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An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients

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Regarding the continuous changes in the diagnostic process and treatment of colorectal cancer (CRC), it is important to evaluate long-term trends which are relevant in giving direction for further research and innovations in cancer patient care. The aim of this study was to analyze developments in incidence, treatment and survival for patients diagnosed with CRC in the Netherlands. For this population-based retrospective cohort study, all patients diagnosed with CRC between 1989 and 2014 in the Netherlands were identified using data of the nationwide population-based Netherlands Cancer Registry (n = 267,765), with follow-up until January 1, 2016. Analyses were performed for trends in incidence, mortality, stage distribution, treatment and relative survival measured from the time of diagnosis. The incidence of both colon and rectal cancer has risen. The use of postoperative chemotherapy for Stage III colon cancer increased (14–60%), as well as the use of preoperative (chemo)radiotherapy for rectal cancer (2–66%). The administration of systemic therapy and metastasectomy increased for Stage IV disease patients. The 5-year relative survival increased significantly from 53 to 62% for colon cancer and from 51 to 65% for rectal cancer. Ongoing advancements in treatment, and also improvement in other factors in the care of CRC patients—such as diagnostics, dedicated surgery and pre- and postoperative care—lead to a continuous improvement in the relative survival of CRC patients. The increasing incidence of CRC favors the implementation of the screening program, of which the effects should be monitored closely.

Introduction

Colorectal cancer (CRC) is one of the most common cancer types in developed countries, with more than 15,000 newly diagnosed patients in the Netherlands in 2016.[1,2] The epidemiology and treatment of CRC have seen major changes over the years.[3] The incidence of CRC in the Dutch population has increased over time and although mortality rates have decreased, CRC is still the second leading cause of cancer-related death, accounting for over 4,900 deaths in 2014.[1] To further decrease mortality rates, the Dutch government introduced a nationwide screening program for CRC in 2014.[4]

Survival rates of CRC patients in the Netherlands have been improving since the end of the 1980s, which has been attributed to major advancements in the diagnostic process and treatment of CRC, ensuring that a successful multimodality management of CRC requires a multidisciplinary approach. CT scanning has become standard for staging with the addition of MRI in rectal cancer patients.[5] Improved surgical techniques as well as subspecialization substantially contributed to the quality of oncological treatment, besides reducing morbidity.[6–8] Preoperative radiotherapy options have increased with several new schedules combining this modality with systemic treatment as induction, concomitant or consolidation therapy.[9,10] The use of postoperative 5-fluorouracil-based chemotherapy has become standard treatment in high-risk Stage II and Stage III colon cancer patients.[11,12] For metastatic CRC, the use of combination chemotherapy, various new systemic and regional multimodality treatments, metastasectomies and other local

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What's new?

To best inform new directions for cancer management, it's important to study historical trends. Here, the authors analyzed 25 years of data in The Netherlands on colorectal cancer incidence, treatment and survival. During the period from 1989 to 2014, both incidence and 5-year relative survival increased. Certain treatments also became more common, such as postoperative chemotherapy for Stage III patients and systemic therapy and surgical removal of metastases for Stage IV patients. Improved diagnostics and treatments have helped more patients survive, and the rising incidence of CRC supports the use of the nationwide screening program, introduced by the Dutch government in 2014.

treatments, such as hyperthermic intraperitoneal chemotherapy, are increasingly being performed.[13–15]

Regarding the continuous changes in the diagnostic process and treatment of CRC, it is important to evaluate both long-term trends and trends during the most recent years, which are relevant to give direction for further research and innovations in cancer patient care. Therefore, the aim of this study was to analyze trends in incidence, mortality, stage distribution, treatment and relative survival for patients diagnosed with CRC between 1989 and 2014 in the Netherlands.

Methods

Data collection

Nationwide population-based data on CRC patients from 1989 onward were obtained from the Netherlands Cancer Registry (NCR). Since 1989, the NCR registers all newly diagnosed malignancies in the Netherlands. The NCR mainly receives notification from the pathology departments of hospitals, all taking part in the automated pathology archive (PALGA), and the National Registry of Hospital Discharge Diagnoses (LMR). Following the notification, trained data managers gather patient, tumor and treatment characteristics directly from the medical records.

Anatomical subsite of the tumor is coded according to International Classification of Diseases for Oncology (ICD-O).[16] The tumor-node-metastasis (TNM) classification was used for stage notification of the primary tumor, according to the edition valid at time of cancer diagnosis.[17] As clinical nodal staging of CRC is rather unreliable with a sensitivity of only 41% and specificity of 84% in daily practice,[18] pathological TNM took precedence over clinical stage except in case of unknown pathological stage. In case of a positive cM, stage was always registered as Stage IV. Patients with CRC Stage 0 were patients with a pathological complete response after preoperative treatment.

All cases of primary CRC diagnosed in the period 1989–2014 were selected for this study. The study period was divided into five time periods of 5 years each (1989–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014). Patients were stratified by tumor localization: colon (C18) and rectum (rectosigmoid and rectum, C19–C20).

Patients' vital status was obtained by linking the NCR to the Municipal Personal Records Database. Follow-up was completed until January 1, 2016.

