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Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989–2006

M.A.G. Elferink [a,*], L.N. van Steenbergen [b], P. Krijnen [c], V.E.P.P. Lemmens [b,d], H.J. Rutten [e], C.A.M. Marijnen [f], I.D. Nagtegaal [g], H.E. Karim-Kos [d], E. de Vries [d], S. Siesling [a,h], On behalf of the Working Group Output of the Netherlands Cancer Registry

[a] Department of Research, Comprehensive Cancer Centre North East, Enschede/Groningen, The Netherlands
[b] Department of Research, Comprehensive Cancer Centre South, P.O. Box 231, 5600 AE Eindhoven, The Netherlands
[c] Comprehensive Cancer Centre West, Schipholweg 5A, 2316 XB Leiden, The Netherlands
[d] Department of Public Health, Erasmus MC University Medical Centre, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands
[e] Department of Surgery, Catharina Hospital, P.O. Box 1350, 5602 ZA Eindhoven, The Netherlands
[f] Department of Clinical Oncology, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands
[g] Department of Pathology, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
[h] Department of Health Technology and Services Research, Twente University, Enschede, The Netherlands

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ABSTRACT

Background: Since the 1990s, treatment of patients with rectal cancer has changed in the Netherlands. Aim of this study was to describe these changes in treatment over time and to evaluate their effects on survival.

Methods: All patients in the Netherlands Cancer Registry with invasive primary rectal cancer diagnosed during the period 1989–2006 were selected. The Cochran–Armitage trend test was used to analyse trends in treatment over time. Multivariate relative survival analyses were performed to estimate relative excess risk (RER) of dying.

Results: In total, 40,888 patients were diagnosed with rectal cancer during the period 1989–2006. The proportion of patients with stages II and III disease receiving preoperative radiotherapy increased from 1% in the period 1989–1992 to 68% in the period 2004–2006 for younger patients (<75 years) and from 1% to 51% for older patients (⩾75 years), whereas the use of postoperative radiotherapy decreased. Administration of chemotherapy to patients with stage IV disease increased over time from 21% to 66% for patients younger than 75 years. Both males and females exhibited an increase in five-year relative survival from 53% to 60%. The highest increase in survival was found for patients with stage III disease. In the multivariate analyses survival improved over time for patients with stages II–IV disease. After adjustment for treatment variables, this improvement remained significant for patients with stages III and IV disease.

Conclusions: The changes in therapy for rectal cancer have led to a markedly increased survival. Patients with stage III disease experienced the greatest improvement in survival.

* *Corresponding author:* Address: Comprehensive Cancer Centre North East, P.O. Box 330, 9700 AH Groningen, The Netherlands. Tel.: +31 0 88 2345500; fax: +31 0 88 2345599.
E-mail address: m.elferink@ikno.nl (M.A.G. Elferink).

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1. Background

Each year, over 3000 new cases of rectal cancer are diagnosed in the Netherlands, with age-standardised incidence rates (European Standard Population, ESR) increasing between 1989 and 2006 from 12.0 to 15.5 per 100,000 person-years. Incidence rates were higher for males than for females (ESR 19.6 versus 11.3 per 100,000 person-years in 2006).[1]

Previous regional Dutch studies have shown improved survival of patients with rectal cancer since 1980.[2,3] Especially since the mid 1990s, this improvement in survival was accompanied by changes in treatment for rectal cancer: a shift from postoperative to preoperative radiotherapy, and introduction of the total mesorectal excision (TME) technique, which replaced conventional blunt dissection of the rectum. The TME technique involves radical resection achieved by sharp dissection under direct vision of the rectum with its mesorectum and the visceral pelvic fascia. The introduction of TME resulted in a decreased local recurrence rate.[4] The Dutch Colorectal Cancer Group (DCCG) investigated the effects of preoperative radiotherapy in combination with standardised TME. This and several other studies showed the survival benefits of preoperative radiotherapy,[5–7] which led to revision of the Dutch national guidelines for the treatment of rectal cancer in 2001.[8] Preoperative radiotherapy became standard practice for all patients with clinical stage T2–T4 tumours.

Since 2004, several studies have reported improved local control with preoperative chemoradiotherapy for clinical stage T3–T4 tumours compared to preoperative radiotherapy and postoperative chemoradiotherapy, but no impact on overall survival was found.[9,10] Based on these results, preoperative chemoradiotherapy became the standard treatment for locally advanced rectal cancer.[8]

The aim of this population-based study is to describe changes in the treatment of patients with rectal cancer during the period 1989–2006 in the Netherlands and the influence of these changes on survival.

