Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial

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Summary

Background **The TME trial investigated the value of preoperative short-term radiotherapy in combination with total mesorectal excision (TME). Long-term results are reported after a median follow-up of 12 years.**

Methods **Between Jan 12, 1996, and Dec 31, 1999, 1861 patients with resectable rectal cancer without evidence of distant disease were randomly assigned to TME preceded by 5×5 Gy radiotherapy or TME alone (ratio 1:1). Randomisation was based on permuted blocks of six with stratification according to centre and expected type of surgery. The primary endpoint was local recurrence, analysed for all eligible patients who underwent a macroscopically complete local resection.**

Findings **10-year cumulative incidence of local recurrence was 5% in the group assigned to radiotherapy and surgery and 11% in the surgery-alone group (p<0·0001). The effect of radiotherapy became stronger as the distance from the anal verge increased. However, when patients with a positive circumferential resection margin were excluded, the relation between distance from the anal verge and the effect of radiotherapy disappeared. Patients assigned to radiotherapy had a lower overall recurrence and when operated with a negative circumferential resection margin, cancer-specific survival was higher. Overall survival did not differ between groups. For patients with TNM stage III cancer with a negative circumferential resection margin, 10-year survival was 50% in the preoperative radiotherapy group versus 40% in the surgery-alone group (p=0·032).**

Interpretation **For all eligible patients, preoperative short-term radiotherapy reduced 10-year local recurrence by more than 50% relative to surgery alone without an overall survival benefit. For patients with a negative resection margin, the effect of radiotherapy was irrespective of the distance from the anal verge and led to an improved cancer-specific survival, which was nullified by an increase in other causes of death, resulting in an equal overall survival. Nevertheless, preoperative short-term radiotherapy significantly improved 10-year survival in patients with a negative circumferential margin and TNM stage III. Future staging techniques should offer possibilities to select patient groups for which the balance between benefits and side-effects will result in sufficiently large gains.**

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Introduction

For rectal cancer treatment, the use of total mesorectal excision (TME) instead of conventional blunt surgery has led to substantial improvements in morbidity and survival.[1] Preoperative short-term radiotherapy in combination with conventional surgery improves local control and survival.[2] To investigate the value of short-term radiotherapy in combination with TME, the Dutch Colorectal Cancer Group initiated the TME trial.[3] For a reliable assessment of the value of preoperative radiotherapy, surgical, pathological, and radiotherapeutical techniques were standardised and controlled for quality. Early results showed a decreased risk of local recurrence for irradiated patients at 2 years (2% *vs* 8%, p<0·001) without a difference in overall survival.[3] After a median follow-up of 6 years, the effect of radiotherapy on local recurrence persisted (6% *vs* 11%, p<0·001), as well as the absence of a survival benefit.[4] Because of the serious consequences associated with local recurrence, guidelines in the Netherlands and several other countries recommend preoperative radiotherapy for all rectal cancer patients with the exception of those with T1 tumours. Unfortunately, preoperative radiotherapy can induce serious side-effects such as faecal incontinence, sexual dysfunction, and secondary malignancies.[5–11] In the absence of a survival benefit, for some patient groups the adverse effects might outweigh the benefits of decreased local recurrence. We report the effect of short-term radiotherapy on local recurrence, distant recurrence, and overall survival from the TME trial after a median follow-up of 12 years.

Methods

Patients

Patients were recruited in 118 European centres and one Canadian centre. Patients were eligible if they had clinically resectable adenocarcinoma of the rectum without evidence of distant disease. Tumours had to be

