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Late side effects of short course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients. A report from the TME trial

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ABSTRACT

Purpose:

Preoperative short term radiotherapy improves local control in patients treated with total mesorectal excision (TME). This study was performed in order to assess the presence and magnitude of long term side effects of preoperative 5x5 Gy and TME. Also, hospital treatment was recorded for diseases possibly related to late side effects of rectal cancer treatment.

Patients and Methods:

Long term morbidity was assessed in patients from the prospective randomized TME trial, investigating the efficacy of 5x5 Gy prior to TME surgery for mobile rectal cancer. Dutch patients without recurrent disease were sent a questionnaire.

Results:

Results were obtained from 597 patients with a median follow up of 5.1 years. Stoma function, urinary function and hospital treatment rates did not differ significantly between the treatment arms. However, irradiated patients reported increased rates of fecal incontinence (62% vs. 38%, $P < 0.001$), pad wearing due to incontinence (56% vs. 33%, $P < 0.001$), anal blood loss (11% vs. 3%, $P = 0.004$) and mucus loss (27% vs. 15%, $P = 0.005$). Satisfaction with bowel function was significantly lower in irradiated patients, and the impact of bowel dysfunction on daily activities was greater in case of radiotherapy.

Conclusion:

Although preoperative short term radiotherapy for rectal cancer results in increased local control, there is more long term bowel dysfunction in irradiated patients than in patients who undergo TME alone. Rectal cancer patients should be informed on late morbidity of both radiotherapy and TME. Future strategies should be aimed at selecting patients for radiotherapy who are at high risk for local failure.

INTRODUCTION

Surgery is the key to cure for patients with rectal cancer. In the past, local recurrence rates after conventional surgery averaged 30% and varied considerably between institutions from 15% to 45%.(1-3) The acknowledgement of the importance of circumferential lateral spread in the occurrence of local failure(4) has led to the introduction of total mesorectal excision (TME).(5) This surgical technique ensures resection of the complete mesorectum in contrast to conventional blunt dissection which is known to leave behind fragments of mesorectal tissue, that frequently contain non-nodal foci of metastatic disease.(6) TME has proven its superiority with regard to local control and survival when compared to historical controls.(7-9)

Apart from surgery, the benefit of radiotherapy, either pre- or postoperatively given, has been established in several randomized trials as well.(10-15) The only randomized trial comparing pre- and postoperative radiotherapy clearly showed the superiority of preoperative radiotherapy regarding side effects and local control.(16) These results were confirmed in a large meta-analysis, including 8507 patients from 22 randomized trials, that concluded that preoperative radiotherapy is superior to postoperative radiotherapy in terms of cancer specific death (45% and 50% respectively, P=0.0003) and reduction of local recurrence risk (46% and 37%, P=0.002).(17) Furthermore, in the Swedish Rectal Cancer trial it was shown that a short-term regimen of high-dose preoperative radiotherapy (5x5 Gy) administered in one week was capable of not only reducing local recurrence rates (27 vs. 11%, P<0.001), but also improving 5 year overall survival (48% vs. 58%, p = 0.004) compared to surgery alone.(15)

The benefit of this radiotherapy regimen in combination with TME surgery was also suggested in the prospective randomized TME trial: after a median follow-up of 2 years, irradiated patients had lower local recurrence rates than patients who underwent radiotherapy alone (2.4% vs. 8.2%, P <0.001). No difference in overall survival could be detected (81.8% vs. 82%, P = 0.84).(18) In a previous report, reporting acute side-effects and complications of 5x5 Gy followed by TME surgery within one week, we showed that radiotherapy is a safe procedure despite a slight increase in complications when compared to TME alone.(19) While acute toxicity of short-term radiotherapy has been examined in several other trials as well(12;13;20), reports on long term morbidity are remarkably scarce. The aim of this study was to evaluate the effect of short-term preoperative radiotherapy and TME surgery on long term side effects in patients with operable rectal cancer.

PATIENTS AND METHODS

Study population

From January 1996 until December 2000, 1861 patients were randomized between preoperative radiotherapy (5x5 Gy) followed by TME and TME alone. Eligibility criteria for trial partici-

pation included histologically confirmed adenocarcinoma of the rectum without evidence of distant metastases. The inferior margin of the tumor had to be located not further than 15 centimetres from the anal verge and below the level of S1-2. Patients with fixed tumors were excluded as well as patients with locally treated (transanal resected) tumors.

