Quality assurance in rectal cancer treatment

Dulk, M. den

Chapter 2

Improved overall survival for patients with rectal cancer since 1990: the effects of TME surgery and preoperative radiotherapy

Marcel den Dulk, Pieta Krijnen, Corrie A.M. Marijnen, Harm J.T. Rutten, Lonneke V. van de Poll-Franse, Hein Putter, Elma Meershoek-Klein Kranenbarg, Marlies L.E.A. Jansen-Landheer, Jan-Willem W. Coebergh, Cornelis J.H. van de Velde

Eur J Cancer 2008; 44: 1710-1716

ABSTRACT

Aim

The aim was to study the effects of the introduction of TME surgery and preoperative radiotherapy on overall survival (OS) by comparing patients treated in the period before (1990-1995), during (1996-1999) and after (2000-2002) the TME trial.

Patients and methods

Patients diagnosed with rectal carcinoma in the region of Comprehensive Cancer Centres South and West were used ($n = 3179$).

Results

Five-year OS was, respectively, 56%, 62% and 65% in the pre-trial, trial and post-trial periods ($P < 0.001$). Preoperative RT was increasingly used over time and significantly related to OS in the post-trial period ($P = 0.002$), but not in the pre-trial and trial periods.

Conclusions

Population-based OS improved markedly since the introduction of TME surgery. With standardised TME surgery, preoperative RT improved OS, whereas withholding preoperative RT was associated with a poorer prognosis. The present study supports that preoperative RT was correctly introduced as a standard treatment before TME surgery in our national guideline.

INTRODUCTION

Since the early 1990s, there have been changes in rectal cancer treatment towards better surgery and/or preoperative radiotherapy (RT). With conventional, blunt dissection of the rectum 5-year local recurrence rates used to be above 20%.[1] However, after total mesorectal excision (TME), which is a sharp dissection under direct vision of the rectum with its mesorectum and the visceral pelvic fascia,[2] local recurrence rates can be less than 10%.[3,4] Moreover, 5-year overall survival (OS) improved from 48% after conventional surgery as performed in the Swedish Rectal Cancer trial to >60% after TME surgery.[1,5,6]

In the Netherlands, a trial was performed between 1996 and 1999 to study the effects of preoperative RT on local control and OS in patients that underwent TME surgery.[7] During this trial, all participating surgeons were trained in the TME technique.[6,8] Instructions were given during workshops, at the dissection table, with booklets and a video tape. Besides, the first five procedures of each participating surgeon were attended by an instructor surgeon. Moreover, RT and pathology examination were also standardised to reduce the variability.[7] The trial resulted in a 5-year local recurrence rate of 5.6% with and 10.9% without preoperative RT, and a 5-year OS rate of 64% in both groups.[6]

TME is now accepted as the golden standard for the curative treatment of rectal carcinoma. In the present study, OS was evaluated in the time periods before, during and after the TME trial to study the effects of the introduction of TME surgery in combination with preoperative RT in the region of Comprehensive Cancer Centres South and West in the Netherlands.

PATIENTS AND METHODS

Patients

Data were derived from the cancer registry of the population-based Comprehensive Cancer Centres South and West. Registration is based on notification of all newly diagnosed malignancies after which data are obtained from clinical records in hospitals. The Dutch regional Cancer Registries have shown to attain a completeness of data exceeding 95%.[9] Patients who underwent a resection for cancer located in the rectum (International Classifications of Diseases-9 154.1) and diagnosed between January 1990 and December 2002 were selected for analysis. Patients with prior invasive adenocarcinoma or with distant metastases diagnosed prior to or during surgery were not included, as were patients who underwent a local excision such as polipectomy or TEM (transanal endoscopic microsurgery). In the Dutch TME trial, patients with T1-T3 and patients with mobile T4 tumours were included. In the registry no details were available on mobility

of the tumour, so all T4 tumours were excluded to limit the current analysis to tumours which could be curatively resected.