2. Methods

2.1. Data collection

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which was started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres, were used. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnoses, haematology departments and radiotherapy institutions.[1] Information on patient characteristics, such as gender and date of birth, as well as tumour characteristics, such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3),[11] histology, stage (TNM classification)[12] and grade, and primary treatment, are collected routinely from the medical records about nine months after diagnosis. The quality of the data is high, due to thorough training of the registrars and computerised consistency checks at regional and national levels. Completeness is estimated to be at least 95%.[13] Vital status of all patients was obtained actively on a regular basis from the integrated database of the municipal registry and the database of deceased persons of the Central Bureau for Genealogy. For the current analyses, the criteria of the International Association of Cancer Registries (IACR) for multiple primaries were applied.[11]

For the present study, all cases of invasive primary rectal cancer (C20.9) diagnosed during the period 1989–2006 in the Netherlands were included. Patients were divided into younger patients (<75 years) and elderly patients ($\geqslant$75 years) for the analyses of treatment. For the survival analyses we used four age groups ($\leqslant$44, 45–59, 60–74 and $\geqslant$75 years).

The study period was divided into four categories: 1989–1993, 1994–1998, 1999–2003 and 2004–2006. Stage was based on the pathological TNM classification, except when the pathological stage was unknown, in which case the clinical TNM was used. For the period 1989–1994, survival data were only available from four regional cancer registries, which were considered representative of the Netherlands as a whole.

2.2. Statistical analyses

Treatment was given as percentages per age group and period. Differences in treatment over time and between the age groups were tested by the Cochran–Armitage trend test.

Follow-up was calculated as the time from diagnosis to death or January 1, 2008. Relative survival was used as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival of the general population with the same age and gender distributions. Relative survival is calculated as the ratio of the observed rates for cancer patients to the expected rates for the general population using the Ederer method.[14] Patients younger than 15 years and older than 95 years at diagnosis were excluded from analysis, as well as cases diagnosed at autopsy. Patients were censored at the age of 100 years old, since follow-up of the very old might be incomplete. For the period 1989–2003 cohort analysis was used. Since follow-up data were only available until January 2008, 5-year follow-up was not feasible for the period 2004–2006, and period analysis was conducted for this period. Overall, 99% of cancers included in the analysis were microscopically verified. The proportion of patients lost to follow-up was less than 1%.

Multivariate relative survival analyses, using Poisson regression modelling, were performed to estimate relative excess risks (RER) of dying for the periods of diagnosis adjusted for follow-up interval and stratified according to stage. Treatment variables were added to investigate the effect of therapy on the RER of dying according to periods of diagnosis. Patients without surgical treatment and patients who received both pre- and postoperative radiotherapy were excluded from the multivariate analyses of patients with stages II and III disease. All analyses were performed using SAS (SAS system 9.2, SAS Institute, Cary, NC).

3. Results

During the period 1989–2006, 40,888 patients were diagnosed with rectal cancer. The proportion of patients aged 45–59 years

Table 1 – Characteristics of patients diagnosed with rectal cancer in the Netherlands in the period 1989–2006 (N = 40,888).

	1989–1993		1994–1998		1999–2003		2004–2006	
	N	%	N	%	N	%	N	%
Gender								
Male	5,185	56	5,979	57	7,248	58	5,123	58
Female	4,010	44	4,509	43	5,174	42	3,660	42
Age at diagnosis								
⩽44 years	377	4	418	4	440	4	303	3
45–59 years	1,676	18	2,070	20	2,795	23	2,031	23
60–74 years	4,027	44	4,524	43	5,348	43	3,788	43
⩾75 years	3,115	34	3,476	33	3,839	31	2,661	30
Stage								
I	2,526	28	2,876	27	3,408	27	2,348	27
II	2,272	25	2,375	23	2,869	23	1,945	22
III	2,020	22	2,361	23	2,987	24	2,145	24
IV	1,257	14	1,535	15	2,038	16	1,574	18
Unknown	1,120	12	1,341	13	1,120	9	771	9
Total	9,195		10,488		12,422		8,783	

increased over time, while the proportion of patients aged 75+ years decreased. During this period, the proportion of patients with stage II disease decreased, whereas the proportion of patients with stages III and IV disease increased (Table 1). The age-standardised incidence rate (ESR) increased over time, whereas the age-standardised mortality rate decreased (Fig. 1).

