

ORIGINAL ARTICLE

Excess mortality after curative surgery for colorectal cancer changes over time and differs for patients with colon versus rectal cancer

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Abstract

Background. Improved management of colorectal cancer patients has resulted in better five-year survival for rectal cancer compared with colon cancer. We compared excess mortality rates in various time intervals after surgery in patients with colon and rectal cancer. **Material and methods.** We analysed all patients with curative resection of colorectal cancers reported in the Cancer Registry of Norway before (1994–1996) and after (2001–2003) national treatment guidelines were introduced. Excess mortality was analysed in different postoperative time intervals within the five-year follow-up periods for patients treated in 1994–1996 vs. 2001–2003. **Results.** A total of 11 437 patients that underwent curative resection were included. For patients treated from 1994 to 1996, excess mortality was similar in colon and rectal cancer patients in all time intervals. For those treated from 2001 to 2003, excess mortality was significantly lower in rectal cancer patients than in colon cancer patients perioperatively (in the first 60 days: excess mortality ratio = 0.46, $p = 0.007$) and during the first two postoperative years (2–12 months: excess mortality ratio = 0.54, $p = 0.010$; 1–2 years: excess mortality ratio = 0.60, $p = 0.009$). Excess mortality in rectal cancer patients was significantly greater than in colon cancer patients 4–5 years postoperatively (excess mortality ratio = 2.18, $p = 0.003$). **Conclusion.** Excess mortality for colon and rectal cancer changed substantially after the introduction of national treatment guidelines. Short-term excess mortality rates was higher in colon cancer compared to rectal cancer for patients treated in 2001–2003, while excess mortality rates for rectal cancer patients was significantly higher later in the follow-up period. This suggests that future research should focus on these differences of excess mortality in patients curatively treated for cancer of the colon and rectum.

Surgery remains the most important treatment modality for curing patients with colorectal cancer (CRC). During the past few decades, management of CRC has changed considerably in terms of pre-operative work-up, imaging and staging, improved surgical techniques, and the introduction of adjuvant therapy. Accordingly, new disease management algorithms have been introduced [1,2], followed by improved survival [3,4]. Recent studies suggest that the observed relative improvement in five-year survival is greater in rectal cancer than in colon cancer [5–7]. Reduced perioperative mortality has been suggested as an important explanation for the observed improvement in long-term survival [8,9].

Survival is usually presented as three- or five-year relative survival. Relative survival and excess mortality estimates are useful for national registry data because of cause of death uncertainty, and these estimates also take into account excess mortality caused by treatment. Relative survival estimates at arbitrarily set follow-up times, such as five-year relative survival, describe cumulative survival during the entire period and are valuable for overall cancer management and outcome. However, these estimates do not reveal temporal variations in mortality rates during the entire follow-up period. Therefore, estimates of excess mortality rates at different postoperative time intervals may reveal important

information about treatment effects by depicting temporal mortality differences during follow-up [10]. Currently, treatment of rectal and colon cancers differ in terms of the surgical approach as well as in the use of radiation and/or chemotherapy. Such differences are likely to influence both short- and long-term postsurgical mortality. Consequently, this study investigated whether there were temporal differences in excess mortality rates at various postoperative time intervals in CRC patients surgically treated for cure in two different time periods. We hypothesised that differences in national treatment strategies for rectal vs. colon cancer would influence disease outcomes for the patients treated in these two time periods; thus, we compared excess mortality in the two patient groups at various time intervals during the five-year follow-up.

Material and methods

In Norway, it is mandatory to report the data of all patients diagnosed with malignant tumours to the government's Cancer Registry of Norway (CRN). This ensures that >98% of all new cancers are recorded [11]. The Norwegian Rectal Cancer Registry (NRCR), which is affiliated with the CRN, was established in 1993, and detailed information regarding diagnosis, stage (TNM classification), treatment, and outcomes for all patients with rectal cancer was recorded prospectively [1,11]. A unique 11-digit personal identification number enables complete follow-up and high data quality.

