

# The TME Trial After a Median Follow-up of 6 Years Increased Local Control But No Survival Benefit in Irradiated Patients With Resectable Rectal Carcinoma

Koen C.M.J. Peeters, MD,\* Corrie A.M. Marijnen, MD, PhD, †‡ Iris D. Nagtegaal, MD, PhD, §  
Elma Klein Kranenborg, MSc,\* Hein Putter, MD, || Theo Wiggers, MD, PhD, ¶  
Harm Rutten, MD, PhD, # Lars Pahlman, MD, PhD, \*\* Bengt Glimelius, MD, PhD, ††§§  
Jan Willem Leer, MD, PhD, |||| and Cornelis J.H. van de Velde, MD, PhD,\*  
for the Dutch Colorectal Cancer Group

**Objective:** To investigate the efficacy of preoperative short-term radiotherapy in patients with mobile rectal cancer undergoing total mesorectal excision (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. Long-term results are reported after a median follow-up of 6 years.

**Methods:** One thousand eight hundred and sixty-one patients with resectable rectal cancer were randomized between TME preceded by  $5 \times 5$  Gy or TME alone. No chemotherapy was allowed. There was no age limit. Surgery, radiotherapy, and pathologic examination were standardized. Primary endpoint was local control.

**Results:** Median follow-up of surviving patients was 6.1 year. Five-year local recurrence risk of patients undergoing a macroscopically complete local resection was 5.6% in case of preoperative radiotherapy compared with 10.9% in patients undergoing TME alone ( $P < 0.001$ ). Overall survival at 5 years was 64.2% and 63.5%, respectively ( $P = 0.902$ ). 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 cm 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.

(*Ann Surg* 2007;246: 693–701)

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.<sup>1–3</sup> 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.<sup>4–13</sup> The Swedish Rectal Cancer Trial showed that short-term high-dose preoperative radiotherapy ( $5 \times 5$  Gy) administered 1 week prior to surgery was capable of reducing 5-year local recurrence rates (27% vs. 11%,  $P < 0.001$ ) and improving 5-year overall survival (48% vs. 58%,  $P = 0.004$ ) compared with surgery alone.<sup>14</sup> The Dutch Colorectal Cancer Group initiated a large prospective randomized multicenter trial to investigate the efficacy of  $5 \times 5$  Gy prior to TME. The Nordic Gastrointestinal Tumor Adjuvant Therapy Group and the European Organisation for

From the Departments of \*Surgery, †Clinical Oncology, Leiden University Medical Center, Leiden, The Netherlands; ‡Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands; §Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; ||Department of Medical Statistics, Leiden University Medical Center, Leiden, The Netherlands; ¶Department of Surgical Oncology, Medical Center Groningen, Groningen, The Netherlands; #Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands; Departments of \*\*Surgery, ††Oncology, Akademiska Sjukhuset, Uppsala; §§Karolinska Institutet, Stockholm, Sweden; and ||||Joint Center for Radiation Oncology, Nijmegen, The Netherlands.

The TME trial has been funded by the Dutch Cancer Society and the Dutch Health Council.

Address for correspondence: Koen C.M.J. Peeters MD, Department of Surgery, Bronovo Ziekenhuis and Leiden University Medical Center, Bronovolaan 5 2597 AX Den Haag, The Netherlands 31 70 312 41 41. E-mail: k.c.m.j.peeters@lumc.nl

Copyright © 2007 by Lippincott Williams & Wilkins

ISSN: 0003-4932/07/24605-0693

DOI: 10.1097/01.sla.0000257358.56863.ce

Research and Treatment of Cancer (EORTC) participated in the trial. Surgical technique was standardized and quality-controlled to assess the value of radiotherapy in addition to TME reliably. Early results showed a reduced risk of local recurrence in irradiated patients at 2 years (2.4% vs. 8.2%,  $P < 0.001$ ) without a difference in overall survival (82.0% vs. 81.8%,  $P = 0.84$ ).<sup>15</sup> 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  $5 \times 5$  Gy followed by TME or TME alone. Tumors had to be below the level of S1/S2 with the inferior tumor margin being 15 cm or less from the anal verge as measured during withdrawal of a flexible colonoscope. Patients with previous treatment of 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.<sup>16</sup> Central and local ethics committee approval for the study was obtained as well as informed consent from included patients. Randomization was performed centrally and based on permuted blocks of 6, with stratification according to center and the expected type of surgery (ie, 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 (eg, a resection without microscopically involved resection margins) compared with 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.<sup>15–18</sup>

