Advances in treatment and new insights in molecular biology of rectal cancer

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Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer

Report of a multicentre randomised trial

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INTRODUCTION

In the treatment of rectal cancer local recurrences are a major problem and the rate varies between 15% and 45%.[1-4] Local recurrences cause severe disabling symptoms and are difficult to treat. In order to reduce local recurrence rates after curative surgery, additional radiotherapy has been given either preoperatively[5-14] or postoperatively.[4,15-18] In a large Swedish trial short term, preoperative radiotherapy resulted in better local control than postoperative radiotherapy (13% vs. 22% local recurrences).[5] All trials with short-term preoperative radiotherapy show lower local recurrence rates in the radiotherapy arm.[7,12,13,19] Results of the Swedish Rectal Cancer Trial (SRCT) even showed an improved overall survival with the short term 5x5 Gy regimen compared to surgery alone, with 58% 5-years survival in the irradiated group versus 48% in the non-irradiated group.[14] However, this beneficial effect of preoperative radiotherapy was observed in combination with conventional surgery. This conventional procedure implies partially blunt dissection of the rectum along the presacral fascia, resulting in incomplete removal of mesorectal tissue. This possible residue of tumour cells was a logical rationale behind application of radiotherapy. The acknowledgement of the important role of circumferential margin involvement in the appearance of local recurrences in rectal cancer has led to the general introduction of total mesorectal excision (TME) surgery, as advocated by Heald[20] and Enker.[21] The main principle of this technique is to achieve a radical resection by sharp dissection within the true pelvis around the intact mesorectum under direct vision, thus enveloping the entire midrectum with the tumour. This technique has shown to reduce the number of local recurrences significantly in retrospective series.[22] A second beneficial effect of TME surgery is the possibility to preserve the autonomic pelvic nerve plexus, resulting in less bladder dysfunction and less sexual morbidity.[23,24]

To answer the question whether preoperative radiotherapy is still beneficial in TME treated patients a randomised, prospective international multicentre trial was conducted under the auspices of the Dutch ColoRectal Cancer Group (DCRCG) to compare the effect of preoperative, hypofractionated radiotherapy combined with TME surgery with TME surgery alone.[25] Any benefit regarding a reduced local recurrence rate and possible improved survival must be weighed against potential adverse effects in both the short- and the long-term. Several trials with preoperative, short-term radiotherapy have shown that preoperative 5x5 Gy followed by surgery within one week is a safe procedure.[12,26-28] In these studies however, the preoperative radiotherapy was combined with conventional surgery.

The present study was undertaken to assess the side effects of short-term, preoperative radiotherapy in rectal cancer patients operated with the TME surgical technique and to study the influence of 5x5 Gy on surgical parameters, postoperative morbidity and mortality in patients randomised in the TME trial.

METHODS

Study population

From January 1996 until December 1999, 1861 patients were randomised to preoperative radiotherapy followed by standardised TME surgery or to TME surgery only in a large international multicentre trial.

Patients entering the trial were required to have biopsy confirmation of a rectal adenocarcinoma, resectable tumours as judged by clinical examination, tumours with the

inferior margin within 15 cm of the anal verge and no hereditary colorectal cancer syndrome. Distant metastases had to be excluded by chest X-ray and ultrasound or CT scan of the liver. Patients in whom previously a malignancy was diagnosed were not included in the study. The World Health Organisation (WHO) performance score had to be less than or equal to two. The patient had to give written or oral informed consent, depending on local hospital regulations.

Stratification took place for institute of surgery and expected type of resection, i.e. Abdomino Perineal Resection (APR) or Low Anterior Resection (LAR). Balanced randomisation lists with a block size of six were used for central randomisation at the Datacentre in Leiden.

The majority of the included patients (1530) were from the Netherlands; the other 331 patients were included by Swedish, other European and Canadian co-investigators. For the final analysis of the trial, all patients will be analysed. Since the Dutch follow-up has been extremely thorough, data about the Dutch patients considering treatment characteristics, toxicity, complications and mortality are very complete and checked by the study coordinators. We therefore only included the Dutch patients in the current analysis.

Preoperative radiotherapy

Patients assigned to preoperative radiotherapy received a total dose of 25 Gy in 5 fractions over 5-7 days. The prescribed dose was specified according to ICRU 50 guidelines.[29] The clinical target volume included the primary tumour and the mesentery with vascular supply containing the perirectal, presacral and the internal iliac nodes (up to the S1/S2 junction).