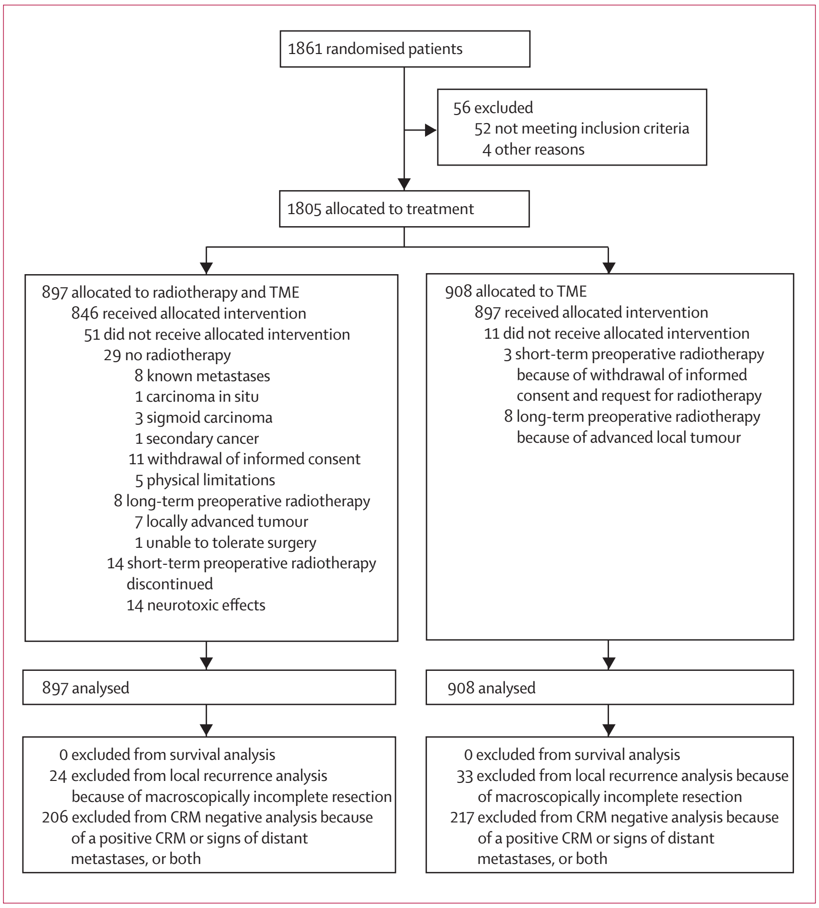

Figure 1: **Trial profile**
TME=total mesorectal excision. CRM=circumferential resection margin.

	RT+TME (n=897)	TME alone (n=908)
Age		
Median (years)	65	66
Range (years)	26–88	23–92
Sex		
Male	573 (64%)	578 (64%)
Female	324 (36%)	330 (36%)
Distance of tumour from the anal verge		
<5 cm	244 (27%)	265 (29%)
5·0–9·9 cm	383 (43%)	359 (40%)
≥10 cm	268 (30%)	283 (31%)
Unknown	2 (<1%)	1 (<1%)
Type of resection		
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	11 (1%)	17 (2%)
I	264 (29%)	243 (27%)
II	251 (28%)	245 (27%)
III	299 (33%)	325 (36%)
IV	62 (7%)	61 (7%)
Unknown	10 (1%)	17 (2%)
CRM involvement		
No	729 (81%)	729 (80%)
Yes	143 (16%)	148 (16%)
Unknown	25 (3%)	31 (3%)

Data are number (%) unless otherwise indicated. RT=radiotherapy. TME=total mesorectal excision. CRM=circumferential resection margin.

Table 1: **Characteristics of eligible patients**

below the level of S1/S2 with an inferior tumour margin located 15 cm or less from the anal verge as measured during withdrawal of a flexible coloscope or a rigid rectoscope. No upper age limit was given. Central and local ethics committees gave approval for the study and included patients gave oral informed consent. The design of the trial was reported previously.[3,4,12]

Randomisation

Patients were randomly assigned to preoperative radiotherapy with 5×5 Gy followed by TME within a week or TME alone (ratio 1:1). Randomisation was computer-generated and based on permuted blocks of six with stratification according to centre and the expected type of surgery. Randomisation was managed centrally at the data centre of the Department of Surgery of Leiden University Medical Centre, Netherlands. For every stratification group and participating centre, a list was printed by the Department of Medical Statistics. Patients were assigned to a treatment by these lists, which were only available in the central data centre. Local investigators enrolling patients had no knowledge of the next assignment in the sequence. The data centre also managed primary and follow-up data on case-report forms that were collected in participating hospitals and by general practitioners. Investigators reviewing primary endpoints were not aware of the allocated treatment and those analysing data were unmasked.