The prescribed radiotherapy consisted of 25 Gy in 5 fractions delivered during 5 to 7 days. The clinical target volume included the primary tumor and its mesentery with vascular supply containing the perirectal, presacral, and internal iliac nodes, up to the S1/S2 junction. A 3 or 4 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 5 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 tumor spread according to the protocol of Quirke and Dixon.<sup>17</sup> A

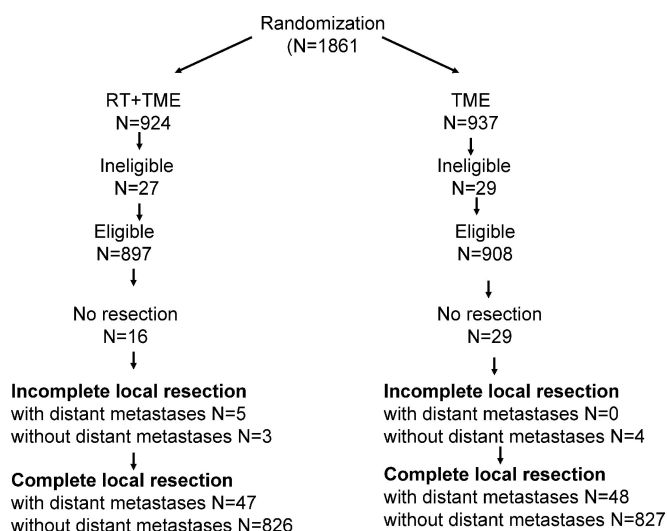
panel of supervising pathologists was installed to review the results of histopathologic examination.<sup>18</sup>

Patients underwent clinical examination every 3 months during the first year after surgery and annually thereafter for the first 2 years after surgery. Liver imaging and endoscopy were mandatory. Local recurrence was defined as evidence of tumor within the pelvic or perineal area. Criteria for distant recurrence involved tumor 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 analyzed 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,<sup>15</sup> 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  $\chi^2$  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 enrollment 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 macroscopic complete local resection and the presence of distant disease, all according to treatment arm. Fifty-six patients were considered ineligible after randomization. Of these ineligible patients, 27 were randomized to receive radiotherapy prior to surgery, the remaining 29 pa-



**FIGURE 1.** Numbers of eligible patients and extent of resection according to randomization. (In)complete resection implies a macroscopic (in)complete resection.

tients to undergo surgery alone. Reasons for ineligibility in the radiotherapy arm were no adenocarcinoma ( $n = 5$ ), tumor treated by transanal resection ( $n = 2$ ), tumor location more than 15 cm from the anal verge ( $n = 4$ ), previous cancer ( $n = 8$ ), coexisting 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 tumor ( $n = 2$ ), tumor location on more than 15 cm from the anal verge ( $n = 1$ ), previous cancer ( $n = 13$ ), coexisting 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 noncompliance with the prescribed anatomic 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.<sup>15</sup> 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 (ie, a local R2 resection). In 95 patients, distant metastases were diagnosed at the time of surgery or after randomization with additional work-up (Fig. 1).