The period of study was divided into three periods: 1990-1995 (pre-trial period), 1996-1999 (trial period) and 2000-2002 (post-trial period). Age was categorised into <60 years, 60-74 years and ≥75 years. Data on tumour stage and data on preoperative and postoperative treatment were obtained from the Cancer Registries. Preoperative RT consisted of both the short, 5 x 5 Gy, schedule and the long schedule, such as 25 x 2 Gy. TNM-classification 4 (UICC,1987) was used before 1999.[10] Since 1999, TNM-classification 5 (UICC, 1997) was used, which classifies node negative patients with less than 12 examined lymph nodes as Nx.[11] Survival data were obtained from hospitals, general practitioners and the Central Bureau for Genealogy, which registers all the deceased persons in the Netherlands.

Statistical analysis

Data were analysed with the SPSS package (SPSS 14.0 for Windows; SPSS Inc., Chicago, IL). Univariate comparisons of categorical variables were performed by a χ^2 test. The following variables were considered as potential confounders for period in the analysis for OS: pathological T-stage, lymph node status, age, gender, (neo)adjuvant treatment, and Comprehensive Cancer Centre region. Potential confounder variables were first univariately tested in a Cox regression model. Confounders with a *P*-value ≤ 0.10 in the univariate analysis were selected and entered in a multivariate Cox regression model together with period of diagnosis. Besides, the model was tested for an interaction between period and statistically significant confounders. To test whether the hazard ratios (HR) were constant across time, the assumption of proportional hazards was studied univariately, and subsequently variables with a significant interaction in these analyses (age, pathological T-stage, nodal status, and (neo)adjuvant treatment) were entered in the previously described multivariate Cox regression model. As the estimates of the HR and *P*-values for >6 months post-surgery in the model with time-dependency were comparable to the model without time-dependency, we chose to report the results without time-dependency. Two-sided *P*-values ≤0.05 were considered statistically significant.

RESULTS

Patient characteristics

In total, 3179 patients were included in the analysis. In the pre-trial period 1150 patients, in the trial period 1084 patients and in the post-trial period 945 patients were analysed. In the trial period, 421 patients (39%) were included in the TME trial. All hospitals in both Comprehensive Cancer Centre regions South and West participated in the TME

Table 1. Patient characteristics by period of diagnosis.

Variable	Pre-trial period (%) *n* = 1150	Trial period (%) *n* = 1084	Post-trial period (%) *n* = 945	Total (%) *n* = 3179	*P*-value
Gender					0.195
Female	495 (43)	451 (42)	370 (39)	1316 (41)	
Male	655 (57)	633 (58)	575 (61)	1863 (59)	
Age					0.369
< 60 years	296 (26)	305 (28)	268 (28)	869 (27)	
60-74 years	535 (47)	512 (47)	426 (45)	1473 (46)	
> 74 years	319 (28)	267 (25)	251 (27)	837 (26)	
pT-stage					0.525
T1	110 (10)	96 (9)	74 (8)	280 (9)	
T2	392 (34)	386 (36)	350 (37)	1128 (36)	
T3	648 (56)	602 (56)	521 (55)	1771 (56)	
Lymph node status					0.019
N0/Nx	825 (72)	720 (66)	640 (68)	2185 (69)	
N+	325 (28)	364 (34)	305 (32)	994 (31)	
(Neo)adjuvant treatment					<0.001
No perioperative treatment	705 (61)	591 (55)	241 (26)	1537 (48)	
Preoperative RT	1 (0)	329 (30)	555 (59)	885 (28)	
Preoperative CRT	0 (0)	17 (2)	50 (5)	67 (2)	
Preop. RT and postop. CT	0 (0)	9 (1)	35 (4)	44 (1)	
Postoperative RT	403 (35)	116 (11)	36 (4)	555 (17)	
Postoperative CRT	27 (2)	5 (0)	5 (1)	37 (1)	
Postoperative CT	14 (1)	17 (2)	23 (2)	54 (2)	
Region					<0.001
CCC South	527 (46)	701 (65)	556 (59)	1784 (56)	
CCC West	623 (54)	383 (35)	389 (41)	1395 (44)	

