

# Impaired anastomotic healing after preoperative radiotherapy followed by anterior resection for treatment of rectal carcinoma

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## Summary

*Background.* Patients with rectal carcinoma undergoing total mesorectal excision (TME) have a lower recurrence rate with preoperative radiotherapy (RT). The aim of this study was to assess the side-effects in patients who had preoperative RT compared with those who did not receive it (because of palliative resections, advanced age or refusal).

*Methods.* From January 2001 to March 2003, 40 patients underwent resection and double-stapled anastomosis for rectal carcinoma. We compared 17 patients who received RT followed by resection and low rectal anastomosis, with 23 patients who did not have RT.

*Results.* After surgery 7/17 of the patients who had received RT developed anastomotic leaks. Anastomotic leakage was seen only once in the patients who did not have RT (41% v. 4%,  $p = 0.006$ ). A protective stoma, which was performed in 11 patients in the RT group, did not prevent anastomotic leakage (4/11 leakage with stoma v. 3/6 leakage without stoma,  $p = 0.64$ ). Median hospital stay was longer in the RT group (17.4 v. 13.7 days,  $p = 0.017$ ). There was no difference in the number of minor postoperative complications between the two groups (24% v. 22%).

*Conclusion.* Compared with surgery alone, preoperative short-term RT increased the number of anastomotic leaks and hospital stay, whether or not a protective stoma was performed.

Since the Dutch total mesorectal excision (TME) trial<sup>1</sup> showed that short-term radiotherapy (RT) before TME in the treatment of rectal carcinoma had an additional effect on local tumour control and overall survival, this strategy has become common in the Netherlands. The positive effect of preoperative RT on survival has been described before.<sup>2,3</sup> Less is known about the side-effects of irradiation on wound and anastomotic healing as shown by the many contrary reports in the existing literature.

As anastomotic leakage can result in a life-threatening situation requiring immediate (surgical) intervention, this complication remains a serious problem. Besides the acute severe complications, anastomotic leakage after surgery results in impaired long-term anorectal function.<sup>4</sup>

We conducted the present study to assess the side-effects of short-term irradiation on anastomotic healing when given before anterior resection.

## Methods

All patients ( $N = 40$ ) who had undergone resection for treatment of colorectal carcinoma in the Department of Surgery at Medisch Centrum Rijnmond Zuid, Rotterdam, between January 2001 and March 2003 were included in this study. Anastomoses were all double-stapled.

Patients were divided into two groups. Group 1 included 17 patients who had received 5 doses of 5 Gy irradiation followed by resection and anastomosis. The other 23 patients had undergone resection and anastomosis without preoperative RT (group 2). TME was performed in 34 patients. In both groups some procedures had a protective ileostomy.

Postoperative complications (in particular, anastomotic leakage) were assessed in relation to preoperative RT. Anastomotic leakage was defined as the presence of rectal contrast material in an extraluminal collection or the formation of presacral abscesses at evaluation with computed tomography (CT) scans or barium enemas. CT scanning or barium enemas were performed when two of the following symptoms were present postoperatively: increased drainage, prolonged ileus, postoperative abdominal pain, fever, or leucocytosis.

Operating time, hospital stay, tumour location, minor postoperative complications and mortality were recorded. A comparison was made of the postoperative results of procedures performed with preoperative RT and those performed without it.

Statistical analysis was done using the Mann-Whitney and Fisher's exact tests. Differences were considered significant at  $p < 0.05$ .



## Results

### Patients

Forty patients were included in the study. Seventeen patients had received preoperative RT (group 1) (Table I) and 23 patients had undergone resection with colorectal anastomosis alone (group 2) (Table II). The latter did not receive preoperative RT for the following reasons: known metastases ( $N = 6$ ), advanced age ( $N = 3$ ), sigmoid carcinoma ( $N = 6$ ) and refusal ( $N = 8$ ). One patient had received long-term RT in the past for treatment of prostate carcinoma.

No differences were found between the two groups in terms of age (group 1: 63 years, range 46 - 75 v. group 2: 62 years, range 38 - 85,  $p = 0.74$ ) and male/female ratio (9/8 v. 13/10, respectively,  $p = 0.71$ ).

The median distance of the tumour from the anal verge was significantly less in the group that received preoperative RT compared with the patients who received surgery alone (10.5 cm, range 5 - 17 v. 14.9 cm, range 6 - 40 cm, respectively,  $p = 0.005$ ) (Tables I and II).

### Postoperative morbidity and mortality

After resection and anastomosis 7 of the 17 patients who had received preoperative short-term RT developed anastomotic leaks and/or presacral abscesses detected at radiological evaluation. Anastomotic leakage was seen only once in the patients (1/23) who had undergone surgery without preoperative radiotherapy (group 1 41% v. group 2 4%,  $p = 0.006$ ) (Table II). All leaks were confirmed by CT scan

( $N = 7$ ) or barium enema ( $N = 1$ ). In 4 patients (2 in both groups) who were clinically suspected of anastomotic leakage, contrast studies did not reveal this.

