation frequency during the day and suffered in a much lower percentages from urgency or needed to wear pads, although up to 85% also had complains of soiling during the day. These results are in concordance with the findings of previous reported studies.²³,²⁴

The evaluation of these inferior functional outcome so far, have not elucidated the underlying mechanisms. One possible explanation may be impaired sphincter function. However, the postoperative anal sphincter resting and squeezing pressures showed no substantial changes as compared with preoperative values and does therefore not explain the less favorable clinical outcome after radiotherapy. Anastomotic height, a variable of major importance for postoperative functional outcome in some studies²⁰,³⁵ and of less importance in others,¹⁹ could also not have influenced the functional outcome in this study as it was not different between the two groups. The only change in sphincter function we observed was a disturbance in slow wave pattern. Short bursts of pressure waves, were observed in a significant higher percentage of patients in the radiotherapy group, whereas the patients in the surgery only group showed an unchanged slow wave pattern with a high amplitude of pressure waves. This type of slow wave patterns has not been reported in healthy volunteers.³⁶ Although, a similar result has been shown in rats who received abdominal irradiation, which lead to clustered bursts of pressure waves in the ileum as compared to controls.³⁷ A definite change in slow wave pattern in the irradiated patients may be suggestive for disturbed or damaged neuromuscular sphincter control.
CHAPTER 3

In addition to the motility changes, a significant decrease in the presence of the RAIR was shown 4 months postoperatively, which recovered substantially in both groups after 12 months. It can be argued that when the RAIR is insufficient, this will not result in relaxation of the sphincter when the neo-rectum is filled with stools. However, when the RAIR has recovered after 12 months, increased pressure in the neo-rectum and/or small amounts of stool will induce a RAIR with further reduction of the basal pressure. If the neo-rectum contracts at that moment, incontinence problems might be expected. As shown in Figure 2, these patients have indeed spontaneous contractions in the neo-rectum followed by an RAIR. In the presence of stool in the neo-rectum, one might expect leakage during such contractions. This can explain why 12 months postoperatively there is a tendency in both groups for more soiling during the night when patients do not consciously experience sensations like desire to defaecate.

Notwithstanding these observations, a complete explanation for the inferior outcome after radiotherapy is not given.

The group that underwent surgery and radiotherapy had a significant lower compliance and therefore smaller volumes at the pressure thresholds to induce the sensations desire to defaecate and intolerable discomfort, which is in agreement with other studies in the literature.\textsuperscript{23,24,38} This can be explained primarily by the fact that the neo-rectum is constructed of sigmoid colon or descending colon which has a lower compliance as compared to normal rectum and is more ‘irritable’ as demonstrated by the neo-rectal contractions during distention.\textsuperscript{39} Secondly the amplitude of rectal contractions during RAIR remained increased 12 months postoperatively in the group that underwent radiotherapy indicating an even more “irritable” neo-rectum than in the group that underwent surgery only. Both the reduced compliance and the increase in irritability may result from inflammation induced by radiotherapy. The fact that 33% of the patients who received radiotherapy still reported macroscopic blood loss indeed suggests the presence of chronic inflammation in these patients. Similar changes in gastrointestinal motility and sensory perception following inflammation have been reported in a variety of mucosal inflammatory conditions of the gut, ranging from peptic esophagitis to ulcerative colitis.\textsuperscript{40} Studies in animal models indicate a causal relationship between the presence of mucosal inflammation and altered sensory-motor function and motility, moreover this alteration persist after recovery from the inflammation.\textsuperscript{41} Similarly, one would expect an increased number of contractions, and/or more powerful contractions during sudden increase of rectal pressure. We do not have a good explanation why this was not observed during barostat distention.
Pressures to induce intolerable discomfort tended to be higher in the group that also underwent radiotherapy. Forty-three percent of these patients experienced this painful sensation at 50 mmHg, 64% of the patients with surgery only. This finding in combination with the fact that the threshold for rectal electrosensitivity was significantly higher after radiotherapy suggests that on the one side the neo-recrum is more “irritable” but tends to be at the same time less “sensible”. An explanation for this could be that local “irritability” is a result of chronic inflammation affecting local intramural neuromuscular function whereas reduced conscious perception of painful stimuli is rather results from afferent nerve fiber injury following radiotherapy. This reduced sensibility can be adventitious to these patients as it will temper their urgency and defaecation frequency and protect them from even worse outcome.

A major drawback of this study is that the number of patients in the group that also underwent radiotherapy is relatively small and that the number of dropouts from follow-up in this groups is relatively large. This type II error is probably the reason why the differences between the two treatment groups, such as in the percentages of patients with urgency, the need to wear a pad and pressures at 12 months to induce intolerable discomfort, are not statistically significant. Larger groups of patients would most likely elucidate more differences between the groups. Bias by dropouts from follow-up can never be ruled out, although the differences preoperatively give no indication for large differences.

Nevertheless, it can not be overlooked that the group that underwent surgery and radiotherapy has a substantial poorer functional outcome as compared to the group that only underwent surgery. Recently, it has been shown that preoperative radiotherapy leads to a significant increase in the five-year survival and reduction of local recurrence. Although it should be considered that the surgical procedures were not standardized. Questionable is therefore, whether similar favorable results can be obtained in a comparative study between standardized surgery with preoperative radiotherapy and standardized surgery alone. Furthermore, it should be considered whether those results are of such magnitude that they can make up for the substantial poorer functional outcome after radiotherapy, especially when preoperative radiotherapy is correlated with a higher risk of postoperative death.

In summary, the group that underwent surgery and radiotherapy had a substantial sustained increase in defaecation frequency, a tendency for more urgency, the need to wear a pad and rectal blood loss. This most likely results from a combination of decreased neo-rectal reservoir capacity, due to decreased compliance, and increased neo-rectal contractility because of increased distention induced contractions. In addition, sensation to distention and to electrical stimuli
was reduced by radiotherapy suggesting afferent nerve injury. Further studies are needed to evaluate whether this inferior functional outcome must be accepted to achieve longer survival and less local recurrence.

References