Based on information from the CRN and the NRCR, we identified all patients ($n = 31\,158$) diagnosed with invasive adenocarcinoma of the colon or rectum between January 1994 and December 2003. Patients diagnosed with more than one colorectal

cancer were registered with their first cancer incident only ($n = 1458$). Patients with both colon and rectal cancer were excluded ($n = 9$).

We excluded patients diagnosed with distant metastases or with cancer of unknown stage at the time of primary diagnosis ($n = 9024$, 28.9%), as well as those treated with non-resection procedures (e.g. endoscopic or trans-anal tumour removal, surgical exploration, or defunctioning stoma as definite treatment) or with non-surgical or unknown treatment ($n = 1595$, 5.1%). The proportion of patients with distant metastases at the time of diagnosis increased significantly from 26.8% in 1994–1996 to 32.8% in 2001–2003 ($p < 0.001$). Details regarding patient selection and exclusion during the two time periods are shown in Table I. Patients identified only on the basis of death certificate or autopsy and 275 (0.9%) patients with unknown tumour site were excluded. Thus, the patients included in this study had major resection for surgical treatment of colon or rectal cancer with curative intent. Enrolment into the CRN was based on the date of diagnosis of colorectal cancer. To obtain complete follow-up data for at least five years for all patients, Statistics Norway (as of December 31, 2008) provided the time of death of deceased patients [12]. Patients who emigrated from Norway ($n = 38$) were censored at the time of emigration.

Evolution of national treatment strategies

Between 1994 and 1996, total mesorectal excision (TME) was implemented as the national standard of surgical care for rectal cancer in Norway [13]. The NRCR was already established (in November 1993), and a centralisation effort was begun to reduce the number of hospitals treating rectal cancer

Table I. Exclusion of colorectal cancer patients who did not undergo curative treatment in 1994–1996 and 2001–2003.

	Total	1994–1996 (%)	2001–2003 (%)	Difference in the proportions for the two time periods (95% CI)
Patients considered for inclusion	18 684*	8769 (28.8)	9915 (31.8)	
Patients excluded for having synchronous/metachronous tumour	1486	373 (4.3%)	508 (5.1%)	0.8 (0.18–1.41)
Patients excluded for having distant metastasis or unknown stage	9024	2294 (27.3)	3060 (32.5)	5.2 (3.85–6.55)
Patients excluded for undergoing non-resectional procedures or non-surgical treatment	1595	638 (10.5)	379 (6.0)	4.5 (3.53–5.48)
Patients included in study	11 437	5464 (28.7)	5973 (31.3)	

*Patients treated in 1997–2000 (12 474 patients) were not included in the current analysis.

Data are not shown for patients identified only on the basis of death certificate or autopsy.

from more than 50 to fewer than 30. Since 2000, preoperative radiotherapy (usually 50 Gy in 25 fractions) followed by TME surgery has been recommended for rectal cancer patients with clinically fixed (i.e. tethered tumours or tumours that were not movable by palpation or with a rigid rectoscope) or T4 rectal tumours (i.e. tumours showing growth into adjacent pelvic structures) [14]. Adjuvant chemotherapy was not part of the national guidelines for rectal cancer during either study period. In contrast, routine adjuvant chemotherapy for colon cancer that was limited to patients with stage III colon cancer who were 75 years of age or younger was recommended in the national guidelines in late 1997 [2].

Based on these changes in the national recommendations, outcomes were analysed for patients treated during the 1994–1996 period (introduction of TME, NRCR, before centralisation of rectal surgery) and the 2001–2003 period (preoperative radiotherapy for fixed/T4 tumours followed by TME, centralised rectal surgery, and adjuvant chemotherapy for colon cancer). While the 1997–2000 time period was considered to be heterogeneous with regard to the introduction of adjuvant treatment for colon cancer, patients treated during that time period were not included.

