Improved overall survival for patients with rectal cancer since 1990: The effects of TME surgery and pre-operative radiotherapy

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ARTICLE INFO

ABSTRACT

Aim: The aim was to study the effects of the introduction of TME surgery and pre-operative 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). Pre-operative 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, pre-operative RT improved OS, whereas withholding pre-operative RT was associated with a poorer prognosis. The present study supports that pre-operative RT was correctly introduced as a standard treatment before TME surgery in our national guideline.

1. Introduction

Since the early nineties, there have been changes in rectal cancer treatment towards better surgery and/or pre-operative 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) im-

proved 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 pre-operative 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 pre-operative RT, and a 5-year OS rate of 64% in both the 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 pre-operative RT in the region of Comprehensive Cancer Centres South and West in The Netherlands.

2. Patients and methods

2.1. 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 the 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 year, 60–74 years and ⩾75 years. Data on tumour stage and data on pre-operative and post-operative treatments were obtained from the Cancer Registries. Pre-operative RT consisted of both the short, 5×5 Gy, schedule and the long schedule, such as 25×2 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.

2.2. 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.

3. Results

3.1. 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 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 post-operative RT, whereas more patients were pre-operatively treated with RT ($p < 0.001$). In the trial and post-trial periods, more patients were diagnosed with N+ disease compared with the pre-trial period.

3.2. Overall survival

Five-year OS in the pre-trial period was 56% (95% 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 ($p = 0.31$).

Table 1 – Patient characteristics by period of diagnosis

	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 (neo) adjuvant treatment	705 (61)	591 (55)	241 (26)	1537 (48)	
Pre-operative RT	1 (0)	329 (30)	555 (59)	885 (28)	
Pre-operative RCT	0 (0)	17 (2)	50 (5)	67 (2)	
Pre-operative RT and post-operative CT	0 (0)	9 (1)	35 (4)	44 (1)	
Post-operative RT	403 (35)	116 (11)	36 (4)	555 (17)	
Post-operative RCT	27 (2)	5 (0)	5 (1)	37 (1)	
Post-operative 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 (2000–2003). Percentages may not add up to 100% due to rounding. RT, radiotherapy; RCT, radiochemotherapy; CT, chemotherapy; CCC, Comprehensive Cancer Centre.

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 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 Fig. 1.

3.3.   The effects of period and treatment on overall survival

In the pre-trial period only one patient is treated with pre-operative 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 Fig. 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 (Fig. 2A), with pre-operative RT (Fig. 2B) and with post-operative RT (Fig. 2C). In the pre-trial period, OS was better for patients treated with post-operative 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 pre-operative RT followed by TME surgery and TME surgery alone (no (neo)adjuvant treatment), both treatments were comparable, whereas patients treated with post-operative RT did worse. In the post-trial period, pre-operative RT was standard treatment, although the treating physician or surgeon could adapt the treatment for each patient. In this period, patients treated with pre-operative RT had the best outcome and patients treated with post-operative 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 pre-operative RT did better in the post-trial period compared with the trial period. Patients treated with post-operative RT did worse in both the trial period and the 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 post-operative RT and the highest survival rate is found for patients treated in the same period with pre-operative 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.

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		
Pre-operative RT	0.77	0.67–0.89	<0.001
Pre-operative RCT	1.35	0.93–1.96	0.111
Pre-operative RT and post-operative CT	0.86	0.51–1.47	0.586
Post-operative RT	1.27	1.12–1.43	<0.001
Post-operative RCT	0.84	0.52–1.36	0.478
Post-operative 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; RCT, radiochemotherapy; CT, chemotherapy; CCC, Comprehensive Cancer Centre.

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		
Post-operative RT	0.80	0.68–0.94	0.005
Post-operative RCT	0.58	0.33–1.04	0.069
Post-operative CT	0.99	0.51–1.92	0.972
(Neo)adjuvant treatment, trial period			0.040
No (neo)adjuvant treatment	1.00		
Pre-operative RT	1.11	0.90–1.36	0.315
Pre-operative RCT	2.38	1.24–4.44	0.007
Pre-operative RT and post-operative CT	0.60	0.19–1.84	0.376
Post-operative RT	1.35	1.02–1.75	0.032
Post-operative RCT	1.99	0.75–5.46	0.174
Post-operative CT	1.14	0.62–2.10	0.683
(Neo)adjuvant treatment, post-trial period			0.001
No (neo)adjuvant treatment	1.00		
Pre-operative RT	0.64	0.49–0.86	0.002
Pre-operative RCT	1.30	0.80–2.17	0.282
Pre-operative RT and post-operative CT	0.84	0.45–1.58	0.590
Post-operative RT	1.59	0.97–2.68	0.066
Post-operative RCT	0.41	0.06–2.95	0.375
Post-operative CT	0.82	0.41–1.63	0.562

RT, radiotherapy; RCT, radiochemotherapy; CT, chemotherapy.
[*] Results for preoperative RT in the pre-trial period not shown (n = 1).