Procedures

Surgeons were taught TME surgery through a complete course of workshops, symposia, and video instructions. A monitoring committee was also installed to ensure adherence to the surgical protocol guidelines. An experienced instructor surgeon supervised the first five TME procedures in every participating hospital. Pathologists were trained to identify tumour spread according to the protocol of Quirke and colleagues.[13] A panel of supervising pathologists was created to review the results of histopathological examination.[14] In case of a positive resection margin in the surgery-alone group, postoperative radiotherapy (28×1·8 Gy) was given.

Patients underwent clinical examination every 3 months during the first year after surgery and annually thereafter. Local recurrence was defined as evidence of tumour within the pelvic or perineal area. Criteria for distant recurrence were tumour growth in any other area, including the colostomy site or inguinal region. All recurrences were confirmed by one of the study coordinators. The primary endpoint was local control. Secondary endpoints were distant recurrence, overall survival, and cancer-specific survival.

Statistical analysis

Data were analysed with PASW Statistics 17.0. All time-to-event variables were calculated from date of surgery. Overall survival analyses were done by intention-to-treat. Local recurrence analyses were done on all eligible patients who underwent a macroscopically complete local resection. Distant recurrence analyses were done on all eligible patients who did not have distant metastases at the time of surgery. Overall recurrence analyses were done on the basis of the number of eligible patients who had a macroscopically complete local resection without distant metastases at the time of surgery. As specified in the trial protocol, secondary analyses were done on patients with a negative circumferential resection margin (>1 mm) and no signs of distant tumour spread. Overall survival was calculated with the Kaplan–Meier method. Analyses for recurrence were reported as cumulative incidences accounting for death as competing risk. Cancer-specific survival was reported as cumulative incidence, accounting for death due to other causes as competing risk. We compared proportions with a χ^2 test and survival and recurrence rates with the log-rank test. We calculated hazard ratios (HR) with the Cox proportional hazards model. We checked the proportional hazards assumption using the methods of Grambsch and Therneau.[15] We used interactions between treatment and prognostic factors in the Cox proportional hazards model to test for the presence of effect modifiers. A two-sided p value of 0·05 or less was considered to show statistical significance.

Role of the funding source

The funding sources of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. WvG, CAMM, EM-KK, HP, and CJHvdV had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between Jan 12, 1996, and Dec 31, 1999, 1861 patients from 84 Dutch, 24 Swedish, ten other European centres, and one Canadian centre were included. 56 patients were considered ineligible after randomisation. The reasons for ineligibility were reported previously.[3,4]

Of the 1805 eligible patients, 62 patients did not receive the intended treatment and 85 patients were treated with postoperative adjuvant treatment against protocol guidelines. Minor violations included extended interval between the end of radiotherapy and surgery (n=110) and non-compliance with the prescribed anatomic borders of the radiotherapy volume (n=127). In accordance with previous reports, patients with major or minor, or both, protocol violations were included in all analyses. Table 1 shows the patient characteristics, which were well balanced across the treatment groups.

Follow-up was continued until July 15, 2010. Median follow-up of surviving patients was 11·6 years (range 1·2–14·1) and did not differ between the two groups.

