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ORIGINAL ARTICLE

Improved survival of colorectal cancer in Denmark during 2001–2012: The efforts of several national initiatives

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ABSTRACT

Background The Danish Colorectal Cancer Group (DCCG) established a national clinical database in 2001 with the aim to monitor and improve outcome of colorectal cancer patients. Since 2000 several national initiatives have been taken to improve cancer outcome. In the present study we used DCCG data to evaluate mortality and survival of CRC patients with focus on comorbidity, stage, and perioperative treatment.

Material and methods Patients notified to the DCCG database from 2001 to 2012 were included. Patients with primary cancer of the colon and rectum were analyzed separately. Analyses were stratified according to gender, comorbidity, Union for International Cancer Control (UICC) stage, and operative priority (elective/emergency/no surgery). Data were stratified into three time periods (2001–2004, 2005–2008, 2009–2012). Mortality and survival were age adjusted.

Results In total 29 385 patients with colon cancer and 15 213 patients with rectal cancer were included. The stage distribution was almost stable over time. The mortality rate per 100 patient year within one year decreased from 32 to 26 in colon cancer and from 26 to 19 in rectal cancer with associated improvements in absolute survival from 73% to 78% in colon cancer and from 78% to 83% in rectal cancer. The five-year relative survival of colon cancer improved from 58% to 63% and in rectal cancer from 59% to 65%. Comorbidity had major negative impact on outcome. Irrespective of tumor location, outcome improved relatively more in patients with stage III and IV disease. The proportion of patients who were spared surgery increased from 8% to 15% in colon cancer and from 13% to 19% in rectal cancer, and these changes were associated with improved outcome for rectal cancer patients, whereas outcome worsened for colon cancer patients.

Conclusion The Danish efforts to improve outcome of cancer have succeeded with improved outcomes in patients with colorectal cancer.

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Colorectal cancer (CRC) is among the three most common cancers in many Western countries. In Denmark with 5.4 million inhabitants, the number of incident cases per year has increased from 3458 in 2002 to 4141 in 2012 [1], the prevalence is about 30 000, and about 2000 patients die every year because of CRC [2].

It has been known for decades that Danish CRC patients have an inferior prognosis as compared to neighboring countries [3–5]. Based on that fact, several national initiatives have been undertaken since the mid-1990s to overcome the poor outcome (Figures 1 and 2). Evidence-based national CRC guidelines for diagnosis and treatment were published in 1998 by the Danish Colorectal Cancer Group (DCCG) and have since been updated regularly [6]. DCCG established a national clinical database in 2001 with the aim to monitor and improve outcome of CRC patients at a national and hospital-specific level. In 2006, DCCG became a multidisciplinary group with participation of surgeons, radiologists, pathologists, and oncologists from all parts of Denmark. To improve healthcare services for cancer patients in general, the National Board of Health initiated a "National Cancer Plan" in 2000 [7], a second in 2005 [8], and a third in 2010 [9]. The cancer plans included proposals for diagnostic and treatment capacity, concentration of the surgical treatment, continuing medical education and supervision of specialists in the cancer area, rehabilitation and palliation, among others. Further, the Danish Government issued a maximum two-week waiting time guarantee from diagnosis to treatment in 2001, fast-track cancer packages in 2008, and revision of the latter in 2012. National screening for CRC was not implemented before March 2014.

The aim of the present study was to evaluate mortality and survival of CRC patients from 2001 to 2012 based on data from

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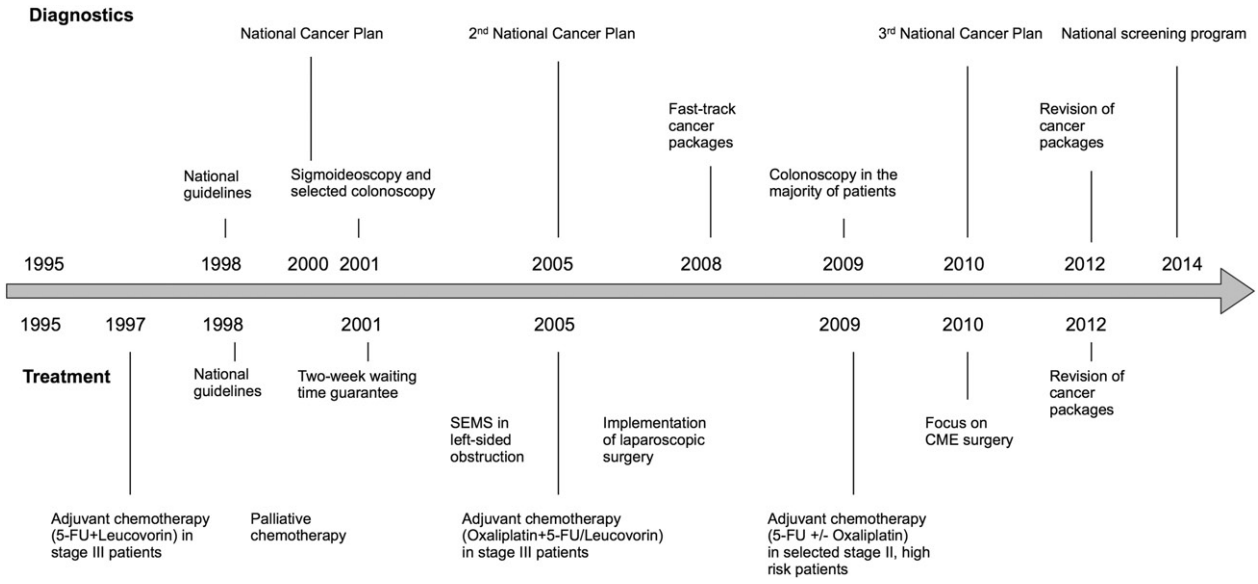

Figure 1. Flow chart on diagnostics and treatment of colon cancer in Denmark, late 1990s–2014.
CME, complete mesocolic excision; 5-FU, 5-fluorouracil; SEMS, self-expandable metallic stent.