The recommended upper border was at the level of the promontory. The perineum was included if an APR was planned, whereas the lower border was 3 cm above the anal verge if the planned operation was a LAR. The treatment was delivered with three portals or with a four-portal "box" technique, depending on the institutes' preference.

Shielding of the lordotic area at the dorsum of the sacrum was recommended. The protocol recommended a treatment time from Monday till Friday, with surgery on the following Monday, Tuesday or Wednesday. In case treatment started on other days and was interrupted during the weekend, the time between the first radiotherapy fraction and the day of surgery was not to exceed 10 days.

In case of resection margins smaller than 1 mm or tumour spill during operation, postoperative radiotherapy was mandatory for the TME only patients.

Treatment details were reported on a radiotherapy form and checked by a radiation oncologist for inconsistencies.

Surgery

All patients underwent surgery according to the Total Mesorectal Excision principle, as advocated by Heald.[20] An extensive structure of workshops, symposia and instruction videos ensured the instruction of this novel technique. In addition, a committee of instructor surgeons was formed to optimise quality. In each participating hospital the first five TME procedures had to be supervised by an instructor surgeon.

A surgery- as well as a post-surgery form, on which all operation characteristics, operative and postoperative complications were recorded, was completed by the operating surgeon. These forms were compared with the operation report and discharge letter by the surgical

trial coordinator and checked for inconsistencies. Additional information was requested when data were not clear or incomplete.

Pathology procedures

Standardised routine pathology examination was performed as described by Quirke et al.[30] Pathologic information on the resected tumour was recorded by pathologists from the referral hospital on a pathology case record form for all patients. A pathology quality manager and a pathology review committee were installed to ensure constant quality of all pathology data and procedures.[31] Tumour staging was performed using the TNM classification.[32]

Side effects and complications

Radiation oncologists were asked to score acute side effects within 3 months from the start of radiotherapy according to the Radiation Therapy Oncology Group (RTOG) scoring system.[33] –In general, grade 0 represents no complaints, whereas grade 5 is any toxicity leading to death. The RTOG system has no scoring system for acute neurological symptoms. Since acute plexopathy was observed in the SRCT,[34] we introduced a scoring system for neurological complaints, with the following categories for painful buttocks or legs: 0: no complaints, 1: mild or intermittent pain not requiring intervention, 2: moderate constant pain requiring narcotics or adjustment of the treatment, 3: intractable severe pain or treatment interruption. This scoring system was introduced in 1997, a year after the start of the trial, explaining the missing data for patients randomised in 1996.

For the postoperative complications, all complications during the first admission were taken into account and the following definitions were used.

Anastomotic leaks included those clinically apparent or after suspicion determined on a contrast-enema. An abscess around the anastomosis was recorded as leakage. Since it is very difficult to discriminate between perineal dehiscence or perineal wound infection these complications were recorded as *perineal wound complication*. Rare complications were classified as *other*. Two categories were used: *moderate* consisting of complications that needed non-invasive treatment or *serious* defined as complications that required reintervention or caused a prolonged hospital stay.

Hospital death was defined as any death occurring during first admission, whereas *postoperative mortality* was defined as any death occurring during the first 30 days after the operation.

A *reintervention* was defined as any surgical procedure that took place in the operating room after the initial operation during the first admission. Only the first reintervention was taken into analysis. Elective procedures like removal of gauzes left behind during the initial operation for bleeding or opening/closure of stoma were not considered as a reintervention. Re-resections for positive margins were not considered as reinterventions.

Data collection and statistics

All case record forms were sent to the central data office in Leiden. After several checking rounds, the data were entered in a database and analysed with SPSS statistical software (version 9.0 for Windows, SPSS, Chicago).

Mann-Whitney tests were used to compare quantitative and ordered variables and Student's t-tests were used to analyse differences in normally distributed data between the two groups.

Chi-square tests were used to compare proportions. A P-value of 0.05 or less was considered statistically significant.

RESULTS

Patients

Of the 1530 Dutch patients included in the trial, 116 turned out to be ineligible. Reasons for ineligibility are recorded in Table 1. In some institutes, a CT-scan for treatment planning of the radiotherapy was performed, leading to detection of metastasis or irresectability. Consequently, more TME only patients turned out to be irresectable or metastasized during the operation. Thus, 1414 patients remained evaluable: 695 in the radiotherapy group and 719 in the surgery alone group. Table 2 shows well balanced clinical and tumour characteristics over both treatment arms. There was also no difference in the distribution in TNM stages or in the percentage of patients with a positive circumferential margin.