Definitions

The rectum was anatomically restricted to the distal part of the large bowel as measured as 15 cm proximal to the anal verge. The remaining parts of the large bowel, including the appendix, comprised the colon. Patients with lymph node metastases were categorised as pN+, and those without lymph node metastases were categorised as pN0.

Postoperative time intervals

To evaluate excess mortality as a function of follow-up time, we estimated the excess mortality rates in various postoperative time intervals: 0–2 months, 2–12 months, 1–2 years, 2–3 years, 3–4 years, and 4–5 years.

Age groups

Adjuvant chemotherapy was offered to colon cancer patients 75 years of age or younger with node-positive disease only; therefore, patient age was categorised as ≤ 75 years and > 75 years of age [2].

Excess mortality

The patients' total mortality rate, also called the hazard rate, $\lambda(t)$, can be modeled as the sum of the

general population mortality rate for a comparable group from the general population, $\lambda_p(t)$, plus the additional mortality rate caused by the disease, also called the excess mortality rate, $\lambda_E(t)$. This can be expressed as follows:

$$\lambda(t) = \lambda_p(t) + \lambda_E(t).$$

The excess mortality rate is the excess instantaneous rate of dying at time t given survival to that point. In this study, we reported the excess mortality rate as the number of excess deaths per 1000 patient years. The estimated excess mortality rate is calculated as the difference between the total mortality rate experienced by the patients and the expected mortality rate of a comparable group from the general population matched with the patients with respect to age, sex, and cohort year. Data for the general population were acquired from actuarial tables that are available from Statistics Norway [12]. A common model for the excess mortality rate is a proportional model of the form:

$$\lambda_E(t) = \lambda_0(t) \exp(\beta x)$$

In this expression, x is a vector of variables with potential impact on excess mortality rate. The baseline excess mortality rate $\lambda_0(t)$ is often estimated as a stepwise function [15] but can also be estimated as a smoothed function [16]. We used a stepwise baseline excess mortality rate, which is constant in each of the defined postoperative time intervals 0–2 months, 2–12 months, 1–2 years, 2–3 years, 3–4 years, and 4–5 years, and compared defined patient groups by calculating excess mortality ratios as the ratio of their respective excess mortality rates for each postoperative time interval. When estimating these mortality ratios, we included sex and age as covariables to adjust for potential age and gender effects and to assure unbiased estimates of excess mortality rates [17].

Statistical analysis

The software packages PASW Statistics 18.0 for Mac (SPSS Inc., Chicago, IL, USA) and R 2.14.2 (<http://www.r-project.org>) were used for the statistical analyses. The R-package "relSurv" version 2.0-1 was used for the excess mortality calculations [18] using the maximum likelihood method for parameter estimation. Categorical data were analysed by cross tabulation and Pearson's χ^2 -test. We compared the 1994–1996 and 2001–2003 study periods with regard to age group, stage of disease, and tumour site. We used a standard 5% significance level. When we simultaneously reported excess mortality ratios for each time interval during the five-year follow-up, we used a 1% level for the inference in each time

Table II. Demographic characteristics and nodal status of 11 437 patients surgically treated with curative intent for colon and rectal cancer in Norway.

	Total n (%)	Site		p-value*
		Colon n (%)	Rectum n (%)	
Number of patients	11 437 (100)	7849 (70)	3421 (30)	<0.001
Sex				
Males	5554 (51)	3534 (45)	1945 (57)	<0.001
Females	5883 (49)	4315 (55)	1476 (43)	
Age				
≤ 75 years	6896 (60)	4492 (57)	2319 (68)	<0.001
> 75 years	4541 (40)	3357 (43)	1102 (33)	
Nodal status				
pN0**	7473 (65)	5240 (67)	2118 (62)	<0.001
pN+**	3964 (35)	2609 (33)	1303 (38)	

*P-value with regard to site of tumour; **pN0 = no lymph node metastases; pN+ = lymph node metastases present.

interval to guard against type 1 errors in multiple testing. This 1% level corresponds to the use of an overall 5% level with a Bonferroni correction for multiple testing.