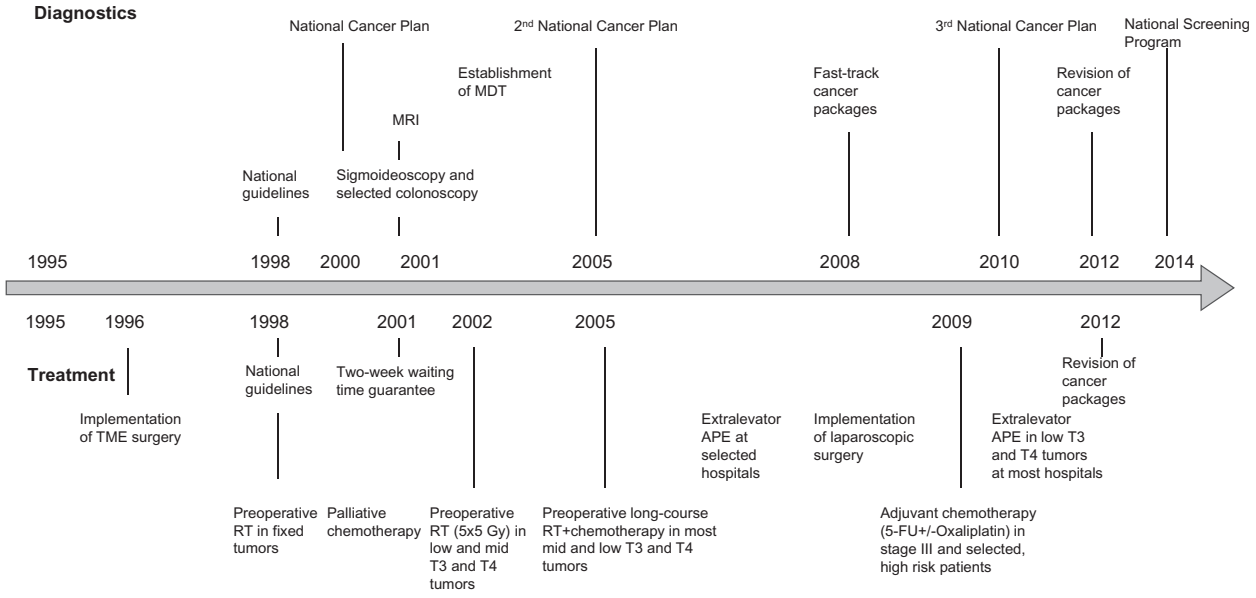

Figure 2. Flow chart on diagnostics and treatment of rectal cancer in Denmark, late 1990s–2014.
APE, abdominoperineal excision; 5-FU, 5-fluorouracil; MDT, multidisciplinary team; MRI, magnetic resonance imaging; RT, radiotherapy; TME, total mesorectal excision.

the national clinical DCCG database which allows detailed analyses concerning comorbidity, stage, and perioperative treatment.

Material and methods

The Danish healthcare system is free and fully financed by tax payment. Every Danish citizen is identified by a unique 10-digit personal number supporting correct vital status (alive or dead) and valid linkage to data in a plethora of registries.

Danish colorectal cancer group database

In 1994 the DCCG established a national database with the aim to improve diagnostic work-up and treatment of rectal cancer patients only. Since May 2001, the clinical quality database has included patients aged 18 years or older with a first-time diagnosis of CRC diagnosed and/or treated at a surgical department at a public Danish hospital. Surgery for CRC is performed at public hospitals in Denmark. Registrations comprise data regarding patient characteristics, diagnostic, preoperative work-up and treatment, surgical treatment, operative priority (emergency or elective surgery or no surgery), post-operative complications, tumor stage according to Union for International Cancer Control (UICC) and Tumor Node Metastasis (TNM) version 5, and pathology (since 2010). All clinical data are notified by the surgeons whereas pathologists enter pathology data. The data entry has been web-based since 2005. Quality indicators, and the

Table 1. Distribution of colon cancer patients by age group, gender, comorbidity level, cancer stage, and priority of surgery (2001–2012), number (percentages).

		Total period N (%)	Calendar period of colon cancer diagnosis N (%)		
	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012
Total	0–1 year	29 385 (100)	8413 (100)	10 245 (100)	10 727 (100)
	0–5 year[2]	19 670 (100)	8413 (100)	10 245 (100)	1012 (100)
Median age (years)		72	72	72	72
Age group					
<45 years	0–1 year	576 (2)	165 (2)	220 (2)	191 (2)
	0–5 year	410 (2)	165 (2)	220 (2)	25 (3)
45–54 years	0–1 year	1805 (6)	546 (7)	637 (6)	622 (6)
	0–5 year	1243 (6)	546 (7)	637 (6)	60 (6)
55–64 years	0–1 year	5399 (18)	1540 (18)	1917 (19)	1942 (18)
	0–5 year	3658 (19)	1540 (18)	1917 (19)	201 (20)
65–74 years	0–1 year	9132 (31)	2519 (30)	3089 (30)	3524 (33)
	0–5 year	5915 (30)	2519 (30)	3089 (30)	307 (30)
≥75 years	0–1 year	12 473 (42)	3643 (43)	4382 (43)	4448 (42)
	0–5 year	8444 (43)	3643 (43)	4382 (43)	419 (41)
Gender					
Men	0–1 year	14 372 (49)	4095 (49)	5005 (49)	5272 (49)
	0–5 year	9609 (49)	4095 (49)	5005 (49)	509 (50)
Women	0–1 year	15 013 (51)	4318 (51)	5240 (51)	5455 (51)
	0–5 year	10 061 (51)	4318 (51)	5240 (51)	503 (50)
Comorbidity level					
CCI = 0 (None)	0–1 year	20 900 (71)	6851 (81)	7142 (70)	6907 (64)
	0–5 year	14 682 (75)	6851 (81)	7142 (70)	689 (68)
CCI = 1 (Low)	0–1 year	3963 (14)	833 (10)	1465 (14)	1665 (16)
	0–5 year	2448 (12)	833 (10)	1465 (14)	150 (15)
CCI = 2 (Medium)	0–1 year	3661 (13)	627 (8)	1341 (13)	1693 (16)
	0–5 year	2101 (11)	627 (8)	1341 (13)	133 (13)
CCI ≥3 (High)	0–1 year	861 (3)	102 (1)	297 (3)	462 (4)
	0–5 year	439 (2)	102 (1)	297 (3)	40 (4)
Cancer stage					
Non-metastatic, M0	0–1 year	19 440 (66)	5675 (68)	6743 (66)	7022 (66)
	0–5 year	13 073 (67)	5675 (68)	6743 (66)	655 (65)
Metastatic, M1	0–1 year	8209 (28)	2121 (25)	2989 (29)	3099 (29)
	0–5 year	5407 (28)	2121 (25)	2989 (29)	297 (29)
Unknown, Mx	0–1 year	1736 (6)	617 (7)	513 (5)	606 (6)
	0–5 year	1190 (6)	617 (7)	513 (5)	60 (6)
UICC cancer stage					
I	0–1 year	2910 (10)	834 (10)	975 (10)	1101 (10)
	0–5 year	1913 (10)	834 (10)	975 (10)	104 (10)
II	0–1 year	9412 (32)	2796 (33)	3194 (31)	3422 (32)
	0–5 year	6314 (32)	2796 (33)	3194 (31)	324 (32)
III	0–1 year	7118 (24)	2045 (24)	2574 (25)	2499 (23)
	0–5 year	4846 (25)	2045 (24)	2574 (25)	227 (22)
IV	0–1 year	8209 (28)	2121 (25)	2989 (29)	3099 (29)
	0–5 year	5407 (28)	2121 (25)	2989 (29)	297 (29)
Unknown	0–1 year	1736 (6)	617 (7)	513 (5)	606 (6)
	0–5 year	1190 (6)	617 (7)	513 (5)	60 (6)
Priority of surgery					
Elective	0–1 year	20 823 (71)	5971 (71)	7331 (72)	7521 (70)
	0–5 year	14 018 (71)	5971 (71)	7331 (72)	716 (71)
Emergency/acute	0–1 year	5037 (17)	1760 (21)	1637 (16)	1640 (15)
	0–5 year	3548 (18)	1760 (21)	1637 (16)	151 (15)
No surgery	0–1 year	3525 (12)	682 (8)	1277 (13)	1566 (15)
	0–5 year	2104 (11)	682 (8)	1277 (13)	145 (14)