Table 1. Patients excluded from analysis.

Randomised	RT+TME n=761	TME n=769	Total n=1530
Ineligible at randomisation	22	27	49
no adenocarcinoma	4	3	7
other/previous malignancy	10	15	25
double tumour	1	5	6
other	7	4	11
Ineligible after randomisation	44	23	67
withdrawn informed consent	11	2	13
sigmoid carcinoma	2	-	2
unresectable on CT-scan	5	-	5
M1 on CT-scan	4	-	4
RT not possible	4	-	4
other	5	1	6
no resection	13	20	33

Radiotherapy

Delivery

In the radiotherapy group, the following minor protocol violations occurred. Treatment was not completed in 14 patients. The interval between the first day of radiotherapy and the day of surgery exceeded 10 days in 11% of the patients (range 11-60). In 85 patients (12%) the upper border of the treatment field was at the level of S1/S2 and in 6 patients the upper border was at the level of L4 or L5 instead of the promontory. In 40 patients undergoing an APR, the perineum was not included in the treatment field. All patients with minor protocol violations were included in the analyses.

Radiotherapy was given with 3 portal fields in 75% of the patients and with four portal fields in 25% of the patients. Fifty-three percent of the patients were treated in supine position. Of the 322 patients treated in prone position, 92 (29%) were treated on a belly board. The dorsal sacrum and lordotic curve was shielded in 90% of all patients.

The median interval between randomisation and surgery was 21 days in the radiotherapy group and 14 days in the surgery group, indicating that postponement of surgery did not occur more often in the radiotherapy group, since it was anticipated that radiotherapy increased the treatment time by a maximum of 10 days.

Table 2. Clinical and pathological characteristics.

	RT+TME n=695		TME n=719		Total n=1414
	n	%	n	%	n
Age (mean, range)	64.1	26-88	64.1	23-92	64.1
Sex					
male	455	65	455	63	910
female	240	35	264	37	504
Tumour level inferior margin					
0-5 cm	202	30	225	32	427
5.1-10 cm	290	42	281	40	571
10.1-15 cm	193	28	204	28	397
missing	10		9		19
Operation type					
APR	214	31	220	30	434
LAR	439	63	465	65	904
Hartmann	42	6	34	5	76
TNM-stage					
0	10	1	15	2	25
I	218	31	203	28	421
II	191	28	190	26	381
III	235	34	272	38	507
IV	41	6	39	6	80
Circumferential margin					
> 1 mm	572	82	578	80	1150
≤ 1 mm	122	18	141	20	263
missing	1				1

Toxicity

During radiotherapy, any kind of side effect was reported in 26% of all irradiated patients (Table 3). Nineteen percent was grade 1 toxicity, representing only minor complaints. In 7% of the patients there was a grade 2 or 3 complication.

Acute transient neurological complaints were recorded in 53 patients, of which 35 had grade 1, not requiring any intervention. In 2 patients the shielding was adjusted and the upper border was lowered in 3 patients. In 13 patients treatment was interrupted due to serious pain in the gluteal region or legs. Remarkably, of these 13 patients, 6 patients were treated in one radiation institute. No relation with number of portals, upper border, treatment position or shielding could be found. Due to the fact that the neurotoxicity score was introduced in 1997, data about neurotoxicity are missing in 178 patients.

In four (<1%) patients other grade 3 toxicity was reported, leading to postponement of the operation in two patients with thrombo-embolic complications. One patient required a catheter due to urinary retention after the radiotherapy. The last patient had anal blood loss 2 months after radiotherapy and proctoscopy confirmed a proctitis.

Table 3. Number of patients with radiotherapy toxicity.

	RTOG grading			
	0	1	2	3
Skin	685	8	2	0
Gastrointestinal	605	75	14	1
Genitourinary	676	16	2	1
Neurological	464	35	5	13
Other	655	31	7	2

Table 4. Surgery characteristics.

