Acta Oncologica, 2010; 49: 784–796

informa
healthcare

ORIGINAL ARTICLE

Trends in colorectal cancer in the south of the Netherlands 1975-2007: Rectal cancer survival levels with colon cancer survival

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Abstract

Objective. In the Netherlands over 11 200 patients are yearly diagnosed with colorectal cancer (CRC), of who about 4 700 are expected to die of the disease ultimately. Investigating long-term trends is useful for clinicians and policy makers to evaluate the impact of changes in practice and will help predict future developments. *Patients.* The 26 826 cases of primary CRC (C18.0–C20.9) diagnosed between 1975 and 2007 in the Dutch population-based Eindhoven Cancer Registry area were included. We analysed trends in incidence, prevalence, stage distribution, treatment, survival, and mortality. *Results.* The age-standardised incidence of colon carcinoma kept increasing, most markedly in males (up to 39 patients per 100 000 inhabitants) and for tumours of the colon ascendens (subsite-specific incidence doubled). The incidence of rectal carcinoma remained stable. The share of patients aged 80 or older rose from 12 to 19% ($p<0.0001$). The proportion of patients diagnosed with distant metastases increased up to 25% for colon carcinoma ($p<0.0001$). Resection rates of the primary tumour remained high except for patients with metastasised disease, showing a decrease since 2000. Recently, the use of adjuvant chemotherapy seemed to level off among patients with stage III colon carcinoma, but the use of neo-adjuvant chemoradiation clearly increased among patients with stage II/III rectal cancer ($p<0.0001$). Five-year relative survival of colon cancer improved from 51% in 1975–1984 to 58% in 2000–2004, for rectal cancer it improved from 44 to 59%. Two-year relative survival of colon cancer in 2005–2006 was 69%, and 77% for rectal cancer. *Conclusions.* The changes in management of rectal cancer led to a superior increase in survival of these patients compared to patients with colon cancer, even surpassing the latter.

In the Netherlands, yearly over 11 200 patients are diagnosed with CRC, of who about 4 700 are expected to ultimately die of the disease [1]. It constitutes 2–3% of total mortality above the age of 40. During the last 35 years, improvements in endoscopy and imaging, advances in surgery and pathology, better pre- and postoperative care, and more frequent use of adjuvant therapies have led to improvements in survival of patients with CRC [2–5].

Investigating long-term and recent trends will help predict future developments, which is important for planning prospective investments in clinical cancer care. Also, it is useful for clinicians and policy makers to evaluate the impact of all the changes that have taken place in the past. In this study, we focus on the trends in incidence, stage distribution, treatment, survival and mortality among patients diagnosed with CRC between 1975 and 2007 in the south of the Netherlands.

Patients and methods

The Eindhoven Cancer Registry collected data on all patients with newly diagnosed cancer in a large part of the southern Netherlands. The registry area nowadays comprises about 2.3 million inhabitants. This population-based registry is notified by six pathology departments, 10 community hospitals (20 at the beginning of the study period but many of them have meanwhile merged) at 17 locations, and two radiotherapy institutions.

Between 1975 and 2007, 26 828 cases of primary CRC (C18.0–C20.9) were diagnosed in the Eindhoven

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(Received 7 September 2009; accepted 25 February 2010)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/02841861003733713

Cancer Registry area, excluding patients with unknown site of primary tumour within the colorectum (1.5% of total). Information on diagnosis, staging, and treatment is routinely extracted from the medical records by specially trained administrators of the cancer registry. Registration takes place six to 18 months after diagnosis. By means of an independent case ascertainment method, the completeness of the registration is estimated to exceed 95% [6]. Vital status of all patients diagnosed until January 1, 2007 was assessed on August 1, 2008 through merging with the Municipal Administrative Databases, where all deceased and emigrated persons in the Netherlands are registered. Disease-specific mortality (as stated on death certificate) was made available at an aggregated level by Statistics Netherlands (CBS). Since cause-of-death was not available at individual patient level, survival was calculated using all-cause mortality.

Analyses

Differences in patient/tumour characteristics between different periods were analysed using a two-sided Cochran-Armitage trend test. Incidence/mortality rates are shown as the 3-year moving average of the number of new patients/deaths per 100 000 inhabitants per year. Trends were estimated from the incidence rates age-standardised to the European standard population (ESR) [7]. For the period 1975–1984 no data on stage distribution and treatment are presented because of incompleteness of these data for the earlier years. Trends in detection and stage are shown as the proportional distribution of the Tumour Node Metastasis (TNM) stage in the respective period (1985–1989, 1990–1994, 1995–1999, 2000–2004, and 2005–2007). Stage is postoperative, except for cases where postoperative stage was unknown, in which case preoperative stage was used. Relative survival was used as an estimation of disease specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same age structure. Relative survival is calculated as the ratio of the observed rates in cancer patients to the expected rates in the general population with the same structure for age and gender [8]. Multivariable relative survival analyses, using Poisson regression modelling, were performed to estimate the relative excess risk (RER) of dying for the respective periods of diagnosis (1975–1984, 1985–1994, 1995–1999, 2000–2006) for patients with stage III and IV colon carcinoma, and stage II/III and IV rectal carcinoma, adjusted for follow-up interval, age, sex, and subsite [9]. Stage IV colon and rectal carcinoma were analysed separately [10]. Treatment variables were added to investigate the effect of therapy on the RER of dying according to period of diagnosis.

Prevalence of patients with CRC up to 10 years at January 1, 1984, 1994, and 2004 was expressed as the age-standardised number of patients alive per 100 000 inhabitants at the respective date.

Results

The age distribution shifted between 1975–1984 and 2005–2007 towards a higher proportion of patients diagnosed at age 80 or older ($p<0.0001$) (Table I). The male-female ratio of incidence increased from 1.03 to 1.14 (p_{trend} 0.004), and a shift occurred towards a more proximal tumour site (colon vs. rectum) (p_{trend} 0.002).

The age-standardised incidence of colon carcinoma among males gradually increased between 1975 and 2007 from 25 to 39 patients per 100 000 inhabitants (Figure 1). The incidence of colon carcinoma among females increased from 23 to 30. The incidence of rectal carcinoma remained more or less stable among males (about 25 per 100 000 inhabitants) and females (about 15).