Statistical analyses

For analyses on patient and tumor characteristics, incidence and mortality, data from all patients were included. The χ^2 test was used to analyze differences in patient and tumor characteristics. Annual incidence and mortality were described per 100,000 person-years and standardized according to the European Standard Population,[19] resulting in the European Standardized Rates (ESR). In addition, analyses of trends in incidence and mortality were achieved by an average annual percentage of change analysis.

For the analyses on treatment and survival, patients with either no histologically confirmed CRC or unknown TNM-stage were excluded. For metachronous primary tumors, the first diagnosed CRC was included. In case of synchronous multiple CRC, the tumor with the most advanced TNM-stage was used. Treatment characteristics were reported as percentages per age group and per time period.

Age-standardized relative survival was calculated for the different age groups as the ratio of the survival observed among the CRC patients to the survival that would have been expected based on age, gender and year of the corresponding general population (Pohar Perme method).[20] The relative survival analyses were performed according to tumor localization and stage.

p values <0.05 were considered statistically significant. Analyses were performed in SAS/STAT® statistical software (SAS system 9.4, SAS Institute, Cary, NC), STATA (version 13.0, Statcorp LP, College Station, TX) and SPSS Statistics for Windows (version 22.0, IBM Corp, Armonk, NY).

Results

Between 1989 and 2014, 267,765 patients were diagnosed with CRC in the Netherlands.

Patient and tumor characteristics are presented in Table 1. There was an increase over time in the proportion of colon tumors compared with rectal tumors. The proportion of males has increased in both colon and rectal cancer. The proportional stage distribution shows a decrease in Stage II, whereas the proportion of Stage IV increased. Moreover, a recent trend is the increasing number of rectal cancer patients with a complete pathological response (Stage 0) after preoperative treatment, starting from the period 2005–2009.

Incidence and mortality (European standardized rates)

The incidence of CRC in the Netherlands increased by 35% in the last 25 years. Figure 1*a* illustrates an increase in age standardized incidence, more pronounced for males, and decrease

Table 1. Tumor site distribution of all patients diagnosed with colorectal cancer, and age, gender, morphology and TNM-stage distribution of all patients diagnosed with colon or rectal cancer in the Netherlands between 1989 and 2014, by period of diagnosis

	Period of diagnosis									
	1989–1994 (%)		1995–1999 (%)		2000–2004 (%)		2005–2009 (%)		2010–2014 (%)	
CRC										
Tumor site										
Colon	30,136	(66)	28,417	(65)	32,486	(65)	40,140	(67)	47,674	(69)
Rectum	15,812	(34)	14,973	(35)	17,114	(35)	19,741	(33)	21,272	(31)
Colon										
Age at diagnosis										
0–49	1,885	(6)	1,583	(6)	1,714	(5)	1,826	(5)	2,047	(4)
50–59	3,418	(11)	3,432	(12)	4,195	(13)	4,878	(12)	5,008	(11)
60–69	7,668	(25)	6,989	(25)	7,793	(24)	10,025	(25)	13,135	(28)
70–79	10,330	(34)	9,935	(35)	11,381	(35)	13,467	(34)	16,254	(34)
80+	6,835	(23)	6,478	(23)	7,403	(23)	9,944	(25)	11,230	(24)
Gender										
Male	13,916	(46)	13,720	(48)	15,938	(49)	20,369	(51)	25,054	(53)
Female	16,220	(54)	14,697	(52)	16,548	(51)	19,771	(49)	22,620	(47)
Morphology										
Adenocarcinoma	22,994	(76)	22,195	(78)	25,945	(80)	32,455	(81)	40,015	(84)
Mucinous adenocarcinoma	5,739	(19)	4,908	(17)	5,141	(16)	5,736	(14)	5,305	(11)
Signet ring cell carcinoma	287	(1)	314	(1)	375	(1)	571	(1)	650	(1)
Other	1,116	(4)	1,000	(4)	1,025	(3)	1,378	(3)	1,704	(4)
TNM-stage										
Stage I[1]	4,674	(16)	4,291	(15)	4,772	(15)	6,286	(16)	8,770	(18)
Stage II	11,267	(37)	10,209	(36)	11,311	(35)	12,579	(31)	13,850	(29)
Stage III	6,637	(22)	6,778	(24)	7,895	(24)	10,001	(25)	11,972	(25)
Stage IV	5,833	(19)	5,433	(19)	6,691	(21)	8,861	(22)	11,211	(24)
Stage X	1,725	(6)	1,706	(6)	1,817	(6)	2,413	(6)	1,871	(4)
Rectum										
Age										
0–49	1,173	(7)	1,030	(7)	1,125	(7)	1,274	(6)	1,315	(6)
50–59	2,278	(14)	2,425	(16)	3,085	(18)	3,430	(17)	3,319	(16)
60–69	4,403	(28)	4,101	(27)	4,838	(28)	5,787	(29)	6,740	(32)
70–79	4,974	(31)	4,718	(32)	5,135	(30)	5,906	(30)	6,391	(30)
80+	2,984	(19)	2,699	(18)	2,931	(17)	3,344	(17)	3,507	(16)
Gender										
Male	8,763	(55)	8,555	(57)	9,970	(58)	11,674	(59)	13,116	(62)
Female	7,049	(45)	6,418	(43)	7,144	(42)	8,067	(41)	8,156	(38)
Morphology										
Adenocarcinoma	13,768	(87)	13,189	(88)	15,115	(88)	17,701	(90)	19,578	(92)
Mucinous adenocarcinoma	1,630	(10)	1,431	(10)	1,550	(9)	1,516	(8)	1,188	(6)
Signet ring cell carcinoma	287	(1)	314	(1)	375	(1)	571	(1)	650	(1)
Other	330	(2)	258	(2)	348	(2)	370	(2)	374	(2)
TNM-stage										
Stage 0	1	(0)	3	(0)	26	(0)	435	(2)	1,017	(5)
Stage I	4,175	(26)	3,845	(26)	4,402	(26)	5,097	(26)	6,076	(29)
Stage II	4,344	(27)	3,837	(26)	4,309	(25)	4,427	(22)	4,106	(19)