Pre-trial period (1990-1995), trial period (1996-1999) and post-trial period (2000-2002). Percentages may not add up to 100% due to rounding. RT = radiotherapy; CRT = chemoradiotherapy; CT = chemotherapy; CCC = Comprehensive Cancer Centre.

trial. Median follow-up of patients alive was 144 (range 108-191), 86 (range 60-119) and 46 months (range 24-72 months), for the pre-trial, trial and post-trial periods, respectively. Patient characteristics are shown in Table 1. In the pre-trial period more patients were included in the region of Comprehensive Cancer Centre West, whereas in the trial and post-trial periods relatively more patients were included from the region of Comprehensive Cancer Centre South. The patients diagnosed in the three periods differed significantly with respect to (neo)adjuvant treatment: over time less patients were treated with postoperative RT, whereas more patients were preoperatively treated with RT ($P < 0.001$). In the trial and post-trial period more patients were diagnosed with N+ disease compared with the pre-trial period.

Overall survival

Five-year OS in the pre-trial period was 56% (95% confidence interval (CI) 53%-59%), compared to 62% (95% CI 60%-65%) and 65% (95% CI 60%-69%) for the trial and post-trial periods respectively ($P < 0.001$). The increase in OS in the trial period compared with the pre-trial period was significant ($P < 0.001$) and did not change significantly thereafter ($P = 0.31$).

The results of the univariate analyses to select confounding variables for OS are shown in Table 2. In this analysis, only region was not found to be associated with OS ($P = 0.993$) and was not entered in the multivariate analysis. All other variables were entered in the multivariate analysis: the results are presented in Table 3. The effects of period, gender, age, pT-stage, lymph node status, and (neo)adjuvant treatment were found to be independently related to the risk of dying. Furthermore, a significant interaction between period and (neo)adjuvant treatment was found ($P < 0.001$). Consequently, the

Table 2. Results of the univariate Cox regression analyses for overall survival.

Variable	Hazard ratio	95% CI	*P*-value
Period of diagnosis			<0.001
Pre-trial	1.00		
Trial	0.81	0.72-0.91	<0.001
Post-trial	0.74	0.64-0.86	<0.001
Gender			0.005
Female	1.00		
Male	1.16	1.05-1.29	
Age			<0.001
< 60 years	1.00		
60-74 years	1.60	1.39-1.84	<0.001
> 74 years	3.14	2.72-3.63	<0.001
pT-stage			<0.001
T1	1.00		
T2	1.31	1.04-1.65	0.021
T3	2.44	1.96-3.03	<0.001
Lymph node status			<0.001
N0/Nx	1.00		
N+	1.89	1.70-2.09	
(Neo)adjuvant treatment			<0.001
No (neo)adjuvant treatment	1.00		
Preoperative RT	0.77	0.67-0.89	<0.001
Preoperative CRT	1.35	0.93-1.96	0.111
Preoperative RT and postoperative CT	0.86	0.51-1.47	0.586
Postoperative RT	1.27	1.12-1.43	<0.001
Postoperative CRT	0.84	0.52-1.36	0.478
Postoperative CT	1.21	0.84-1.76	0.311
Region			0.993
CCC South	1.00		
CCC West	1.00	0.90-1.11	