Follow-up was continued until November 2005. Median follow-up of surviving patients was 6.1 year (range 1.2 to 9.5 years) and did not differ between the 2 randomization arms (6.0 vs. 6.1 year,  $P = 0.760$ ). Among 1748 patients who underwent a macroscopically complete resection, 129 pa-

tients 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 local recurrence risk at 5 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, tumor location, type of surgery, TNM stage, and circumferential resection margin (CRM) involvement were predictors of local recurrence risk. Multivariate Cox regression analysis revealed that randomization arm, tumor 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 randomization revealed no significant interaction between type of surgery and treatment group assignment, nor between TNM stage and treatment group assignment. This suggests that the effects of radiotherapy did not differ between these subgroups. Moreover, sample sizes of the subgroups are probably too small to yield significant  $P$  values, as differences in local recurrence rates may amount up to 11% (ie, TNM stage IV) without showing any statistical significance.

Distant recurrence was diagnosed in 201 cases that were assigned to radiotherapy compared with 222 patients in the surgery alone arm. Distant recurrence risk at 5 years was 25.8% and 28.3%, respectively ( $P = 0.387$ ) (Fig. 3).

As of November 1, 2005, 748 patients had died. Of these patients, 374 (50.2%) died with recurrent disease. At 5 years, the overall survival rate in irradiated patients was 64.2% which did not differ significantly from the survival rate in patients who underwent TME alone (63.5%,  $P = 0.902$ , Fig. 4). Respective cancer specific survival rates were 75.4% and 72.4% ( $P = 0.260$ ) (Fig. 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 with TME surgery alone. This risk reduction at 5 years is smaller when compared with the relative risk reduction of 71% at a median follow-up of 2 years.<sup>15</sup> 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 3 years after surgery.<sup>19,20</sup> In fact, in patients assigned to TME alone, only 9 (10%) of 87 local recurrences appeared after 3 years of

**TABLE 1.** Patient and Tumor Characteristics According to Randomization of 1805 Eligible Patients\*

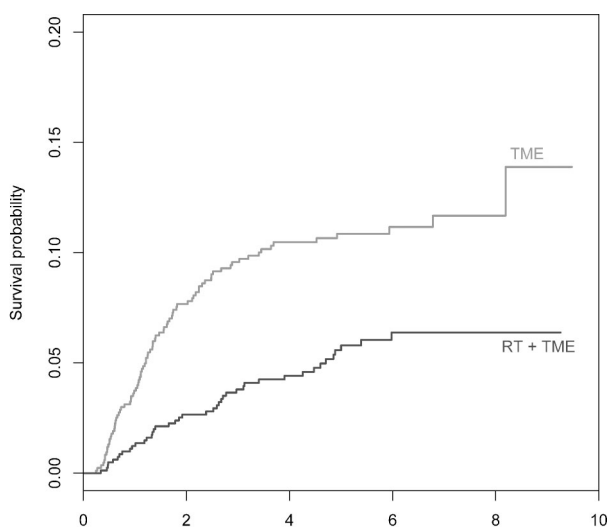
	RT + TME		TME Alone		P
	n = 897	%	n = 908	%	
Age (yr)					0.79
Median	65.0		66.0		
Range	26–88		23–92		
Sex					0.92
Male	573	64	578	64	
Female	324	36	330	36	
Distance tumor from anal verge (cm)					0.37
≥10.1					
5.1–10.0	268	30	283	31	
≤5	383	43	359	40	
Unknown	244	27	265	29	
	2	<1	1	<1	
Type of resection					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.

follow-up, compared with 13 (31%) 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 tumor burden, prolonging the time to macroscopic 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.<sup>21</sup> In the Swedish trial, only a total of 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 tumor burden that possibly needs less time to become apparent as a clinical 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%,  $P < 0.001$ ) was related to a significant improvement in 5-year overall survival (58% vs. 48%, respectively,  $P = 0.004$ ),<sup>14</sup> 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%,  $P < 0.001$ ) and this continues to improve overall survival after a long follow-up period (38% vs. 30%,  $P = 0.008$ ).<sup>21</sup> The fact that there is no survival benefit of radiotherapy in TME-treated patients should give rise to the search for other treatment modalities to improve survival. This is all the more the case as radiotherapy is responsible for significant long-term bowel dysfunction.<sup>22</sup> Now that both TME and radiotherapy have improved local control substantially, adjuvant chemotherapy may have a role in reducing systemic failure and thus improving survival. Indeed, distant failure is common, also in the TME trial without any difference in irradiated and nonirradiated patients (25.8% vs. 28.3%,  $P = 0.387$ ).