Results

In 1994–1996 and 2001–2003, a total of 11 437 patients (5464 in 1994–1996 and 5973 patients in 2001–2003) underwent curative resection for CRC. The baseline characteristics of the cohort have been reported previously [5]. Patient demographics and nodal status are shown in Table II. The proportion of patients aged >75 years increased from 37% in the 1994–1996 period to 42% in the 2001–2003 period ($p = 0.001$), as did the proportion of patients with pN+ disease (32% in 1994–1996 vs. 36% in 2001–2003; $p < 0.001$). Although the proportion of patients who were surgically treated with curative intent decreased by 2.1% (62.3% in 1994–1996 vs. 60.2% in 2001–2003; $p = 0.003$), the proportion of

patients with colon and rectal cancer were similar during the two periods. There were significantly more rectal resections performed according to TME principles in 2001–2003 than in 1994–1996 (96% vs. 82%, $p < 0.001$), and radiotherapy was given to significantly more rectal cancer patients that were treated in 2001–2003 (18% vs. 8%, $p < 0.001$).

Temporal changes in the two study periods

Excess mortality rates during the perioperative time interval (0–2 months postoperatively) remained unchanged for patients with colon or rectal cancer in the two study periods. However, colon cancer patients treated in 2001–2003 had significantly lower excess mortality rates at 2–3 years than those treated in 1994–1996 (Table III, Figure 1a). Rectal cancer patients treated in 2001–2003 showed significantly lower excess mortality rates than those treated in 1994–1996 at 2–12 months, 1–2 years, and 2–3 years after surgery (Table III and Figure 1b). There were no significant differences in the survival of rectal cancer patients treated in two study periods (3–4 years or 4–5 years after surgery).

Colon vs. rectal cancer

For patients treated in the 1994–1996 study period, there were no differences in excess mortality rates for colon vs. rectal cancer in any of the time intervals (Table III, Figure 2a). However, for patients treated in the 2001–2003 study period, those with rectal cancer had a perioperative excess mortality rate that was less than 50% of that for colon cancer patients (excess mortality ratio 0.46, $p = 0.007$). Rectal cancer patients also showed significantly lower excess mortality than colon cancer patients during the 2–12-month postoperative interval (excess mortality ratio 0.54; $p = 0.01$) and in the second year after surgery (excess mortality ratio 0.6; $p = 0.01$) (Table III and Figure 2b). No other significant differences were observed until the final follow-up interval, when

Table III. Excess hazard at different postoperative time intervals during the five-year follow-up period, reported as per excess deaths per 1000 person years. Excess hazard figures are provided for the 1994–1996 and 2001–2003 periods.

	All patients				Lymph node-positive ≤ 75 y				Lymph node-positive > 75 y			
	Colon		Rectum		Colon		Rectum		Colon		Rectum	
	1994–96	2001–03	1994–96	2001–03	1994–96	2001–03	1994–96	2001–03	1994–96	2001–03	1994–96	2001–03
0–2 mo	123	143	70	66	64	112	52	49	337	388	291	171
2–12 mo	70	53	61	28	131	63	104	38	224	220	124	132
1–2 y	63	61	72	36	152	100	156	78	185	200	303	102
2–3 y	80	51	79	49	195	104	172	79	131	91	309	119
3–4 y	50	43	66	54	120	85	150	91	109	108	55	78
4–5 y	37	20	42	45	77	32	102	90	72	40	139	18