Most patients (n = 1530) were Dutch. The remaining patients were included by Swedish, other European and Canadian centers. Only Dutch patients were considered in the present analysis as accurate collection and verification of data on late side effects was for logistical reasons feasible for these patients only. Secondly, only those patients were included who were present in the analysis of acute toxicity as well. In- and exclusion for this analysis has been reported previously.(19) Patients had to be free of local or distant recurrent disease in order to avoid confounding due to symptoms caused by disease recurrence. Finally, only those patients who had responded to the quality of life questionnaires, that were sent 18 and 24 months after surgery received a questionnaire about toxicity.

Treatment

Radiotherapy consisted of a total dose of 25 Gy given in 5 fractions over 5-7 days. A three or four-portal technique was used and the clinical target volume included the primary tumor and the mesentery containing the perirectal, presacral and internal iliac nodes up to the S1/S2 junction. The anal sphincter was included in the clinical target volume only if an abdominoperineal resection was planned. This resulted in an upper border at the level of the promontory, and lateral borders 1.5 cm over the pelvic inlet. In the lateral fields, the entire sacrum had to be included and the anterior border included the posterior part of the prostate or the vagina. Treatment was delivered with a three or four portal box technique, depending on the institutes' preference. The protocol prescribed an overall treatment time of at most 10 days. It was advised to give the radiotherapy on 5 consecutive days. Other details on radiotherapy have been described previously. (19)

All patients underwent surgery according the principles of TME surgery. Workshops, symposia and video instructions were organised to ensure quality controlled surgery. Moreover, in each participating center, the first five TME procedures had to be supervised by an instructing surgeon. Both radiotherapy and surgical procedures have been reported in detail in earlier instance.(18;20)

Measurements

Late morbidity was assessed using a questionnaire that was mailed to all patients in April and May 2003. The questionnaire was accompanied with a letter that explained the purpose of the study. In a pilot study, the questionnaire was tested for readability and understanding among 20 eligible patients. Patients that did not respond initially were sent one reminder. Table 1 shows the items of the questionnaire regarding bowel, stoma and urinary function. Patients could indicate the severity of dysfunction on a four-point scale ranging from "no, never" to

Table 1. Questions asked to assess bowel, stoma and urinary function

Bowel function
mean bowel frequency at day and night
anal blood and mucus loss
fecal incontinence at day and night
pad wearing due to fecal incontinence
Stoma function
peristomal skin irritation
stoma smell
stoma bleeding
stoma leakage
painful stoma
noisy stoma
Urinary function
mean urinary frequency at day and night
hematuria
dysuria
urinary incontinence
use of pads for urinary incontinence
need to urinate again within 2 hours
stream hesitation
difficulty to postpone urination
weak urinary stream
Impact of bowel and urinary dysfunction on
work or household activities
activities outside the house like shopping or paying visits
social activities like theatre or cinema visiting
Satisfaction with bowel, stoma and urinary function

"sometimes" (less than once a week), to often (more than once a week, but not every day) to "yes, always" (every day) for time dependent symptoms, and from "no, not at all" to "a little" to "pretty much" to "very seriously" for time independent symptoms. Data from four-point scale answers were transformed into binary outcome measures (i.e. signs yes/no present). Only if there were no complaints at all, the item was scored as not present. Level of satisfaction with bowel and urinary function was assessed using a 3 point verbal scale including "satisfied, neutral feelings, or unsatisfied". Because of previously reported neurogenic pain and subacute nerve damage using a fraction size of 5 Gy (21), questions regarding neurological function were included: patients were asked for the presence of back/buttock ache or pain in one or both legs, hip stiffness or pain, walking difficulties and the use of walking aids. In addition, patients were asked to rate their overall perceived health during the week prior to receipt of the questionnaire by means of a visual analogue scale (a 100 mm horizontal line, anchored at the extremes by 'best imaginable quality of life' and 'worst imaginable quality of life').(22)

Patients were further asked whether they were treated in the hospital (either on a in- or outpatient basis) since rectal cancer surgery for any of the following disorders: bowel obstruc-

tion, herniae cicatricales, delayed wound healing, anastomotic stenosis, stoma problems like parastomal hernia, stenosis and prolaps, chronic cystitis, fracture of hip and/or pelvis, and finally, myocardial infarction or stroke. Only those groups of diseases that were considered possible late side effects of treatment were specifically mentioned. In addition, patients were requested to report any other treatment in the hospital. Data on hospital treatment were added with information obtained from the regular follow-up of the TME trial.

Data Collection and Statistics

All questionnaires were sent to the central data centre in Leiden. Data were entered in a database and analysed with SPSS statistical software (version 11.5 for Windows, SPSS, Chicago). Chi-square tests were used to compare proportions. Student t-testing was applied for testing differences between continuous variables. A two-sided P-value of 0.05 was considered significant. No correction for multiple testing was applied.