Numbers at risk:		Years since surgery				
		0	2	4	6	8
TME	: 873	697	542	277	49	0
RT + TME	: 871	719	572	284	42	0

**FIGURE 2.** Rates of local recurrence among 1748 eligible patients who underwent macroscopically complete local resection, according to randomization.

**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
Randomization			<0.001
RT + TME	1.00		
TME alone	2.11	1.46–3.04	
Distance tumor from anal verge (cm)			0.001
≥10.1	1.00		
5.1–10.0	1.71	1.06–2.78	0.02
≤5	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	

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 favor of preoperative treatment,  $P = 0.006$ ). In parallel, there was no difference between the 2 randomization arms in 5-year overall survival rates (76% vs. 74%,  $P = 0.80$ ).<sup>23</sup>

**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
Randomization			<0.001
RT + TME	1.00		
TME alone	2.18	1.47–3.25	
Distance tumor from anal verge (cm)			0.031
≥10.1	1.00		
5.1–10.0	1.18	1.11–3.20	0.019
≤5	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	

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 favorable, 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 pathologic 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 when compared with 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 (5 × 5 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%,  $P = 0.17$ ),<sup>23a</sup> despite the fact that there was more downsizing after prolonged treatment.<sup>24</sup> 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 tumors 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 pathologic response),<sup>25</sup> leading to a significant reduction in local recurrence risk (17.1% vs. 8.7% at 5 years).<sup>25a</sup> 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).<sup>25b</sup> Although the addition of chemotherapy to radiotherapy seems justifiable on

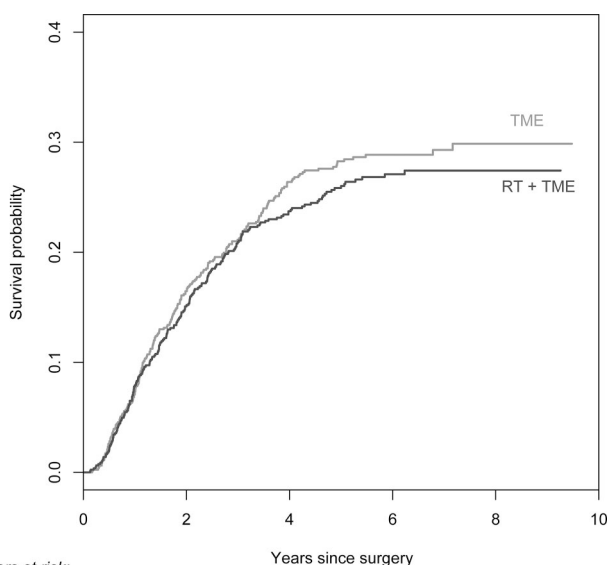
**TABLE 4.** Univariate Log Rank Analyses of 5-Year Local Recurrence Risk According to Randomization Arm Among 1748 Eligible Patients Who Underwent Macroscopically Complete Local Resection

	RT + TME		TME Alone		P	P Interaction
	Number at Risk	Local Recurrence at 5 yr	Number at Risk	Local Recurrence at 5 yr		
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 tumor from anal verge (cm)						0.032
≥10.1	262	3.7	271	6.2	0.122	
5.1–10.0	372	3.7	350	13.7	<0.001	
≤5	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	