However, over time in all age groups more pre-operative RT was given: 47% of patients aged ⩾80 years and 62% of patients aged <75 years in the post-trial period.

4. 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, pre-operative short course RT was already in use in some parts of The Netherlands. In the TME trial, the effects of the addition of pre-operative 5×5 Gy RT in combination with standardised TME surgery were studied. This cohort study demonstrates that population-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

the 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 pre-operative RT. In other words: with good quality – TME-surgery survival improves and with good surgery pre-operative RT does matter for outcome. In the remaining discussion, we will use the adjusted OS when mentioning OS, unless indicated differently.
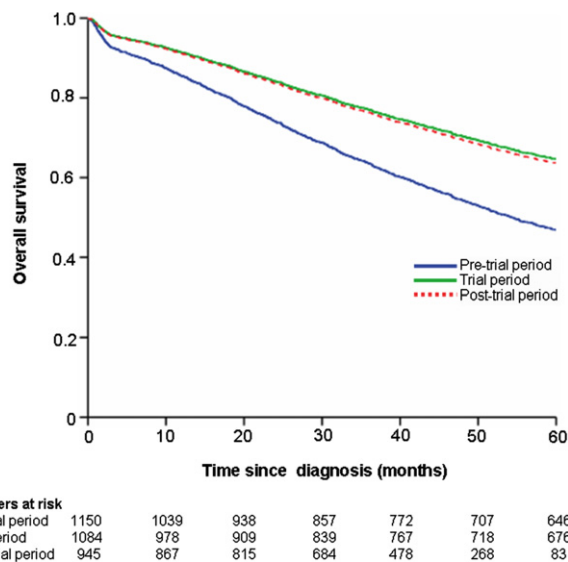
Fig. 1 – Cox regression curves for overall survival (OS) for resectable rectal cancer by period adjusted for gender, age, pT-stage, lymph node status, (neo)adjuvant treatment and the interaction between treatment and period.

Table 4 – Unadjusted five-year overall survival rate (%) per period for patients treated with no (neo)adjuvant treatment, pre-operative RT and post-operative RT			
Period	No (neo) adjuvant treatment (95% CI)	Pre-operative RT (95% CI)	Post-operative 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)
RT, radiotherapy; n.a., not available. [*]Results for preoperative RT in the pre-trial period not shown (n = 1).			