Table I. Age, gender, and tumour site distribution of all patients diagnosed with colorectal cancer in the south of the Netherlands between 1975 and 2007, by period of diagnosis.[1]

	Period of diagnosis				
	1975–1984	1985–1994	1995–1999	2000–2004	2005–2007
Age (years)					
19–49	282 (9)	553 (8)	340 (7)	420 (6)	229 (5)
50–64	965 (31)	2 168 (28)	1 466 (28)	1 893 (29)	1 299 (28)
65–79	1 485 (48)	3 488 (48)	2 527 (49)	3 234 (49)	2 244 (49)
80+	368 (12)	1 130 (15)	876 (15)	1 040 (16)	819 (19)
Gender					
Male	1 562 (50)	3 824 (52)	2 746 (53)	3 534 (54)	2 459 (54)
Female	1 538 (50)	3 515 (48)	2 463 (47)	3 053 (46)	2 132 (46)
Tumour site					
Colon	1 877 (61)	4 589 (63)	3 245 (62)	4 203 (64)	2 955 (64)
Rectum	1 223 (39)	2 750 (37)	1 964 (38)	2 384 (36)	1 636 (36)

[1]Data are absolute numbers with percentages between parentheses.

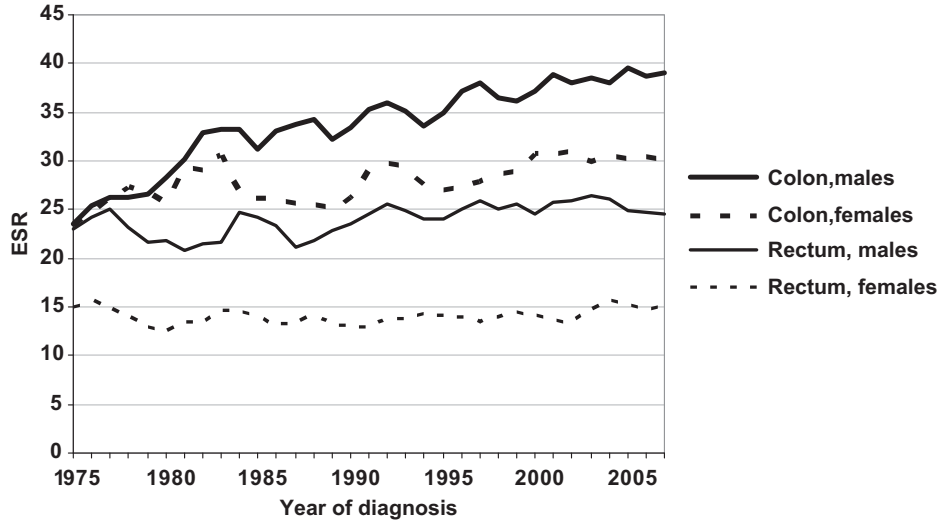


Figure 1. Age-standardised incidence of CRC in the south of the Netherlands, according to gender and tumour site (3-year moving average; Incidence rates age-standardised to the European standard population (ESR)).

The subsite-specific incidence rates showed a marked increase for carcinomas situated in the colon ascendens, among both males and females, and for carcinoma situated in the colon descendens and sigmoideum especially among males (Figure 2a and b).

The proportional stage distribution of patients with colon carcinoma showed a slightly decreasing proportion of stage II patients, and an increased proportion of patients with stage III and IV disease ($pT_{any}N1\text{-}2M0$) ($p<0.0001$) (Figure 3). Comparing proportions of patients diagnosed with stage II and III only, there is a shift towards a higher proportion of patients with stage III disease since 1995–1999 ($p=0.01$). In the most recent period, an increase in the proportion of stage IV patients could be noted for both colon (up to 25% and rectum (up to 22%). The proportion of patients with unknown stage remained stable for both colon (2–3%) and rectal cancer (3–5%) (results not shown). Among patients without lymph node metastases (N0), the proportion of patients with T1 tumours decreased from 11 to 5%, the proportion T2 decreased from 28 to 17%, and the proportion T3 increased from 54 to 69% ($p<0.0001$) (results not shown). The proportion of patients with a clinically (preoperative) unknown stage decreased between 1985–1994 and 2005–2007: cTx decreased from 89 to 71%, cNx from 89 to 59%, and cMx from 26 to 12% ($p<0.0001$) (results not shown).

Almost all patients with stage I–III ($pT_{any}N_{any}M0$, if unknown then $cT_{any}N_{any}M0$) colon carcinoma underwent resection, regardless of period of diagnosis and age (ranging from 92 to 100%) (Table IIa). Since the mid 1990s, adjuvant chemotherapy was increasingly administered among all age groups of stage III colon carcinoma patients, but to a lesser extant among the older age groups. Only 5% of patients aged 80 years or older received adjuvant chemotherapy in the most recent period. The use of adjuvant chemotherapy seemed to level of since 2000 among patients younger than 70 years. In 2005–2007, 22% of patients younger than 50 years with stage II disease received adjuvant chemotherapy. Resection rates of the primary tumour initially increased over time among patients younger than 50 years with colon carcinoma stage IV ($T_{any}N_{any}M1$), but decreased again in the most recent period, especially among elderly patients. Metastasectomy was performed in less than 5% percent of patients with stage IV disease. Chemotherapy was increasingly administered to patients with stage IV disease, also for patients over 80 years of age.

Patients with rectal carcinoma increasingly underwent surgery, except for the oldest patients, where surgery rates decreased somewhat since the beginning of the 90's (Table IIb). The use of radiotherapy among stage II/III patients increased between 1985–1989 and 1990–1994 (postoperative radiotherapy), decreased in the subsequent period (transition to preoperative radiotherapy), and increased again in the most recent period (preoperative radiotherapy). With rising age, the use of radiotherapy decreased. Chemoradiation, especially in the neo-adjuvant setting, was markedly administered more often in the most recent period, especially among patients younger than 70 years old. Stage IV patients less frequently underwent resection, particularly in the most recent period. Opposite to that the use of chemotherapy among these patients rose clearly, even among the older patients, although less pronounced.