(Continues)

Table 1. (Continued)

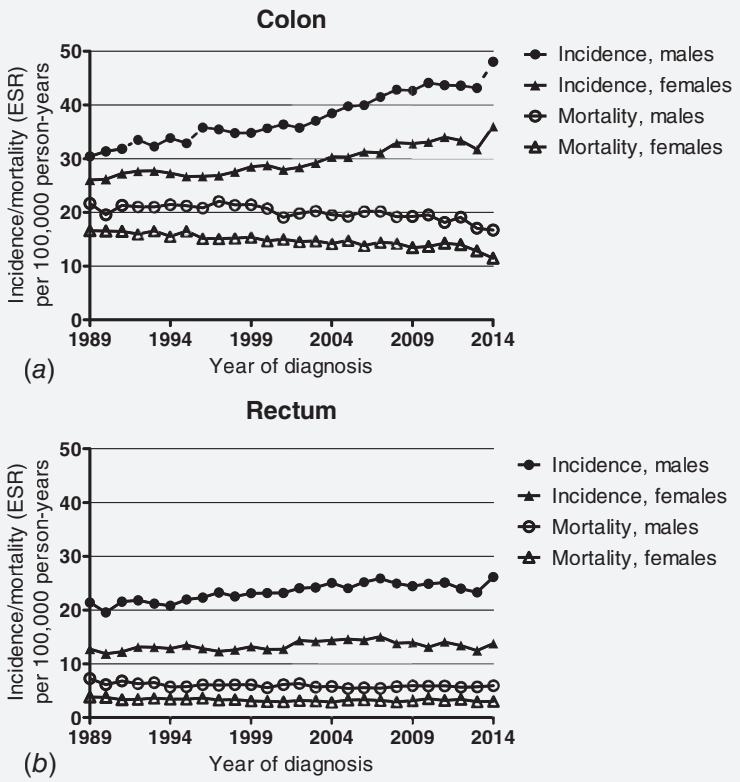
	Period of diagnosis									
	1989–1994 (%)		1995–1999 (%)		2000–2004 (%)		2005–2009 (%)		2010–2014 (%)	
Stage III	3,573	(23)	3,614	(24)	4,278	(25)	4,945	(25)	5,214	(25)
Stage IV	2,436	(15)	2,427	(16)	3,078	(18)	3,901	(20)	4,236	(20)
Stage X	1,283	(8)	1,247	(8)	1,021	(6)	936	(5)	623	(3)

Data are absolute numbers with percentages between parentheses.
[1]0.2% of these patients were Stage pT0, the majority of the pT0 patients were colon sigmoideum patients of which 51% had neo-adjuvant treatment.

in mortality for colon cancer patients. The same trends in incidence and mortality as for colon cancer patients can be seen for rectal cancer patients, although they are less obvious (Fig. 1*b*). For all groups, a strong increase in incidence is seen in 2014 following the introduction of the national screening program.

Treatment

In Table 2, trends in treatment for colon and rectal cancer are presented. Almost all patients diagnosed with Stages I–III colon cancer underwent resection (including local excisions). Administration of postoperative systemic therapy increased in patients with Stages II and III colon cancer. In patients



Note.

		Estimated average annual percentage of change			
		Incidence		Mortality	
Colon					
	Male (Confidence Interval (CI))	1.54	(1.37 to 1.71)	-0.73	(-0.97 to -0.49)
	Female (CI)	1.06	(0.85 to 1.26)	-1.02	(-1.22 to -0.82)
Rectum					
	Male (CI)	0.75	(0.54 to 0.95)	-0.59	(-0.83 to -0.34)
	Female (CI)	0.37	(0.09 to 0.65)	-0.58	(-0.94 to -0.23)

Figure 1. European age standardized (ESR) incidence and mortality rates per 100,000 person-years, according to gender and tumor site.