3.1. *Treatment*

3.1.1. *Surgery*

The proportion of patients with stage I rectal cancer who underwent a polypectomy or TEM (Transanal Endoscopic Microsurgery) increased over time with a steeper increase for the elderly patients (⩾75 years). The resection rate among younger patients (<75 years) with stages I–III disease remained stable during the study period, but decreased in the elderly from 91% during the period 1989–1993 to 81% during the period 2004–2006. Among patients with stage IV disease, the resection rate for the primary tumour decreased over time, mainly among the elderly patients. Younger patients underwent a metastasectomy more frequently over time (Table 2).

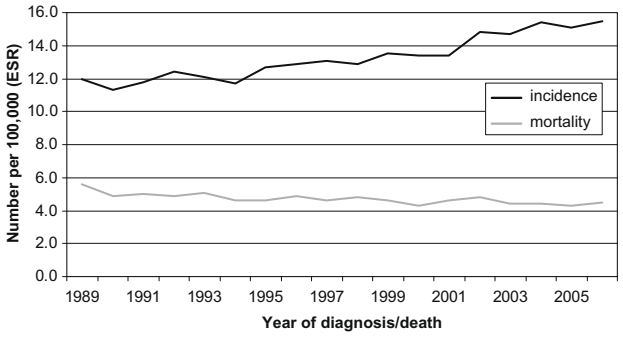

Fig. 1 – Age-standardised incidence and mortality rates (European Standardised Rate, ESR) of rectal cancer in the Netherlands, 1989–2006.

3.1.2. *Radiotherapy*

The proportion of patients with stages II and III disease receiving preoperative radiotherapy increased sharply from 1% in the period 1989–1993 to 68% in the period 2004–2006 among the younger patients. For elderly patients the proportion increased from 1% to 51%. Postoperative radiotherapy decreased substantially among patients with stages II and III disease, from 46% in 1989–1993 to 4% in 2004–2006 for younger patients and from 23% to 3% for elderly patients.

In the period 1994–1998 neoadjuvant radiotherapy combined with chemotherapy was administered to 1% of the younger patients with stages II and III disease, this proportion increased to 9% in the period 2004–2006. Elderly patients with stages II and III disease received neoadjuvant radiotherapy combined with chemotherapy (3%) less often in 2004–2006 (Table 2).

3.1.3. *Chemotherapy*

The proportion of patients with stage III disease who received adjuvant chemotherapy increased sharply, particularly among younger patients. The use of chemotherapy for patients with stage IV disease increased over time from 21% in the period 1989–1993 to 66% in the period 2004–2006 for younger patients and from 2% to 25% for elderly patients (Table 2).

3.2. *Survival*

Five-year relative survival for patients with rectal cancer increased for both sexes between the periods 1989–1993 and 2004–2006, from 53% to 60% for males and from 53% to 59% for females (Table 3).

The 5-year survival of patients with stage I rectal cancer was stable over time at around 90% for both sexes. For both males and females with stage II disease, there was a large improvement in 5-year survival, from 63% in 1989–1993 to

Table 2 – Treatment of patients with rectal cancer according to period of diagnosis and age at diagnosis.

Treatment	Age at diagnosis	1989–1993		1994–1998		1999–2003		2004–2006		P[a]
		N	%	N	%	N	%	N	%	
Surgery										
Polypectomy or TEM, stage I										
	<75 years	65	4	257	13	349	14	279	17	<0.001
	⩾75 years	47	6	134	15	170	18	160	23	<0.001
Resection, stages I–III										
	<75 years	4,433	94	4,851	93	6,034	92	4,207	93	<0.001
	⩾75 years	1,934	91	2,076	87	2,278	85	1,525	81	<0.001
Resection[b], stage IV										
	<75 years	473	54	606	56	748	49	507	44	<0.001
	⩾75 years	162	43	181	41	187	36	122	28	<0.001
Metastasectomy, stage IV										
	<75 years	8	1	45	4	69	5	85	7	<0.001
	⩾75 years	2	1	9	2	8	2	8	2	0.22
Radiotherapy										
Preoperative RT, stages II–III										
	<75 years	37	1	523	16	2,183	53	1,958	68	<0.001
	⩾75 years	9	1	145	10	683	40	615	51	<0.001
Postoperative RT, stages II–III										
	<75 years	1,376	46	976	30	375	9	114	4	<0.001
	⩾75 years	310	23	247	17	91	5	36	3	<0.001
Neoadjuvant RT and CT, stages II–III										
	<75 years	0	0	28	1	165	4	268	9	<0.001
	⩾75 years	0	0	0	0	14	1	40	3	[c]
Chemotherapy										
Adjuvant CT, stage III										
	<75 years	131	9	374	22	577	26	462	29	<0.001
	⩾75 years	3	1	14	2	20	3	27	5	<0.001
Chemotherapy, stage IV										
	<75 years	181	21	348	32	779	51	753	66	<0.001
	⩾75 years	7	2	8	2	44	8	108	25	<0.001