	RT+TME n=695		TME n=719		
	n	%	n	%	P
Operation characteristics					
time (median, range)	180	65-390	180	70-380	ns
blood loss (median, range)	1100	50-20000	1000	20-15000	<0.001
LAR	1025		800		<0.001
APR	1200		1300		ns
hospital stay (median, range)	15.0	3-179	14.0	0-169	ns
Operation type when LAR planned					
LAR	408	85	435	89	ns
APR	45	9	35	7	
Hartmann	30	6	21	4	
Stoma in LAR patients					
no stoma	176	36	216	43	0.05
stoma	263	64	249	57	
Anastomosis in LAR patients					
side-end	261	60	278	60	ns
end-end	54	12	50	11	
pouch	122	28	132	29	
missing	2		5		

Operation time in minutes, blood loss in ml and hospital stay in days. ns=not significant

Surgery

Surgical characteristics

To evaluate whether preoperative radiotherapy influences operation procedures, surgery characteristics are compared in Table 4. There was no significant difference in median operation time or median hospital stay between both treatment arms. Total blood loss was slightly increased (100 ml) in the irradiated (RT+) group (P<0.001). Subset analysis revealed that the difference in median blood loss was mainly present in the LAR patients: 1025 ml in the RT+ group vs. 800 ml in the non-irradiated (RT-) group (P<0.001), whereas median blood loss in the APR patients was not significantly different over the treatment arms.

Of the patients planned to undergo a LAR operation, 9% in the RT+ group and 7% of the patients in the RT- group underwent an APR. In APR patients, conversion to a sphincter saving procedure took place in 20% of the irradiated patients and in 19% of the TME alone group. A pouch reconstruction was done in 28% of the irradiated patients undergoing a

LAR vs. 29% of the non-irradiated patients.

More RT+ patients received a temporary diverting stoma at the time of TME surgery than RT- patients did (64% vs. 57%, P=0.05). Postoperatively, slightly more RT- patients required a stoma due to complications, resulting in a not significantly different overall number of temporary stomas in both groups (68% vs. 63%, P=0.2), as is shown in Figure 1.

Complications

There was no difference in the percentage of patients with complications during the operation. Bleeding during operation occurred in 13% of the patients in both groups. In 8% of the irradiated patients and in 7% of the non-irradiated patients, an unintended organ injury occurred.

All reported postoperative complications are listed in Table 5. For most complications there was no difference between the two treatment arms. The overall postoperative complication rate was 48% in the irradiated group vs. 41% in the non-irradiated group (P=0.008). This difference was mainly attributable to the difference in perineal wound healing.

In APR patients, perineal wound complications were significantly increased in the irradiated patients (29% vs. 18%, P=0.008), whereas there was no difference in the abdominal wound complications. Application of an omentoplasty did not lead to a reduction in perineal complications. In 40 irradiated APR patients the perineum was not included in the treatment field. Seven of these patients (18%) had perineal problems, vs. 54 (31%) of the 174 patients in which the perineum was included in the treatment field.

The percentage of LAR patients showing clinical leakage postoperatively was 11% (n=105) and was not statistically different for irradiated and non-irradiated patients (11% vs. 12%). Leakage was less common in patients with a diverting stoma (8% vs. 16%, P=0.001). In patients with an end-end anastomosis leakage occurred in 16% of the LAR patients, whereas only 9% of the patients with a pouch reconstruction experienced anastomotic failure. In patients with a side-end anastomosis this percentage was 12%. There was no influence of the distance of the tumour from the anal verge or age on the occurrence of leakage. Twenty percent of the patients with leakage were treated conservatively, whereas 80% required a surgical reintervention.

In total, 201 patients (14%) underwent one or more reinterventions with 103 patients in the RT+ group and 98 in the RT- group. Indications for reinterventions are listed in Table 6. No difference between the number of reinterventions in the LAR or APR patients was observed.

Twenty-eight patients (4%) died in hospital in the RT+ group vs. 24 (3.3%) in the RT- group (P=0.49). Postoperative mortality (<30 days) was 3.5% in the RT+ group vs. 2.6% in the RT- group (P=0.38). There was a strong correlation between age and hospital death (P<0.001, Figure 2). Causes of hospital death are given in Table 7. In the RT+ group 10 patients died of cardiac problems versus 3 patients in the RT- group (P=0.04). Anastomotic leakage contributed to postoperative mortality in 12 patients (23% of all in-hospital mortalities).