Table 2. Trends in primary treatment for patients with colon or rectal cancer in the Netherlands, according to postoperative stage

Treatment	Stage	Period of diagnosis									
		1989–1994 (%)		1995–1999 (%)		2000–2004 (%)		2005–2009 (%)		2010–2014 (%)	
Colon											
Resection	I–III	21,389	(98)	19,952	(99)	22,333	(98)	26,653	(98)	31,693	(98)
Postoperative chemotherapy	II	251	(2)	297	(3)	438	(4)	877	(7)	1,024	(8)
	III	918	(14)	2,465	(38)	4,019	(53)	5,621	(58)	6,855	(60)
Resection of primary tumor only	IV	3,341	(59)	2,624	(50)	2,295	(35)	2,097	(24)	1,812	(17)
Use of systemic therapy only	IV	299	(5)	384	(7)	889	(14)	1,947	(23)	3,112	(30)
Both resection of the primary tumor and systemic therapy	IV	671	(12)	1,061	(20)	1,841	(28)	2,779	(32)	3,471	(33)
Metastasectomy	IV	104	(2)	264	(5)	391	(6)	915	(11)	1,810	(17)
Rectum											
Resection	0–III	11,439	(96)	10,593	(96)	12,141	(95)	13,774	(95)	14,581	(92)
Preoperative radiotherapy	0–III	196	(2)	1,590	(14)	5,634	(44)	6,552	(45)	5,578	(35)
Preoperative chemoradiation	0–III	11	(0)	88	(1)	391	(3)	2,751	(19)	4,964	(31)
Postoperative radiotherapy	II/III	2,315	(30)	1,218	(17)	478	(6)	225	(2)	163	(2)
Postoperative chemotherapy	II/III	295	(4)	688	(9)	1,142	(14)	1,495	(16)	899	(10)
Resection of primary tumor only	IV	1,192	(49)	958	(40)	776	(26)	556	(15)	434	(11)
Use of systemic therapy only	IV	149	(6)	226	(9)	593	(20)	1,377	(36)	1,778	(43)
Both resection of the primary tumor and systemic therapy	IV	236	(10)	418	(18)	748	(25)	936	(24)	833	(20)
Metastasectomy	IV	54	(2)	127	(5)	212	(7)	550	(14)	939	(23)

Data are presented as absolute numbers with percentages of patients who underwent the respective treatment between parentheses.

diagnosed with Stage IV colon cancer, the combination of systemic therapy and resection, the use of only systematic therapy and the use of metastasectomy increased.

The primary tumor in nonmetastasized rectal cancer was almost always resected. The use of preoperative radiotherapy and chemoradiotherapy increased over time. The administration of postoperative chemotherapy increased until 2005–2009 in patients with Stage II/III rectal cancer, but decreased in more recent years. In patients with Stage IV rectal cancer, similar trends can be seen as for colon cancer.

Survival

Relative survival is depicted in Figure 2 and has improved over time for both colon and rectal cancer. For patients with Stage I colon cancer, the relative survival remained stable over time. Relative survival improved during all periods for patients with Stages II or III colon cancer, being most pronounced increase in the latter with an improvement in 5-year survival from 45 to 68%. The 5-year survival for patients with Stage IV colon cancer increased from 4 to 12%.

Also for patients with Stages I or II rectal cancer, an improvement in survival can be seen. For patients with Stage III rectal cancer, no further increase was observed in 5-year survival in 2010–2014. The improvement in survival for patients with Stage IV rectal cancer was similar to the improvement in survival for Stage IV colon cancer. The 5-year survival increased for all colon cancer stages combined from 53 to 62%, and for all rectal cancer stages combined from 51 to 65%.

Discussion

This large population-based study provides an overview of the vast changes in incidence, mortality, treatment and survival of CRC in the Netherlands in the period 1989–2014. Changes in treatment were seen next to a significant increase in overall as well as stage-specific relative survival for both colon and rectal cancer patients. Furthermore, intensified treatment of Stage IV CRC has also resulted in better outcome for metastasized patients with a generally poor prognosis.

The incidence of CRC in the Netherlands increased by 35% in the last 25 years. The implementation of a nationwide bowel screening program in the Netherlands explains the steep increase in the incidence of both colon and rectal cancer in 2014, which is expected to continue for several years.[21] The annual CRC mortality in the Netherlands has decreased modestly over the years, and is expected to decrease further because of the screening program, resulting in earlier diagnosis and thereby more curative treatment options.[22] The trend of increasing incidence and decreasing mortality of CRC patients is in line with trends in other Western countries