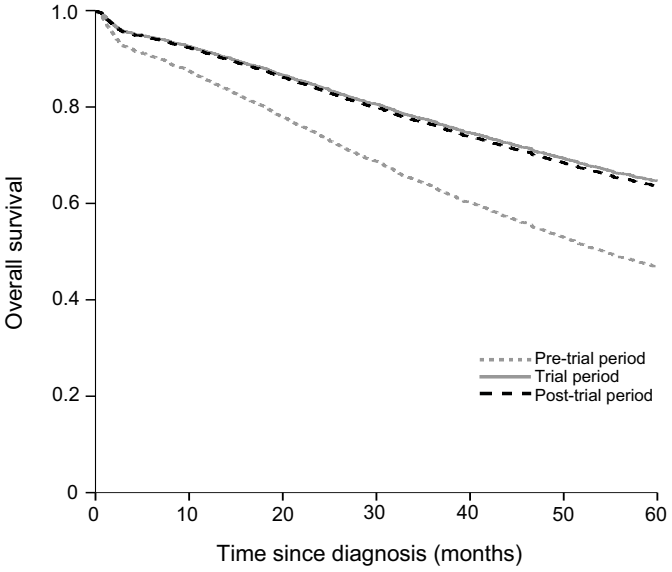
RT = radiotherapy; CRT = chemoradiotherapy; CT = chemotherapy; CCC = Comprehensive Cancer Centre; CI = confidence interval.

Table 3. Results of the multivariate Cox regression analysis for overall survival.

Variable	Hazard ratio	95% CI	*P*-value
Period of diagnosis			<0.001
Pre-trial	1.00		
Trial	0.66	0.56-0.77	<0.001
Post-trial	0.79	0.63-1.00	0.049
Gender			<0.001
Female	1.00		
Male	1.26	1.13-1.40	
Age			<0.001
< 60 years	1.00		
60-74 years	1.71	1.48-1.97	<0.001
> 74 years	3.44	2.96-4.00	<0.001
pT-stage			<0.001
T1	1.00		
T2	1.22	0.96-1.54	0.094
T3	2.02	1.61-2.54	<0.001
Lymph node status			<0.001
N0/Nx	1.00		
N+	1.88	1.68-2.10	
(Neo)adjuvant treatment, pre-trial period *			0.046
No (neo)adjuvant treatment	1.00		
Postoperative RT	0.80	0.68-0.94	0.005
Postoperative CRT	0.58	0.33-1.04	0.069
Postoperative CT	0.99	0.51-1.92	0.972
(Neo)adjuvant treatment, trial period			0.040
No (neo)adjuvant treatment	1.00		
Preoperative RT	1.11	0.90-1.36	0.315
Preoperative CRT	2.38	1.24-4.44	0.007
Preoperative RT and postoperative CT	0.60	0.19-1.84	0.376
Postoperative RT	1.35	1.02-1.75	0.032
Postoperative CRT	1.99	0.75-5.46	0.174
Postoperative CT	1.14	0.62-2.10	0.683
(Neo)adjuvant treatment, post-trial period			0.001
No (neo)adjuvant treatment	1.00		
Preoperative RT	0.64	0.49-0.86	0.002
Preoperative CRT	1.30	0.80-2.17	0.282
Preoperative RT and postoperative CT	0.84	0.45-1.58	0.590
Postoperative RT	1.59	0.97-2.68	0.066
Postoperative CRT	0.41	0.06-2.95	0.375
Postoperative CT	0.82	0.41-1.63	0.562

RT = radiotherapy; CRT = chemoradiotherapy; CT = chemotherapy; CI = confidence interval. * Results for preoperative RT in the pre-trial period not shown ($n = 1$).

effect of (neo)adjuvant treatment is presented separately for each period in Table 3. Moreover, period of treatment itself was significantly associated with OS. Adjusted OS in the trial period was significantly improved compared to the pre-trial period (OR 0.66, $P < 0.001$). In contrast, adjusted OS was lower in the post-trial period compared with the trial period although not statistically significant (OR = 1.20, $P = 0.141$ for post-trial period compared to trial period). Adjusted Cox regression curves for OS are shown in Figure 1.



Numbers at risk							
Pre-trial period	1150	1039	938	857	772	707	646
Trial period	1084	978	909	839	767	718	676
Post-trial period	945	867	815	684	478	268	83

Figure 1. Cox regression curves for overall survival (OS) for resectable rectal cancer by period adjusted for gender, age, pT-stage, lymph node status, (neo)adjuvant treatment, and the interaction between treatment and period.

