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The randomized controlled TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma A report from the TME trial

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ABSTRACT

Objective. To investigate the efficacy of preoperative short term radiotherapy in patients with mobile rectal cancer undergoing TME surgery.

Summary Background Data. Local recurrence is a major problem in rectal cancer treatment. Preoperative short term radiotherapy has shown to improve local control and survival in combination with conventional surgery. The TME trial investigated the value of this regimen in combination with total mesorectal excision (TME). Long term results are reported after a median follow-up of 6 years.

Methods. 1861 patients with resectable rectal cancer were randomized between TME preceded by 5x5 Gy or TME alone. No chemotherapy was allowed. There was no age limit. Surgery, radiotherapy as well as pathological examination were standardized. Primary end-point was local control.

Results: Median follow-up of surviving patients was 6·1 years. Five year local recurrence risk of patients undergoing a macroscopically complete local resection was 5·6% in case of preoperative radiotherapy compared to 10.9% in patients undergoing TME alone ($P < 0{\cdot}001$). Overall survival at 5 years was 64·2% and 63·5% respectively ($P = 0{\cdot}902$). Subgroup analyses showed significant effect of radiotherapy in reducing local recurrence risk for patients with nodal involvement, for patients with lesions between 5 and 10 centimetres from the anal verge, and for patients with uninvolved circumferential resection margins.

Conclusions. With increasing follow-up, there is a persisting overall effect of preoperative short term radiotherapy on local control in patients with clinically resectable rectal cancer. However, there is no effect on overall survival. Since survival is mainly determined by distant metastases, efforts should be directed towards preventing systemic disease.

INTRODUCTION

For rectal cancer, surgery is the principal treatment leading to cure. In particular, surgical technique determines treatment outcome to a great extent. With the introduction of total mesorectal excision (TME) involving resection of the fatty tissue around the rectum, local control and survival rates have improved substantially.[1-3] In recent years, TME has become the standard in many countries and has replaced conventional blunt dissection that is known to leave behind mesorectal tissue, exposing patients to high risk of local recurrence and thus, poor survival.

Apart from the advances made in surgery, pre-or postoperative treatment has shown to be a significant contributor to improved local control and survival as well. The benefits of (chemo)radiation either given pre- or postoperatively have all been established in combination with conventional surgery.[4-13] The Swedish Rectal Cancer Trial showed that short-term high-dose preoperative radiotherapy (5x5 Gy) administered one week prior to surgery was capable of reducing 5 years local recurrence rates (27% vs. 11%, P < 0·001) and improving 5 year overall survival (48% vs. 58%, P = 0·004) compared to surgery alone.[14] The Dutch Colorectal Cancer Group initiated a large prospective randomized multicenter trial to investigate the efficacy of 5x5 Gy prior to TME. The Nordic Gastrointestinal Tumour Adjuvant Therapy Group and the European Organisation for Research and Treatment of Cancer (EORTC) participated in the trial. Surgical technique was standardized and quality-controlled in order to assess the value of radiotherapy in addition to TME reliably. Early results showed a reduced risk of local recurrence in irradiated patients at two years (2·4% vs. 8·2%, P < 0.001) without a difference in overall survival (82·0% vs. 81·8%, P = 0·84).[15] In this article, we report on the results of the TME trial after a median follow-up of 6 years with a focus on subgroup analyses.

METHODS

Patients with clinically resectable adenocarcinoma of the rectum without any evidence of distant disease were randomly assigned to preoperative radiotherapy using 5x5 Gy followed by TME or TME alone. Tumours had to be below the level of S1/S2 with the inferior tumour margin being 15 centimetres or less from the anal verge as measured during withdrawal of a flexible coloscope. Patients with previous treatment for rectal cancer were excluded from trial participation, as well as patients who had previous chemo- or radiotherapy to the pelvis. There was no age limit. Other inclusion and exclusion criteria have been reported previously.[16] Central and local ethics committee approval for the study was obtained as well as informed consent from included patients. Randomisation was performed centrally and based on permuted blocks of six, with stratification according to centre and the expected

type of surgery (i.e. low anterior resection or abdominoperineal resection). Primary endpoint was local control. The trial design was based on a local recurrence rate of 5% at 5 years in the radiotherapy group for patients who underwent a curative resection (e.g. a resection without microscopically involved resection margins) compared to 10% in patients assigned to surgery alone. Secondary outcome parameters included distant recurrence, overall and cancer specific survival. No interim analysis was planned or performed. Trial design, surgery and radiotherapy technique as well as pathology procedures have been described in detail elsewhere.[17-20]