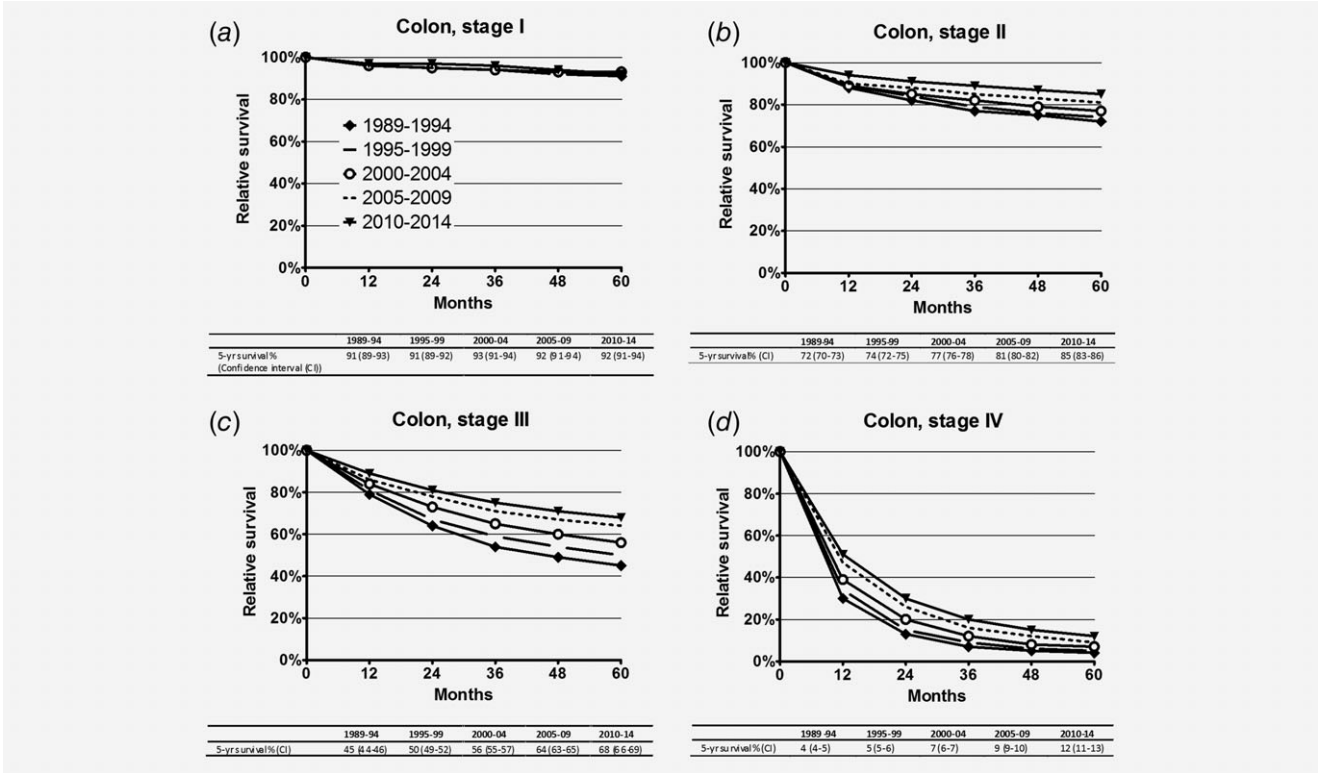


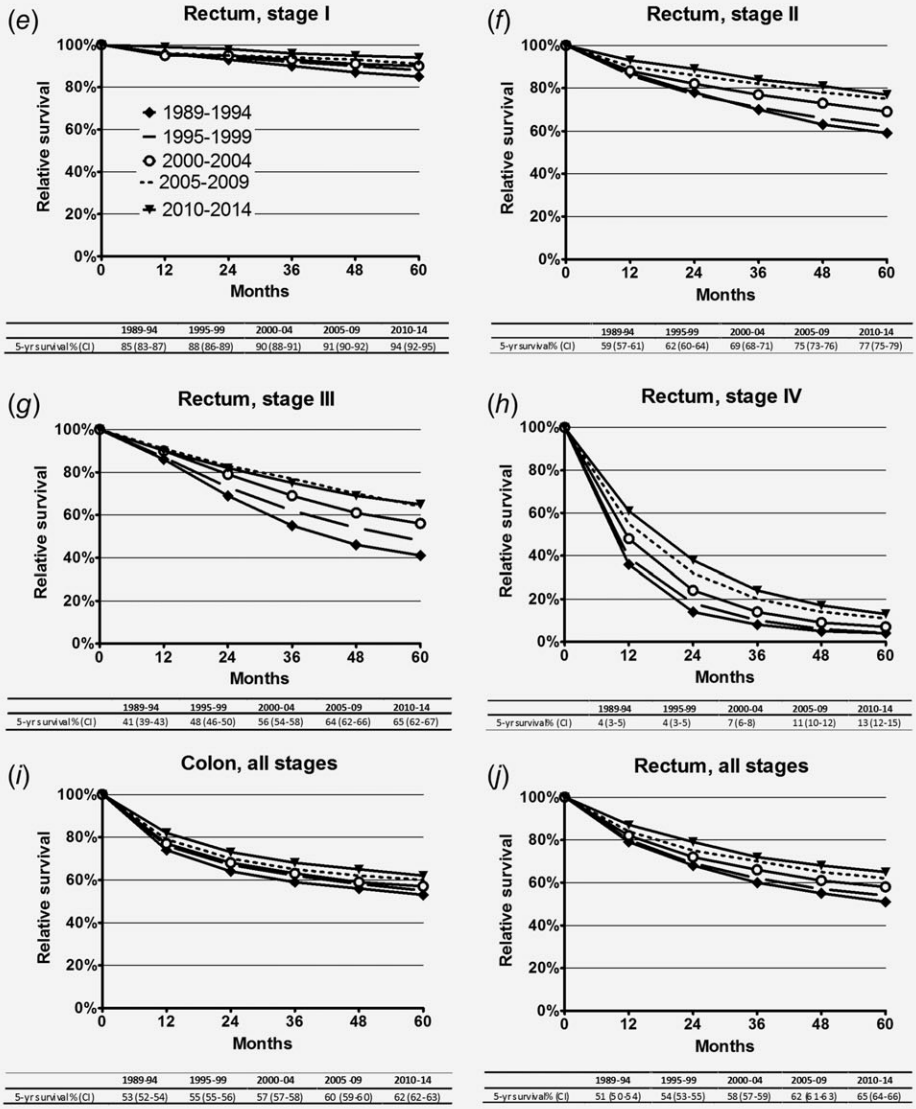
Figure 2. Stage-specific relative survival and relative survival for all stages combined for colon and rectal cancer, according to postoperative stage. (*a*) Relative survival among patients with postoperative Stage I colon cancer (including postoperative Stage 0). (*b*) Relative survival among patients with postoperative Stage II colon cancer. (*c*) Relative survival among patients with postoperative Stage III colon cancer. (*d*) Relative survival among patients with postoperative Stage IV colon cancer. (*e*) Relative survival among patients with postoperative Stage I rectal cancer (including postoperative Stage 0). (*f*) Relative survival among patients with postoperative Stage II rectal cancer. (*g*) Relative survival among patients with postoperative Stage III rectal cancer. (*h*) Relative survival among patients with postoperative Stage IV rectal cancer. (*i*) Relative survival among patients with colon cancer, all postoperative stages and ages. (*j*) Relative survival among patients with rectal cancer, all postoperative stages and ages.