[1]The calendar year 2001 includes May–December, both included;
[2]Follow-up for 5 years could not be reached for all patients from the calendar period 2009–2012.
CCI, Charlson Comorbidity Index.

corresponding data needed to be collected, are regularly revised by a multidisciplinary board consisting of surgeons, radiologists, pathologists, and oncologists. A clinical epidemiologist has recently been added to the board. Such revisions are especially created following major changes of the national guidelines.

Patient completeness has always been high, close to 95% until 2010 and thereafter 99% [10]. The high completeness is achieved through linkage to the Danish National Patient Register (monthly) and Danish Cancer Registry (until 2006). Discrepancies disclosed by the linkages are listed and sent to the surgeons and pathologists in order to evaluate whether or not apparently missing patients fulfill the criteria for notification to the DCCG database. Patients without histological diagnosis are only recorded if surgeons confirm a ''clinical'' CRC diagnosis. Pathologists' participation in notification since 2010 has ensured that only patients with the correct histological type are included, whereby, e.g. appendix cancers, anal

Table 2. One- and 5-year age-adjusted mortality rate for colon cancer patients. Overall estimates (entire cohort) and stratified by gender, comorbidity level, cancer stage, and priority of surgery.

		Total period	Calendar period of colon cancer diagnosis			
Mortality rate, per 100 patient year (95% CI)	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012	p-value
All	0–1 year	29 (28–30)	32 (31–34)	30 (29–31)	26 (25–27)	0.001
	0–5 year	16 (16–17)	17 (17–18)	16 (15–16)	15 (13–16)	0.001
Gender						
Men	0–1 year	31 (30–32)	35 (33–37)	31 (29–33)	26 (25–28)	0.001
	0–5 year	18 (17–18)	19 (18–20)	17 (16–17)	16 (14–18)	0.001
Women	0–1 year	27 (26–28)	29 (28–31)	28 (27–30)	25 (23–26)	0.001
	0–5 year	15 (15–15)	15 (15–16)	15 (14–15)	14 (12–15)	0.058
Comorbidity level						
CCI = 0 (None)	0–1 year	26 (26–27)	30 (28–31)	27 (26–28)	22 (21–23)	0.001
	0–5 year	15 (15–15)	16 (16–17)	14 (14–15)	13 (12–15)	0.001
CCI = 1 (Low)	0–1 year	32 (31–34)	44 (39–50)	31 (28–35)	29 (26–31)	0.001
	0–5 year	19 (18–20)	22 (20–24)	17 (15–18)	20 (15–24)	0.001
CCI = 2 (Medium)	0–1 year	37 (34–39)	45 (39–52)	40 (36–44)	32 (29–35)	0.001
	0–5 year	21 (20–22)	23 (21–26)	21 (20–23)	16 (12–21)	0.102
CCI ≥3 (High)	0–1 year	58 (52–65)	66 (48–90)	62 (51–74)	55 (47–64)	0.257
	0–5 year	39 (35–43)	42 (33–52)	35 (30–40)	39 (25–58)	0.265
Cancer stage						
Non-metastatic, M0	0–1 year	12 (11–12)	14 (13–15)	13 (12–14)	9 (8–10)	0.001
	0–5 year	9 (9–9)	10 (9–10)	8 (8–9)	7 (6–8)	0.001
Metastatic, M1	0–1 year	81 (78–83)	97 (92–102)	81 (77–85)	72 (68–76)	0.001
	0–5 year	62 (61–64)	71 (68–75)	58 (56–60)	57 (50–65)	0.001
Unknown, Mx	0–1 year	49 (45–53)	53 (47–60)	45 (38–52)	51 (44–58)	0.605
	0–5 year	19 (17–20)	22 (19–24)	16 (14–18)	21 (14–31)	0.500
UICC cancer stage						
I	0–1 year	7 (6–8)	10 (8–12)	8 (6–10)	5 (4–6)	0.001
	0–5 year	5 (4–5)	5 (5–6)	5 (4–5)	4 (2–6)	0.052
II	0–1 year	10 (9–11)	12 (11–13)	11 (9–12)	8 (7–9)	0.001
	0–5 year	7 (7–8)	8 (7–8)	7 (6–7)	7 (5–8)	0.003
III	0–1 year	16 (15–17)	19 (17–21)	18 (16–19)	12 (11–13)	0.001
	0–5 year	13 (13–14)	15 (14–16)	12 (11–13)	11 (9–14)	0.001
IV	0–1 year	81 (78–83)	97 (92–102)	81 (77–85)	72 (68–76)	0.001
	0–5 year	62 (61–64)	71 (68–75)	58 (56–60)	57 (50–65)	0.001
Unknown	0–1 year	49 (47–51)	53 (50–57)	45 (42–48)	51 (48–54)	0.604
	0–5 year	19 (18–19)	22 (20–23)	16 (15–17)	21 (18–25)	0.500
Priority of surgery						
Elective	0–1 year	17 (17–18)	23 (22–24)	19 (18–20)	12 (11–13)	0.001
	0–5 year	12 (12–12)	13 (13–14)	11 (11–12)	9 (8–11)	0.001
Emergency/acute	0–1 year	53 (50–55)	55 (51–60)	54 (50–58)	49 (45–53)	0.016
	0–5 year	30 (29–31)	30 (29–32)	30 (28–32)	32 (26–38)	0.526
No surgery	0–1 year	96 (92–100)	88 (80–98)	90 (84–97)	106 (99–113)	0.302
	0–5 year	46 (44–49)	41 (38–45)	48 (45–51)	67 (55–80)	0.001