The effects of period and treatment on overall survival

In the pre-trial period only one patient is treated with preoperative RT, therefore this patient is not included in the following analyses. Unadjusted, 5-year survival rates per period and treatment are shown in Table 4. In Figure 2, Cox regression curves for OS are shown adjusted for gender, age, pT-stage, and lymph node status. The curves are presented separately for patients treated without (neo)adjuvant treatment (Figure 2A), with preoperative RT (Figure 2B) and with postoperative RT (Figure 2C). In the pre-trial period, OS was better for patients treated with postoperative RT compared with patients treated without (neo)adjuvant treatment ($P = 0.005$, Table 3). In the trial period, in which 39% of patients were included in the TME trial and randomised between preoperative

Table 4. Unadjusted 5-year overall survival rate (%) per period for patients treated with no (neo)adjuvant treatment, preoperative radiotherapy (RT), and postoperative RT.

Period	No (neo)adjuvant treatment % (95% CI)	Preoperative RT % (95% CI)	Postoperative RT % (95% CI)
Pre-trial	57.9 (54.2-61.6)	n.a.*	52.6 (47.7-57.5)
Trial	65.0 (61.1-68.9)	62.3 (57.0-67.6)	54.3 (45.3-63.3)
Post-trial	59.5 (66.8-52.2)	70.5 (65.6-75.4)	49.8 (33.3-66.3)

n.a. = not available. *Results for preoperative RT in the pre-trial period not shown ($n = 1$).

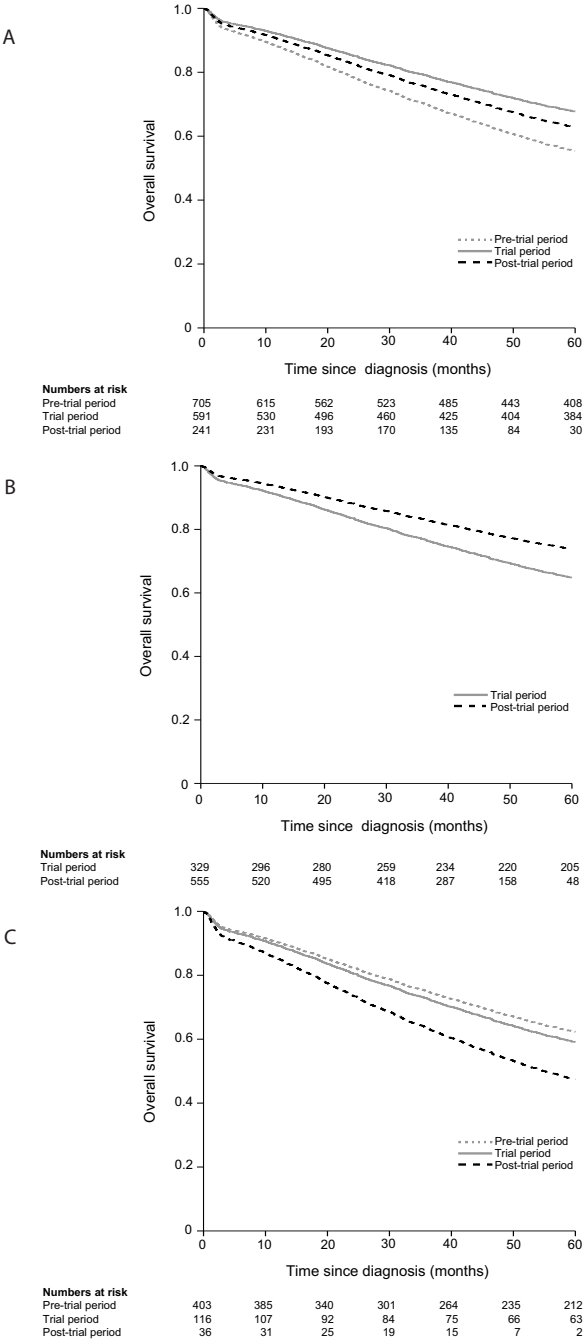


Figure 2. Cox regression curves for overall survival (OS) shown separately for patients treated without (neo)adjuvant treatment (A), with preoperative radiotherapy (RT) (B) and with postoperative RT (C) in the pre-trial, trial and post-trial period. The curves are adjusted for gender, age, pT-stage, and lymph node status. The results for preoperative RT in the pre-trial period is not shown ($n = 1$).