Unadjusted relative survival rates increased for colon and for rectal cancer patients during the

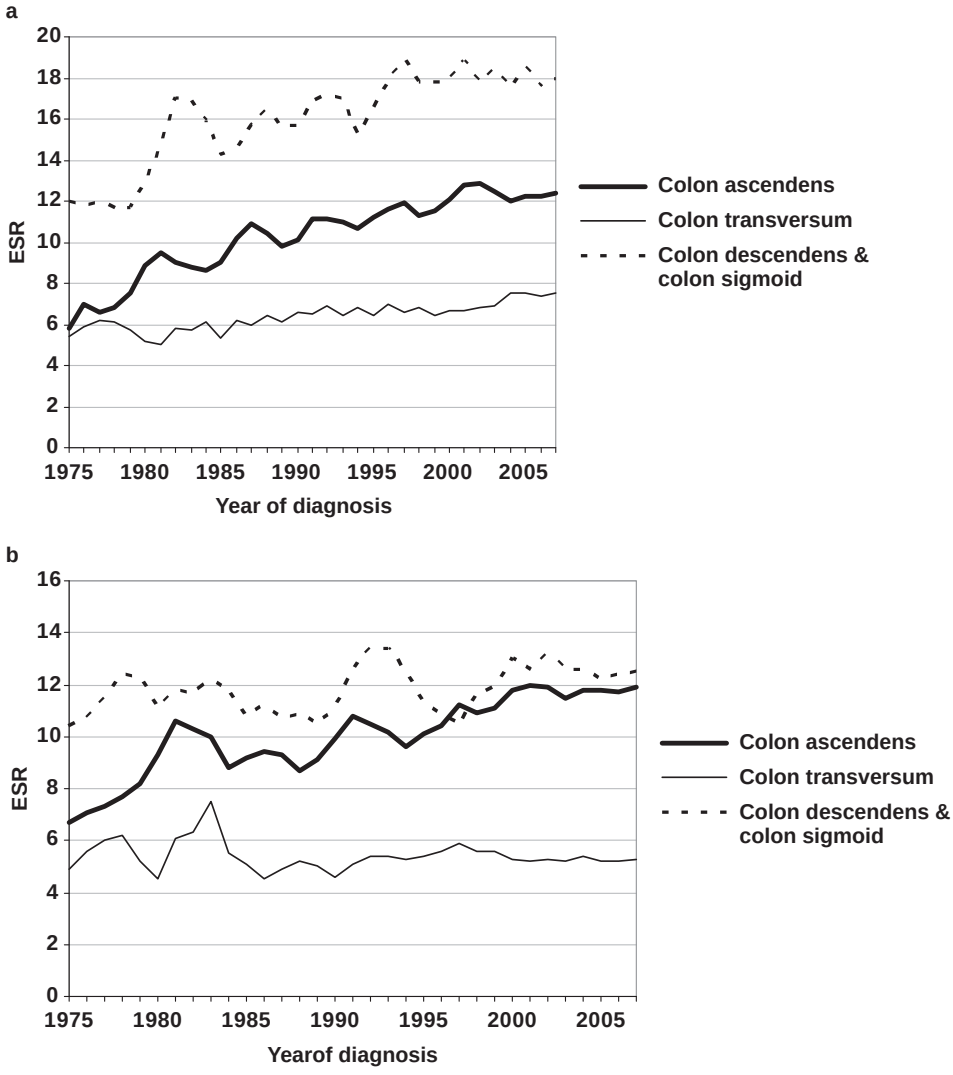


Figure 2. (a) Age-standardised incidence of colon cancer among males in the south of the Netherlands, according to subsite (3-year moving average; Incidence rates age-standardised to the European standard population). (b) Age-standardised incidence of colon cancer among females in the south of the Netherlands, according to subsite (3-year moving average Incidence rates age-standardised to the European standard population).

30 year period. For stage I and II colon cancer (Figure 4a and 4b), survival improved markedly until 1995–1999, but remained stable afterwards. There was a dramatic improvement in 5-year survival for stage III colon cancer: from 37 to 55% (Figure 4c). Among stage IV patients, there appeared to be an increase in median survival in 1995–1999 (Figure 4d).

Five-year survival of stage I rectal cancer increased drastically between 1985 and 1994, and improved afterwards at a slower rate up to 91% in 2000–2004 (Figure 4e). Stage II also exhibited vast improvements in survival between 1975–1984 and 1995–1999, without further improvement in 2000–2004 (Figure 4f). The developments in survival among stage III rectal cancer patients equalled the improvements seen among stage III colon cancer, with large improvements in 1995–1999 (Figure 4g). There was also a noteworthy improvement in 2-year survival among stage IV rectal cancer patients, especially since the mid 1990s (Figure 4h). The unadjusted cancer survival rate among patients younger than 70 years with colon cancer showed an increasing trend throughout the whole study period, for elderly patients only up to 1995–1999 (Figure 4i and j). Among younger patients with rectal cancer, every period exhibited a survival improvement except for 2000–2004, in contrast to the elderly where this improvement in 5-year relative survival was more moderate (Figure 4k and l). Five-year survival of all colon cancer patients improved from 51% in 1975–1984 to 58% in 2000–2004; 5-year survival of all rectal cancer patients improved from 44 to 59% in that period (Figure 4m and n). Two-year relative survival of colon cancer in 2005–2006 was 69%, and 77% for rectal cancer.

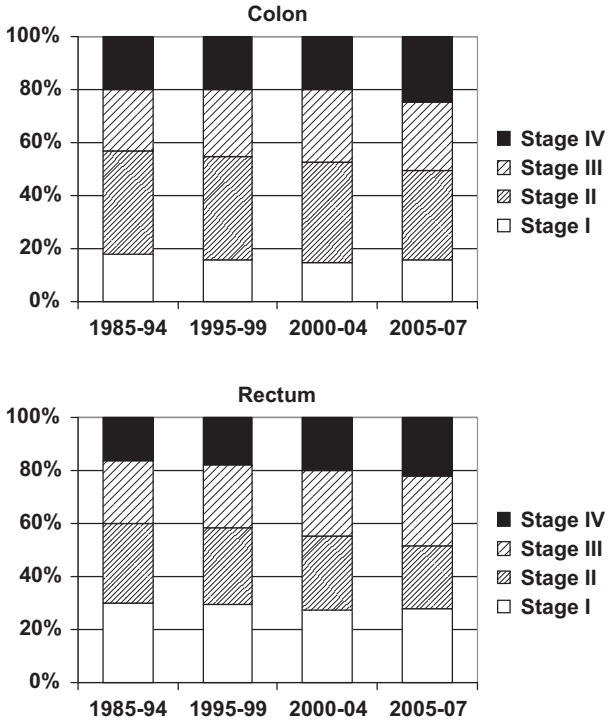


Figure 3. Trends in stage distribution of CRC in the south of the (excluding unknown stage).

The multivariable relative survival analyses among stage III colon cancer patients aged younger than 70 showed that without treatment added to the model, there is decreased risk of death over time (Table IIIa). However, with the addition of adjuvant treatment to the model, this effect largely disappeared. There also was a significant improvement over time among the older age group, although somewhat more moderate than among younger patients. Among stage II and III rectal cancer patients, there was a marked and significant reduction in death risk over time for both patients younger and older than 70 years, both without and with treatment in the model. Among younger patients with stage IV colon or rectal cancer the risk of death decreased over time (Table IIIb). After inclusion of treatment there was still an effect of period of diagnosis, albeit lower than without treatment added to the model. Among older patients with stage IV colon or rectal cancer, no clear effect of period of diagnosis could be noted.