In group 1 the anastomotic leaks and presacral abscesses were managed via percutaneous drainage ( $N = 3$ ), operative drainage of the abscess ( $N = 1$ ), ileostomy and operative drainage of the abscess ( $N = 2$ ), and colostomy ( $N = 1$ ). The presacral abscess in the patient in group 2 with anastomotic leakage was treated by percutaneous drainage.

In 11 patients in group 1 the surgical procedure was performed with a protective stoma. Nevertheless anastomotic leakage occurred in 4 of these patients (36%) (Table I). Hence, we found no benefit of a protective stoma in the reduction in anastomotic leakage rate after RT and low anterior resection (36% v. 50% (3/6 leakage without protective stoma),  $p = 0.64$ ). Also the rate of leakage requiring surgery did not decrease after a protective stoma was performed (2/4 patients with a protective stoma required surgery for anastomotic leakage v. 2/3 patients without a stoma).

There was no significant difference found in the number of other (minor) complications between the two groups (24% in patients with RT and surgery v. 22% in patients with surgery alone,  $p = 0.59$ ). Minor complications were postoperative ileus ( $N = 2$ ), urogenital infection ( $N = 4$ ) and limited wound infection ( $N = 3$ ). One patient in group 2 died after aspiration pneumonia.

### Operation time and hospital stay

Surgery took nearly half an hour longer in the irradiated group (group 1: 298 minutes, range 208 - 548 minutes v.

**TABLE I. RESULTS OF RESECTION AND ANASTOMOSIS AFTER PREOPERATIVE RADIOTHERAPY IN RELATION TO TUMOUR HEIGHT AND STAGE**

N	Age (yrs)	Type of surgery	Tumour height (cm)	Tumour stage	Operation time (min)	Hospital stay (days)	Complications
1	69	AR*	15	T3N0	238	10 (1)	
2	50	AR*	10	T3N0	257	9 (1)	
3	60	AR*	15	T3N0	208	10 (0)	
4	59	AR*	10	T2N0	262	13 (1)	Presacral abscess
5	72	AR*	12	T3N0	315	5 (0)	Anastomotic leakage, necrotic ileostomy
6	67	AR*	7	T3N1	239	32 (0)	Anastomotic leakage, abscess
7	50	AR* and hysterectomy, splenectomy, ileostomy	7	T3N0	324	14 (0)	
8	72	AR* and ileostomy	11	T3N0	448	32 (5)	Anastomotic leakage, abscess
9	46	Laparoscopic AR*	12	T1N0	353	15 (0)	Presacral abscess
10	63	AR* and ileostomy	13	T2N0	342	11 (0)	
11	56	AR* and ileostomy	6	T3N2	246	9 (0)	
12	63	AR* and ileostomy	5	T3N0	253	34 (0)	
13	63	AR* and ileostomy	7	T2N1	237	31 (0)	Presacral abscess
14	67	AR* and ileostomy	10	T3N1	336	15 (1)	
15	56	AR* and ileostomy	11	T3N1	233	11 (1)	
16	74	AR* and splenectomy and ileostomy	10	T3N2	223	25 (2)	
17	74	Rectosigmoid resection and ileostomy	17	T2N0	548	14 (1)	Anastomotic leakage, decubitus

AR = anterior resection (\*total mesorectal excision).

**TABLE II. RESULTS OF RESECTION AND ANASTOMOSIS IN RELATION TO TUMOUR HEIGHT AND STAGE WITHOUT PREOPERATIVE RADIOTHERAPY**

N	Age (yrs)	Type of surgery	Tumour height (cm)	Tumour stage	Operation time (min)	Hospital stay (days)	Complication
1	57	AR* with ileostomy	7	T3N0	206	59 (7)	Venous bleeding
2	85	AR* with ileostomy	10	T2N1	401	19 (5)	
3	64	AR*	6	T3N1	430	10 (1)	Enterocutaneous fistula
4	71	AR*	15	T2N1	112	12 (0)	
5	38	AR*	15	T3N1M1	235	20 (0)	
6	53	AR*	8	T3N2M1	236	8 (1)	Wound infection
7	75	AR*	14	T2N0	219	8 (1)	
8	66	AR*	8	T3N0M1	312	5 (1)	Death after aspiration
9	63	AR*	15	T3N1	206	11 (1)	
10	81	AR*	15	T2N0	181	7 (0)	Presacral abscess
11	52	Rectosigmoid resection	25	T3N0M1	292	35 (3)	
12	83	AR* with ileostomy	12	T2N0	326	14 (0)	
13	55	AR* with ileostomy	14	T3N0	306	14 (1)	Ileus
14	68	Rectosigmoid resection	40	T4N2M1	358	9 (0)	
15	63	AR*	15	T2N0	195	10 (0)	Pneumonia
16	75	AR*	15	T3N1	142	7 (0)	
17	56	AR	17	T2N0	225	12 (0)	
18	48	AR and appendectomy	18	T3N2	230	4 (0)	Wound infection
19	42	AR*	18	T3N2	186	7 (0)	
20	67	AR*	20	T3N1M1	117	5 (0)	Anastomotic stenosis
21	69	AR	20	T3N0	250	8 (0)	
22	47	Rectosigmoid resection	20	T3N0	183	8 (0)	
23	43	AR*	20	T3N0	344	7 (1)	