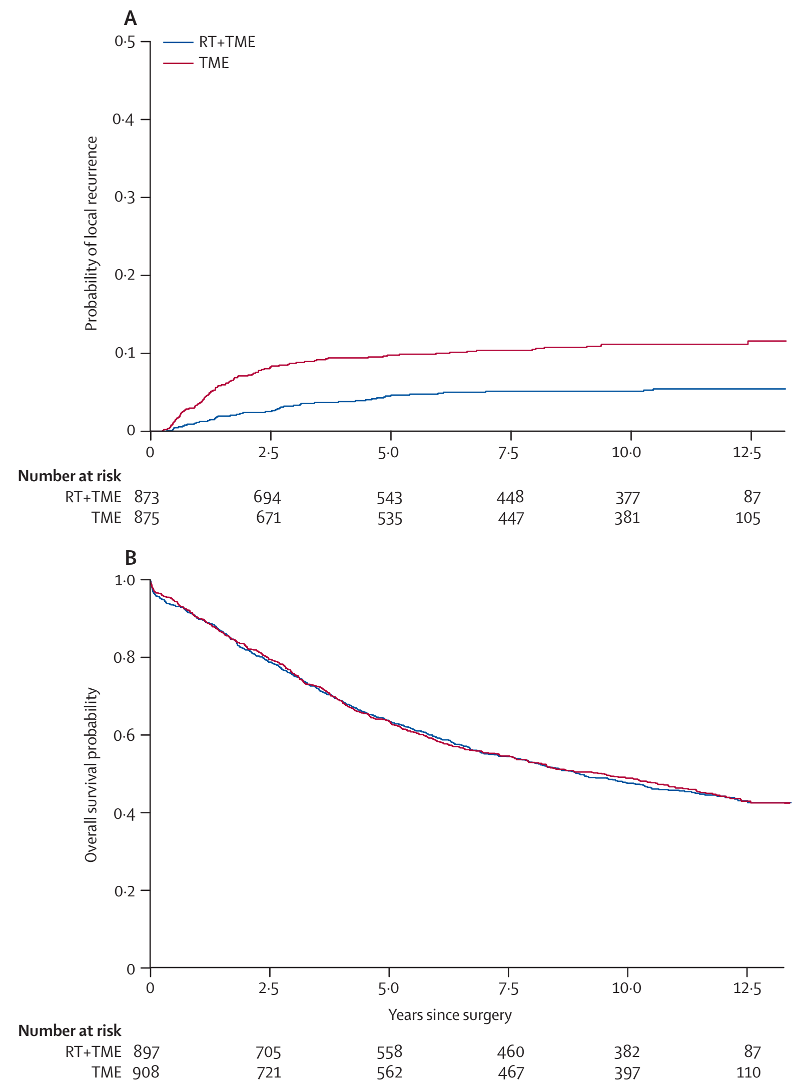

Figure 2: **Local recurrence and overall survival in the two treatment groups**
(A) Probability of local recurrence in the 1748 eligible patients who underwent a macroscopically complete local resection. (B) Probability of overall survival in the 1805 eligible patients. RT=radiotherapy. TME=total mesorectal excision.

	RT+TME (n=315)	TME alone (n=319)
Rectal cancer	119 (38%)	152 (48%)
Radiotherapy complications	2 (<1%)	0 (0%)
Surgery complications	20 (6%)	16 (5%)
Secondary malignancy	43 (14%)	30 (9%)
Cardiovascular cause	46 (15%)	45 (14%)
Pulmonary cause	16 (5%)	15 (5%)
Infectious cause	3 (1%)	2 (<1%)
Neurological cause	4 (1%)	4 (1%)
Ileus	3 (1%)	2 (<1%)
Other	39 (12%)	32 (10%)
Unknown	20 (6%)	21 (7%)

Data are number (%). Pearson χ^2 test between all causes of death p=0·448. RT=radiotherapy. TME=total mesorectal excision.

***Table 2:* Causes of death in patients who were operated with a negative circumferential margin**

Of the 1805 eligible patients, 57 had a macroscopically incomplete resection and consequently never reached local control. Of the 1748 patients who underwent a macroscopically complete resection, 143 patients had local disease recurrence (46 in the radiotherapy-surgery group and 97 in the surgery-alone group). At 10 years, the cumulative incidence of local recurrence was 5% in the radiotherapy-surgery group and 11% in the surgery-alone group (p<0·0001; figure 2A). Of the 1683 (835 in the radiotherapy-surgery group, 848 in the surgery-alone group) eligible patients without distant metastases at time of surgery, 442 patients developed a distant recurrence (207 in the radiotherapy-surgery group and 235 in the surgery-alone group). The cumulative incidence of distant recurrence at 10 years was 25% in the radiotherapy-surgery group and 28% in the surgery-alone group (p=0·21). Of the 1652 (825 in the radiotherapy-surgery group, 827 in the surgery-alone group) patients who underwent a macroscopically complete resection without distant metastases at the time of surgery, overall recurrence at 10 years was significantly lower in the irradiated group (26% *vs* 32%, p=0·03).