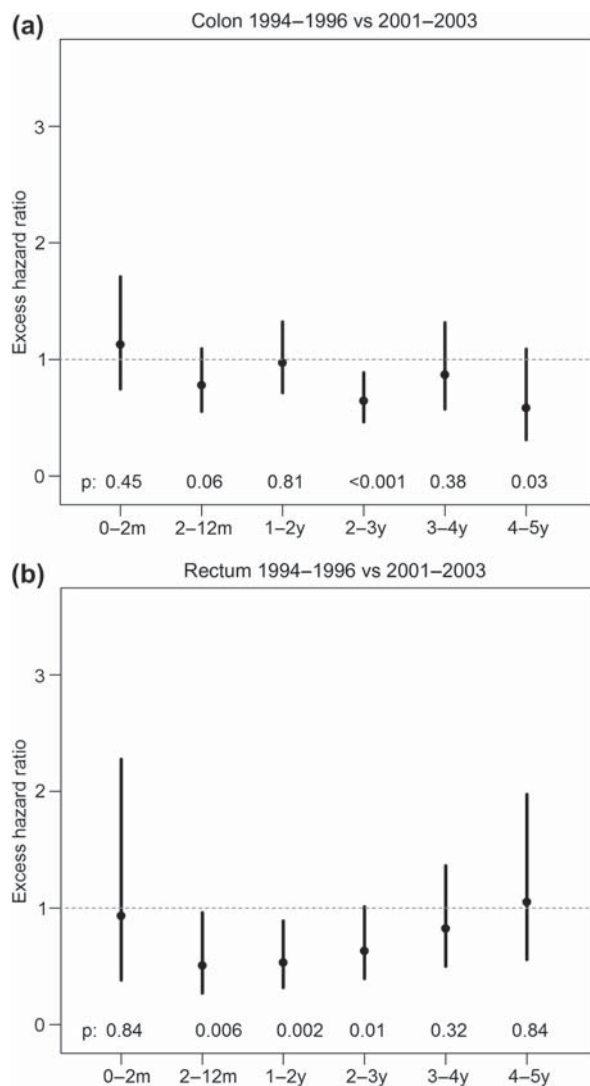


Figure 1. Excess hazard ratio with 99% confidence intervals (CI) in the 1994–1996 period compared with the 2001–2003 period for different postoperative time intervals (0–2 months, 2–12 months, 1–2 years, 2–3 years, 3–4 years, and 4–5 years). A ratio < 1 indicates a lower mortality in the 2001–2003 period compared with the 1994–1996 period. A. Colon cancer. B. Rectal cancer.

the excess mortality rate in rectal cancer patients was more than twice that of colon cancer patients (excess mortality ratio 2.18; $p = 0.003$).

Lymph node status and age

Excess mortality rates were similar for colon and rectal cancer patients without lymph node metastases (pN0) who were treated during the two study periods. However, in node-positive colon cancer patients (pN+) ≤ 75 years of age, excess mortality was significantly lower for patients treated during the 2001–2003 period at all time intervals except at 0–2 months and 3–4 years (Table III, Figure 3a).