[a] Cochrane–Armitage trend test.
[b] Excluding metastasectomy.
[c] Not analysed.

72% in 2004–2006 for males and from 59% to 71% for females. The increase in survival was highest for stage III disease. Five-year relative survival for stage III disease for males increased from 44% in 1989–1993 to 56% in 2004–2006, and from 38% to 54% for females. For male patients with stage IV disease, a sharp increase in 1-year survival was seen, from 29% in 1989–1993 to 55% in the period 2004–2006. A similar improvement was found for female patients, from 31% to 48%. Similarly, for both males and females, 5-year survival according to depth of invasion (pT) increased, especially for patients with pT2 and pT3 tumours. Five-year relative survival for pT2 tumours in males improved from 79% in 1989–1993 to 85% in 2004–2006, and from 78% to 86% for females. For male patients with a pT3 tumour, 5-year relative survival increased from 51% in 1989–1993 to 57% in 2004–2006. For female patients with a pT3 tumour, 5-year relative survival increased from 47% to 57%. The increase in survival of male patients was the largest in the age group 45–59 years. Five-year relative survival improved from 57% to 67%. For female patients the increase was the largest for patients younger than 44 years, from 55% in 1989–1993 to 64% in 2004–2006.

3.2.1. *Multivariate relative excess risk of dying*

In all multivariate relative survival models for all stages survival decreased with increasing age. The multivariate model for patients with rectal cancer stage I without treatment included in the model, revealed no differences in survival over time. Adding treatment (resection or no resection) to the model had no effect on survival according to period of diagnosis (Table 4). Survival among patients with stage II disease improved over time. This significant increase disappeared after introducing radiotherapy to the model, indicating that the survival probabilities improved due to changes in radiotherapy. Compared to patients who did not receive radiotherapy, patients receiving preoperative or postoperative radiotherapy exhibited a better survival rate (RER 0.51, 95% CI 0.44–0.59 and RER 0.75, 95% CI 0.64–0.89, respectively) (Table 5). In the multivariate model for patients with stage III disease without treatment, survival also improved over time. This remained significant after adding (preoperative and postoperative) radiotherapy and adjuvant chemotherapy to the model. Patients with stage III disease receiving preoperative radiotherapy had a better survival (RER 0.79, 95%

Table 3 – Five-year relative survival according to period of diagnosis, stage and age at diagnosis.

	1989–1993 (SE)	1994–1998 (SE)	1999–2003 (SE)	2004–2006[a] (SE)
Males				
Total	53 (1.3)	54 (0.8)	57 (0.7)	60 (0.9)
Stage				
I	87 (2.5)	88 (1.5)	90 (1.2)	90 (1.5)
II	63 (2.8)	62 (1.8)	67 (1.5)	72 (1.9)
III	44 (2.6)	48 (1.7)	52 (1.4)	56 (1.8)
IV	[b]	4 (0.7)	6 (0.7)	7 (1.1)
Age at diagnosis				
⩽44 years	58 (4.7)	63 (3.6)	60 (3.2)	67 (3.9)
45–59 years	57 (2.5)	58 (1.5)	59 (1.3)	67 (1.6)
60–74 years	53 (1.8)	56 (1.2)	59 (1.0)	62 (1.2)
⩾75 years	50 (3.2)	48 (2.1)	53 (1.9)	55 (2.3)
Females				
Total	53 (1.4)	57 (0.9)	58 (0.8)	59 (1.0)
Stage				
I	88 (2.3)	90 (1.5)	91 (1.3)	91 (1.6)
II	59 (2.9)	65 (2.0)	68 (1.7)	71 (2.2)
III	38 (2.6)	50 (1.9)	53 (1.6)	54 (2.1)
IV	[b]	4 (0.9)	5 (0.9)	7 (1.2)
Age at diagnosis				
⩽44 years	55 (6.1)	70 (3.5)	60 (3.5)	64 (4.4)
45–59 years	58 (2.9)	65 (1.8)	64 (1.5)	66 (1.8)
60–74 years	56 (2.0)	60 (1.4)	60 (1.2)	64 (1.6)
⩾75 years	48 (2.7)	48 (1.8)	50 (1.7)	47 (2.0)