[1]The calendar year 2001 includes May–December, both included.
CCI, Charlson Comorbidity Index.

cancers, neuroendocrine carcinomas, intestinal lymphomas and melanomas, metastases, mesenchymal tumors, are excluded from the DCCG database.

Despite revision of the TNM classification, DCCG has maintained registration according to version 5, thus allowing a consistent TNM classification over time. Only pTNM is registered.

Patients classified as having distant metastases within 120 days after diagnosis of CRC, according to the Danish National Patient Register, are classified as UICC stage IV (since 2008). Thereby, the proportion of patients with uncertain stage is reduced because most patients with, i.e. unspecific pulmonary nodules, are recommended to have a re-evaluating computed tomography scan within 90 days.

National patient register

The Danish National Patient Register was established in 1977 and collect data from hospital services including dates of admission and discharge, treatment codes including surgical procedures, and up to 20 discharge diagnoses classified according to the ICD-10. In 2000, the Danish healthcare authorities implemented a reimbursement structure based on Diagnosis Related Groups (DRG), which may have provided stronger incentives to record concomitant conditions.

Data on comorbidity for calculation of Charlson's Comorbidity Index (CCI) was retrieved from the National Patient Register using patient histories up to 10 years prior to the cancer diagnosis date. ICD-10 codes for CRC were not included in the CCI. The positive predictive value of the ICD-10 coding in the Danish National Patient Register for the conditions included in the CCI has been reported to be above 90% [11].

Patients

All patients registered in the DCCG database from May 2001 through 2012 were included and checked for vital status (alive/

Table 3. One- and 5-year absolute, age-adjusted survival for colon cancer patients. Overall estimates (entire cohort) and stratified by gender, comorbidity level, cancer stage, and priority of surgery.

		Total period	Calendar period of colon cancer diagnosis			
Absolute survival % (95% CI)	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012	p-value
All	0–1 year	76 (75–77)	73 (72–75)	75 (73–77)	78 (76–80)	0.001
	0–5 year	49 (48–50)	47 (45–48)	50 (48–51)	52 (48–57)	0.001
Gender						
Men	0–1 year	75 (73–76)	72 (69–74)	74 (72–77)	78 (75–78)	0.001
	0–5 year	46 (44–47)	43 (41–45)	48 (46–50)	50 (44–57)	0.001
Women	0–1 year	77 (75–78)	75 (73–78)	76 (74–79)	79 (76–81)	0.001
	0–5 year	51 (50–53)	51 (49–53)	52 (50–54)	55 (48–62)	0.090
Comorbidity level						
CCI = 0 (None)	0–1 year	78 (76–79)	75 (73–77)	77 (75– 79)	81 (79–83)	0.001
	0–5 year	51 (50–52)	49 (47–50)	53 (51– 54)	55 (50–61)	0.001
CCI = 1 (Low)	0–1 year	74 (71–76)	68 (62–73)	75 (70–79)	76 (72–81)	0.001
	0–5 year	45 (43–48)	43 (38–47)	49 (45–53)	49 (39–62)	0.003
CCI = 2 (Medium)	0–1 year	71 (68–74)	67 (61–74)	70 (65–74)	74 (70–78)	0.001
	0–5 year	41 (38–43)	40 (35–45)	42 (38–45)	56 (44–71)	0.088
CCI ≥3 (High)	0–1 year	60 (55–65)	59 (45–76)	61 (53–71)	61 (54–69)	0.460
	0–5 year	26 (22–32)	26 (17–38)	32 (26–39)	41 (23–66)	0.251
Cancer stage						
Non-metastatic, M0	0–1 year	89 (88–91)	87 (85–90)	88 (86–90)	92 (90–94)	0.001
	0–5 year	65 (64–67)	63 (61–65)	67 (65–69)	71 (64–78)	0.001
Metastatic, M1	0–1 year	47 (45–48)	41 (38–43)	47 (45–50)	50 (48–53)	0.001
	0–5 year	10 (9–11)	8 (6–9)	12 (11–13)	13 (9–17)	0.001
Unknown, Mx	0–1 year	64 (60–68)	62 (56–68)	67 (60–75)	64 (58–71)	0.686
	0–5 year	47 (43–51)	42 (37–47)	53 (47–59)	55 (38–77)	0.604
UICC cancer stage						
I	0–1 year	93 (90–97)	91 (85–98)	92 (86–99)	95 (90–100)	0.001
	0–5 year	79 (75–83)	78 (72–84)	80 (74–85)	84 (67–100)	0.067
II	0–1 year	91 (89–93)	89 (86–93)	90 (87–94)	93 (89–96)	0.001
	0–5 year	71 (69–73)	69 (66–72)	72 (69–75)	74 (65–84)	0.004
III	0–1 year	86 (83–88)	83 (79–87)	84 (81–88)	89 (85–93)	0.001
	0–5 year	54 (52–56)	49 (46–52)	57 (54–60)	61 (51–72)	0.001
IV	0–1 year	47 (45–48)	41 (38–43)	47 (45–50)	50 (48– 53)	0.001
	0–5 year	10 (9–11)	8 (6–9)	12 (11–13)	13 (9–17)	0.001
Unknown	0–1 year	64 (62–66)	62 (58–65)	67 (64–70)	64 (62–67)	0.686
	0–5 year	47 (45–48)	42 (39–45)	53 (50–55)	55 (47–64)	0.604
Priority of surgery						
Elective	0–1 year	84 (83–86)	80 (78–83)	83 (81–86)	89 (87–91)	0.001
	0–5 year	57 (56–58)	54 (52–56)	59 (57–61)	64 (58–71)	0.001
Emergency/acute	0–1 year	62 (59–64)	60 (57–64)	61 (57–65)	64 (60–68)	0.060
	0–5 year	30 (28–32)	30 (27–32)	30 (28– 33)	32 (24–42)	0.683
No surgery	0–1 year	42 (40–44)	46 (41–52)	45 (41–49)	38 (35–41)	0.040
	0–5 year	21 (19–23)	24 (21–28)	20 (18–23)	19 (13–28)	0.072