Up to July 15, 2010, 973 patients died. 485 were in the radiotherapy-surgery group and 488 in the surgery-alone group, with 10-year overall survival probabilities of 48% and 49%, respectively (p=0·86; figure 2B). Cumulative incidence of cancer-specific death at 10 years was 28% for patients who had radiotherapy and surgery and 31% for patients who underwent surgery alone (p=0·20).

Of the 1382 patients with a negative circumferential resection margin and no signs of distant metastases during surgery, 82 patients had a local recurrence (22 of 691 in the radiotherapy-surgery group and 60 of 691 in the surgery-alone group). The 10-year cumulative incidence of local recurrence was 3% in the radiotherapy-surgery group and 9% in the surgery-alone group (p<0·0001). 300 patients developed a distant recurrence (134 of 691 in the radiotherapy-surgery group and

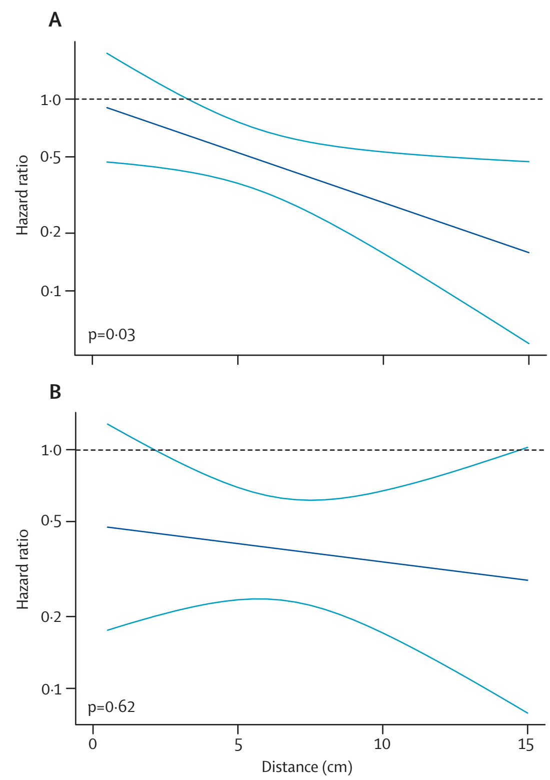

***Figure 3:* Relation between the effect of radiotherapy on local recurrence and the distance of the tumour from the anal verge**

(A) Analysis of the 1748 eligible patients. (B) Analysis of the 1382 patients with negative circumferential resection margins. Interaction measured with Cox proportional hazards model.

166 of 691 in the surgery-alone group); the 10-year probability of distant recurrence was 19% and 24% respectively (p=0·06). Overall, recurrence at 10 years was significantly less common in the irradiated group than in the surgery-alone group (20% *vs* 27%, p=0·01).

Up to July 15, 2010, 634 patients with negative circumferential resection margin had died (315 in the radiotherapy-surgery group and 319 in the surgery-alone group; table 2), corresponding to 10-year survival probabilities of 56% and 57% respectively (p=0·88).

The cumulative incidence of cancer-specific death at 10 years was 17% (119 of 691) for irradiated patients and 22% (152 of 691) for patients who underwent surgery alone (p=0·04). The causes of death are shown in table 2. Irradiated patients died less often from rectal cancer than did non-irradiated patients. Conversely, other causes of death were more frequent in irradiated patients, resulting in equal overall survival rates in both groups.

Adverse events that led to patient death (table 2) were updated in this 12-year follow-up; however, non-mortal adverse events have not been updated since previously reported.[6]

The relation between the distance of the tumour from the anal verge and the effect of radiotherapy on local

	10-year local recurrence					10-year overall survival				
	n	RT+TME (%)	TME (%)	p	Interaction	n	RT+TME (%)	TME (%)	p	Interaction
All eligible patients					p=0·312					p=0·262
TNM I	507	<1%	3%	0·027	..	507	65%	72%	0·321	..
TNM II	491	5%	8%	0·212	..	496	50%	55%	0·242	..
TNM III	622	9%	19%	<0·0001	..	624	39%	37%	0·526	..
Patients with a negative CRM					p=0·15					p=0·027
TNM I	497	<1%	3%	0·027	..	497	65%	72%	0·293	..
TNM II	421	4%	7%	0·355	..	421	51%	57%	0·213	..
TNM III	435	5%	17%	<0·0001	..	435	50%	40%	0·032	..