SE = standard error.
[a] The survival rates of this period were based on period analysis.
[b] Not analysed, $N < 10$ cases.

Table 4 – Relative excess risk (RER) of dying for patients with rectal cancer stage I.

	Multivariate model without treatment variables		Multivariate model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989–1993	1.00	Reference	1.00	Reference
1994–1998	0.96	0.71–1.29	0.92	0.68–1.25
1999–2003	0.85	0.63–1.14	0.82	0.61–1.10
2004–2006	0.73	0.51–1.07	0.71	0.49–1.03
Age at diagnosis				
⩽44 years	0.46	0.25–0.85	0.45	0.24–0.83
45–59 years	0.62	0.48–0.82	0.62	0.48–0.81
60–74 years	1.00	Reference	1.00	Reference
⩾75 years	1.76	1.41–2.21	1.75	1.40–2.19
Resection				
No			1.00	Reference
Yes			0.76	0.58–1.00

CI 0.71–0.88), but there was no survival benefit for patients receiving postoperative radiotherapy (RER 0.95, 95% CI 0.86–1.06). A better survival was found for patients receiving adjuvant chemotherapy (RER 0.65, 95% CI 0.58–0.73) (Table 6). Similarly, survival of patients with stage IV disease increased over time. After adding the treatment variables adjuvant chemotherapy, primary resection and metastasectomy to the model, the improvement in survival according to period of diagnosis remained significant for the periods 1999–2003 and 2004–2006 (Table 7).

4. Discussion

This nationwide population-based study focussed on trends in treatment and survival of patients with rectal cancer in the Netherlands during the period 1989–2006. There were

Table 5 – Relative excess risk (RER) of dying for patients with rectal cancer stage II.[a]

	Multivariate model without treatment variables		Multivariate model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989–1993	1.00	Reference	1.00	Reference
1994–1998	0.91	0.78–1.07	0.95	0.80–1.12
1999–2003	0.77	0.66–0.90	0.98	0.82–1.16
2004–2006	0.60	0.49–0.73	0.86	0.69–1.08
Age at diagnosis				
⩽44 years	0.68	0.50–0.94	0.73	0.53–1.01
45–59 years	0.78	0.67–0.90	0.81	0.70–0.94
60–74 years	1.00	Reference	1.00	Reference
⩾75 years	1.64	1.45–1.86	1.58	1.40–1.79
Radiotherapy				
No			1.00	Reference
Preoperative			0.51	0.44–0.59
Postoperative			0.75	0.64–0.89

[a] Patients without surgical treatment and patients with both pre- and postoperative radiotherapy were excluded.

Table 6 – Relative excess risk (RER) of dying for patients with rectal cancer stage III.[a]

	Multivariate model without treatment variables		Multivariate model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989–1993	1.00	Reference	1.00	Reference
1994–1998	0.82	0.73–0.92	0.87	0.77–0.98
1999–2003	0.70	0.62–0.78	0.82	0.72–0.93
2004–2006	0.50	0.43–0.58	0.63	0.53–0.75
Age at diagnosis				
⩽44 years	0.71	0.59–0.86	0.75	0.62–0.91
45–59 years	0.82	0.74–0.90	0.84	0.77–0.93
60–74 years	1.00	Reference	1.00	Reference
⩾75 years	1.41	1.28–1.56	1.31	1.18–1.45
Radiotherapy				
No			1.00	Reference
Preoperative			0.79	0.71–0.88
Postoperative			0.95	0.86–1.06
Adjuvant chemotherapy				
No			1.00	Reference
Yes			0.65	0.58–0.73

[a] Patients without surgical treatment and patients with both pre- and postoperative radiotherapy were excluded.

several changes in treatment, which contributed to an improvement in survival, particularly for patients with stage III rectal cancer.