(e.g., Canada, Sweden and the United Kingdom). The rising incidence rates may be accounted for by major risk factors such as lifestyle, obesity and dietary habits.[23] Interestingly, the incidence of CRC patients has been declining in other Western countries such as the US, France and Australia. Even though this difference is often attributed to the adoption of a western lifestyle and the long-term effects of screening for CRC, no concluding explanation exists.[23,24] In the United States, a rise in younger individuals being diagnosed with CRC has been shown, whereas the total incidence of CRC is declining.[24] Data from this study show that in the Netherlands, there is no such opposite trend but a rise in the incidence of CRC incidence in both younger and elderly patients.

The increasing incidence and decreasing annual CRC mortality points toward an improvement in survival of CRC patients, which has been attributed previously to advancements in treatment.[3] Results from this study show that resection is the cornerstone in the treatment of nonmetastatic CRC, and the introduction of screening programs will increase the use of less-invasive procedures such as polypectomies and local excisions.

Since the 1990s, the use of postoperative systemic therapy is recommended for Stage III colon cancer, and the administration has continued to increase during more recent time periods.[25,26] Considering Stage II colon cancer, Dutch, European and American guidelines recommend the use of postoperative chemotherapy only in high-risk patients.[12,27] Unfortunately, it was not possible to select for high-risk Stage II in the NCR database, but a previous Dutch study found that only 16% of high-risk Stage II patients received postoperative chemotherapy in 2008–2012.[12] Following the Dutch guidelines, Stage III and high-risk Stage II patients postoperatively receive a combination chemotherapy of fluoropyrimidine and oxaliplatin.

Compared with colon cancer, rectal cancer treatment changed significantly over recent decades. Since 2001, the total mesorectal excision technique became the standard for rectal cancer surgery in the Netherlands and contributed to an improved survival.[7,28] Simultaneously, preoperative (chemo) radiotherapy was implemented in the treatment for Stage II/III rectal cancer in the Netherlands.[7] The addition of preoperative (chemo)radiotherapy has not demonstrated an overall



	1989-94	1995-99	2000-04	2005-09	2010-14
5-yr survival% (CI)	85 (83-87)	88 (86-89)	90 (88-91)	91 (90-92)	94 (92-95)

	1989-94	1995-99	2000-04	2005-09	2010-14
5-yr survival% (CI)	59 (57-61)	62 (60-64)	69 (68-71)	75 (73-76)	77 (75-79)

	1989-94	1995-99	2000-04	2005-09	2010-14
5-yr survival% (CI)	41 (39-43)	48 (46-50)	56 (54-58)	64 (62-66)	65 (62-67)

	1989-94	1995-99	2000-04	2005-09	2010-14
5-yr survival% (CI)	4 (3-5)	4 (3-5)	7 (6-8)	11 (10-12)	13 (12-15)

	1989-94	1995-99	2000-04	2005-09	2010-14
5-yr survival% (CI)	53 (52-54)	55 (55-56)	57 (57-58)	60 (59-60)	62 (62-63)

	1989-94	1995-99	2000-04	2005-09	2010-14
5-yr survival% (CI)	51 (50-54)	54 (53-55)	58 (57-59)	62 (61-63)	65 (64-66)

Figure 2. (Continued)

survival benefit in randomized trials, although a more tailored application for high-risk groups might impact survival based on subgroup analysis.[29]

The findings for metastasized CRC show a continuation of the trends in treatment described previously in the Dutch population, with a shift from resection of the primary tumor alone to either systemic therapy alone or in combination with surgery of the primary tumor, and an increase in the use of metastasectomy.[3,13] The exact type of received chemotherapy is not registered in the NCR database, but the Dutch guidelines recommend fluoropyrimidine monotherapy for patients who are likely to receive multiple-line therapy, or combination chemotherapy (i.e., fluoropyrimidine and oxaliplatin) for patients who are not. Previous Dutch studies have shown that combination chemotherapy is not superior to sequential therapy in Stage IV CRC patients, and that both combination and sequential treatment regimens are prescribed in daily practice in the Netherlands, which is in line with current guidelines.[30]