The prescribed radiotherapy consisted of 25 Gy in 5 fractions delivered during 5 to 7 days. The clinical target volume included the primary tumour and its mesentery with vascular supply containing the perirectal, presacral and internal iliac nodes, up to the S1/S2 junction. A three or four portal "box" technique was recommended. The upper boarder was at the level of the promontory. The perineum was included in the treatment field only if the operating surgeon anticipated performing an abdominoperineal resection.

Surgery was scheduled to take place in the week after radiotherapy. Surgeons were taught to perform proper TME surgery through an extensive structure of workshops, symposia and video instruction. Also, a monitoring committee was installed to ensure adherence to the strict surgical protocol guidelines. The first five TME procedures in each participating hospital were supervised by an experienced instructor surgeon. The administration of concomitant or adjuvant chemotherapy was not allowed.

Pathologists were trained to identify lateral tumour spread according to the protocol of Quirke and Dixon.[19] A panel of supervising pathologists was installed to review the results of histopathological examination.[21]

Patients underwent clinical examination every three months during the first year after surgery and annually thereafter for the first two years after surgery. Liver imaging and endoscopy were mandatory. Local recurrence was defined as evidence of tumour within the pelvic or perineal area. Criteria for distant recurrence involved tumour growth in any other area, including the colostomy site or inguinal region. All recurrences were confirmed by one of the study coordinators by checking all original pathology and radiology reports.

Central data management was done at the Data Center at the Department of Surgery of the Leiden Medical University Medical Center, the Netherlands. Information from participating hospitals was collected on case report forms that were sent to the central office. Data were checked and entered in a database and analysed using the SPSS program (version 11.5 for Windows SPSS Inc, Chicago, IL). A two-sided P value of 0·05 or less was considered to indicate statistical significance. In accordance with our previous report, event-free times were recorded from the day of surgery until day of local or distant recurrence, or death, or day of last follow-up. Overall survival analyses comprised all eligible patients and were thus performed on an intention-to-treat basis. In accordance with our previous report[22], only patients who underwent a macroscopically complete local resection were included when calculating local

recurrence rates. Distant recurrence rates were based on all eligible patients who did not have distant metastasis at the time of surgery. Overall recurrence rate was calculated on the basis of the number of eligible patients who had a macroscopically complete local resection without distant metastasis at the time of surgery. Patient data were censored when at last follow-up contact the patient was alive or had no evidence of disease. The χ^2 test was applied to evaluate differences in proportions. Univariate survival analyses were carried out by the Kaplan-Meier method. The log-rank test was used for comparison of the Kaplan Meier curves. The Cox proportional hazard model was applied to calculate hazard ratios. All variables with a P-value of less than 0·10 were entered in a multiple regression analysis. For subgroup analyses, no adjustment for multiple testing was applied. Results of subgroup analyses have to be judged with care: any significant results must be viewed as generating hypotheses that require validation in subsequent studies. In case of subset analyses, a P value of 0·05 may not be accurate enough.

RESULTS

Recruitment of patients started in January 1996 and lasted until December 1999 with the enrollement of 1861 patients from 84 Dutch and 24 Swedish hospitals, as well as from 1 Canadian and 10 other European centers. Figure 1 shows characteristics for eligible and ineligible patients, as well as rates of complete local and distant resection, according to treatment arm.