Age-standardised mortality from colon cancer among males fluctuated between 20 to 25 deaths per 100 000 inhabitants during the whole study period (Figure 5). Among females, colon cancer mortality rates showed a steady decrease from 22 deaths per 100 000 inhabitants in 1975, to 16 in 2007. A similar trend could be observed for rectal cancer mortality rates; a decline from 13 deaths per 100 000 inhabitants to seven among males, and from eight to four among females.

The 10-years prevalence of patients with CRC clearly increased between 1984 and 2004, especially among males (Table IV). Per community hospital in the Eindhoven cancer registry area, this means an increase from 800 colorectal cancer patients per hospital to almost 1 300 patients.

Discussion

The epidemiology of CRC has changed strikingly in the south of the Netherlands during the period 1975–2007. First of all, there has been a gradual increase in incidence of colon cancer, which was most marked among males and for proximal tumours. Furthermore, survival increased dramatically, especially among patients with rectal cancer. This went together with changes in treatment; particularly since the mid-1990s, a growing proportion of predominantly younger patients underwent adjuvant chemo- or radiotherapy, next to changes in surgical management. The advances in survival led in turn to decreased mortality rates, and consequently to increased prevalence rates. The changes in stage distribution suggested more accurate staging procedures for N and M disease over time, with no evidence that patients diagnosed more recently are diagnosed at an earlier stage of the disease.

The rising age-standardised incidence of CRC in the south of the Netherlands, predominantly among males, is in concordance with patterns of incidence found in many other European countries [11]. Changes in major risk factors such as lifestyle, including physical activity, diet and obesity may account for the rising trend [11,12]. These trends are however in contrast to patterns found in the US, where overall incidence rates have been steadily declining over the past two decades [13]. One explanation for this reversed trend may be the more extensive implementation of opportunistic CRC screening in the US [13]. The trends in stage distribution as shown by the current study support this hypothesis; no clear shift towards an earlier stage at diagnosis was observed in the south of the Netherlands, which would be expected in case of higher uptake of screening activities. Added to that, one can only speculate about any effect on stage distribution of an increased polypectomy of premalignant adenomas over time.

As in many Western countries, a shift towards more proximal tumour site was observed [14–18]. This has been related to the use of sigmoidoscopy (and related polypectomy) as a screening tool [14,19]. However, our data show that the shift towards proximal tumour site is the result of an increase in age-adjusted incidence of proximal tumours, and not

Table IIa. Trends in primary treatment for patients with colon cancer in the south of the Netherlands, according to age[a].

		Period of diagnosis				
Treatment	Age (yrs)	1985–89 %	1990–94 %	1995–99 %	2000–04 %	2005–07 %
Resection, stage I–III						
	19–49	99	99	92	99	99
	50–59	100	99	95	98	100
	60–69	99	99	98	98	99
	70–79	97	99	97	97	98
	80+	96	98	97	97	98
Adjuvant chemotherapy, stage II						
	19–49	0	14	2	10	22
	50–59	0	5	5	5	12
	60–69	1	6	2	4	16
	70–79	0	0	1	2	3
	80+	0	0	0	0	0
Adjuvant chemotherapy, stage III						
	19–49	2	47	72	93	85
	50–59	1	34	60	83	79
	60–69	0	32	52	76	80
	70–79	0	8	25	36	49
	80+	0	0	1	4	5
Resection of primary tumour, stage IV						
	19–49	76	69	85	83	64
	50–59	80	78	73	70	61
	60–69	82	83	70	70	67
	70–79	78	75	71	68	59
	80+	78	71	69	64	47
Chemotherapy, stage IV						
	19–49	17	38	60	68	82
	50–59	11	33	44	63	75
	60–69	5	20	28	50	69
	70–79	2	3	12	32	39
	80+	0	0	1	3	10

[a]Percentages of patients who underwent the respective treatment.

merely a decline in distal tumour site. Possibly changes in diet and lifestyle, and maybe also the use of medications such as aspirin and non-steroidal anti-inflammatory drugs, and hormone replacement therapy in women, are responsible for the rightward shift in CRC incidence through differential effects of these risk factors on the respective subsites.

There was a vast improvement in 5-year relative survival for both colon and rectal cancer, being largest in the latter and among stage III patients. A number of other European population-based studies already earlier reported on these remarkable improvements [20–23]. The low relative excess risks related to adjuvant chemotherapy among patients with stage III colon carcinoma and those related to systemic treatment among patients with stage IV colon or rectal carcinoma are however prone to bias in this retrospective analysis: patients who are fit are more likely to be treated with chemotherapy [24]. The fact that the RER for adjuvant or palliative chemotherapy was alike or even lower among older patients suggests that selection bias influenced our results.

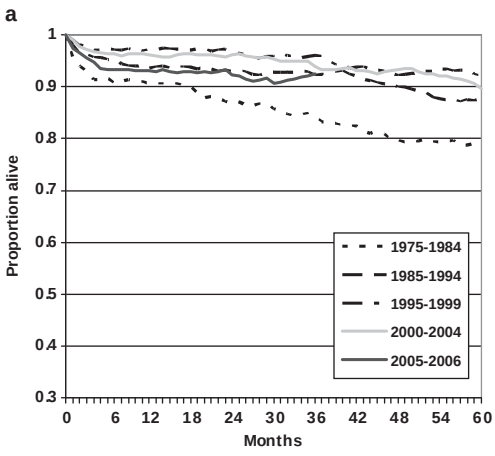
The current study demonstrated that the increase in survival was more pronounced among patients younger than 70. Our observation that survival also improved for older patients with rectal cancer is in contradiction with other Dutch studies using somewhat older data [2,25]. Indeed, our data did also not show an improvement among these patients during the 1990s. Our finding that recent survival of elderly patients has improved is in line with a SEER registry-based study [26]. For stage III colon cancer patients, the increased use of effective adjuvant chemotherapy regimens for these patients probably largely accounted for the dramatic improvement. Among elderly stage III patients, survival increased more moderately. Adjuvant chemotherapy was administered to only 5% of those aged 80 or older in the period 2005–2007, although several studies have demonstrated the benefit of this therapy at higher ages [27]. Besides age as well as hospital, also comorbidity, gender, and socio-economic status influenced administration of adjuvant chemotherapy in the south of the Netherlands [24].

Table IIb. Trends in primary treatment for patients with rectal cancer in the south of the Netherlands, according to age[a].