RESULTS

Patients

Of all 1530 randomized Dutch patients, 116 were excluded for the assessment of acute radiotherapy toxicity.(19) These patients were also excluded for the present analysis. Other reasons for exclusion were death (n = 517), recurrent disease (n = 83) and no compliance with the completion of a previous quality of life questionnaire (n = 106). Thus, 708 patients remained evaluable. Median follow-up of these patients was 5.09 years since surgery and did not differ significantly between irradiated and non-irradiated patients. Of these patients, 597 returned the questionnaire, resulting in a response rate of 84%. Distribution of patients and clinical characteristics was well balanced between irradiated and non-irradiated patients as shown in table 2.

At the time of filling out the questionnaires, 362 patients did not have a stoma. Of these patients, mean bowel frequency during the day was significantly higher in irradiated patients compared to patients who underwent surgery alone (3.69 vs. 3.02, P = 0.011). Mean bowel frequency during the night did not differ statistically between the two randomisation arms (0.48 vs. 0.35, P = 0.207). Figure 1 shows significantly increased rates in irradiated patients of fecal incontinence at day and night, anal blood and mucus loss, as well as higher rates of pad wearing due to fecal incontinence. The severity of fecal incontinence for the two randomisation arms is shown in figure 2. Irradiated patients reported more signs of severe incontinence: daily incontinence was 5% in TME alone patients and 14% in irradiated patients. Figure 3 shows the degree of fecal incontinence depending on tumor distance from the anal verge: incontinence at day was significantly more reported after radiotherapy for patients with

Table 2. Clinical and pathological patients characteristics over both treatment arms. Of 1 one irradiated patient, tumor location was unknown

	RT+TME n=306		TME n=291		Total n=597
	n	%	n	%	Total
Age (mean, range)	63.06 (34-86)		61.60 (27-84)		
Sex					
male	199	65	170	58	369
female	107	35	121	42	228
Tumor location(*)					
≤5 cm	86	28	95	33	181
5.1-10.0 cm	123	40	109	38	232
≥10.1 cm	96	32	87	30	183
Operation type					
APR	91	30	86	30	177
LAR	200	65	197	68	397
Hartmann	15	5	8	3	23
TNM stage					
0	8	3	10	3	18
I	140	46	123	42	263
II	84	28	82	28	166
III	74	24	76	26	150
Stoma present					
No	177	58	185	64	362
Yes	129	42	106	36	235
Median follow-up (yrs)	4.98	2.6 – 7.6	5.18	2.7 – 7.5	5.09

tumors between 5 and 10 centimeters from the anal verge. The difference was not statistically significant for proximal lesions up to 15 centimeters.

More irradiated patients reported an impact of bowel dysfunction on daily activities like work and/or household (34% vs. 22%, P = 0.01) and activities outside the house (52% vs. 40%, P = 0.04). Although statistical significance was not reached, there was an increased impact on social activities (46% vs. 37%, P = 0.15) in irradiated patients.

Two hundred and thirty-five patients had a stoma at the time of completing the questionnaire. There were no statistical significant differences in stoma related difficulties although slightly more problems were seen in irradiated patients (table 3). Overall reported stoma complaints were 87% in irradiated and 82% in TME alone patients (P = 0.06). The impact of stoma (dys)function on work/household activities (31% vs. 33%, P = 0.77), activities outside the house (35% vs. 28%, P = 0.27) and social activities (35% vs. 28%, P = 0.29) did not differ significantly between the treatment arms, but was much lower than for patients without a stoma.