Table 5. Postoperative complications.**

	RT+TME n=695		TME n=719	
	n	%	n	%
Infectious				
wound infection	43	6	45	6
abscess	31	5	20	3
haematoma	7	1	2	<1
sepsis/fever	63	9	50	7
other	2	<1	2	<1
Any infectious complication	120	17	105	15
General				
cardiac	36	5	22	3 #
multi-organ failure	11	2	10	1
pulmonary	53	8	57	8
thrombo-embolism	11	2	12	2
line-sepsis	9	1	9	1
neurological	10	1	12	2
psychological disorders	28	4	10	1 *
renal	4	1	6	1
other	25	4	23	3
Any general complication	161	23	30	18 #
Surgical				
leakage (LAR)	49	11	56	12
perforation	8	1	7	1
intestinal necrosis	6	1	7	1
fistula	8	1	14	2
stoma complications	14	2	12	2
bleeding	23	3	29	4
abdominal dehiscence	16	2	25	4
perineal complications (APR)	61	29	39	18
diarrhoea	11	2	2	<1 #
ileus	37	5	48	7
other	22	3	10	1 #
Any surgical complication	209	30	191	27
Any complication	336	48	297	41 *

# P<0.05

* P<0.01

** The numbers and percentages of the separate complications do not summate "any complication" since some patients had more than one complication. They were registered for each separate complication, but for "any complication" they were counted as one.

Table 6. Indications reintervention.

	RT+TME	TME	Total
Anastomotic leakage	23	31	54
Abscess	27	13	40
Bleeding	11	16	27
Abdominal dehiscence	8	13	21
Perineal complications	4	2	6
Complications stoma	3	4	7
Other complications surgery	6	6	12
Peritonitis or sepsis	7	2	9
Ileus	11	9	20
Other	3	2	5
Total	103	98	201

Table 7. Causes of hospital mortality.

	RT+TME	TME	Total
Abscess	1	1	2
Anastomotic leakage	4	8	12
Bleeding	1	1	2
Perforation bowel	3	1	4
Complications mechanic ileus	-	3	3
Necrosis bowel	2	2	4
Sepsis	1	2	3
ARDS	1	-	1
Cardiac	10	3	13
Pulmonary embolism	2	2	4
Pneumonia	3	1	4
Total	28	24	52

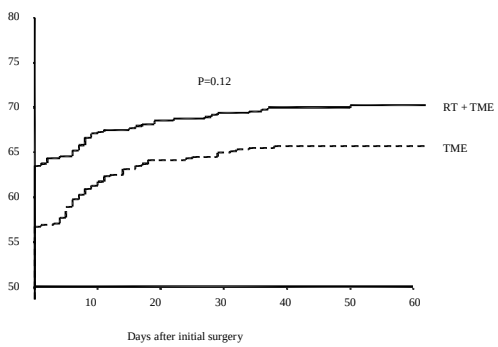

Figure 1. Percentage of LAR patients with a diverting stoma per randomisation group (P=0.12).

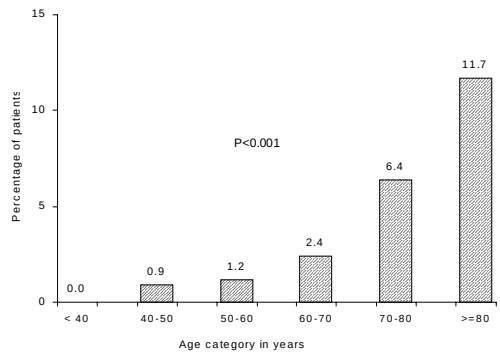

Figure 2. Percentage of hospital deaths per age category (P=0.001).

DISCUSSION

The results of this study indicate that short-term, preoperative radiotherapy does not complicate TME surgery, although there is a slight increase in complications in the preoperatively irradiated patients.

Acute side effects of preoperative, hypofractionated radiotherapy include nausea, diarrhoea and skin erythema. These side effects develop to some degree in most patients, but usually resolve within a few weeks. In this trial, few early side effects for radiotherapy were reported. This may be attributed to the fact that most patients were operated in the week after radiotherapy and not seen by the radiation oncologist until several weeks after the operation. By this time, most side effects will have resided.

Lumbosacral plexopathy was a major cause of concern in the Swedish Rectal Cancer Trial (SRCT) since six patients developed long-standing pain and/or neurological symptoms at the level of the lower lumbar plexus.[34] These six patients all complained about pain during the radiotherapy. An extensive study on dose distribution showed that these patients might have received a higher dose (112%) at the level of the lumbar vertebrae, when the dorsal shields were inappropriately placed.

In our study, 53 patients had pain or a feeling of discomfort in the legs or in the gluteal region, of which 18 needed medication or treatment interruption. In these patients, a careful evaluation of the treatment fields and the dorsal shielding was done and adjustments were made in 5 patients. As precaution, treatment was interrupted in 14 patients. So far, with a median follow up of 25.4 months, there are no reports of longstanding pain or neurological symptoms. This might be attributed to the fact that the upper border of the radiation field was defined as L5/S1, as opposed to mid L4 in the Swedish trials. This prevents the irradiation of the lower dorsal lumbar roots.