[1]The calendar year 2001 includes May–December, both included.
CCI, Charlson Comorbidity Index.

dead) in the Danish Civil Registration Service at 23 May 2014. Approval from the ethical committee is not required in register-based studies according to Danish law.

Statistical methods

Analyses were performed for colon cancer and rectal cancer separately and were grouped by year of diagnosis (2001–2004; 2005–2008; 2009–2012). Patients were followed from diagnosis until death or end of follow-up (23 May 2014). The outcome measures were estimated for the first year after diagnosis, and the full five-year period after diagnosis, respectively; for the latter estimates were included only patients with the potential of follow-up for the full five-year period of diagnosis. All estimates were based on all-cause mortality and were standardized by age and sex according to the ICSS cancer population weights (cluster 1) [12].

The outcome measures comprised: (1) The absolute mortality rate (per 100 patient-years), defined as the number of deaths divided by the sum of the patient-time at risk over the follow-up period concerned; (2) Absolute survival, defined as the proportion of patients surviving to the end of the relevant follow-up period; and (3) Relative survival, defined as the ratio of absolute survival divided by the expected survival.

All outcomes were calculated for the total patient population as well as after stratification by selected variables. Confidence intervals (95%-level) were calculated based on the approximated Poisson distribution and χ^2 statistics were used to assess heterogeneity across the diagnosis cohorts.

Results

Colon cancer

In total 29 385 patients with colon cancer were registered in the database from May 2001 to 2012. The number of patients per time period increased slightly during the study period (Table 1). Median age was 72 years. The age distribution was almost stable except a minor increase of patients aged 65–74 years in 2009–2012. The proportion of patients with comorbidity, CCI ≥1, increased from 19% to 36%. For the whole

Table 4. One- and 5-year absolute, age-adjusted relative survival for colon cancer patients. Overall estimates (entire cohort) and stratified by gender, comorbidity level, cancer stage, and priority of surgery.

		Total period	Calendar period of colon cancer diagnosis			
Relative survival % (95% CI)	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012	p-value
All	0–1 year	78 (77–79)	76 (74–78)	78 (76–79)	80 (79–82)	0.001
	0–5 year	60 (58–61)	58 (56–60)	61 (59–62)	63 (58–69)	0.001
Gender						
Men	0–1 year	78 (76–79)	75 (72–77)	77 (75–80)	80 (78–83)	0.001
	0–5 year	58 (56–60)	55 (52–58)	60 (58–63)	62 (55–71)	0.001
Women	0–1 year	79 (77–80)	78 (75–80)	78 (76–81)	81 (78–83)	0.001
	0–5 year	61 (59–63)	61 (58–63)	61 (59–63)	64 (57–73)	0.062
Comorbidity level						
CCI = 0 (None)	0–1 year	80 (79–81)	78 (76–80)	80 (77–82)	83 (81–85)	0.001
	0–5 year	62 (61–64)	60 (58–62)	64 (62–66)	67 (60–74)	0.001
CCI = 1 (Low)	0–1 year	76 (73–79)	70 (64–76)	77 (73–82)	79 (74–83)	0.001
	0–5 year	55 (52–59)	53 (48–59)	60 (56–64)	60 (47–75)	0.001
CCI = 2 (Medium)	0–1 year	73 (71–76)	70 (63–77)	72 (67–77)	76 (72–81)	0.001
	0–5 year	50 (46–53)	49 (43–56)	51 (47–55)	68 (54–86)	0.121
CCI ≥3 (High)	0–1 year	62 (57–67)	61 (47–79)	63 (55–73)	63 (56–71)	0.466
	0–5 year	32 (27–39)	32 (21–47)	39 (31–47)	49 (28–79)	0.209
Cancer stage						
Non-metastatic, M0	0–1 year	92 (91–93)	90 (88–93)	91 (89–93)	94 (92–97)	0.001
	0–5 year	80 (78–82)	77 (75–80)	82 (79–84)	85 (78–93)	0.001
Metastatic, M1	0–1 year	48 (47–50)	42 (39–45)	49 (46–51)	52 (49–55)	0.001
	0–5 year	12 (11–13)	9 (8–11)	14 (13–16)	15 (11–21)	0.001
Unknown, Mx	0–1 year	66 (62–70)	64 (58–71)	69 (62–77)	66 (60–73)	0.739
	0–5 year	58 (53–63)	52 (46–59)	65 (57–73)	67 (46–94)	0.240
UICC cancer stage						
I	0–1 year	96 (92–100)	94 (88–101)	95 (89–102)	98 (92–103)	0.001
	0–5 year	96 (92–101)	96 (89–103)	97 (90–104)	101 (81–120)	0.145
II	0–1 year	94 (92–96)	92 (89–96)	93 (90–97)	95 (92–99)	0.001
	0–5 year	87 (84–89)	85 (82–89)	87 (84–91)	89 (78–101)	0.001
III	0–1 year	88 (86–91)	86 (82–90)	87 (83–91)	92 (88–95)	0.001
	0–5 year	66 (64–69)	61 (57–65)	69 (66–73)	73 (62–87)	0.001
IV	0–1 year	48 (47–50)	42 (39–45)	49 (46–51)	52 (49–55)	0.001
	0–5 year	12 (11–13)	9 (8–11)	14 (13–16)	15 (11–21)	0.001
Unknown	0–1 year	66 (64–68)	64 (61–68)	69 (66–73)	66 (64–69)	0.739
	0–5 year	58 (55–60)	52 (49–56)	65 (61–68)	67 (57–78)	0.240
Priority of surgery						
Elective	0–1 year	87 (86–88)	83 (81–85)	86 (84–88)	92 (89–94)	0.001
	0–5 year	69 (68–71)	67 (64–69)	71 (69–73)	77 (70–84)	0.001
Emergency/acute	0–1 year	64 (61–66)	63 (59–67)	63 (59–67)	66 (62–70)	0.071
	0–5 year	37 (34–39)	37 (33–40)	37 (34–40)	39 (28–51)	0.764
No surgery	0–1 year	43 (41–45)	48 (43–54)	46 (42–50)	39 (36–42)	0.027
	0–5 year	25 (23–28)	30 (26–35)	25 (22–28)	23 (15–33)	0.038