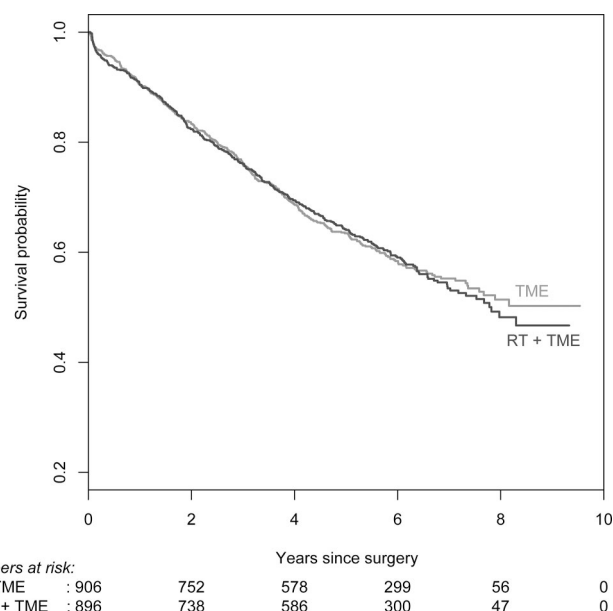
the basis of these data, acute and late toxicity may be more pronounced after combined treatment.

Discrepancies between trial results are most likely related to selection biases due to suboptimal staging, rather than

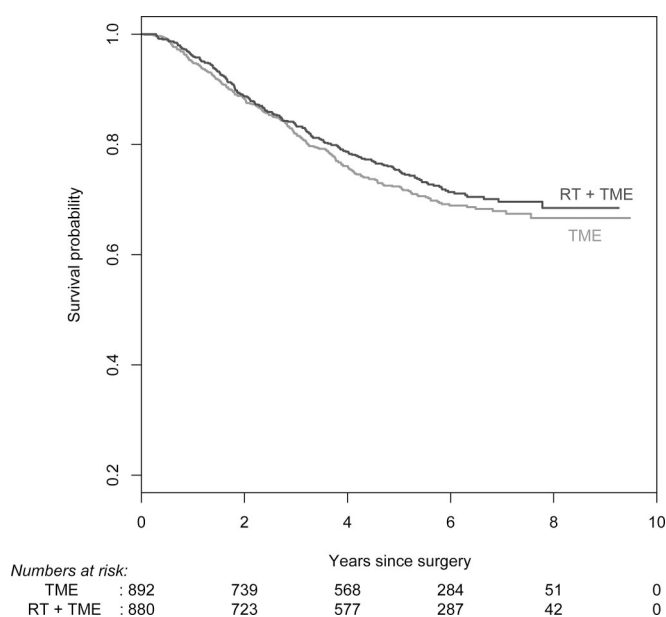
to differences in biologic behavior. Preoperative clinical staging applying digital rectal examination and/or endorectal ultrasonography is increasingly replaced by magnetic resonance imaging, facilitating appropriate selection for the right type of neoadjuvant therapy.<sup>26</sup> Thus, the differences in pa-



**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 randomization.



**FIGURE 5.** Rates of cancer specific survival among 1805 eligible patients according to randomization.

tient 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 tumor shrinkage and thus, sphincter preservation for distal rectal lesions. A prolonged overall time of irradiation, as well as 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%,  $P = 0.57$ ).<sup>24</sup> 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.<sup>22</sup>

Clinical practice 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 (ie, 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 favored in Japan<sup>27–30</sup> seems unnecessary with radiotherapy treating nodal spread sufficiently in a noninvasive manner.

Preferably, patients with lymph node involvement are to be identified prior to treatment to avoid over treatment. Although the use of novel MRI contrast agents to predict nodal involvement prior to treatment seems promising,<sup>31</sup> presently, the use of these agents is merely experimental and requires further investigation, especially for suspected nodes smaller than 5 mm.<sup>32</sup> 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 tumor: patients with proximal tumors 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 tumors in the middle and upper part.<sup>33</sup> Possibly, the completeness of mesorectal excision that might be less in case of proximal lesions is an explanatory factor. For patient with low tumors up to 5 cm 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.<sup>21</sup> Also, the Swedish Rectal Cancer Register has demonstrated a significant effect on local recurrence rates by applying  $5 \times 5$  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.<sup>34</sup> 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 with 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 tumor location is often difficult to assess prior to treatment: discrepancies between colonoscopy measurements, CT and MRI and intraoperative findings are often encountered and indicate the difficulty of determining exact tumor position and the a priori chance of local failure. Therefore, these subgroup analyses provide limited support to withhold radiotherapy from pa-

tients 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 with results from conventional blunt dissection. Future efforts should be directed towards optimal preoperative imaging 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 optimized by both TME and short-term preoperative radiotherapy.