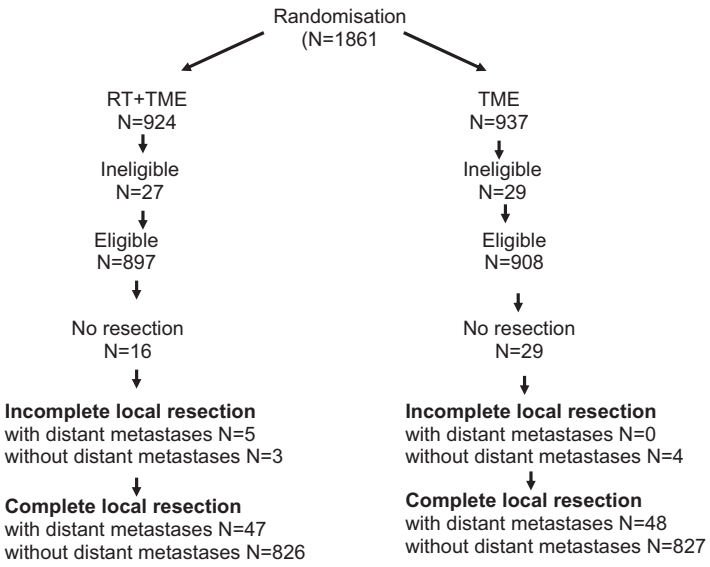

Figure 1. Numbers of eligible patients and extent of resection according to randomisation. (In)complete resection implies a macroscopic (in)complete resection.

Table 1. Patient and tumour characteristics according to randomisation of 1805 eligible patients*

	RT + TME		TME alone		P-value
	(n=897)	%	(n=908)	%	
Age (yrs)					0·79
Median	65.0		66.0		
Range	26 – 88		23 - 92		
Sex					0·92
Male	573	64	578	64	
Female	324	36	330	36	
Distance tumour from anal verge					0·37
≥10.1 cm					
5.1-10.0 cm	268	30	283	31	
≤5 cm	383	43	359	40	
Unknown	244	27	265	29	
	2	<1	1	<1	
Type of resection					0·11
None	16	2	29	3	
Low anterior	579	65	604	67	
Abdominoperineal	251	28	235	26	
Hartmann	50	6	39	4	
Unknown	1	<1	1	<1	
TNM stage					0·51
0	11	1	17	2	
I	264	30	243	27	
II	251	28	245	27	
III	299	34	325	36	
IV	62	7	61	7	
Unknown or no resection	10	<1	17	2	
CRM involvement					0·34
No	729	81	729	80	
Yes	143	16	148	16	
Unknown	25	3	31	3	

* Characteristics were unknown in some cases because not all case reports were received.

Fifty-six patients were considered ineligible after randomisation. Of these ineligible patients, 27 were randomized to receive radiotherapy prior to surgery, the remaining 29 patients to undergo surgery alone. Reasons for ineligibility in the radiotherapy arm were no adenocarcinoma (n = 5), tumour treated by transanal resection (n = 2), tumour location on more than 15 centimetres from the anal verge (n = 4), previous cancer (n = 8), coexisiting cancer (n = 4), previous large-bowel surgery, pelvic radiotherapy and/or chemotherapy (n = 2) and incomplete information on eligibility (n = 2). In the surgery alone arm reasons for ineligibility were no adenocarcinoma (n = 3), fixed tumour (n = 2), tumour location on more than 15 centimetres from the anal verge (n = 1), previous cancer (n = 13), coexisiting cancer (n = 7), previous large-bowel surgery, pelvic radiotherapy and/or chemotherapy (n = 1) and incomplete information

on eligibility (n = 2). Among the 1805 eligible patients, there were 139 patients with major protocol violations including no administration of the intended treatment (n = 54) or delivery of postoperative adjuvant treatment against protocol guidelines (n = 85). Minor violations included prolonged interval between the end of radiotherapy and surgery (n = 110) and non-compliance with the prescribed anatomical borders of the clinical target radiotherapy volume (n = 127). Specifics on major and minor protocol violations, as well as postoperative morbidity and mortality have been described before.[23] Patients with major and/or minor protocol violations were included in all the analyses. Table 1 shows patient characteristics that were well balanced across the treatment groups.

Forty-five eligible patients had no resection at all, 12 patients underwent a local resection with macroscopically involved resection margins (i.e. a local R2 resection). In 95 patients, distant metastases were diagnosed at the time of surgery or after randomisation with additional work-up (figure 1).