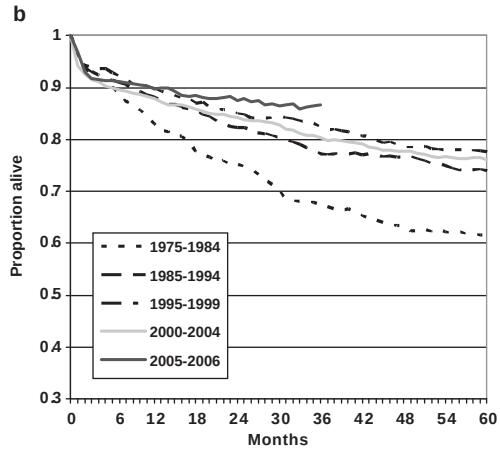
		Period of diagnosis				
Treatment	Age (yrs)	1985–89 %	1990–94 %	1995–99 %	2000–04 %	2005–07 %
Resection, stage I–III						
	19–49	96	95	94	98	97
	50–59	99	97	97	97	98
	60–69	98	99	97	96	97
	70–79	96	96	94	95	97
	80+	89	96	93	88	88
Pre/postoperative radiotherapy[b], stage II/III						
	19–49	55	63	58	77	80
	50–59	67	61	54	73	80
	60–69	46	57	47	71	77
	70–79	31	43	37	58	69
	80+	15	20	19	42	55
(Neo-) adjuvant chemotherapy plus radiotherapy, stage II/III						
	19–49	0	11	14	37	43
	50–59	2	6	11	27	27
	60–69	0	2	4	22	21
	70–79	0	1	1	9	10
	80+	0	0	0	1	3
Resection of primary tumour, stage IV						
	19–49	53	50	57	66	21
	50–59	72	54	69	56	20
	60–69	75	55	63	60	44
	70–79	63	63	55	42	35
	80+	78	40	36	31	19
Chemotherapy, stage IV						
	19–49	5	17	54	76	93
	50–59	9	36	49	65	70
	60–69	17	10	35	53	65
	70–79	2	7	17	31	42
	80+	0	0	0	4	7

[a]Percentages of patients who underwent the respective treatment.
[b]Since mid-1990s, postoperative radiotherapy was replaced by preoperative radiotherapy.

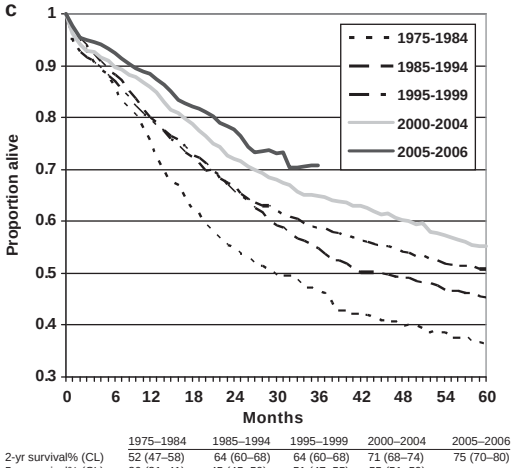
Large changes in treatment have taken place among rectal cancer patients: implementation of Total Mesorectal Excision (TME) and a shift from post- to preoperative radiotherapy together with increased administration of (neo-adjuvant) chemotherapy [3,5,28]. The increase in survival for rectal cancer in general was large, and when the survival in the period 1965–1974 (33%) is also taken into account, the relative improvement in survival was the largest of all adult tumours. Also for stage IV CRC patients survival improved; responsible is an increased use of and changes in chemotherapy, and probably a more adequate selection of patients eligible for surgery [4]. Partly, the improved stage-specific survival in these and other patients might be the results of stage migration, as a consequence of more adequate staging procedures [29]. The increased proportions of patients with stage III and IV disease over time underline these developments. Better and more widely applied imaging techniques (MRI, CT-scan) and increasingly adequate pathology (more thorough search for lymph nodes by pathologists) are very likely to have an effect on all stage-specific survival analyses besides stage I. The fact that after adjustment for treatment, still an effect of period of diagnosis could be noted in the multivariable relative survival analyses, suggests that stage migration has played a role here. However, the improvements seen in non-stage specific survival, especially among patients younger than 70 years, suggests that not only stage migration is responsible for the improvements in stage-specific survival. In most recent years, there has been a regionalisation of the surgical expertise for treating locally advanced rectal carcinoma and liver metastases. As opposed to the use of adjuvant chemotherapy among patients with stage III colon cancer, in our multivariable analyses the survival improvements for stage II/III rectal cancer patients could not be explained by the increased use of preoperative radiotherapy. The majority of studies showed



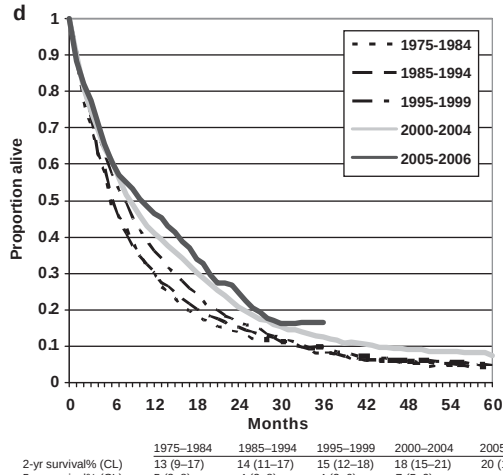
	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (confidence limits (CL)	87 (82–92)	94 (91–97)	96 (93–99)	97 (94–100)	92 (87–97)
5-yr survival% (CL)	79 (73–85)	88 (83–93)	92 (87–97)	89 (85–94)	not applicable
(n.a.)					



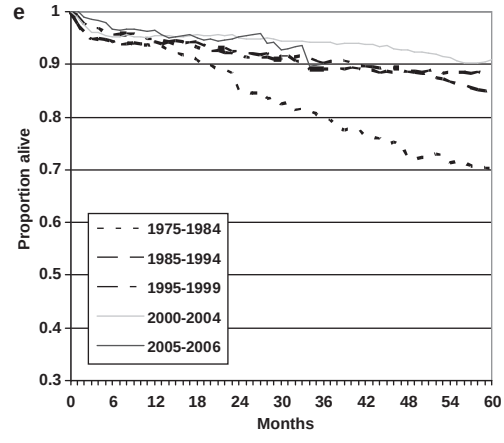
	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	74 (69–79)	82 (79–85)	85 (82–88)	83 (81–85)	88 (85–92)
5-yr survival% (CL)	61 (55–67)	74 (70–78)	77 (73–81)	76 (73–79)	n.a.