[1]The calendar year 2001 includes May–December, both included.
CCI, Charlson Comorbidity Index.

period, local disease (UICC stage I + II) was present in 42% of patients, regional disease (stage III) in 24% of patients, and 28% had metastatic disease. Six percent of patients were classified with unknown stage. A total of 21% of patients underwent emergency surgery in 2001–2004 compared to 16% and 15% in the two subsequent periods, whereas 8% of patients had no surgical treatment in 2001–2004 compared to 13% and 15%, respectively, in 2005–2008 and 2009–2012.

Age-standardized mortality per 100 patient-years within first year after diagnosis decreased from 32 in 2001–2004 to 26 in 2009–2012, and the five-year mortality rate per 100 patient-years decreased from 17 to 15 (Table 2). Correspondingly, the one-year age-adjusted absolute survival increased from 73% to 78% and five-year absolute survival from 47% to 52% (Table 3). Taking mortality of the general population into account one-year age-adjusted relative survival increased from 76% to 80% and five-year relative survival from 58% to 63% (Table 4).

Men experienced a more pronounced reduction in one-year mortality rate from 35 to 26 as compared to women (from 29 to 25), and with similar trends in the five-year figures. Changes in absolute and relative survival showed similar favorable trends (Tables 3 and 4).

Comorbidity had significant negative influence on mortality and survival rates (Tables 2–4). Mortality rates for patients with severe comorbidity (CCI ≥3) were at least double as high as those in patients without comorbidity (CCI = 0) in all three periods. During the study period statistically significant improvements in one-year estimates were only observed in patients with CCI = 0, CCI = 1, and CCI = 2, and in five-year estimates in patients with CCI = 0 and CCI = 1.

Stage-specific one- and five-year mortality and survival rates improved statistically significantly during the study period for all stages except the five-year estimates of the minor group of patients with stage I disease (Tables 2–4). The largest, relative increases were observed in patients with stage III and IV disease with five-year relative survival rates increasing from 61% to 73% and from 9% to 15%, respectively. Corresponding estimates within stage I and II disease resulted in increments from 96% to 101% and from 85% to 89%, respectively (Figure 3).

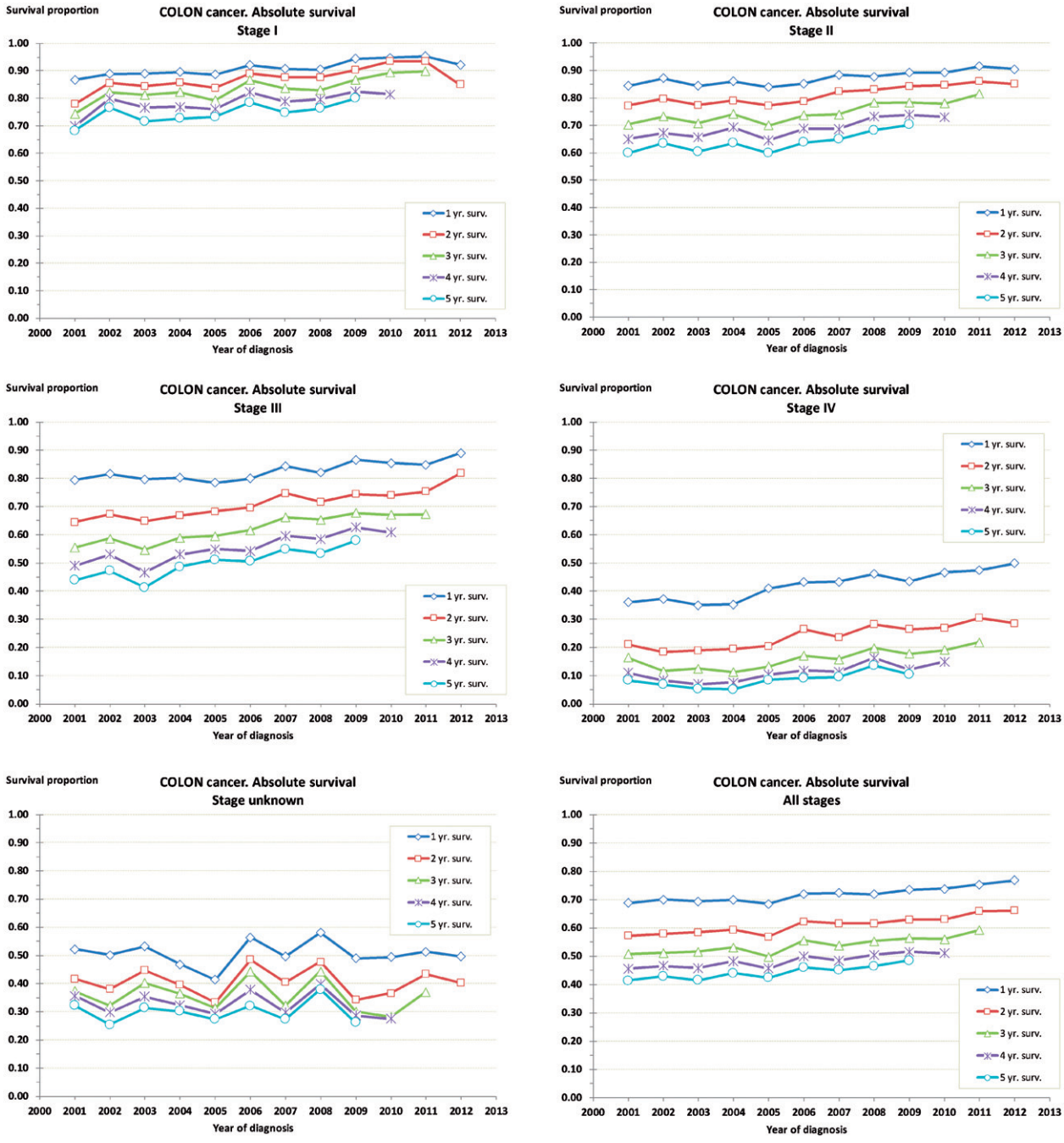

Figure 3. Trends in unadjusted, absolute survival proportions by year at diagnosis. Colon cancer.