Follow-up was continued until November 2005. Median follow-up of surviving patients was 6·1 years (range 1·2 to 9·5 years) and did not differ between the two randomisation arms (6·0 vs. 6·1 years, P=0·760). Among 1748 patients who underwent a macroscopically complete resection, 129 patients had local disease recurrence. Of these patients, 83 (63·4%) patients had both local and distant relapse. Figure 2 shows Kaplan-Meier curves for relapse risk with

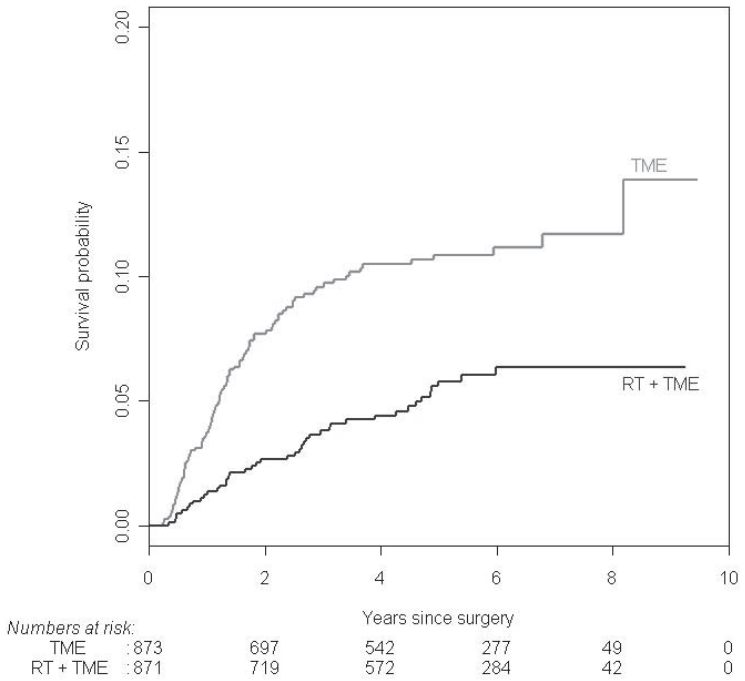

Figure 2. Rates of local recurrence among 1748 eligible patients who underwent macroscopically complete local resection, according to randomisation

Table 2. Univariate Cox regression analysis of local recurrence risk among 1748 eligible patients who underwent macroscopically complete local resection

	Hazard ratio	95% CI	P-value
Randomisation			<0·001
RT+TME	1·00		
TME alone	2·11	1·46 – 3·04	
Distance tumour from anal verge			0·001
≥10·1 cm	1·00		
5·1-10·0 cm	1·71	1·06 – 2·78	0·02
≤5 cm	2·44	1·50 – 3·95	<0·001
Type of resection			0·009
Low anterior	1·00		
Abdominoperineal	1·72	1·20 – 2·46	0·003
Hartmann	1·43	0·62 – 3·28	0·259
TNM stage			<0·001
I	1·00		
II	5·45	2·26 – 13·12	<0·001
III	13·61	5·94 – 31·20	<0·001
IV	22·60	8·44 – 60·57	<0·001
CRM involvement			<0·001
No	1·00		
Yes	4·03	2·82 – 5·76	

Table 3. Multivariate Cox regression analysis of local recurrence risk among 1748 eligible patients who underwent macroscopically complete local resection

	Hazard ratio	95% CI	P-value
Randomisation			<0·001
RT+TME	1·00		
TME alone	2·18	1·47 – 3·25	
Distance tumour from anal verge			0·031
≥10·1 cm	1·00		
5·1-10·0 cm	1·18	1·11 – 3·20	0·019
≤5 cm	2·31	1·16 – 4·64	0·018
Type of resection			0·942
Low anterior	1·00		
Abdominoperineal	1·06	0·60 – 1·89	0·839
Hartmann	1·15	0·49 – 2·69	0·751
TNM stage			<0·001
I	1·00		
II	4·08	1·65 – 10·09	0·002
III	9·92	4·25 – 23·16	<0·001
IV	20·26	7·43 – 55·28	<0·001
CRM involvement			<0·001
No	1·00		
Yes	2·16	1·46-3·19	

Table 4. Univariate log-rank analyses of 5 year local recurrence risk according to randomisation arm among 1748 eligible patients who underwent macroscopically complete local resection