The increase in 5-year survival in the more recent periods seems remarkable as there have been no major changes in treatment and most of the trends in treatment have leveled off for localized disease, except for the use of preoperative chemoradiation. The treatment of metastases has developed further over time with the use of metastasectomy and evolved systemic therapy regimens. However, the minority of patients with metastasized disease can be treated with curative intent by metastasectomy, and these treated patients have a 5-year survival of ~50%.[31,32] Systemic therapy in Stage IV CRC yields a 5-year survival of <10%,[32] and of all Stages I–III CRC

patients, only ~10–30% will develop metastases.[33] Therefore, the potential influence of these systemic treatment options on 5-year survival is considered to be small.

Besides developing treatment strategies, other mechanisms might play a role in the increasing survival rates. First, the gain in 1-year survival in this study suggests a substantial improvement in the management of factors associated with short-term mortality, by means of better pre- and postoperative care, and dedicated surgery.[34,35] Second, improvement of diagnostic imaging tools may have led to stage migration due to detection of small lymph nodes and distal metastases which were previously missed (the Will Rogers phenomenon). Third, preoperative chemoradiotherapy in rectal cancer might have shifted stage-specific outcome, as postoperative stage has been used in this study. Patients who respond well to preoperative treatment have been downstaged, thereby deteriorating survival rates in the higher stages. This might explain the stagnation in survival improvement of Stage III rectal cancer in 2010–2014. Besides the effect of downstaging, this stagnation in survival in 2010–2014, relative to the major gains in 2000–2004 and 2005–2009, could also be explained by the nationwide implementation of TME-surgery in those earlier periods.[28] Last, the improvement in survival in the more recent years could also be caused by lead-time bias due to earlier diagnosis through various regional screening programs.[36] Importantly, survival of all stages combined still improved, showing that the increase of survival in the present data is not only the result of stage migration.

Another interesting finding is that over time, rectal cancer survival has caught up with colon cancer survival and even surpassed the latter in the more recent periods of the study. This has previously been described, and results of this study show a progression of this trend.[3,37]

Even though there are persistent differences in relative survival of CRC across Europe, similar increases in relative survival were observed for both colon and rectal cancer across different regions. Compared to other regions in Europe, Western Europe (including the Netherlands) has superior survival rates for CRC patients, with only slight differences in survival between countries in this region.[38] It is plausible that the trends described in this study are also applicable to other West-European countries. Overarching European guidelines are increasingly incorporated into national guidelines, with an increase toward multinational collaborative research with rapid implementation of gained knowledge and new treatment strategies.

High-quality, long-term nationwide population-based data were used for this study, making it possible to describe trends in recent years in the context of long-term trends. However, there are also some limitations to this study. Comorbidity, socioeconomic status and ethnicity were missing, which might have influenced survival in CRC patients. Also, we decided to use postoperative stage for our analyses, encountering a dilemma because treatment strategies are based on clinical stage. Also, downstaging may have occurred after preoperative treatment with chemoradiotherapy or after preoperative short-course radiotherapy followed by a long interval to surgery.[39] However, the majority of patients in this database that received short-course radiotherapy had surgery within an interval of 10 days after preoperative therapy, and downstaging is not observed in this group.[40,41] Most importantly, postoperative staging is the gold standard and clinical staging using CT and MRI is rather unreliable, especially regarding lymph node staging.[18,42]

Last, yp-TNM and p-TNM are grouped together for the analyses in this study to give a global overview of the epidemiology of CRC in the Netherlands. However, it should be taken into account that differences in survival between p-TNM and yp-TNM are not fully comparable. Bosch et al. described that not only survival was different between p-TNM and yp-TNM patients, but also clinical staging significantly differed between these patient groups making comparison difficult.[43]

In conclusion, this study showed an increase in incidence and an ongoing improvement in survival. This improvement in survival is a continuum, which is partly due to evolving cancer treatment, but also to other factors in the organization of care for CRC patients. The increasing incidence of CRC favors the implementation of the national screening program. It is to be expected that further patient tailored treatment based on better insight into tumor heterogeneity, and the screening program, will further improve survival in the coming years, but the effects should be monitored closely.

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References

1. Registry NC. www.cijfersoverkanker.nl, 2018.
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136: E359–86.
3. Lemmens V, van Steenbergen L, Janssen-Heijnen M, et al. Trends in colorectal cancer in the south of The Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. *Acta Oncol* 2010;49:784–96.
4. Toes-Zoutendijk E, van Leerdam ME, Dekker E, et al. Real-time monitoring of results during first year of dutch colorectal cancer screening program and optimization by altering fecal immunochemical test cut-off levels. *Gastroenterology* 2016;154 (4):767–77.
5. Bokkerink GM, Buijs EF, de Ruijter W, et al. Improved quality of care for patients undergoing an abdominoperineal excision for rectal cancer. *Eur J Surg Oncol* 2015;41: 201–7.
6. Bonjer HJ, Deijen CL, Haglind E. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015;373:194.
7. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638–46.
8. Buunen M, Veldkamp R, Hop WC, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. *Lancet Oncol* 2009;10:44–52.