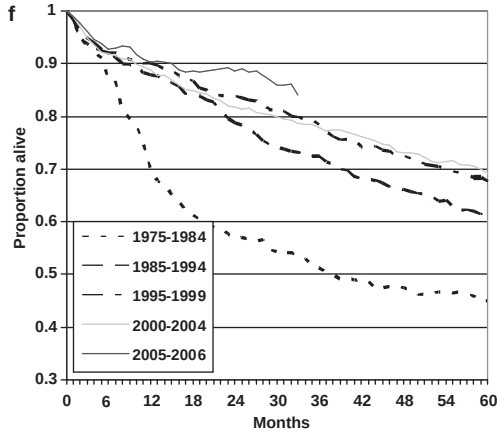
	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	52 (47–58)	64 (60–68)	64 (60–68)	71 (68–74)	75 (70–80)
5-yr survival% (CL)	36 (31–41)	45 (45–50)	51 (47–55)	55 (51–59)	n.a.



	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	13 (9–17)	14 (11–17)	15 (12–18)	18 (15–21)	20 (16–21)
5-yr survival% (CL)	5 (2–8)	4 (2–8)	4 (2–6)	7 (5–9)	n.a.

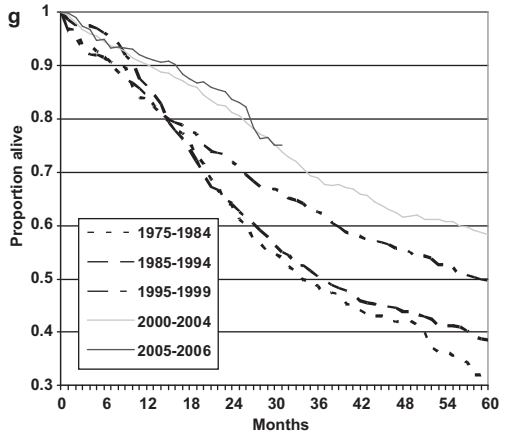


	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	84 (79–89)	92 (88–96)	91 (88–94)	95 (92–98)	96 (92–100)
5-yr survival% (CL)	70 (63–77)	86 (81–91)	88 (83–93)	91 (87–95)	n.a.

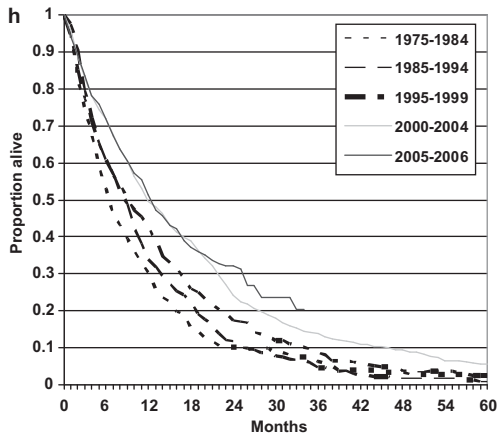


	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	57 (50–64)	78 (74–82)	83 (79–87)	81 (77–85)	89 (84–94)
5-yr survival% (CL)	45 (37–53)	61 (56–66)	67 (62–73)	68 (63–73)	n.a.

Figure 4. *(Continued)*.

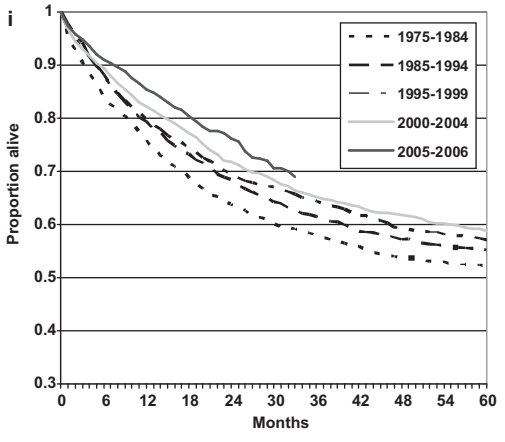


	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	59 (52–65)	61 (56–66)	70 (65–75)	80 (76–84)	82 (76–88)
5-yr survival% (CL)	30 (24–36)	38 (33–43)	50 (44–56)	58 (53–63)	n.a.

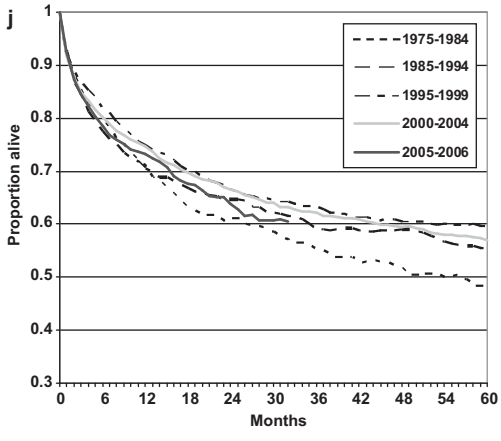


	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	10 (6–14)	9 (6–12)	17 (13–21)	21 (17–25)	30 (23–37)
5-yr survival% (CL)	*	*	*	6 (3–9)	n.a.

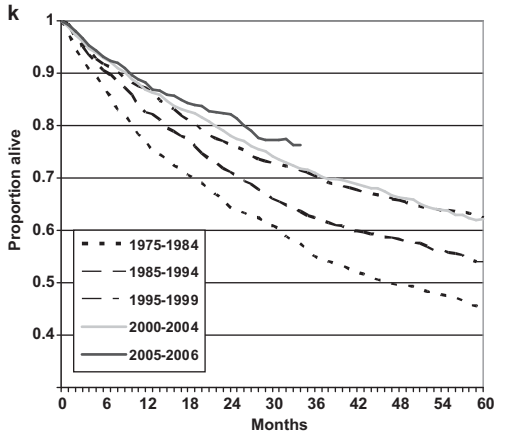
*** = effective number at risk at 60 months lower than 10**



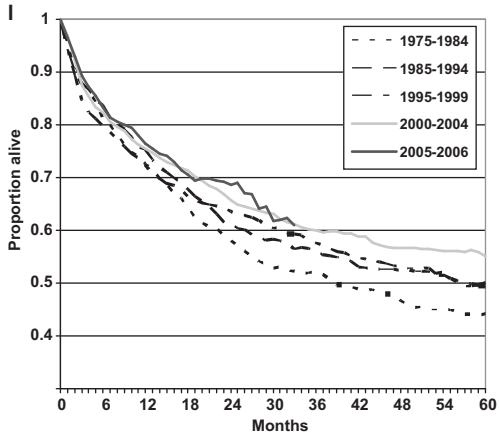
	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	63 (60–66)	67 (65–70)	69 (67–71)	71 (69–73)	76 (73–79)
5-yr survival% (CL)	52 (49–55)	55 (52–58)	57 (54–60)	59 (57–61)	n.a.