Data are shown for patients for whom the TNM stage was known. RT=radiotherapy. TME=total mesorectal excision. CRM= circumferential resection margin.

Table 3: **Local recurrence and survival in patients specified per TNM stage and treatment group**

recurrence was analysed for all eligible patients and for patients with a negative circumferential resection margin (figure 3). For all eligible patients, the effect of radiotherapy became stronger as the distance from the anal verge increased, with a significant distance by treatment interaction (p=0·03, figure 3A). However, when patients with a positive circumferential resection margin were excluded from the analyses, the relation between distance from the anal verge and the effect of radiotherapy disappeared, with a non-significant interaction (p=0·62, figure 3B).

Local recurrence and overall survival were calculated for TNM stages I, II, and III for all eligible patients and for patients with negative circumferential resection margin (table 3). Although no significant interaction between treatment and TNM stage was noted for local recurrence, the effect of radiotherapy was most convincing in patients with TNM stage III tumours. Irrespective of the status of circumferential resection margin, radiotherapy had no significant effect on patients with TNM stage II tumours. Although radiotherapy decreased local recurrence significantly for patients with TNM stage I tumours, it was with a low absolute risk reduction of 2·6% for all eligible patients and 2·7% for those with a negative circumferential margin.

Radiotherapy was not associated with an increase in overall survival when the entire trial population was considered. For overall survival of patients with negative circumferential resection margin, the two treatment groups differed significantly (p=0·027; table 3). Only for patients with a negative circumferential resection margin and with a TNM stage III tumour was 10-year overall survival better in the radiotherapy group than in the surgery alone group (table 3). Figure 4 shows a forest plot with HR of radiotherapy and surgery compared with surgery alone for overall survival in subgroups of patients with a negative circumferential resection margin.

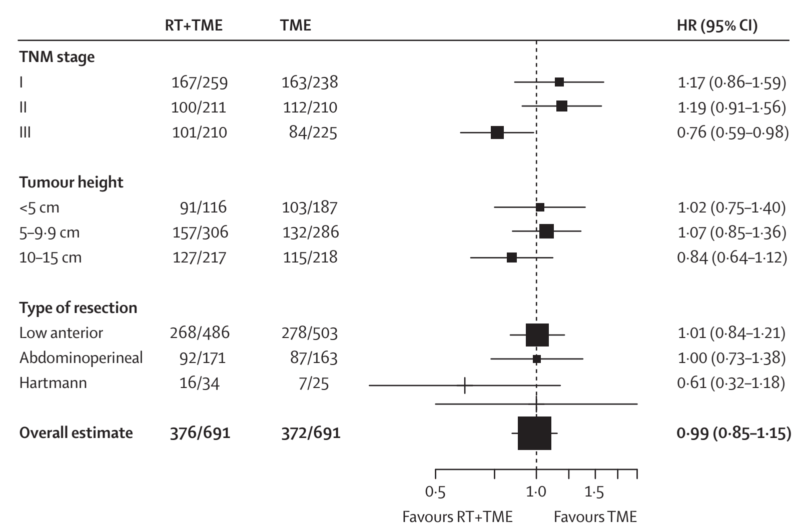

Figure 4: **Forest plot analysis of overall survival of subgroups of patients with a negative circumferential resection margin.**
RT=radiotherapy. TME=total mesorectal excision. HR=hazard ratio.

Discussion

After a median follow-up of 12 years, preoperative short-term radiotherapy for patients with resectable rectal cancer decreases local recurrence rates by more than 50% relative to surgery alone, with a decreased overall recurrence rate. Compared with the results after a follow-up of 6 years, the relative risk reduction remains stable at about 50%. In previous reports of this trial,[3,4] the possibility that in some cases radiotherapy might not prevent but merely postpone local recurrence could not be excluded. However, after 12 years of follow-up, no signs of this phenomenon appeared, which is a similar result to the long-term follow-up of the Swedish rectal cancer trial.[16] The proportion of local recurrence presenting later than 5 years after surgery was 11% (11/97) in the surgery-alone group and 9% (4/46) in the irradiated group. The effect of radiotherapy is even stronger for patients with a negative circumferential resection margin, with a relative risk reduction of 64% for local recurrence. As shown previously,[3,4] radiotherapy had no significant effect on distant recurrence rates.