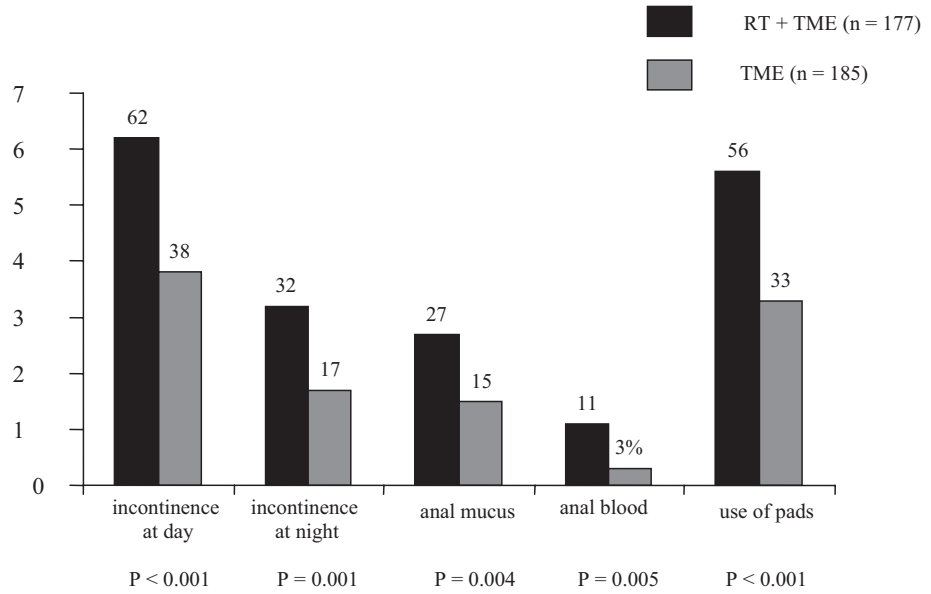

Figure 1. Bowel function in eligible patients at risk without a stoma

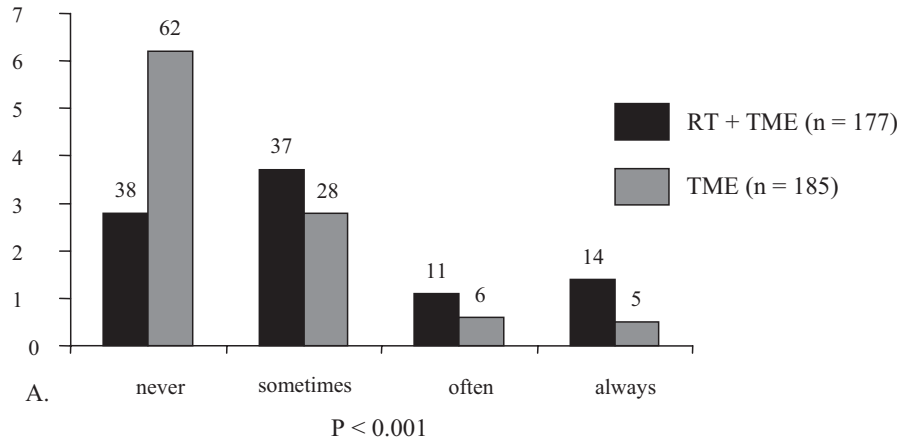

Figure 2. Degree of fecal incontinence at day in patients at risk without a stoma who reported some degree of fecal incontinence (n = 362). Sometimes was defined as once a week or less; often as more than once a week and always as every day

Patients with a stoma were more satisfied about their bowel functioning than patients without a stoma, whether they had received radiotherapy or not (figure 4). In stoma patients there was no difference in satisfaction between the randomization arms. In patients without a stoma, irradiated patients were less satisfied than non-irradiated patients (50% vs. 60%, p=0.008).

Table 4 summarizes results from urinary function assessment and shows no significant differences in voiding problems between the two treatment arms. However, around 39%

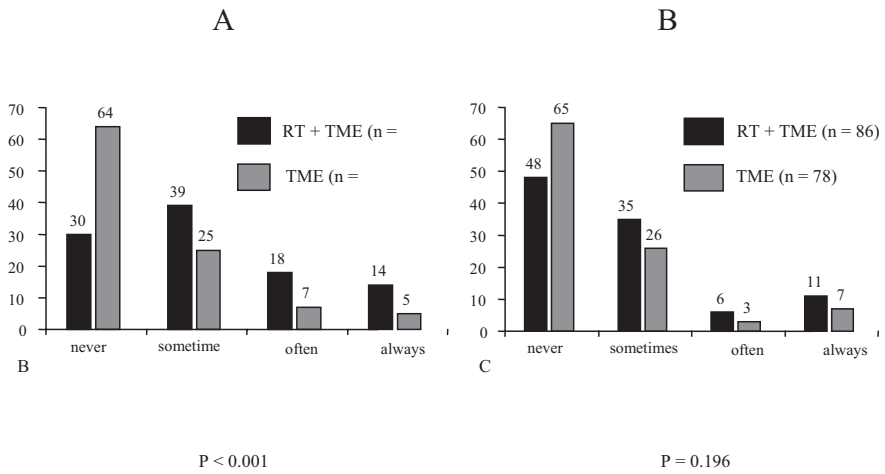

Figure 3. Degree of fecal incontinence at day in patients at risk without a stoma who reported some degree of fecal incontinence (n = 362) A. Patients without a stoma with tumors between 5.1 and 10 centimeters from the anal verge B. Patients without a stoma with tumors between 10.1 and 15 centimeters from the anal verge. Sometimes was defined as once a week or less; often as more than once a week and always as every day