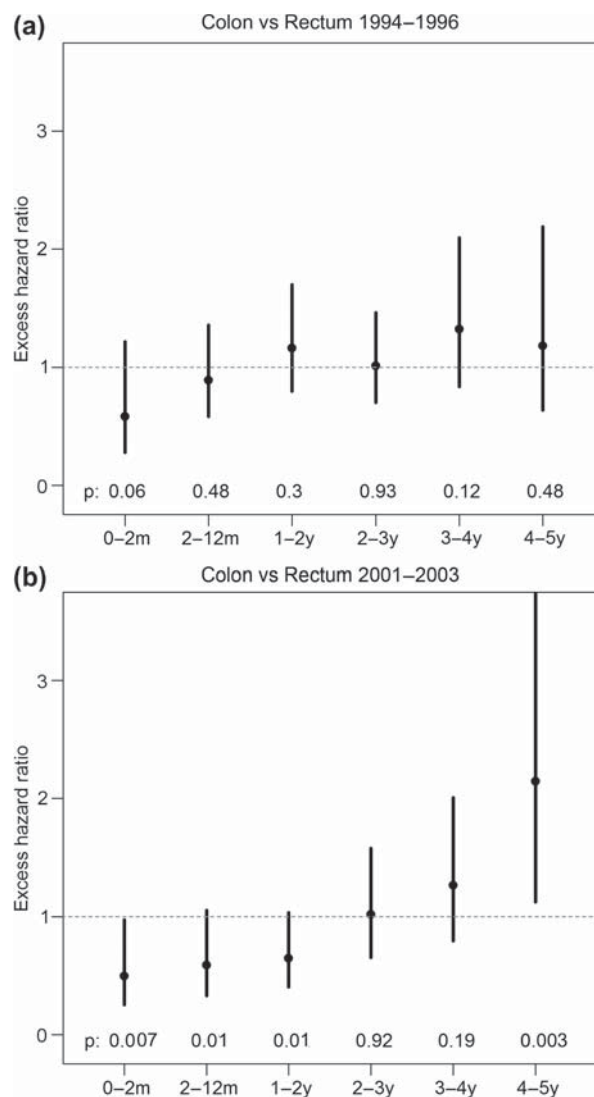


Figure 2. Excess hazard ratio with 99% confidence intervals (CI) for colon cancer compared to rectal cancer for different postoperative time intervals (0–2 months, 2–12 months, 1–2 years, 2–3 years, 3–4 years, and 4–5 years). A. 1994–1996 period. B. 2001–2003 period.

No differences were observed for patients > 75 years of age (Table III, Figure 3b).

Excess mortality rates were significantly lower in patients with rectal cancer vs. colon cancer in patients ≤ 75 years of age (months 2–12, years 1–2 and 2–3; Table III, Figure 3c) and those aged > 75 years (years 1–2 and 2–3; Table III, Figure 3d). No differences in excess mortality were observed four or five years after surgery.

Discussion

Investigating excess mortality rates in different intervals after curative surgery in patients treated in two time periods revealed significant changes over