	RT+TME		TME alone		P-value	P-value Interaction
	Number at risk	Local recurrence at 5 years	Number at risk	Local recurrence at 5 years		
Overall	873	5·6	875	10·9	<0·001	
Sex						0·943
Male	555	5·8	557	10·9	0·002	
Female	318	5·3	318	10·9	0·007	
Distance tumour from anal verge						0·032
≥10·1 cm	262	3·7	271	6·2	0·122	
5·1-10·0 cm	372	3·7	350	13·7	<0·001	
≤5 cm	237	10·7	253	12·0	0·578	
Type of resection						0·375
Low anterior	577	4·2	603	9·7	<0·001	
Abdominoperineal	248	9·2	232	13·4	0·147	
Hartmann	47	2·7	39	13·2	0·196	
TNM stage						0·659
I	265	0·4	244	1·7	0·091	
II	251	5·3	241	7·2	0·331	
III	298	10·6	324	20·6	<0·001	
IV	47	15·9	48	26·9	0·207	
CRM involvement						0·029
Yes	136	19·7	144	23·5	0·393	
No	715	3·4	717	8·7	<0·001	

local recurrence risk at five years being 5·6% in the group assigned to radiotherapy before surgery and 10·9% in TME alone patients ($P < 0·001$), implying a relative risk reduction of 49% in patients assigned to preoperative radiotherapy. In the univariate analyses (table 2), treatment group assignment, tumour location, type of surgery, TNM stage and circumferential resection margin (CRM) involvement were predictors of local recurrence risk. Multivariate Cox regression analysis revealed that randomisation arm, tumour location, TNM stage and (CRM) were independent predictors of local recurrence risk (table 3). Univariate log-rank analyses of 5 year local recurrence risk is displayed in table 4. According to these subgroup analyses, radiotherapy did not have a significant effect in patients with proximal and distal lesions, in patients who underwent a abdominoperineal resection or Hartmann procedure, nor in patients with TNM stage I,II or IV disease. However, interaction analyses in the Cox regression analysis between the respective covariates and randomisation revealed no significant interaction between type of surgery and treatment group assignment, nor between TNM

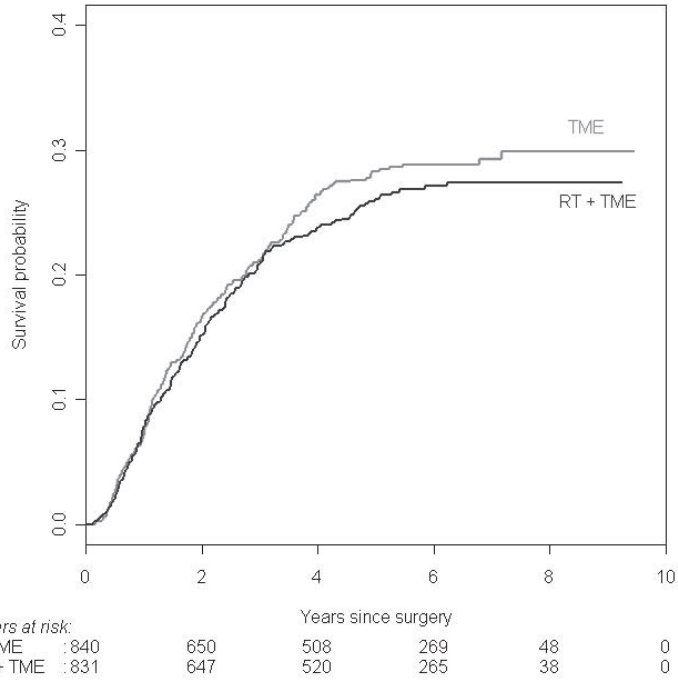

Figure 3. Rates of distant recurrence among all eligible patients who did not have distant metastasis at the time of surgery