Table 3. Stoma functioning in irradiated and non-irradiated patients

	RT+TME n=129			TME n=106			
	n	%	missing	n	%	missing	P-value
Peristomal skin irritation	48	39	5	32	31	4	0.251
Stoma smell	65	55	9	46	47	7	0.233
Stoma bleeding	45	39	12	34	34	7	0.531
Stoma leakage	34	30	14	23	24	8	0.317
Painful stoma	20	17	14	12	12	8	0.295
Noisy stoma	83	68	6	62	61	5	0.342
Any stoma problem	**110**	**87**	**2**	**82**	**78**	**1**	**0.063**
Impact on work/household activities	39	31	4	34	33	3	0.771
Impact on activities outside the house	44	35	2	29	28	2	0.271
Impact on social activities	42	35	9	28	28	7	0.289
Satisfaction about defecation							
satisfied	95	74		78	75		
neutral	30	23	1	22	21	2	0.783
unsatisfied	3	2		4	4		

reported to be incontinent for urine in both groups, and 57% of the patients wore pads due to urine incontinence.

There was no increase in the readmission rates in irradiated patients for the indications as displayed in figure 5. In particular, the number of cardiovascular accidents was not increased

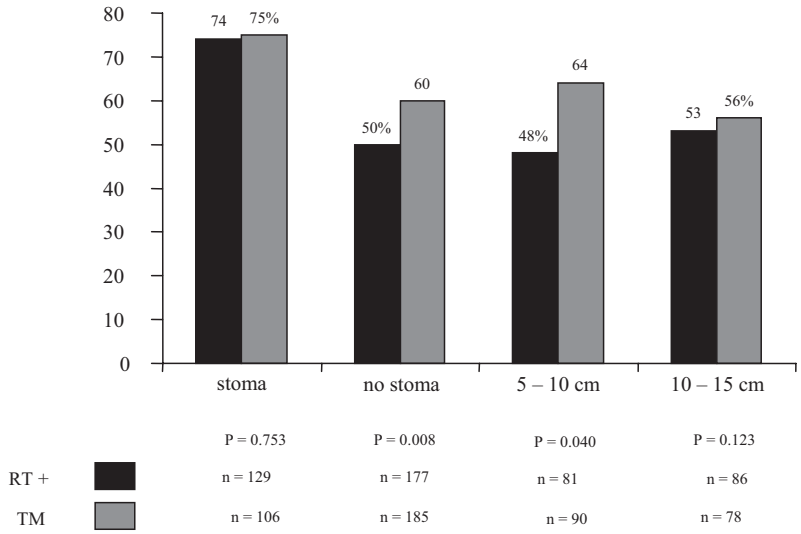

Figure 4. Proportion of patient subgroups that indicated to be satisfied with bowel function

Table 4. Urinary function

	RT+TME n=306			TME n=291			P-value
	n	%	missing	n	%	missing	
Median urinary frequency at day	6.21		21	5.97		11	0.270
Median urinary frequency at night	1.51		6	1.41		4	0.260
Hematuria	5	2	7	2	1	8	0.286
Dysuria	27	9	7	22	8	8	0.585
Urinary incontinence	118	39	6	109	38	3	0.711
Use of pads for incontinence	67	57	5	62	57	5	0.983
Sensation of uncompleted bladder emptying	139	47	13	134	48	9	0.985
Need to urinate again within 2 hours	203	70	16	195	71	18	0.710
Stream hesitation	131	45	15	136	49	13	0.315
Difficulty to postpone urination	152	53	17	141	52	17	0.788
Weak urinary stream	158	55	17	144	52	15	0.552
Need to push or stain to urinate	77	26	13	92	33	12	0.079
Satisfaction about urinary function							
satisfied	207	68		194	68		
neutral	74	24	6	75	26	5	0.903
unsatisfied	19	6		17	6		