	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	61 (57–65)	65 (62–68)	66 (63–69)	66 (64–68)	63 (59–67)
5-yr survival% (CL)	48 (43–53)	56 (52–60)	60 (56–64)	57 (54–60)	n.a.



	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	64 (60–68)	70 (67–73)	76 (73–79)	77 (75–79)	81 (77–85)
5-yr survival% (CL)	45 (41–49)	54 (51–57)	62 (59–65)	62 (59–65)	n.a.



	1975–1984	1985–1994	1995–1999	2000–2004	2005–2006
2-yr survival% (CL)	57 (52–62)	60 (56–64)	63 (59–67)	65 (61–69)	69 (64–47)
5-yr survival% (CL)	44 (38–50)	49 (44–54)	50 (56–55)	55 (50–60)	n.a.

Figure 4. *(Continued)*.

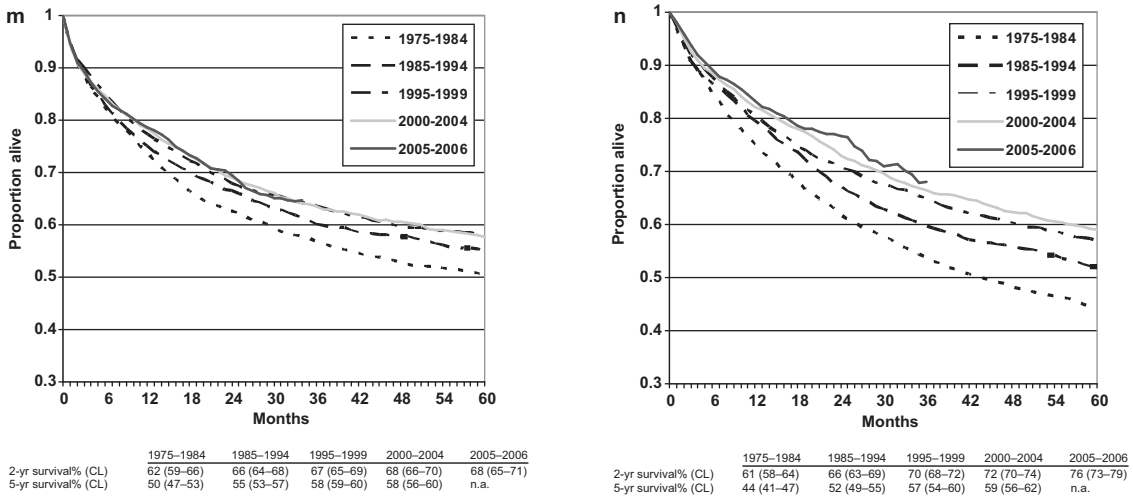


Figure 4. (a) Relative survival among patients with stage I colon cancer. (b) Relative survival among patients with stage II colon cancer. (c) Relative survival among patients with stage III colon cancer. (d) Relative survival among patients with stage IV colon cancer. (e) Relative survival among patients with stage I rectal cancer. (f) Relative survival among patients with stage II rectal cancer. (g) Relative survival among patients with stage III rectal cancer. (h) Relative survival among patients with stage IV rectal cancer. (i) Relative survival among patients with colon cancer, all stages, younger than 70 years. (j) Relative survival among patients with colon cancer, all stages, 70 years or older. (k) Relative survival among patients with rectal cancer, all stages, younger than 70 years. (l) Relative survival among patients with rectal cancer, all stages, 70 years or older. (m) Relative survival among patients with colon cancer, all stages and ages. (n) Relative survival among patients with rectal cancer, all stages and ages. * = effective number at risk at 60 months lower than 10.

a clear effect of preoperative radiotherapy on local control, but the effect of preoperative radiotherapy on overall survival was less unambiguous [5,30]. No significant survival improving effects have been reported for preoperative chemoradiation (5-fluoruracil-based) among patients with locally advanced rectal carcinoma, but also here the beneficial effects on local control are well documented [31,32]. Anyway, changes in surgical management, more accurate staging procedures by surgeon and pathologist, perioperative care, and the establishment of multidisciplinary teams probably all have contributed to the improved survival of rectal carcinoma. Especially the TME-trial, in which a large number of hospitals in the Eindhoven Cancer Registry area participated actively, has had a large influence on quality of rectal cancer treatment [3,5,33]. However, already before the start of the TME-trial, a number of surgeons already performed their resections in a TME-like fashion. The increased survival of patients with rectal carcinoma seen already long before the introduction of TME surgery suggests that other mechanisms and developments play a role, such as more general learning curves in diagnostics and surgery. This is also true for colon cancer, where an increase in survival could be noted already before the widespread introduction of adjuvant chemotherapy. The large effect of for example improved surgical management on long-term survival of both colon and rectal cancer has been reported in a French population-based study; it was calculated that a reduction of 30-day mortality from 18 to 8% had led to a relative improvement of 27.5% in 5-year survival [34].

Although adherence to clinical guidelines is generally considered a measure of quality of care, deviating from these guidelines in case of an elderly patient is not necessarily indicating inferior quality of care. The large proportion of elderly patients presenting with comorbidity, and the inherent lack of evidence-based guidelines for this group, often call for pragmatic individualised treatment [35,36]. In view of the growing proportion of elderly CRC patients—partly because of the rising incidence rates

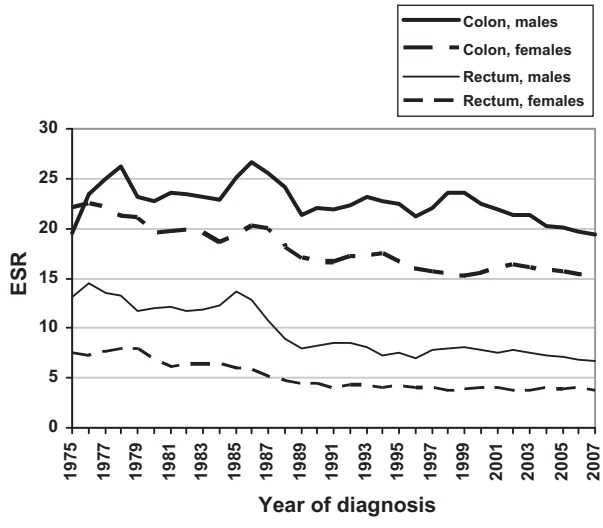


Figure 5. Age-standardised mortality of CRC in the south of the Netherlands (3-year moving average), according to gender and tumour site.

Table IIIa. Multivariable relative survival analysis of patients with stage III colon and stage II/III rectal cancer.