Table 5. (Neo)adjuvant treatments shown separately for patients aged < 75 years, 75-79 years and ≥ 80 years.

Period	(Neo)adjuvant treatment	Age < 75 years *n* (%)	Age 75-79 years *n* (%)	Age ≥ 80 years *n* (%)
Pre-trial	No (neo)adjuvant treatment	465 (56.0)	192 (65.8)	138 (84.1)
	Preoperative RT	1 (0.1)	0 (0.0)	0 (0.0)
	Postoperative RT	326 (39.2)	51 (32.9)	26 (15.9)
	Other (neo)adjuvant treatment	39 (4.7)	2 (1.6)	0 (0.0)
Trial	No (neo)adjuvant treatment	403 (49.3)	95 (66.4)	93 (75.0)
	Preoperative RT	269 (32.9)	37 (25.9)	23 (18.5)
	Postoperative RT	97 (11.9)	11 (7.7)	8 (6.5)
	Other (neo)adjuvant treatment	48 (5.9)	0 (0.0)	0 (0.0)
Post-trial	No (neo)adjuvant treatment	133 (19.2)	53 (37.9)	55 (49.5)
	Preoperative RT	431 (62.1)	72 (51.4)	52 (46.8)
	Postoperative RT	26 (3.7)	6 (4.3)	4 (3.6)
	Other (neo)adjuvant treatment	104 (15.0)	9 (6.4)	0 (0.0)

RT = radiotherapy.

RT followed by TME surgery and TME surgery alone (no (neo)adjuvant treatment), both treatments were comparable, whereas patients treated with postoperative RT did worse. In the post-trial period, preoperative RT was standard treatment, although the treating physician of surgeon could adapt the treatment for each patient. In this period, patients treated with preoperative RT had the best outcome and patients treated with postoperative RT the worst outcome. Moreover, the influence of the introduction of TME surgery can be seen by the improvement of OS in the TME period, which is stable in the post-trial period. Patients treated with preoperative RT did better in the post-trial period compared with the trial period. Patients treated with postoperative RT did worse in both the trial period and post-trial period compared with the pre-trial period. Overall, the lowest survival rate is found for patients in the post-trial period treated with postoperative RT and the highest survival rate is found for patients treated in the same period with preoperative RT.

The relationship between age and (neo)adjuvant treatment per period is shown in Table 5. In general, less (neo)adjuvant treatment is given to patients aged ≥ 80 years. However, over time in all age groups more preoperative RT was given: 47% of patients aged ≥ 80 years and 62% of patients aged <75 years in the post-trial period.

DISCUSSION

Between 1996 and 1999, the TME trial was conducted in the Netherlands, resulting in a nationwide standardised and quality-controlled introduction of TME surgery.[12] Incidentally, preoperative short course RT was already in use in some parts of the Netherlands. In the TME trial, the effects of the addition of preoperative 5 x 5 Gy RT in combination with standardised TME surgery were studied. This cohort study demonstrates that pop-

ulation-based OS of patients with rectal cancer improved over time. An earlier study of Comprehensive Cancer Centre South showed that, compared to the period 1980-1989, OS in this region had already improved in the period 1990-1994, and continued to improve during the study period of the TME trial.[13] Interestingly, the present cohort study shows that the OS improved in the period 1996-1999 and 2000-2002 compared with the period 1990-1995, suggesting that the introduction of TME surgery has improved survival further. Moreover, after adjusting for gender, age, pT-stage, nodal status, and (neo) adjuvant treatment, OS in the post-trial period mainly increased for patients treated with preoperative RT. In other words: with good quality TME surgery survival improves and with good surgery preoperative RT does matter for outcome. In the remaining discussion, we will use the adjusted OS when mentioning OS, unless indicated differently.