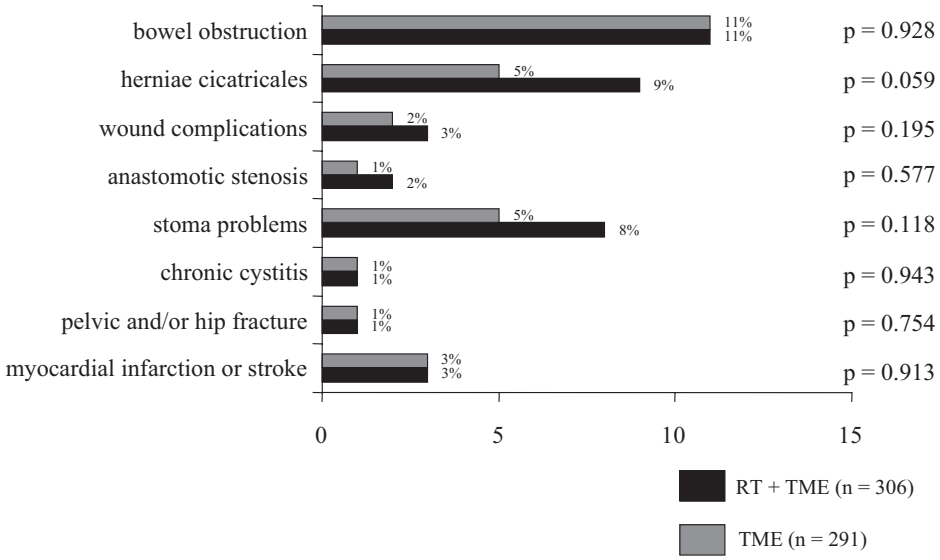

Figure 5. Rates of hospital treatment in all responding patients

in irradiated patients. Moreover, there were not more angina pectoris complaints after radiotherapy (12% vs. 16%, P = 0.17).

Back/buttock ache or pain in one or both legs was reported by 52% of the irradiated patients and 58% of the patients who underwent TME alone (P = 0.20). Hip stiffness or pain occurred in 34% of patients who underwent radiotherapy compared to 37% in case of TME alone (P = 0.423). Respective figures for walking difficulties were 43% and 46%, P = 0.79.

Median score on the visual analogue scale for overall perceived health was 82.0 for irradiated patients (range 13 – 100) and 81.0 for patients without radiotherapy (range 4 – 100) (P = 0.38). For patients with fecal incontinence, median VAS score was 79.0 (range 16 – 100) compared to 84.0 (range 13 – 100) for patients who were continent (P < 0.001). Of the continent patients, 68% was satisfied with their bowel function. For incontinent patients, this figure was still 44% (P < 0.001).

DISCUSSION

Short term preoperative radiotherapy has been successfully used to reduce local recurrence rates in TME treated rectal cancer patients.(18) This benefit of radiotherapy has to be balanced against the acute and late side effects of irradiation. We previously demonstrated that there is hardly an increase of acute toxicity after preoperative hypofractionated radiotherapy.(19) Concerning late side effects, there are only few reports available.(23;24) This study evaluated for the first time late sequela of radiotherapy and TME surgery within the framework of a randomized prospective trial. There were no significant differences in voiding and stoma

function, nor in symptoms possibly related to pelvic surgery or late side effects of radiotherapy. However, there were clear differences in bowel function between irradiated patients and patients who underwent TME alone.

In contrast to earlier radiotherapy studies (19;24), we detected no increased rates in irradiated patients of small bowel obstruction, urinary tract disease, femoral neck and pelvic fractures and arterial disease. The only randomized trial comparing pre- to postoperative radiotherapy, reported an increase in bowel obstruction in patients assigned to postoperative irradiation.(16) We now demonstrate that short-term preoperative radiotherapy does not lead to an increase in small bowel obstruction compared to surgery alone. This might be explained by the fact that in preoperative radiotherapy the pelvic cavity is still occupied by large bowel, thus creating a "natural spacer" for the small bowel, which consequently is not exposed to irradiation. This is in contrast to radiotherapy after pelvic surgery, in which case the small bowel descends into the small pelvis due to the created open space.

Also, there was no difference in the number of femoral head or pelvic fractures. This is in contrast with data from the Stockholm trials that showed 5.3% of femoral neck or pelvic fractures after radiotherapy, compared to 2.4% in patients without radiotherapy ($P = 0.03$)(24). In the Stockholm I trial, a two field technique was used that was replaced in the Stockholm II trial by a four-field box technique. Concomitant with this change in radiotherapy technique, there was a drop in the incidence of femoral neck and pelvic fractures. In our study, a three or four field technique was routinely used, which most likely explains the non-significant difference in fractures in our study population.

Long term urinary function was not deteriorated in irradiated patients compared to TME alone patients, which is in agreement with results from the Stockholm I and II trial, in which there was no statistical difference in urinary function between irradiated and non-irradiated patients. A small study (n=42) in male rectal cancer patients undergoing TME with or without preoperative radiotherapy demonstrated no significant difference in urinary function between irradiated and non-irradiated patients.(26) Although there is no statistical significant difference between both treatment arms in urinary incontinence rates, it is noteworthy to have incontinence reported in as much as up to 40% in both groups. One has to bare in mind however, that for the present study, loosing urine involuntarily once a week or less, was scored as urinary incontinence. Yet, there was an impact of urinary incontinence on overall perceived health: patients with urinary incontinence had a median VAS score of 77 (range 11 – 100) compared to 84 (range 4 – 100) for patients without urinary incontinence ($P < 0.001$).