Surgery performed in an elective setting was associated with statistically significant decreases of mortality rates and increases of survival rates during the study period (Tables 2–4). The one-year mortality rate was almost halved from 23 to 12, and the five-year mortality was reduced from 13 to 9. In patients who underwent emergency surgery, however, the one-year mortality fell only from 55 to 49, although significantly, and five-year mortality did not change. The proportion of patients, who had no surgical treatment, increased over the period, and for these patients, mortality rates increased and survival rates decreased statistically significantly. Thus, the five-year relative survival decreased from 30 to 23.

The trends over time in unadjusted, absolute survival rates are depicted in Figure 3 and illustrate the steadily increasing rates in stage-specific survival, irrespective of stage, and overall survival. For stages II and III, the five-year curves exhibit steeper slopes than the one-year curves.

Rectal cancer

In total 15 213 patients with rectal cancer were identified and with increasing number of patients across the time periods (Table 5). Median age was 69 years and the proportion of patients aged 65–74 years increased. Rectal cancer occurred more frequently among men, 60%. Comorbidity was diagnosed

Table 5. Distribution of rectal cancer patients by age group, gender, comorbidity level, cancer stage, and priority of surgery (2001–2012), number (percentages).

		Total period N (%)	Calendar period of rectal cancer diagnosis N (%)		
	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012
Total	0–1 year	15 213 (100)	4545 (100)	5240 (100)	5428 (100)
	0–5 year[2]	10 305 (100)	4545 (100)	5240 (100)	520 (100)
Median age (years)		69	70	69	68
Age group					
<45 years	0–1 year	344 (2)	95 (2.1)	121 (2)	128 (2)
	0–5 year	228 (2)	95 (2.1)	121 (2)	12 (2)
45–54 years	0–1 year	1317 (9)	384 (8)	476 (9)	457 (8)
	0–5 year	908 (9)	384 (8.4)	476 (9)	48 (9)
55–64 years	0–1 year	3493 (23)	1042 (23)	1249 (24)	1202 (22)
	0–5 year	2418 (24)	1042 (23)	1249 (24)	127 (24)
65–74 years	0–1 year	4875 (32)	1403 (31)	1611 (31)	1861 (34)
	0–5 year	3176 (31)	1403 (31)	1611 (31)	162 (31)
≥75 years	0–1 year	5184 (34)	1621 (36)	1783 (34)	1780 (33)
	0–5 year	3575 (35)	1621 (36)	1783 (34)	171 (33)
Gender					
Men	0–1 year	9100 (60)	2670 (59)	3104 (59)	3326 (61)
	0–5 year	6110 (59)	2670 (59)	3104 (59)	336 (65)
Women	0–1 year	6113 (40)	1875 (41)	2136 (41)	2102 (39)
	0–5 year	4195 (41)	1875 (41)	2136 (41)	184 (35)
CCI = 0 (None)	0–1 year	11 694 (77)	3914 (86)	3935 (75)	3845 (71)
	0–5 year	8237 (80)	3914 (86)	3935 (75)	388 (75)
CCI = 1 (Low)	0–1 year	1744 (12)	346 (8)	660 (13)	738 (14)
	0–5 year	1066 (10)	346 (8)	660 (13)	60 (12)
CCI = 2 (Medium)	0–1 year	1441 (10)	239 (5)	526 (10)	676 (13)
	0–5 year	825 (8)	239 (5)	526 (10)	60 (12)
CCI ≥3 (High)	0–1 year	334 (2)	46 (1)	119 (2)	169 (3)
	0–5 year	177 (2)	46 (1)	119 (2)	12 (2)
Cancer stage					
Non-metastatic, M0	0–1 year	9858 (65)	2903 (63.9)	3422 (65.3)	3533 (65.1)
	0–5 year	6654 (65)	2903 (63.9)	3422 (65.3)	329 (63.3)
Metastatic, M1	0–1 year	3729 (25)	1030 (22.7)	1333 (25.4)	1366 (25.2)
	0–5 year	2514 (24)	1030 (22.7)	1333 (25.4)	151 (29.0)
Unknown, Mx	0–1 year	1626 (11)	612 (13.5)	485 (9.3)	529 (9.7)
	0–5 year	1137 (11)	612 (13.5)	485 (9.3)	40 (7.7)
UICC cancer stage					
I	0–1 year	2804 (18)	737 (16)	958 (18)	1109 (20)
	0–5 year	1798 (17)	737 (16)	958 (18)	103 (20)
II	0–1 year	3547 (23)	1072 (24)	1228 (23)	1247 (23)
	0–5 year	2420 (24)	1072 (24)	1228 (23)	120 (23)
III	0–1 year	3507 (23)	1094 (24)	1236 (24)	1177 (22)
	0–5 year	2436 (24)	1094 (24)	1236 (24)	106 (20)
IV	0–1 year	3729 (25)	1030 (23)	1333 (25)	1366 (25)
	0–5 year	2514 (24)	1030 (23)	1333 (25)	151 (29)
Unknown	0–1 year	1626 (11)	612 (14)	485 (9)	529 (10)
	0–5 year	1137 (11)	612 (14)	485 (9)	40 (8)
Priority of surgery					
Elective	0–1 year	12 321 (81)	3824 (84)	4208 (80)	4289 (79)
	0–5 year	8442 (82)	3824 (84)	4208 (80)	410 (79)
Emergency/acute	0–1 year	412 (3)	150 (3)	132 (3)	130 (2)
	0–5 year	293 (3)	150 (3)	132 (3)	11 (2)
No surgery	0–1 year	2480 (16)	571 (13)	900 (17)	1009 (19)
	0–5 year	1570 (15)	571 (13)	900 (17)	99 (19)

[1]The calendar year 2001 includes May–December, both included;
[2]Follow-up for 5 years could not be reached for all patients from the calendar period 2009–2012.
CCI, Charlson Comorbidity Index.

more frequently over time just like in patients with colon cancer. The stage distribution changed slightly. The proportions of patients with stage I disease increased from 16% to 20%, stage II disease remained stable at 23%, stage III disease decreased from 24% to 22%, and stage IV disease increased from 23% to 25%. Very few patients (3%) had emergency surgery. Like in colon cancer, a higher proportion of patients did not receive surgical treatment during the study period, 13% in 2001–2004 and 19% in 2009–2012.