Several studies found that preoperative RT resulted in better local control compared with postoperative RT.[14,15] Besides, compliance to postoperative treatment was only about 50% which was often related to surgical complications.[14-16] In a meta-analysis, it was concluded that preoperative RT could be safely used and resulted in a better local control compared to postoperative treatment (37% less local recurrences, $P = 0.002$).[17] In addition, the authors of the meta-analysis found that fewer patients who had preoperative RT died from rectal cancer than did those who had surgery alone (45% versus 50%, respectively, $P = 0.0003$). In the Dutch TME trial, it was found that local recurrence rates could be further reduced with the addition of preoperative RT to TME surgery, whereas OS remained the same.[6,12] These findings resulted in the adjustment of the national treatment guidelines for rectal cancer in the Netherlands: the National Committee on Gastrointestinal Cancer decided to implement 5 x 5 Gy preoperative RT in combination with TME surgery as standard practice in the treatment of resectable T2-4 rectal carcinoma in 2001. The present analysis also showed that patients who were treated with preoperative RT had a better outcome than patients treated with postoperative treatment.

The effect of RT on survival changed over time. In the trial period, 39% of patients were treated within the trial and randomly assigned to preoperative RT followed by TME surgery or TME surgery alone. Similar to the findings in the TME trial,[6,12] treatment with preoperative RT did not significantly improve OS in this period ($P = 0.315$). In contrast, in the post-trial period, preoperative RT was significantly related to OS ($P = 0.002$). In this period, preoperative RT was the standard, although for some patients preoperative RT was omitted according to the judgement of the treating physician or surgeon. For example, preoperative RT was more frequently used in younger patients than in older patients. However, the multivariate analysis showed that after adjustment for age, gender, pT-stage, and lymph node status, preoperative RT was associated with an increased survival in the post-trial period. According to the results, preoperative RT was withheld in 32% (305/945) of patients in the post-trial period, resulting in a poorer prognosis in

this subset of patients. Unfortunately, no information on comorbidity was available in this study. Also for patients treated without preoperative RT but with postoperative RT survival was less, although for these patients selection of tumour related parameters could have played a role. It should be noted that postoperative radiotherapy has been used differently over time: in the trial and post-trial periods it was mainly indicated for patients with a positive circumferential resection margin (CRM), whereas in the pre-trial period it was used for more patients such as patients with pT3 disease or positive lymph nodes. Due to these differences in selection, comparisons between the periods should be done with caution. Nevertheless, the question arises whether patients treated without preoperative RT did receive the most optimal treatment. We think that the aim should be to treat all patients with preoperative RT, although for the elderly patients the effect of preoperative treatment on survival is less clear than for younger patients.[18,19]

Circumferential resection margin (CRM) involvement has been found to be associated with an increased risk of local recurrence and decreased OS in several trials.[20-22] However, not only involvement of the CRM, commonly defined as tumour within 1 mm of the CRM, but even tumour within 1 cm of the CRM is associated with increased local recurrence rates and decreased survival.[22] Therefore, it is necessary to preoperatively identify patients with a tumour that is located in proximity to the mesorectal fascia, the surgical border of the TME resection. The MERCURY study group reported recently that magnetic resonance imaging (MRI) is accurate in predicting whether the CRM will be clear or affected by tumour.[23] Burton et al. showed that if only a MRI-scan is performed but not discussed in a multidisciplinary team meeting, poor prognostic factors were missed in 50% of patients.[24] Therefore, preoperative MRI-based multidisciplinary team meetings are necessary to select patients in whom the treatment plan should be adapted to a more extended resection and/or to a long schedule of (chemo)radiotherapy to downstage or downsize the tumour to perform a curative resection with an uninvolved CRM.[25,26]