Despite the undisputable improvements in radiotherapy technique and application in time, the adverse effect on long term bowel function and its impact on daily activities remains an important issue for concern. Dahlberg et al.(23) retrospectivally investigated the effect of preoperative high-dose radiotherapy in the Swedish Rectal Cancer Trial(15) and showed increased bowel frequency, incontinence, urgency and emptying difficulties in irradiated patients. In a recent report involving 124 patients undergoing anterior rectal resection, Welsh

et al.(27) showed higher incontinence scores in patients undergoing 5x5 Gy prior to TME. Data of these studies are in line with our results and indicate that there is price to pay for increased local control, even with adjusted radiotherapy technique. According to the TME radiotherapy protocol, the clinical target volume excluded the anal sphincter in case of an anterior resection with the lower border being 3 centimeters above the anal verge. Despite sparing of the anal sphincter, fecal incontinence rates were increased in irradiated patients. Apart from anal sphincter function, compliance of the rectal remnant is probably important for fecal continence as well. The latter might be decreased by radiotherapy due to aspecific changes in surrounding tissues.

As shown in figure 2, the proportion of patients expressing signs of fecal incontinence is considerable, especially in case of irradiation. Rates of fecal incontinence up to 62% in irradiated patients might appear unsurpassed when compared to previous studies. It needs to be stressed however, that even when the patient reported soiling once a week or less, the patient was considered as incontinent for the present study. Thus, comparison with previous reports should be made with care. Nevertheless, 14% of the irradiated patients mentioned to suffer from fecal incontinence every day compared to 5% of the TME alone patients, making the additional toxic effect of radiotherapy unnegligible.

Based upon subgroup analyses from the TME trial at a median follow-up of two years, radiotherapy is most effective for patients with tumors between 5.1 and 10 centimeters with local recurrence rates dropping from 10.1% to as low as 1.0% after preoperative radiotherapy ($P < 0.001$).(18) Figure 3 shows that the increase in incontinence rates due to radiotherapy is statistically significant in patients with mid-rectal carcinomas. This is not the case for patients with proximal lesions 10-15 centimeters from the anal verge. Thus, late term bowel dysfunction due to irradiation is more explicit in patients who seem to benefit most from radiotherapy.

It is not clear to what extent patients' quality of life is affected by impaired bowel function. In a concomitant study of our group, measuring health related quality of life on different time points up to 24 months after surgery, there were only few differences in quality of life between patients with and without preoperative radiotherapy, despite the presence significantly more fecal incontinence and sexual dysfunction in irradiated patients.(28) The current analysis of functional outcome was performed later in time and did not include a complete quality of life assessment. Nevertheless, overall perceived health was measured in this study: the median score of the Visual Analogue Scale was not significantly different between irradiated and nonirradiated patients without a stoma: 83.0 vs. 80.5 ($P = 0.374$), indicating that the increased rate of bowel dysfunction after radiotherapy is not expressed in a significantly worse VAS score for the whole population. However, we showed that impairment of bowel function had a significant effect on daily and social activities and this difference is translated in the overall perceived health, because the median VAS score was significantly lower for incontinent patients compared to continent patients (84.0 vs. 79.0, $P = 0.05$). In addition,

we demonstrated a statistical significant difference in satisfaction between irradiated and non-irradiated patients without a stoma: 50% vs. 60% respectively (P = 0.008).

We found no significant increase in stoma related problems in irradiated patients. In the analysis of acute radiotherapy toxicity, there was no increase of anastomtic dehiscence in irradiated patients.(19) Apparently, anastomotic bowel healing is not influenced by radiotherapy. In parallel to this finding, in the long run, stoma healing and function is neither affected adversely by radiotherapy. As shown in figure 4, irradiated stoma patients were satisfied with bowel function in 74% of the cases, versus 75% of non-irradiated patients (P = 0.753). Apart from the effect of radiotherapy, it is remarkable to note the distinction in satisfaction rates between patients with and without a stoma: patients reported to be satisfied with bowel function in 74% (n = 173) and 55% (n = 199) respectively (P < 0.001). Sphincter saving rectal surgery, often accompanied with long term bowel dysfunction, does not seem the ultimate goal that should be aimed for in every rectal cancer patient.