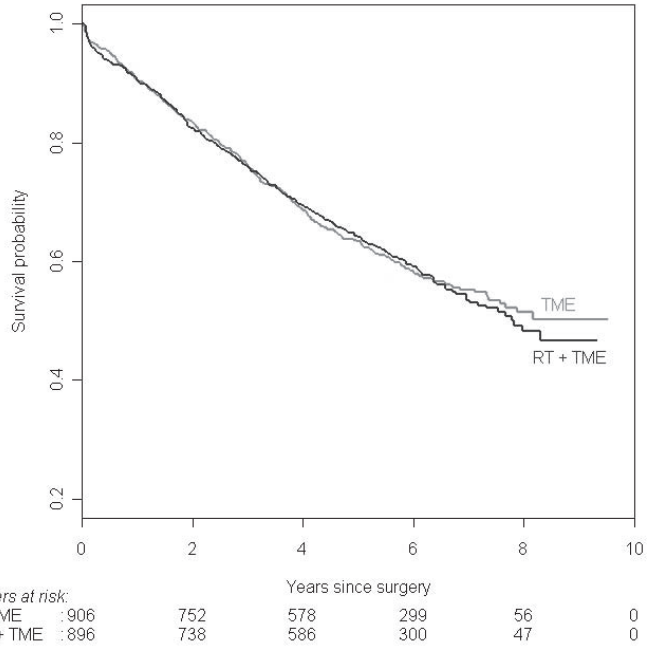

Figure 4. Rates of overall survival among 1805 eligible patients according to randomisation

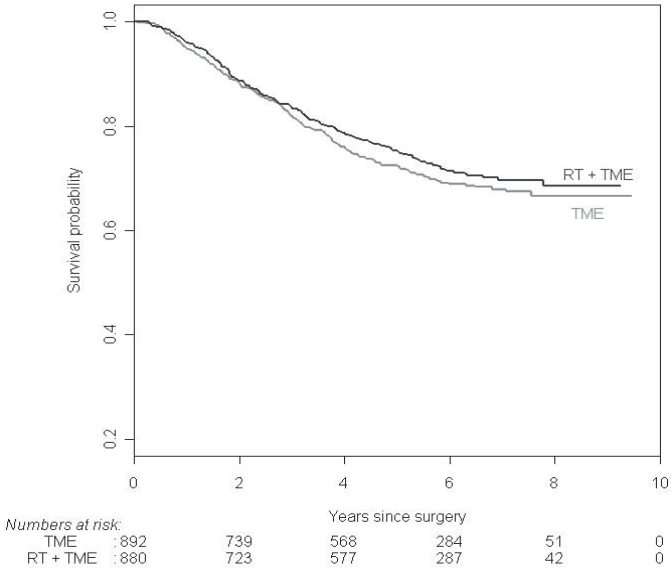

Figure 5. Rates of cancer specific survival among 1805 eligible patients according to randomisation

stage and treatment group assignment. This suggests that the effects of radiotherapy did not differ between these subgroups.

Distant recurrence was diagnosed in 201 cases that were assigned to radiotherapy compared to 222 patients in the surgery alone arm. Distant recurrence risk at five years was 25·8% and 28·3%, respectively (P = 0·387) (figure 3).

As of November 1st 2005, 748 patients had died. Of these patients, 374 (50·2%) died with recurrent disease. At five years, overall survival rates in irradiated patients were 64·2% which did not differ significantly from survival rates in patients who underwent TME alone (63·5%, P = 0·902, see figure 4). Respective cancer specific survival rates were 75·4% and 72·4% (P = 0·260) (Figure 5).

DISCUSSION

Short term preoperative radiotherapy results in improved local control for patients with resectable rectal cancer undergoing TME. Local control was chosen as primary endpoint in the present trial, since local recurrence is responsible for substantial morbidity and death. Local recurrence rates are significantly lower in irradiated patients, with a relative risk reduction of 49% when compared to TME surgery alone. This risk reduction at 5 years is smaller when compared to the relative risk reduction of 71% at a median follow-up of 2 years.[24] Figure 2 shows that a significant number of local recurrences occur beyond a follow-up period of 3 years in case of preoperative radiotherapy. This is in contrast to previously released data

that indicated that the majority of local recurrences become overt within three years after surgery.[25,26] In fact, in patients assigned to TME alone, only 9 (10%) out of 87 local recurrences appeared after 3 years of follow-up, compared to 13 (31%) out of 42 local recurrences in case of preoperative radiotherapy. Apparently, in a proportion of irradiated patients, radiotherapy does not prevent but merely postpones local recurrence. Hypothetically, radiotherapy decreases tumour burden, prolonging the time to macroscopically outgrowth. These results are in contrast to long-term follow-up data on the Swedish Rectal Cancer Trial where no delay was seen in irradiated patients.[27] In the Swedish trial, only a total 5 patients developed a local recurrence at 5 years after surgery. Four of these did not undergo radiotherapy. An explanation for this discrepancy might be the fact that, unlike the present trial, no TME was performed in the Swedish study. Conventional surgery results in a larger postoperative residual tumour burden that possibly needs less time to become apparent as a clinically recurrence.