In conclusion, population-based OS of patients with curatively resected rectal cancer improved since the nationwide introduction of TME surgery. The training of surgeons in this new technique was done successfully, with lasting effects. Furthermore, after TME surgery, preoperative RT resulted in an increased survival rate, whereas withholding of preoperative RT was associated with a poorer prognosis. In the latest Dutch national guideline, a preoperative MRI scan is recommended as standard preoperative work-up for all patients with a >T1 tumour. Besides, all patients should be discussed preoperatively in a multidisciplary team meeting. Preoperative short-course RT is advised for all patients with a >T1 curable rectal tumour. If all future patients will be treated according to these recommendations, it is likely that further improvements in OS are within reach.

REFERENCES

1. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997; 336: 980-987.
2. Enker WE. Total mesorectal excision - the new golden standard of surgery for rectal cancer. *Ann Med* 1997; 29: 127-133.
3. Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg* 1995; 181: 335-346.
4. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; 327: 1479-1482.
5. Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, van Houwelingen HC, et al. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. *Eur J Surg Oncol* 1999; 25: 368-374.
6. Peeters KC, Marijnen CAM, Nagtegaal ID, Klein Kranenbarg E, Putter H, Wiggers T, et al. 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. *Ann Surg* 2007; 246: 693-701.
7. Kapiteijn E, Klein Kranenbarg E, Steup WH, Taat CW, Rutten HJ, Wiggers T, 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.
8. Klein Kranenbarg E, van de Velde CJH. Surgical trials in oncology. the importance of quality control in the TME trial. *Eur J Cancer* 2002; 38: 937-942.
9. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, the Netherlands. *Int J Epidemiol* 1993; 22: 369-376.
10. Hermanek P, Sobin LH. TNM classification of malignant tumours (4th edition). Berlin: Springer-Verlag, 1987.
11. Sobin LH, Wittekind Ch. TNM classification of malignant tumours (5th edition). New York: John Wiley & Sons, Inc., 1997.
12. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001; 345: 638-646.
13. Martijn H, Voogd AC, van de Poll-Franse LV, Repelaer van Driel OJ, Rutten HJ, Coebergh JW. Improved survival of patients with rectal cancer since 1980: a population-based study. *Eur J Cancer* 2003; 39: 2073-2079.
14. Påhlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. *Ann Surg* 1990; 211: 187-195.
15. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351: 1731-1740.
16. Kapiteijn E, Marijnen CA, Colenbrander AC, Klein Kranenbarg E, Steup WH, van Krieken JH, et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. *Eur J Surg Oncol* 1998; 24: 528-535.
17. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001; 358: 1291-1304.

18. Rutten H, den Dulk M, Lemmens V, Nieuwenhuijzen G, Krijnen P, Jansen-Landheer M, et al. Survival of elderly rectal cancer patients not improved: analysis of population based data on the impact of TME surgery. *Eur J Cancer* 2007; 43: 2295-2300.
19. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. *Eur J Cancer* 2006; 42: 3015-3021.
20. Baik SH, Kim NK, Lee YC, Kim H, Lee KY, Sohn SK, et al. Prognostic significance of circumferential resection margin following total mesorectal excision and adjuvant chemoradiotherapy in patients with rectal cancer. *Ann Surg Oncol* 2007; 14: 462-469.
21. den Dulk M, Collette L, van de Velde CJ, Marijnen CA, Calais G, Mineur L, et al. Quality of surgery in T3-4 rectal cancer: involvement of circumferential resection margin not influenced by preoperative treatment. Results from EORTC trial 22921. *Eur J Cancer* 2007; 43: 1821-1828.
22. Nagtegaal ID, Marijnen CA, Klein Kranenbarg E, van de Velde CJH, van Krieken JH. 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.
23. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006; 333: 779.
24. Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? *Br J Cancer* 2006; 94: 351-357.
25. Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results - EORTC 22921. *J Clin Oncol* 2005; 23: 5620-5627.
26. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, 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.