Several studies found that pre-operative RT resulted in a better local control compared with post-operative RT.[14,15] Besides, compliance to post-operative treatment was only about 50% which was often related to surgical complications.[14–16] In a meta-analysis, it was concluded that pre-operative RT could be safely used and resulted in a better local control compared to post-operative treatment (37% less local recurrences, $p = 0.002$).[17] In addition, the authors of the meta-analysis found that fewer patients who had pre-operative 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 pre-operative 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 5×5 Gy pre-operative 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 pre-operative RT had a better outcome than patients treated with post-operative 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 pre-operative RT followed by TME surgery or TME surgery alone. Similar to the findings in the TME trial,[6,12] treatment with pre-operative RT did not significantly improve OS in this period ($p = 0.315$). In contrast, in the post-trial period, pre-operative RT was significantly related to OS ($p = 0.002$). In this period, pre-operative RT was the standard, although for some patients pre-operative RT was omitted according to the judgement of the treating physician of surgeon. For example, pre-operative 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, pre-operative RT was associated with an increased survival in the post-trial period. According to the results, pre-operative 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 pre-operative RT but with post-operative RT survival was less, although for these patients selection of tumour related parameters could have played a role. It should be noted that post-operative 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 pre-operative RT did receive the most optimal treatment. We think that the aim should be to treat all patients with pre-operative RT, although for the elderly the effect of pre-operative 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 pre-operatively 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, pre-operative 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
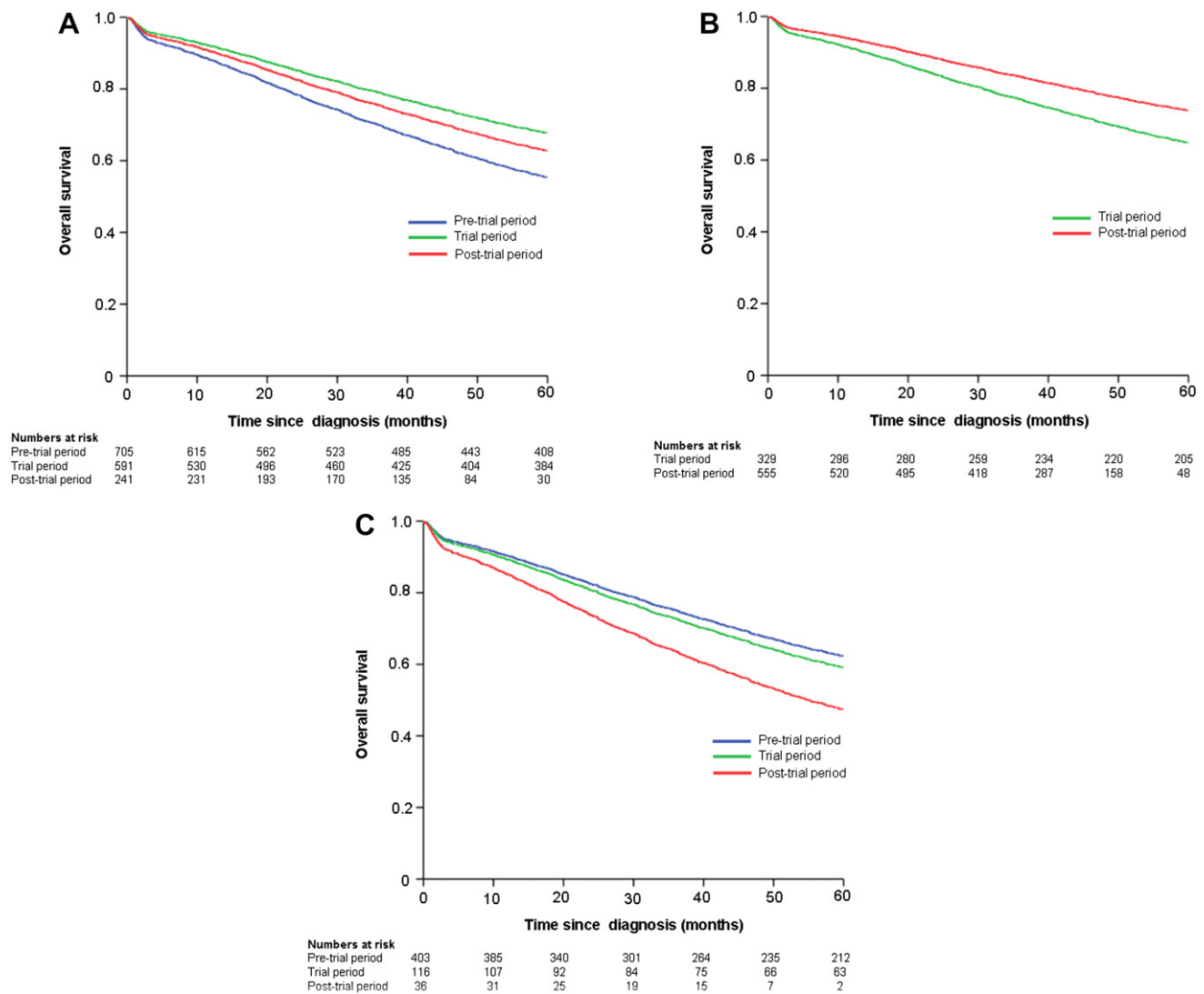
Fig. 2 – Cox regression curves for overall survival (OS) shown separately for patients treated without (neo)adjuvant treatment (A), with pre-operative radiotherapy (RT) (B) and with post-operative RT (C) in the pre-trial, trial and post-trial periods. The curves are adjusted for gender, age, pT-stage and lymph node status. The results for pre-operative RT in the pre-trial period are 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)
	Pre-operative RT	1 (0.1)	0 (0.0)	0 (0.0)
	Post-operative 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)
	Pre-operative RT	269 (32.9)	37 (25.9)	23 (18.5)
	Post-operative 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)
	Pre-operative RT	431 (62.1)	72 (51.4)	52 (46.8)
	Post-operative 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.				

new technique was done successfully, with lasting effects. Furthermore, after TME surgery, pre-operative RT resulted in an increased survival rate, whereas withholding of pre-operative RT was associated with a poorer prognosis. In the latest Dutch national guideline, a pre-operative MRI scan is recommended as a standard pre-operative work-up for all patients with a >T1 tumour. Besides, all patients should be discussed pre-operatively in a multidisciplinary team meeting. Pre-operative 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.

Conflict of interest statement

The authors declare to have no conflict of interest.

Financial interests

None.

Acknowledgements

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