In our study, increased local control in irradiated patients does not lead to a detectable improved overall survival. Although local recurrences are known to be an important cause of death, apparently, an absolute difference in local recurrence rates of 5·3% is too small to have a significant impact on survival. For comparison, in the Swedish Rectal Cancer Trial, an absolute reduction of 16% in local recurrence risk in irradiated patients (from 27% to 11%, $P < 0{\cdot}001$) was related to a significant improvement in 5 year overall survival (58% vs. 48%, respectively, $P = 0{\cdot}004$)[28], presuming local failure to be an important cause of death. In a recent survey of the Swedish Rectal Cancer Trial with a minimum follow-up of 14 years the difference in local recurrence rate is persistent (9% vs. 26%, $P<0{\cdot}001$) and this continues to improve overall survival after a long follow-up period (38% vs. 30%, $P = 0{\cdot}008$).[27]

In the recently published German randomized trial comparing preoperative to postoperative chemoradiation in patients with locally advanced disease, local recurrence rates were comparable to those of the current study (6% vs. 13% in favour of preoperative treatment, $P = 0{\cdot}006$). In parallel, there was no difference between the two randomisation arms in five year overall survival rates (76% resp. 74%, $P = 0{\cdot}80$).[29] Although trial results should be compared with care due to differences in case mix, it has to be noted that survival rates in the German study appear more favourable, despite the advanced stage of disease at presentation. However, the fact that as much as 18% of the patients, assigned to postoperative treatment turned out at pathological examination to have stage I disease, indicates that not only patients with locally advanced disease were included. Moreover, in the German study there was an upper age limit of 75 years excluding trial participation compared to no age limit in the TME trial. Differences in patient selection due to different staging techniques hinder adequate comparison of trial results. For example, the Polish trial comparing short term preoperative radiotherapy (5x5 Gy) to chemoradiation (50·4 Gy, 1·8 Gy per fraction plus bolus 5FU/LV) in patients with locally advanced rectal cancer accessible to digital examination, showed no difference in local recurrence risk (9% vs. 14%, $P=0{\cdot}17$)[30], despite the fact that there was more downsizing after prolonged treatment.[31] These results demonstrate that for the patients selected in this trial,

a short course of radiotherapy is at least as good as chemoradiation, indicating that not all patients with locally advanced tumours require a prolonged radiotherapy schedule. According to the EORTC 22921 trial, response rate is increased by the addition of chemotherapy to prolonged irradiation (14% vs. 5%, complete pathological response)[32], leading to a significant reduction in local recurrence risk (17·1% vs. 8·7% at 5 years).[33] This is in line with data from the FFCD 9203 trial that showed not only more complete responses after combined treatment (11·7% vs. 3·7%, P<0·001), but also a 2-fold reduction in local recurrence risk (16.5% vs. 8%, no P-value mentioned.[34] Although the addition of chemotherapy to radiotherapy seems justifiable on the basis of these data, acute and late toxicity may be more pronounced after combined treatment.

Discrepancies between trial results are most likely related to selection biases due to suboptimal staging, rather than to differences in biological behaviour. Preoperative clinical staging applying digital rectal examination and/or endorectal ultrasonography is increasingly replaced by magnetic resonance imaging, facilitating appropriate selection for the right type of neoadjuvant therapy.[35] Thus, the differences in patient characteristics between all these trials are difficult to appreciate, applying the current standards of local staging.

A potential advantage of prolonged neoadjuvant treatment over short term preoperative irradiation is tumour shrinkage and thus, sphincter preservation for distal rectal lesions. A prolonged overall time of irradiation, as well a protracted interval between radiotherapy and surgery is considered to be associated with downsizing, facilitating low-lying anastomosis. However, the aforementioned randomized trial comparing conventionally fractionated chemoradiation to preoperative short-term irradiation showed no difference in rates of sphincter preservation (58% vs. 61%, P = 0·57).[31] This might relate to the hypothesis that surgeons were reluctant to alter their initial surgical planning on the basis of response to neoadjuvant treatment. Sphincter preservation and thus, avoidance of a permanent stoma are thought to be of benefit for rectal cancer patients. However, in a recent study of our group investigating the late toxic effects of radiotherapy on functional outcome, patients with a (permanent) stoma were more satisfied with bowel functioning than patients who had undergone a low anterior resection and had no stoma.[36]