Panel: **Research in context**

Systematic review

Until the mid-1990s, several trials reported benefits of preoperative radiotherapy in combination with conventional blunt surgery for rectal cancer.[2,33–35] At that time, total mesorectal excision (TME) surgery was popularised worldwide and brought low local recurrence rates with improved survival compared with conventional surgery. No evidence existed that preoperative radiotherapy had added value in combination with TME surgery. The TME trial was the first trial to investigate this question. No systematic review had been done before the start of the TME trial. However, relevant evidence was described in detail in the trial protocol.

Interpretation

The long term follow-up of the TME trial showed that preoperative short-term radiotherapy reduced local recurrence in combination with TME surgery. A negative circumferential resection margin was of crucial importance because radiotherapy could not compensate for a positive margin. Cancer-specific survival was significantly higher when short-term radiotherapy was followed by surgery with negative resection margins but did not translate into an improved overall survival because of the toxic effects of radiotherapy. In patients with negative resection margins, preoperative radiotherapy for TNM stage III patients resulted in an overall-survival benefit whereas for patients with a good prognosis on preoperative imaging, the consequences of adverse effects induced by radiotherapy outweighed the benefits. For some patients, high quality surgery suffices and for others a combination of radiotherapy, chemotherapy, and surgery is needed. Improvements in imaging and biological markers will enable a more personalised approach. Consequently, patients with rectal cancer should be carefully staged preoperatively and discussed multidisciplinary to enable an optimal tailor-made treatment approach.

Nevertheless, overall recurrence was significantly lower in the group of irradiated patients.

In the previous report of this trial,[4] radiotherapy seemed only effective for tumours located between 5 and 10 cm from the anal verge. In this report, distance from the anal verge was analysed as a continuous factor rather than with arbitrary cutoff points. When all eligible patients were analysed, the effect of radiotherapy was not significant for distal tumours; however, the benefit of radiotherapy became significant as the distance from the anal verge increased. But, because of the absence of preoperative imaging, a substantial proportion of patients with distal tumours had a positive circumferential resection margin, a condition for which preoperative short-term radiotherapy cannot compensate.[17,18] When those patients with positive margins were excluded, the effect of radiotherapy on the reduction of local recurrence was independent of the distance of the tumour from the anal verge.

Preoperative short-term radiotherapy had no effect on overall survival or cancer-specific survival when all randomised patients were included in the analyses. However, in patients operated with a negative circumferential resection margin, radiotherapy significantly improved cancer-specific survival. Unfortunately, this benefit was offset by an increase in other causes of death, resulting in an equal overall survival compared with surgery alone. In view of several non-fatal but serious side-effects of radiotherapy such as faecal incontinence, sexual dysfunction, and bowel dysfunction, the overall benefits of radiotherapy for an unselected patient group are disputable.

While subgroup analyses should always be interpreted with care, our secondary outcomes clearly show that the balance between benefit and harm induced by radiotherapy differs between patient groups. Despite a significant decrease of the local recurrence rate in TNM stage I patients, an absolute reduction of 2·6% for all eligible patients implies that 38 patients have to be exposed to radiotherapy to save one patient a local recurrence without any survival benefit. By contrast, for TNM stage III patients, less than ten patients have to be treated with radiotherapy to save one patient a local recurrence. Additionally, radiation improved survival among TNM III patients with a negative circumferential resection margin, in whom only ten patients have to be treated to save one life. The significant interaction between TNM stage and the treatment groups suggests that these results can be interpreted as a true difference in treatment outcomes compared with the trial population as a whole.