## REFERENCES

- Martling AL, Holm T, Rutqvist LE, et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet*. 2000;356:93–96.
- Wibe A, Moller B, Norstein J, et al. A national strategic change in treatment policy for rectal cancer—implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum*. 2002;45:857–866.
- 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*. 2002;89:1142–1149.
- Boullis-Wassif S, Gerard A, Loygue J, et al. Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *Cancer*. 1984; 53:1811–1818.
- 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*. 1988;208:606–614.
- Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst*. 1988;80:21–29.
- Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med*. 1991;324:709–715.
- 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*. 1994;30A:1602–1606.
- 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*. 1995;75:2269–2275.
- Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Medical Research Council Rectal Cancer Working Party. *Lancet*. 1996;348:1610–1614.
- Tveit KM, Guldvog I, Hagen S, et al. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer. Norwegian Adjuvant Rectal Cancer Project Group. *Br J Surg*. 1997;84: 1130–1135.
- Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst*. 2000;92: 388–396.
- Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control—final report of intergroup 0114. *J Clin Oncol*. 2002;20:1744–1750.
- Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med*. 1997;336: 980–987.
- Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345:638–646.
- 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*. 1999;165:410–420.
- 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*. 1986;2: 996–999.
- Nagtegaal ID, Kranenbarg EK, Hermans J, et al. Pathology data in the central databases of multicenter randomized trials need to be based on pathology reports and controlled by trained quality managers. *J Clin Oncol*. 2000;18:1771–1779.
- Abulafi AM, Williams NS. Local recurrence of colorectal cancer: the problem, mechanisms, management and adjuvant therapy. *Br J Surg*. 1994;81:7–19.
- Holm T, Cedermark B, Rutqvist LE. Local recurrence of rectal adenocarcinoma after 'curative' surgery with and without preoperative radiotherapy. *Br J Surg*. 1994;81:452–455.
- Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol*. 2005;23:5644–5650.
- Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch colorectal cancer group study. *J Clin Oncol*. 2005; 23:6199–6206.
- Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351: 1731–1740.
- Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg*. 2006;93:1215–1223.
- Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiother Oncol*. 2004;72: 15–24.
- Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. *J Clin Oncol*. 2005;23:5620–5627.
- Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med*. 2006;355:1114–1123.
- Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol*. 2006;24:4620–4625.
- Brown G, Davies S, Williams GT, et al. Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? *Br J Cancer*. 2004;91: 23–29.
- Fujita S, Yamamoto S, Akasu T, et al. Lateral pelvic lymph node dissection for advanced lower rectal cancer. *Br J Surg*. 2003;90:1580–1585.
- Moriya Y, Sugihara K, Akasu T, et al. Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. *World J Surg*. 1997;21:728–732.
- Mori T, Takahashi K, Yasuno M. Radical resection with autonomic nerve preservation and lymph node dissection techniques in lower rectal



- cancer surgery and its results: the impact of lateral lymph node dissection. *Langenbecks Arch Surg.* 1998;383:409–415.
30. Steup WH, Moriya Y, van de Velde CJ. Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. *Eur J Cancer.* 2002;38:911–918.
  31. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med.* 2003;348:2491–2499.
  32. Koh DM, Cook GJ, Husband JE. New horizons in oncologic imaging. *N Engl J Med.* 2003;348:2487–2488.
  33. Sauer R, Rodel C. Author reply. *N Engl J Med.* 2005;352:509–511.
  34. Nagtegaal ID, Marijnen CA, Kranenburg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol.* 2002;26:350–357.