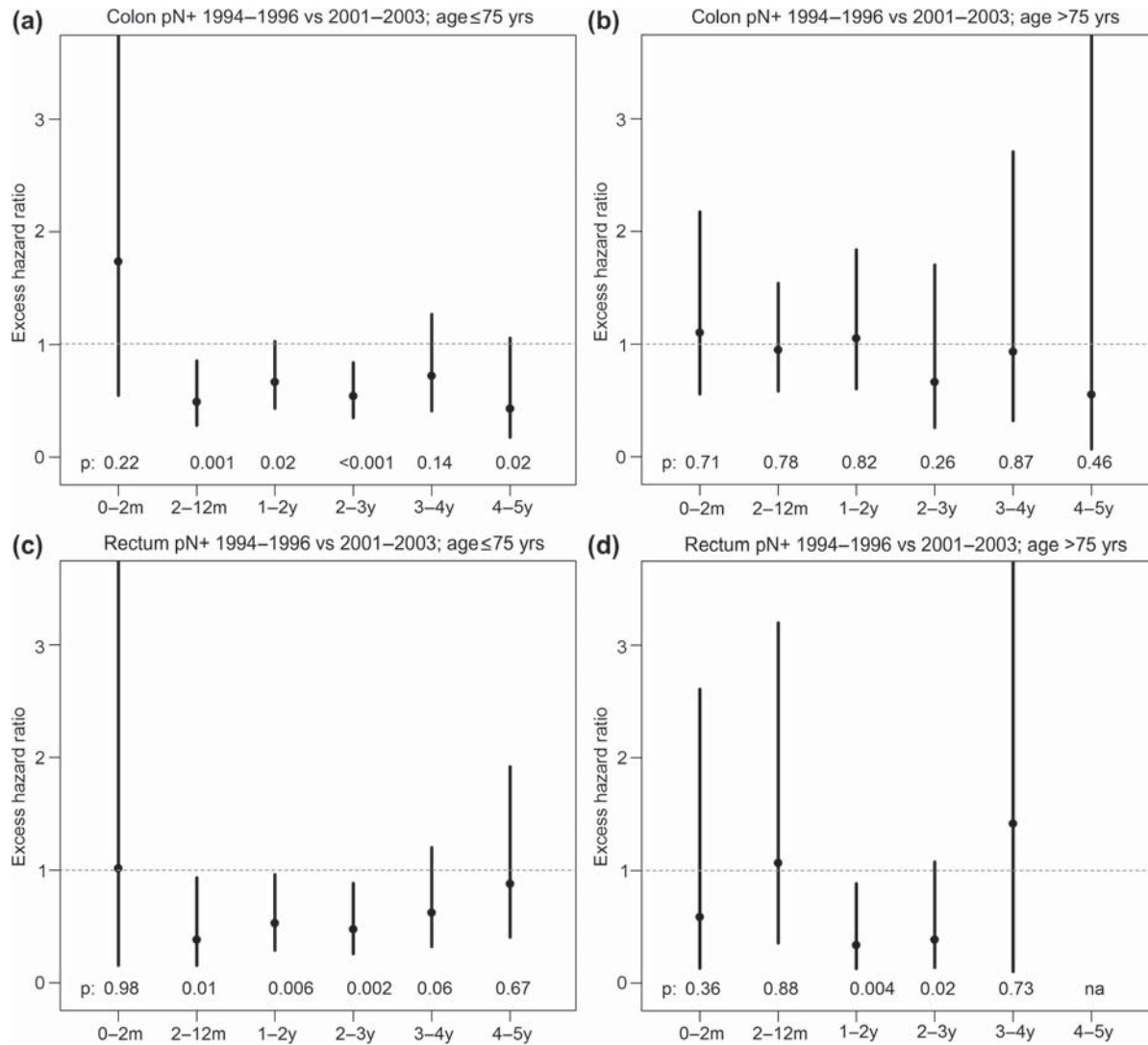


Figure 3. Excess hazard ratio with 99% confidence interval (CI) in the 1994–1996 period compared with the 2001–2003 period for patients with lymph node-positive disease during different postoperative time intervals (0–2 months, 2–12 months, 1–2 years, 2–3 years, 3–4 years, and 4–5 years) after curative surgery. For rectal cancer patients aged >75 years, there were too few incidents to generate a CI for the 4–5 year time interval. A. Colon cancer patients ≤75 years. B. Colon cancer patients >75 years. C. Rectal cancer patients ≤75 years. D. Rectal cancer patients >75 years.

time. Patients treated during the 1994–1996 study period (before implementation of nationwide standards of management) exhibited no remarkable differences in excess mortality. In contrast, patients treated for rectal and colon cancer in the 2001–2003 study period showed clear temporal differences in excess mortality, most likely reflecting the contemporary state-of-the-art management of CRC. Notably, during the 2001–2003 period, excess mortality rates for the perioperative time interval and during the first three postoperative years were significantly lower for patients with rectal cancer compared to patients with colon cancer (Figure 2b). A turning point was observed during the fifth year after surgery: at this time, the excess mortality rate of rectal cancer patients was twice that of colon cancer patients.

The observation of short-term lower excess mortality rates for rectal cancer followed by an unparalleled long-term increase in excess mortality rates may reflect low perioperative risk and good initial disease control, both of which are overcome later by increased deaths. These findings correspond to treatment changes that focused mainly on local tumour control such as TME, preoperative radiotherapy, centralisation of surgery, and regular national audits. Previously, local recurrence typically occurred during the first three postoperative years. However, in line with national data, there was a significant reduction in local rectal cancer recurrence in patients treated in the 2001–2003 study period [13,14]. We believe that patients with rectal cancer likely benefited more than those with colon cancer from these