In conclusion, late term adverse effects of hypofractioned preoperative radiotherapy and TME surgery on functional outcome are considerable, using our strict criteria for dysfunction. However, an age-matched control group without a history of pelvic disease and treatment is lacking in the current study. Studying a control group, would possibly reveal a certain degree of dysfunction as well, making the real contribution of radiotherapy and surgery to functional outcome more clear. The results of our study, however, enable physicians to inform their patients reliably about the side effects of both radiotherapy and surgery in rectal cancer. Compared to radiotherapy, TME surgery is the main contributor to late bowel dysfunction. However, surgery is the only option that can lead to cure in contrast to radiotherapy that has merely benefits in terms of increased local control. The substantial additional long term side effect of radiotherapy on bowel dysfunction urges to tailor radiotherapy to those patients only who are most likely to benefit from it. In this way, unnecessary exposure to the described late side effects is avoided. However, pretreatment staging modalities presently used are incapable of identifying patients at risk for local failure accurately. Considering the significant increase in local control after preoperative radiotherapy for TME treated rectal cancer patients, 5x5 Gy remains a valuable treatment regimen.

REFERENCE LIST

1. Kapiteijn E, Marijnen CA, Colenbrander AC, et al: Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. Eur J Surg Oncol 24(6):528-535, 1998
2. Phillips RK, Hittinger R, Blesovsky L, et al: Local recurrence following 'curative' surgery for large bowel cancer: II. The rectum and rectosigmoid. Br J Surg 71(1):17-20, 1984
3. Porter GA, Soskolne CL, Yakimets WW, et al: Surgeon-related factors and outcome in rectal cancer. Ann Surg 227(2):157-167,1998
4. Quirke P, Durdey P, Dixon MF, et al: Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 2(8514):996-999, 1986
5. Heald RJ: A new approach to rectal cancer. Br J Hosp Med 22(3):277-281,1979
6. Reynolds JV, Joyce WP, Dolan J, et al: Pathological evidence in support of total mesorectal excision in the management of rectal cancer. Br J Surg 83(8):1112-1115, 1996
7. Aitken RJ: Mesorectal excision for rectal cancer. Br J Surg 83(2):214-216, 1996
8. Enker WE: Total mesorectal excision--the new golden standard of surgery for rectal cancer. Ann Med 29(2):127-133, 1997
9. Kapiteijn E, Putter H, van de Velde CJ: Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. Br J Surg 89(9):1142-1149, 2002
10. Gerard A, Buyse M, Nordlinger B et al: Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg 208(5):606-614, 1988
11. O'Connell MJ, Martenson JA, Wieand HS et al: Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331(8):502-507, 1994
12. Cedermark B, Johansson H, Rutqvist LE et al: The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. Cancer 75(9):2269-2275, 1995
13. Goldberg PA, Nicholls RJ, Porter NH et al: Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. Eur J Cancer 30A(11):1602-1606, 1994
14. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Medical Research Council Rectal Cancer Working Party. Lancet 348(9042):1610-1614, 1996
15. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 336(14):980-987, 1997
16. Frykholm GJ, Glimelius B, Pahlman L: Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum 36(6):564-572, 1993
17. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 358(9290):1291-1304, 2001
18. Kapiteijn E, Marijnen CAM, Nagtegaal ID et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. New England Journal of Medicine 345(9):638-646, 2001
19. Marijnen CA, Kapiteijn E, van de Velde CJ et al: Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002 20(3):817-825, 2002
20. Kapiteijn E, Kranenbarg EK, Steup WH et al: Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. Eur J Surg 165(5):410-420, 1999
21. Frykholm GJ, Sintorn K, Montelius A et al: Acute lumbosacral plexopathy during and after preoperative radiotherapy of rectal adenocarcinoma. Radiother Oncol 38(2):121-130, 1996

22. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. Br J Cancer 62(6):1034-1038, 1990
23. Dahlberg M, Glimelius B, Graf W et al: Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study. Dis Colon Rectum 41(5):543-549, 1998
24. Holm T, Singnomklao T, Rutqvist LE et al: Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. Cancer 78(5):968-976, 1996
25. Pahlman L, Glimelius B, Graffman S: Pre- versus postoperative radiotherapy in rectal carcinoma: an interim report from a randomized multicentre trial. Br J Surg 72(12):961-966, 1985
26. Bonnel C, Parc YR, Pocard M et al: Effects of preoperative radiotherapy for primary resectable rectal adenocarcinoma on male sexual and urinary function. Dis Colon Rectum 45(7):934-939, 2002
27. Welsh FK, McFall M, Mitchell G et al: Pre-operative short-course radiotherapy is associated with faecal incontinence after anterior resection. Colorectal Dis 5(6):563-568, 2003
28. Marijnen CA, van de Velde CJH, Putter H et al: Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 20;23(9):1847-58, 2005