Although the secondary analyses of patients with negative resection margin were planned in the trial design, conclusions based on resection margin status are open to some criticisms. Results were based on a subgroup selected with pathological data, whereas a negative circumferential resection margin can only be predicted up front and decisions about neoadjuvant treatment can only be based on preoperative staging. Recent improvements in preoperative imaging and improved surgical techniques for distal resections has greatly reduced the number of operations with positive resection margins.[19,20] During accrual of this trial, most surgeons assessed resectability of the tumour solely with a digital rectal examination whereas nowadays preoperative MRI is standard in most western European hospitals. MRI allows the careful identification of tumours that impede a negative circumferential resection margin, allowing downstaging therapy before surgery.[21] As a result, the proportion of patients with a positive circumferential resection margin in the Netherlands dropped from 16% in the TME trial to 6% in the 2009 report of the Dutch Surgical Colorectal Audit.[4,22] When MRI results are discussed in a preoperative multidisciplinary team, rates of positive resection margins can be as low as 1%.[23]

Long-course chemoradiation is the therapy of choice for patients needing preoperative downstaging or downsizing, but its use is questionable for other patients. The efficacy of preoperative short-term radiotherapy seen in this trial was also reported for other trials. First, results from the Polish rectal cancer trial showed that short-term radiotherapy was as effective as long-course chemoradiotherapy.[24] Furthermore, in the British MRC CR07 trial, short-term preoperative radiotherapy was better than selective postoperative chemoradiotherapy.[18]

Additionally, results from an interim analysis of the Stockholm III trial showed that short-term radiotherapy in combination with delayed surgery is feasible and has a downstaging effect.[25] Finally, results from the Australian intergroup trial showed that short-term radiotherapy seemed equally effective as long-course chemoradiotherapy for clinically staged T3 rectal cancer.[26] However, the finding that radiotherapy might not be necessary to achieve excellent results in selected patient groups is also supported by other publications. A 5-year local recurrence of 3% was achieved after surgery alone in 122 patients from the MERCURY trial classified to have a good prognosis on MRI.[27] Population-based data from Norway showed a 5-year local recurrence of 7% in 921 patients with rectal cancer operated between 2002 and 2004 without radiotherapy.[28]

Although currently rectal cancers are mainly assessed on their primary closeness to the mesorectal fascia, results from this trial show that nodal involvement should be another important factor to decide which patients should be treated with preoperative radiotherapy. Therefore, a reliable technique is needed to detect positive lymph nodes before surgery. Although nodal staging has improved with use of morphological criteria, accuracy is still inadequate. Studies with contrast agents for MRI have reported improved sensitivity and specificity for the detection of metastatic lymph nodes in rectal carcinoma.[29,30] These results suggest that contrast-enhanced MRI could improve preoperative nodal staging in the future. Together with improved imaging techniques, new biomarkers can also help to select those patients who will benefit most from radiotherapy. Research on tissue samples obtained from the TME trial showed that both the level of caspase-3 activity and the presence of mutations in the *PIK3CA* gene could be used to identify patients with an increased risk of local recurrence.[31,32]

To our knowledge, the TME trial is the first trial in which the value of short-term radiotherapy before quality-controlled TME surgery was investigated (panel). The importance of the quality of the resected TME specimen has been reported several times and is best shown by the status of circumferential resection margin, defined as positive when it is equal to or higher than 0·10 cm. However, even after good surgery, a positive resection margin can occur because growth adjacent to, at, or through the mesorectal fascia is missed by inadequate or absent preoperative imaging techniques. Because MRI was not available in most participating hospitals between 1996 and 1999, resectabillty was mostly judged by rectal digital examination, which explains the large proportion of patients with positive circumferential resection margins in this trial. The interaction between treatment and TNM stage for overall survival points towards a differential treatment effect for different TNM stages within patients with negative resection margins. Thus, it is most likely not a subgroup analysis issue, although the possibility of a statistical type-1 error cannot be entirely excluded.

Extensive quality-of-life variables recorded for this trial have contributed to a much improved understanding of the effect of surgery and radiotherapy on patients' lives. However, for the present follow-up, quality-of-life data have not been updated and were subsequently not included in this report. Future staging techniques should offer possibilities to select patient groups for which the balance between benefits and side-effects favours gains and simultaneously identify patients for whom radiotherapy can safely be omitted.

Contributors

WvG, CAMM, HP, EM-KK, and CJHvdV participated in the analysis, interpretation, and writing of this report. IDN, TW, HJTR, LP, and BG participated in the interpretation and writing of this report. All authors approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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