The incidence of rectal cancer increased in the Netherlands whereas the mortality decreased, pointing to an increase in survival possibly caused by effective treatment.[15] However, there were other changes in the management of patients with rectal cancer that contributed to improved survival as well, such as better pre-operative diagnostic planning, better multidisciplinary decision making and thorough pathological investigation. Both the concentration of rectal cancer treatment within surgical groups leading to a higher surgeon volume and improvements in the treatment of recurrences may have played a role in the improved survival as well. Unfortunately, we do not have data on these factors and could only evaluate the effect of changes in treatment on survival.

The improvement in survival might be attributed partly to a shift from postoperative to preoperative radiotherapy, in combination with improved (TME) surgery. The TME technique has replaced conventional blunt dissection. In 1979 Heald was the first European surgeon who reported low local recurrence rates due to this technique. With conventional blunt dissection local recurrence rates varied between 7% and 50%,[16] whereas Heald found a local recurrence rate of 6% at 5 years with the TME technique.[17] A Swedish study

Table 7 – Relative excess risk (RER) of dying for patients with rectal cancer stage IV.

	Multivariate model without treatment variables		Multivariate model with treatment variables	
	RER	95% CI	RER	95% CI
Period of diagnosis				
1989–1993	1.00	Reference	1.00	Reference
1994–1998	0.80	0.73–0.89	0.93	0.84–1.02
1999–2003	0.71	0.64–0.78	0.84	0.76–0.93
2004–2006	0.60	0.54–0.67	0.76	0.68–0.84
Age at diagnosis				
⩽44 years	0.86	0.75–0.99	0.96	0.83–1.11
45–59 years	0.84	0.78–0.91	0.92	0.86–0.99
60–74 years	1.00	Reference	1.00	Reference
⩾75 years	1.51	1.41–1.62	1.18	1.09–1.26
Chemotherapy				
No			1.00	Reference
Yes			0.62	0.58–0.66
Resection of primary tumour				
No			1.00	Reference
Yes			0.42	0.40–0.45
Metastasectomy				
No			1.00	Reference
Yes			0.38	0.31–0.46

demonstrated similar results.[18] In the Netherlands, TME surgery was introduced within the framework of the TME trial. After this trial, it became standard surgery in the Netherlands. Unfortunately, information about which surgical technique was used (TME or no TME) is not available in the NCR. Therefore, we could only show trends for surgery in general instead of trends for TME surgery.

Thorough examination of the resection specimen by a pathologist is important for adequate staging and adjuvant treatment, but also for feedback to the surgeons about their performance. The results of the TME trial showed the prognostic implication of evaluation of the mesorectum by pathologists. Patients with incomplete resection of the mesorectum developed a recurrence more often. This implies an important role for pathologists in evaluating the TME specimen.[19]

The value of discussing patients preoperatively in multidisciplinary team meetings increased with the development of new treatment strategies. Furthermore, preoperative investigations have become increasingly important for identifying patients with a possibly positive circumferential resection margin (CRM) and selecting these patients for more extensive treatment. A study from the United Kingdom demonstrated a reduced number of patients with a positive circumferential resection margin when the MRI was discussed preoperatively within a multidisciplinary team.[20]

In our results, a change from postoperative to preoperative radiotherapy was found for patients with stages II and III disease in the mid 1990s. After the start of the TME trial in 1996 preoperative radiotherapy was used increasingly in the Netherlands. It increased in both age groups, although more sharply for patients younger than 75 years. The TME trial showed a reduced risk of local recurrence for patients who received preoperative radiotherapy (5×5 Gy) followed by TME surgery within one week after radiotherapy. However, no improvement in overall survival was seen between TME surgery and TME surgery with preoperative radiotherapy.[7] The results of this population-based study showed, however, an increase in overall survival for stage II rectal cancer and a better survival for patients who received preoperative radiotherapy. In addition, our results showed a significantly better survival for patients with stage II disease, but not for patients with stage III disease who received postoperative radiotherapy compared to patients who did not receive radiotherapy. However, a decreasing risk of dying over time was found for stage III disease, also after adding preoperative radiotherapy, suggesting an effect of TME surgery combined with the preoperative radiotherapy. Because information about the surgical technique (TME or no TME) is missing in the NCR, we were not able to discriminate between the effect of preoperative radiotherapy and that of TME surgery. A Swedish trial also demonstrated the benefits of preoperative radiotherapy with a lower local recurrence rate and an improved 5-year overall survival rate after preoperative radiotherapy.[5] The stage distribution of the current study demonstrated a decrease in stage II and an increase in stages III and IV over time, suggesting a role for stage-migration in the improved stage-specific survival as well. However, survival according to pT stage also increased, suggesting a role for other factors, such as better treatment, as well.