9. Jobsen J, Aarts MJ, Siesling S, et al. Use of primary radiotherapy for rectal cancer in The Netherlands between 1997 and 2008: a population-based study. *Clin Oncol (R Coll Radiol)* 2012; 24:e1–8.
10. Smith JJ, Garcia-Aguilar J. Advances and challenges in treatment of locally advanced rectal cancer. *J Clin Oncol* 2015;33:1797–808.
11. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109–16.
12. Verhoeff SR, van Erning FN, Lemmens VE, et al. Adjuvant chemotherapy is not associated with improved survival for all high-risk factors in stage II colon cancer. *Int J Cancer* 2016;139:187–93.
13. van der Pool A, Damhuis RA, IJzermans JN, et al. Trends in incidence, treatment and survival of patients with stage IV colorectal cancer: a population-based series. *Color Dis* 2012;14:56–61.
14. Simkens LH, van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. *Lancet* 2015;385:1843–52.
15. Klaver CE, Musters GD, Bemelman WA, et al. Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial. *BMC Cancer* 2015;15:428.
16. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, S W. *International Classification of Diseases for Oncology (ICD-O)* ed. Geneva: World Health Organization, 2000.
17. Wittekind CGF, Hutter R, Klimpfinger M, L. S. *TNM atlas* ed. Berlin: Springer-Verslag, 2004.
18. Brouwer NPM, Stijns RCH, Lemmens VEPP, et al. Clinical lymph node staging in colorectal cancer; a flip of the coin? *Eur J Surg Oncol* 2018; 44(8):1241–6.
19. European Standard Population. In: WHO, ed., 1976.
20. Perme MP, Stare J, Esteve J. On estimation in relative survival. *Biometrics* 2012;68:113–20.
21. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603–7.
22. McClements PL, Madurasinghe V, Thomson CS, et al. Impact of the Uk colorectal cancer screening pilot studies on incidence, stage distribution and mortality trends. *Cancer Epidemiol* 2012;36:e232–42.
23. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683–91.
24. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. *J Natl Cancer Inst* 2017; 109:1–6.
25. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990;322:352–8.
26. Benson AB 3rd, Venook AP, Bekaii-Saab T, et al. Colon cancer, version 3.2014. *J Natl Compr Cancer Netw* 2014;12:1028–59.
27. Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Ann Oncol* 2012;23:2479–516.
28. den Dulk M, Krijnen P, Marijnen CA, et al. Improved overall survival for patients with rectal cancer since 1990: the effects of TME surgery and pre-operative radiotherapy. *Eur J Cancer* 2008;44:1710–6.
29. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;355: 1114–23.
30. Mol L, Koopman M, van Gils CW, et al. Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands. *Acta Oncol* 2013;52:950–5.
31. de Ridder JA, Lemmens VE, Overbeek LI, et al. Liver resection for metastatic disease; a population-based analysis of trends. *Dig Surg* 2016;33:104–3.
32. van der Geest LG, Lam-Boer J, Koopman M, et al. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis* 2015;32:457–65.
33. Elferink MA, de Jong KP, Klaase JM, et al. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Color Dis* 2015;30:205–12.
34. van Gestel YR, Lemmens VE, de Hingh IH, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. *Ann Surg Oncol* 2013;20:371–80.
35. Gooiker GA, Dekker JW, Bastiaannet E, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Ann Surg Oncol* 2012;19:2428–34.
36. Bretthauer M, Kaminski MF, Loberg M, et al. Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. *JAMA Intern Med* 2016;176: 894–902.
37. Fischer J, Hellmich G, Jackisch T, et al. Outcome for stage II and III rectal and colon cancer equally good after treatment improvement over three decades. *Int J Color Dis* 2015;30: 797–806.
38. Holleczek B, Rossi S, Domenic A, et al. EUROCARE-5 Working Group. On-going improvement and persistent differences in the survival for patients with Colon and rectum cancer across Europe 1999-2007 Results from the EUROCARE-5 study. *Eur J Cancer* 2015;51: 2158–68.
39. Rombouts AJM, Hugen N, Verhoeven RHA, et al. Tumor response after long interval comparing 5x5Gy radiation therapy with chemoradiation therapy in rectal cancer patients. *Eur J Surg Oncol* 2018;44:1018–24.
40. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009;373:811–20.
41. Marijnen CA, Nagtegaal ID, Klein Kranenbarg E, et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001;19:1976–84.
42. Nerad E, Lahaye MJ, Maas M, et al. Diagnostic accuracy of CT for local staging of colon cancer: a systematic review and meta-analysis. *AJR Am J Roentgenol* 2016;207:984–5.
43. Bosch SL, Verhoeven RHA, Lemmens VEPP, Poortmans P, de Wilt JHW, Nagtegaal ID. Type of preoperative therapy and stage-specific survival after surgery for rectal cancer: a nationwide population-based cohort study. 2018. Submitted for publication.

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