nationwide efforts to standardise and improve treatment, possibly explaining the lower mortality rates observed in rectal cancer patients during the first three postoperative years. The benefit of reduced excess mortality at the early time intervals in rectal cancer was likely hampered by increased mortality related to late relapses, which are characterised by either distant spread or late local recurrences. In accordance with the national guidelines, rectal cancer patients with pN+ disease do not receive adjuvant chemotherapy [19,20]. Our observations may suggest the occurrence of metastatic disease at the end of follow-up. Supporting this view, the current study demonstrated lower excess mortality for pN+ colon cancer patients ≤ 75 years who were eligible for adjuvant chemotherapy according to the national guidelines. While the impact of radiotherapy on local recurrence is not controversial, the effect on survival is more unclear. The Dutch TME trial showed no effect of radiotherapy on long-term survival [21], although the risk of local recurrence was reduced. A Cochrane review concluded that radiotherapy results in a 2% increase in survival [22]. Radiotherapy may decrease tumour burden, thus prolonging the time to macroscopic tumour growth [23].

In contrast, with regard to colon cancer treatment, there were no major changes in care guidelines except for the introduction of adjuvant chemotherapy for pN+ patients ≤ 75 years of age. Our study only showed a major improvement for colon cancer survival in lymph node-positive patients younger than 75 years of age, which is the subgroup that received adjuvant chemotherapy. This suggests that the use of adjuvant chemotherapy should be considered in patients > 75 years with pN+ colon cancer who may benefit from this treatment.

The observed difference in excess mortality in the immediate perioperative time interval in colon vs. rectal cancer patients may reflect the more frequent need for emergency surgery in colon cancer patients than in rectal cancer patients due to perforation or bowel obstruction. Recent studies report emergency operations in 25% of colon cancer patients but only in 1–3% of rectal cancer patients [24,25]. As the incidence of acute clinical presentation was likely similar for both study periods, the current findings suggest that excess mortality related to the perioperative time interval for rectal cancer was reduced in the 2001–2003 period.

The current study has recognised shortcomings associated with most registry studies. The selection criteria of patients for curative surgery may have changed from after the 1994–1996 study period, as more patients were diagnosed with distant metastases in the 2001–2003 period. This led to a greater proportion of patients being excluded and may have

contributed to the improvement in survival. We think that this difference in survival reflects changes treatment decisions in metastasised disease in the 2001–2003 period, since at that time, more effective chemotherapy was available than in the 1994–1996 period. Furthermore, the quality of pathology examinations and biopsy reports may have been higher in 2001–2003 when the focus on pN status had strongly increased as the key criterion for adjuvant treatment. Accordingly, the difference in diagnosed tumour stages may be a result of stage migration rather than a true biological change. Unfortunately, we have no information regarding elective or emergency surgery.

The two time periods in this study were based on the date of diagnosis of colorectal cancer, not on the date of surgery, which may have influenced mortality in the early postoperative time interval (i.e. 0–2 months). However, it is likely that the great majority of patients were treated within a very short time after their diagnosis. Accordingly we think that the time between diagnosis and surgery was probably quite short and would have a negligible influence on our findings. Furthermore, an increased proportion of rectal cancer patients (18% vs. 10% of colon cancer patients) received preoperative radiotherapy during the 2001–2003 period. This delayed surgery and might have influenced excess mortality during the early (0–2 month) interval. Finally, information regarding the de facto use of chemotherapy outside of guideline recommendations was unavailable at this time.

This study revealed considerable statistically significant differences in excess mortality in patients with curative resection for cancer of the colon and rectum before and after the implementation of national treatment guidelines. Our findings clearly demonstrate the effect of these guidelines at the population level. Furthermore, our analysis of excess mortality rates during various time intervals within the five years after surgery demonstrates significant changes. Of particular concern are the significantly higher mortality of rectal cancer patients during the fifth year after treatment and of patients with pN+ colon cancer > 75 years who are not eligible for adjuvant treatment. These findings mandate increased attention to research on these patient groups to continuously improve the treatment of patients with cancer of the colon and rectum.

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