Neoadjuvant chemoradiation was introduced in the Netherlands around 2004, although some patients received this therapy already in the mid 1990s. Before 2004, no benefits were demonstrated for the use of preoperative chemoradiation compared to preoperative radiotherapy alone.[21] In the last decade, however, several studies have shown reduction of the local recurrence rate for patients with T3–T4 or N+ tumours using preoperative chemoradiation, but no improvement in overall survival was observed.[9,10] Preoperative

radiotherapy combined with chemotherapy has only recently been introduced, mainly after our study period. However, our study demonstrated an improvement in overall survival of stages II and III disease in the period 2004–2006 which may be partly due to neoadjuvant chemoradiation.

In many countries, adjuvant chemotherapy is standard therapy for rectal cancer patients with positive lymph nodes. In the Dutch guidelines it is not recommended.[8] Currently, the SCRIPT (Simply Capecitabine in Rectal Cancer After Irradiation Plus TME) study is investigating the effect of adjuvant therapy after preoperative radiotherapy and TME.[22] In our population-based study we found a positive effect of adjuvant chemotherapy on survival for patients with stage III disease.

In metastatic rectal cancer, the increased use of chemotherapy and the improvement in surgery could be explanations for the improved survival of these patients. After adjustment for treatment variables, the improvement in survival over time remained, suggesting a role for upstaging. New developments in diagnostic imaging techniques may lead to the detection of small metastases which would otherwise have been unidentified.[23]

In Europe, a slower increase in survival of the elderly was found for almost all cancers, leading to a gap in survival between younger and older patients.[24] Our results showed no survival benefits of the improvements in treatment for patients 75 years and older. Two other retrospective Dutch studies did not find improvements in survival for elderly patients either.[25,26] Comorbidity and treatment-related complications, such as pneumonia and cardiac complications, were possible explanations for the worse prognosis for elderly patients. Furthermore, complications with a comparable occurrence in younger patients as in elderly patients were associated with a higher mortality in elderly patients.[27] However, according to results of the Dutch TME-study elderly patients exhibited a good response to preoperative radiotherapy.[25] Furthermore, the EUROCARE study showed a similar prognosis for elderly patients who survived the first year compared to middle-aged patients.[24] Therefore, individualised treatment plans should be used for elderly patients, whereby patients with a good health status could benefit from the same treatment chosen for younger patients and extensive treatment of elderly patients with a poor health status will be avoided.

An increase in survival of patients with rectal cancer has also been seen in other countries. In two French regions, Normandy and Burgundy, 5-year relative survival increased from 35% in the period 1978–1981 to 57% in the period 1985–1989.[28] Five-year survival for women in England and Wales was 39% in the period 1986–1990 and 51% in the period 1996–1999.[29] According to EUROCARE-4, 5-year relative survival for rectal cancer in the period 1995–1999 was 53% for the whole of Europe. However, these estimates varied across Europe, from 39% to 61%.[30] The Netherlands belonged to the countries with the highest survival rates.

A limitation of this study is that we used the pathological stage instead of the clinical stage to describe trends in treatment. However, treatment plans are based on the clinical stage. Furthermore, after a long interval between preoperative radiotherapy and surgery, downstaging might occur.[31] Our choice of the pathological stage was made because the clinical T-stage was often unknown in the NCR, due to an unclear description of the extent of the invasion in the report of the MRI or the MRI was not performed. In addition, our results show a decrease in stage II and an increase in stage III, pointing to a low frequency of downstaging.

In conclusion, this nationwide population-based study of more than 40,000 patients revealed a marked improvement in survival for patients with rectal cancer, especially for patients with stages II and III disease. A shift from postoperative to preoperative radiotherapy, improved (TME) surgery and, for stage III patients, adjuvant chemotherapy have played an important part in the enhanced survival. Further improvement in survival can be expected in future years due to new therapies, such as neoadjuvant chemoradiation for patients with locally advanced rectal carcinoma.

Conflict of interest statement

None declared.

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