Clinical practise should not be based on the results of subgroup analyses: power is often too low to detect clinically relevant differences, and it is difficult to differentiate between subgroups prior to treatment. Nevertheless, subgroup analyses may be of interest for the development of future trials. According to the univariate analyses of local control (table 4), only patients with positive lymph nodes (i.e. TNM stage III) benefited from radiotherapy. Apparently, with the involved nodes having removed, preoperative radiotherapy is able to treat (microscopic) nodal disease beyond the plane of surgical resection. Lateral pelvic lymphadenectomy, as favoured in Japan[37-40] seems unnecessary with radiotherapy treating nodal spread sufficiently in a non-invasive manner. Preferably, patients with lymph node involvement are to be identified prior to treatment in order to avoid overtreatment. Although

the use of novel MRI contrast agents to predict nodal involvement prior to treatment seems promising[41], presently, the use of these agents is merely experimental and requires further investigation, especially for suspected nodes smaller than 5 millimeters.[42] Although subgroup analyses indicate a nonsignificant effect of radiotherapy for TNM stage I,II and IV, caution is warranted not to irradiate these patients considering the absence of significant interaction between TNM stage and treatment group assignment.

The efficacy of the investigated radiotherapy regimen depends on the location of the tumour: patients with proximal tumours do not benefit significantly from radiotherapy as becomes clear in table 3. Apart from the absence of a statistical difference, the number of events is rather low in patients with proximal lesions, making the number of patients needed to treat to prevent one local recurrence considerably high. Surprisingly, in the aforementioned German trial, there is no difference in local relapse risk between patients with tumours in the middle and upper part.[43] Possibly, the completeness of mesorectal excision that might be less in case of proximal lesions is an explanatory factor. For patient with low tumours up to 5 centimetres from the anal verge, there is neither a significant effect to the benefit of short course irradiation. This contradicts data from the Swedish Rectal Cancer Trial that showed an effect of radiotherapy for this group of patients.[27] Also, the Swedish Rectal Cancer Register has demonstrated a significant effect on local recurrence rates by applying 5 x 5 Gy preoperatively for patients with low lying rectal cancer. (Swedish Rectal Cancer Register (2004) http://www.SOS.se/mars/kvaflik.htm (Swe). A possible important confounding factor for this patient subset is the substantial proportion of patients with positive CRM involvement. Unfortunately, Swedish data on margin involvement are not available, but hypothetically, CRM involvement occurs less often in Sweden. Especially for patients with distal lesions, incomplete resection constitutes a major problem: as shown earlier, positive CRM is the most important independent predictor for local failure.[44] Table 4 shows unacceptable high rates of local recurrence in case of positive CRM. For these patients, radiotherapy has no significant effect (19·7% vs. 23·5%, P = 0·393). In particular, for patients requiring APR, complete resection seems a major challenge: in this subgroup, as much as 30% had involved CRM compared to 11% of the patients undergoing LAR (P < 0.001). Hypothetically, a cylindrical resection in stead of "coning in" towards the distal margin is appropriate in an attempt to avoid incomplete resection. Alternatively, as mentioned before, prolonged (chemo)radiation may result in downsizing facilitating curative resection. Again, speculations based upon subgroup analyses require validation in future studies. Precise tumour location is often difficult to assess prior to treatment: discrepancies between coloscopy measurements, CT and MRI imaging and intraoperative findings are often encountered and indicate the difficulty of determining exact tumour position and the a priori chance of local failure. Therefore, these subgroup analyses provide limited support to withhold radiotherapy from patients with proximal rectal cancer or to apply a prolonged radiotherapy schedule for patients with distal rectal cancer.

In conclusion, with increasing follow-up, there is still a highly significant effect of short term preoperative radiotherapy on local recurrence rates. There is no detectable effect on overall survival. TME surgery contributes significantly to superior local control and survival compared to results from conventional blunt dissection. Future efforts should be directed towards optimal preoperative imaging in order to differentiate between rectal cancers where a free CRM can be obtained or not. In the latter a more aggressive approach is warranted. In the future, adjuvant chemotherapy might gain a role for patients with clinically resectable rectal cancer in an attempt to improve survival, now that local treatment has been optimised by both TME and short term preoperative radiotherapy.

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