AR = anterior resection (\*total mesorectal excision).

group 2: 272 minutes, range 112 - 765 minutes,  $p = 0.048$ ). Mean hospital stay was also longer after irradiation (17.4 days, range 9 - 34 days, compared with 13.7 days, range 4 - 34 days). This is a significant difference ( $p = 0.017$ ).

Because of the formation of presacral abscesses 5 patients (4 patients in group 1 and 1 patient in group 2) had to be readmitted to hospital.

No difference was found in median stay in the intensive care unit (ICU) (group 1: 0.8 days, range 0 - 5 v. group 2: 1.0 days, range 0 - 7 days,  $p = 0.46$ ).

## Discussion

In the treatment of rectal carcinoma preoperative RT has been shown to improve local control and survival.<sup>2,3,5,6</sup> Even when optimal surgical techniques such as TME are used, preoperative RT provides additional benefit.<sup>1,7</sup> However, preoperative irradiation also increases morbidity. Irradiation increases the rate of intestinal obstruction,<sup>8</sup> postoperative fistulas,<sup>9</sup> perineal complications after abdominoperineal resection<sup>10</sup> and incontinence of loose stool, urgency and emptying difficulties and impairment of social life due to other bowel dysfunction.<sup>11,12</sup>

In this study we observed an increased number of anastomotic leakages after short-term RT before resection with low rectal anastomosis compared with surgery alone, whether or not a protective stoma was performed. About 41% of the patients who received preoperative irradiation developed

an anastomotic leak and/or a presacral abscess. This resulted in prolonged hospital stay and a higher readmission rate, compared with the patients who did not receive preoperative irradiation. Our findings are not in accordance with those of a similar study undertaken by Friedmann *et al.*<sup>13</sup> who compared 40 patients with a moderate dose of preoperative RT followed by anterior resection and primary anastomosis with 93 patients without preoperative RT. They found no significant difference between the two groups with regard to anastomotic leak rates or overall rate of complications.

In the current literature controversy still exists about the effect of irradiation on rectal anastomotic healing. Milsom *et al.*<sup>14</sup> concluded that preoperative RT results in an early and persistent decrease in colorectal mural blood flow independent of anastomotic technique, which leads to impaired anastomotic healing and an increased number of anastomotic complications. In contrast, Leupin *et al.*<sup>15</sup> found that despite acute severe inflammation of the bowel after short-term irradiation, none of their 34 patients developed peri- or postoperative complications.

As anastomotic leakage is a major problem particularly in operations for low rectal cancer (e.g. impaired long-term anorectal function<sup>16</sup>) several procedures were invented to prevent this complication. Marusch *et al.*<sup>17</sup> conducted a prospective multicentre study to investigate whether a protective stoma could reduce the number of leaks. They concluded that the overall anastomotic leakage rate was not decreased in patients receiving a protective stoma, but the

rate of leakage requiring surgery was significantly lower. Merad *et al.*<sup>18</sup> showed that prophylactic drainage of the pelvis did not diminish the number of leaks or the severity of complications. Finally, the safety of different methods of low rectal anastomosis revealed no differences between single-stapled, double-stapled or handsewn anastomosis regarding leak rate or other postoperative complications.<sup>19-22</sup> In our study the distance of the tumour from the anal verge in the group of patients who had received preoperative radiotherapy (group 1) was significantly less than in the group that underwent surgery alone (group 2). Another study by Marusch *et al.*<sup>23</sup> showed an increased anastomotic leakage rate and postoperative morbidity with anastomosis less than 7 cm from the anal verge. Meanwhile, a significant reduction in overall postoperative morbidity and complications was found after resection of tumours located further than 8 cm from the anal verge. In our study the mean distance of the tumour from the verge was more than 8 cm in both groups (Tables I and II). Although 5 patients in the irradiation group had their primary rectal tumour located within 7 cm of the anal verge, only 2 of them developed an anastomotic leak.

The relatively large amount of anastomotic leakage found in the preoperatively irradiated patients in this study raises the question whether all patients with rectal carcinoma should receive short-term RT before surgery, especially when considering that there was no beneficial effect of preoperative RT in patients with TNM stage I and IV tumours according to the Dutch Colorectal Cancer Group.<sup>1</sup> Therefore, patients should be informed carefully about the advantages and disadvantages of neoadjuvant RT. Perhaps patients with stage I carcinoma, advanced age, or known metastases should not be offered preoperative RT.

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