		Model excl. treatment[1]		Model incl. treatment[1]	
		RER	cl	RER	cl
Colon, stage III, <70 yrs	Period of diagnosis				
	1975–1984	2.0	1.63–2.52	1.0	0.80–1.35
	1985–1994	1.6	1.32–2.00	0.9	0.71–1.16
	1995–1999	1.3	1.10–1.64	1.1	0.88–1.33
	2000–2006[2]	1.0		1.0	
	Treatment				
	Surgery[2]	–		1.0	
	Surgery + adj. chemotherapy	–		0.4	0.36–0.52
Colon, stage III, 70+ yrs	Period of diagnosis				
	1975–1984	1.8	1.38–3.00	1.4	1.07–1.80
	1985–1994	1.2	0.96–1.52	1.0	0.77–1.22
	1995–1999	1.2	0.97–1.48	1.1	0.89–1.36
	2000–2006[2]	1.0	0.01	1.0	
	Treatment				
	Surgery[2]	–		1.0	
	Surgery + adj. chemotherapy	–		0.4	0.28–0.52
Rectum, stage II/III, <70 yrs	Period of diagnosis				
	1975–1984	2.8	2.24–3.43	3.1	2.42–3.85
	1985–1994	1.9	1.55–2.29	2.1	1.68–2.53
	1995–1999	1.3	1.08–1.63	1.4	1.14–1.78
	2000–2006[2]	1.0		1.0	
	Treatment				
	Surgery[2]	–		1.0	
	Surgery + preop. radiotherapy	–		1.1	0.91–1.26
Rectum, stage II/III, 70+ yrs	Period of diagnosis				
	1975–1984	2.0	1.51–2.59	2.1	1.51–2.85
	1985–1994	1.4	1.07–1.73	1.4	1.09–1.92
	1995–1999	1.2	0.91–1.50	1.2	0.91–1.63
	2000–2006[2]	1.0		1.0	
	Treatment				
	Surgery[2]	–		1.0	
	Surgery + preop. radiotherapy	–		0.9	0.7–1.09

RER = relative excess risk.
cl = 95% confidence limits.
[1]Adjusted for follow-up time, age, gender, subsite, and variables shown.
[2]Reference category.

but especially because of the aging population—clinicians will more and more often face difficult decisions regarding adjuvant therapy. However, a growing specific knowledge of CRC care of the elderly is probably shifting the approach towards elderly patients towards more aggressive treatment and multimodal therapy [27], as partly confirmed by our data.

The aging of the population and hence the rise in absolute numbers of patients with CRC together with the increased survival rates will also lead to a large number of individuals who were diagnosed with CRC five or more years ago. A report of the Dutch National Cancer Society estimated the prevalence of CRC patients in the Netherlands to increase from 60 000 in 2005 to 100 000 in 2015 [37]. These patients have to be followed-up, which will further claim endoscopy capacity, and part of these patients will need extra care, i.e. because of a permanent stoma. Furthermore, patients who have survived several years also have an excess risk of developing a subsequent primary cancer.

The strength of the current study is the availability of long-term, high quality population-based data [38]. Studying long-term trends enables an evaluation of implemented care and eventual screening activities, and an anticipation of developments in the near future. The results of our study showed that the workload of all clinicians involved in the diagnosis, staging, treatment, and follow-up of CRC will keep increasing considerably in the near future. Not only the steady increase in age-adjusted incidence, but especially the demographic changes of the Dutch population and the likely future implementation of CRC mass screening will necessitate investments with relation to education, recruitment, materials, and infra-structure. In many other European countries, the situation is the same

Table IIIb. Multivariable relative survival analysis of patients with stage IV colon or rectal cancer.

		Model excl. treatment[1]		Model i\ncl. treatment[1]	
		RER	cl	RER	cl
Colon,stage IV, <70 yrs	Period of diagnosis				
	1975–1984	1.7	1.44–1.99	1.4	1.20–1.69
	1985–1994	1.4	1.19–1.59	1.2	1.01–1.37
	1995–1999	1.2	1.09–1.42	1.1	1.00–1.31
	2000–2006[2]	1.0		1.0	
	Treatment				
	No systemic therapy[2]	–		1.0	
	Systemic therapy	–		0.7	0.62–0.79
Colon, stage IV, 70+ yrs	Period of diagnosis				
	1975–1984	0.9	0.75–1.15	0.8	0.60–0.97
	1985–1994	1.2	1.01–1.39	1.0	0.83–1.15
	1995–1999	1.1	0.97–1.33	1.0	0.83–1.15
	2000–2006[2]	1.0		1.0	
	Treatment				
	No systemic therapy[2]	–		1.0	
	Systemic therapy	–		0.5	0.43–0.62
Rectum, stage IV, <70 yrs	Period of diagnosis				
	1975–1984	2.3	1.82–2.80	2.0	1.58–2.48
	1985–1994	1.9	1.61–2.36	1.6	1.34–2.02
	1995–1999	1.4	1.14–1.66	1.3	1.06–1.55
	2000–2006[2]	1.0		1.0	
	Treatment				
	No systemic therapy[2]	–		1.0	
	Systemic therapy	–		0.7	0.61–0.84
Rectum, stage IV, 70+ yrs	Period of diagnosis				
	1975–1984	1.0	0.74–1.33	0.8	0.60–1.09
	1985–1994	1.0	0.79–1.29	0.8	0.65–1.09
	1995–1999	1.2	0.96–1.50	1.1	0.88–1.37
	2000–2006[2]	1.0		1.0	
	Treatment				
	No systemic therapy[2]	–		1.0	
	Systemic therapy	–		0.5	0.41–0.68

RER = relative excess risk.
cl = 95% confidence limits.
[1]Adjusted for follow-up time, age, gender, subsite, and variables shown.
[2]Reference category.

[11]. Nevertheless, this study demonstrated large improvements in management and survival of CRC patients between 1975 and 2007. The changes in management of rectal cancer lead to a superior increase in survival of these patients compared to patients with colon cancer, even surpassing the latter.

Table IV. Ten-years prevalence (ESR) of patients with CRC at January 1, 1984, 1994, and 2004, respectively, in the south of the Netherlands.[1]

		Prevalence (ESR)		
		01-01-1984	01-01-1994	01-01-2004
Males	Colon	101	138	167
	Rectum	70	104	128
Females	Colon	96	118	145
	Rectum	51	59	75

[1]Age-standardised number of patients alive, diagnosed with colorectal cancer up to 10 years before the respective date, per 100 000 inhabitants.

Acknowledgements

The authors thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection. This work was carried out with grants from the Dutch Cancer Society (KWF) (IKZ 2006-3588).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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