Although there was initial concern that irradiation would hamper the operation, this was not reflected in the parameters of the surgical procedure. There was no increase in the duration of the operation and although the difference in blood loss was significant, an increase of 100 ml is not a serious clinical problem. Irradiation did not influence the choice of the surgeon to perform a LAR or an APR procedure.

The relatively high incidence of postoperative complications in our trial (45%) might be explained by the great effort taken to meticulously register all possible complications. Apart from data from the case record forms as recorded by the surgeon, data from operation notes and discharge letters were taken into account as well. Similar complication rates were reported in a prospective comparison of conventional and TME surgery.[35]

The mortality rate in the Stockholm I trial with 5x5 Gy was 2% in the RT- group vs. 8% in the RT+ group.[27] In the Imperial Cancer Research Fund (ICRF) trial where patients were treated with 3x5 Gy, these percentages were 7% vs. 12%, respectively.[7] The difference could mainly be contributed to an increase in cardiovascular deaths, particularly in patients aged over 75 years. Therefore, patients elder than 80 years were excluded from the Stockholm II trial and the SRCT. The explanation for the increased mortality rates in the Stockholm I trial and the ICRF trial is possibly the suboptimal treatment technique. In these trials, the treatment was given by two opposed fields, which increases the volume treated with 25 Gy considerably. Later trials therefore requested a three or four portal technique in order to reduce the treated volume. In the SRCT 48 patients were treated with a two-portal technique and those patients showed a higher mortality rate than the patients treated with three or four

portals.[26] In the Stockholm II trial there was no longer a difference in mortality within 30 days between the two treatment arms: 2% in the irradiated group vs. 1% in the non-irradiated group. In-hospital mortality rates in the SRCT were 4% in the RT+ vs. 3% in the RT- group. The in-hospital mortality rate in our trial showed no difference between the treatment arms and was 4% in the RT+ group vs. 3.3% in the RT- group. This can be considered as a satisfying result, taking into account that patients above the age of 80 were included in our trial. Our results demonstrate that the introduction of TME surgery after preoperative radiotherapy does not lead to an increase in the postoperative mortality rate, as long as at least three portals are used for the radiotherapy.

The two major causes of postoperative mortality in our trial were cardiovascular problems and complications due to anastomotic failure in LAR patients. Anastomotic leakage is a major clinical problem in rectal or anal anastomoses. The reported clinical leakage rate after anterior resection varies from 3% to 11%.[36-39] Karanjia et al. showed that a diverting colostomy is an important measure in reducing the complications of anastomotic leakage.[37] After TME surgery, an increase in serious anastomotic leakage has been reported as compared to conventional surgery.[35,40] This increase can be partly explained by the removal of the pain-sensitive peritoneum, which prevents early detection of anastomotic failure.[37] In our study, the number of patients with clinical anastomotic leakage was 105 (11%). This is consistent with other reports in which TME surgery was applied. It is particularly reassuring since this trial was a large multicentre study, whereas most other reports concern single institution experience. No difference in clinical leakage rate between the RT+ and RT- patients was observed, which is in agreement with previous reports about preoperative radiotherapy.[11,12,27,28] Since patients with a diverting colostomy developed fewer leaks, we recommend a diversion in case there is any doubt about the quality of the anastomosis.

Increase in perineal dehiscence after preoperative RT has been observed by several authors, both after short-term as well as after long-term preoperative radiotherapy. Although results are difficult to compare, due to various definitions of perineal dehiscence, a twofold increase is generally reported after RT.[11,12,26-28] In our study, 100 patients suffered from perineal complications with 18% in the RT- group vs. 29% in the RT+ patients. When the perineum was not included in the target volume, there was no increase of perineal complications as compared to the non-irradiated patients. However, avoidance of irradiation of the perineum is not desirable in APR patients since this might lead to an increase in local recurrences.

In conclusion, our results show that although application of short term, preoperative radiotherapy in combination with TME surgery leads to an increase in overall postoperative complication rate when compared to TME surgery alone, the number of complications leading to reintervention or even mortality are similar in both treatment arms. Although follow-up is too short to comment on the occurrence of late side effects, long term results from the SRCT give no reasons for concern so far. Therefore, preoperative hypofractionated RT is to be considered a safe procedure also in patients treated with TME surgery, despite a slight increase in complications when compared to TME surgery only.

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