The one- and five-year mortality rates for all patients decreased as seen in colon cancer, although the mortality rates were lower (Table 6). The one- and five-year rates of absolute survival increased statistically significantly from 78% to 83% and from 47% to 53%, respectively (Table 7), and the corresponding rates for one- and five-year relative survival increased from 81% to 85% and 59% to 65%, respectively (Table 8).

Men's mortality and survival rates improved statistically significantly across the time periods and more than observed in women, resulting in almost similar figures for the two genders for one- and five-year mortality, one-year absolute survival, and one- and five-year relative survival in 2009–2012 among men

Table 6. One- and 5-year age-adjusted mortality rate for rectal cancer patients. Overall estimates (entire cohort) and stratified by gender, comorbidity level, cancer stage, and priority of surgery.

		Total period	Calendar period of rectal cancer diagnosis			
Mortality rate, per 100 patient year (95% CI)	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012	p-value
All	0–1 year	22 (21–23)	26 (24–27)	22 (20–23)	19 (18–21)	0.001
	0–5 year	15 (15–15)	16 (16–17)	14 (13–14)	14 (12–16)	0.001
Gender						
Men	0–1 year	23 (22–24)	26 (24–28)	22 (20–24)	20 (18–22)	0.001
	0–5 year	16 (15–16)	17 (16–18)	15 (14–16)	15 (13–17)	0.001
Women	0–1 year	21 (20–22)	25 (23–27)	21 (19–23)	19 (17–20)	0.001
	0–5 year	14 (13–14)	16 (15–17)	12 (12–13)	13 (10–16)	0.001
Comorbidity level						
CCI = 0 (None)	0–1 year	20 (19–21)	23 (22–25)	19 (18–21)	17 (15–18)	0.001
	0–5 year	14 (13–14)	15 (15–16)	12 (12–13)	13 (11–15)	0.001
CCI = 1 (Low)	0–1 year	24 (22–27)	32 (25–39)	25 (21–29)	22 (18–26)	0.001
	0–5 year	18 (17–20)	22 (20–26)	17 (16–19)	17 (11–25)	0.006
CCI = 2 (Medium)	0–1 year	35 (32–39)	50 (40–61)	32 (27–38)	32 (27–37)	0.001
	0–5 year	22 (20–24)	29 (25–34)	20 (18–23)	17 (11–25)	0.001
CCI ≥3 (High)	0–1 year	51 (43–61)	100 (64–149)	55 (40–74)	45 (34–59)	0.007
	0–5 year	37 (31–44)	53 (37–75)	36 (29–45)	41 (9–115)	0.149
Cancer stage						
Non-metastatic, M0	0–1 year	9 (8–9)	10 (9–11)	9 (8–10)	7 (6–8)	0.001
	0–5 year	8 (8–9)	9 (9–10)	8 (7–8)	6 (5–8)	0.001
Metastatic, M1	0–1 year	61 (58–64)	72 (66–78)	61 (56–66)	55 (50–59)	0.001
	0–5 year	52 (50–54)	58 (54–62)	49 (46–52)	44 (36–52)	0.001
Unknown, Mx	0–1 year	39 (36–43)	48 (42–55)	33 (27–39)	37 (31–43)	0.010
	0–5 year	22 (20–24)	27 (24–30)	16 (14–18)	21 (13–32)	0.001
UICC cancer stage						
I	0–1 year	6 (5–7)	8 (6–10)	5 (3–6)	6 (4–8)	0.018
	0–5 year	5 (4–5)	5 (5–6)	4 (4–5)	5 (3–7)	0.017
II	0–1 year	8 (7–9)	9 (7–11)	10 (8–12)	6 (5–8)	0.001
	0–5 year	7 (7–8)	8 (7–9)	7 (7–8)	7 (5–10)	0.069
III	0–1 year	11 (10–12)	14 (12–16)	11 (10–14)	9 (7–11)	0.008
	0–5 year	13 (12–14)	15 (13–16)	12 (11–13)	9 (6–13)	0.001
IV	0–1 year	61 (58–64)	72 (66–78)	61 (56–66)	55 (50–59)	0.001
	0–5 year	52 (50–54)	58 (54–62)	49 (46–52)	44 (36–52)	0.001
Unknown	0–1 year	39 (37–41)	48 (43–53)	33 (29–36)	37 (33–41)	0.010
	0–5 year	22 (21–23)	27 (25–29)	16 (15–17)	21 (17–26)	0.001
Priority of surgery						
Elective	0–1 year	14 (13–15)	19 (17–20)	13 (12–15)	10 (9–11)	0.001
	0–5 year	12 (11–12)	14 (13–14)	10 (10–11)	9 (8–11)	0.001
Emergency/acute	0–1 year	91 (80–104)	92 (73–115)	108 (86–135)	76 (58–97)	0.047
	0–5 year	55 (49–63)	49 (41–59)	63 (51–75)	91 (21–247)	0.390
No surgery	0–1 year	71 (67–75)	84 (75–94)	70 (63–77)	69 (63–75)	0.012
	0–5 year	52 (50–55)	58 (53–64)	49 (45–52)	65 (52–81)	0.003

[1]The calendar year 2001 includes May–December, both included.
CCI, Charlson Comorbidity Index.

and women (Tables 6–8). In women, only one-year mortality and survival improved statistically significantly.

The CCI had negative impact on mortality and survival as in colon cancer, but, nevertheless, with improvements of mortality and survival observed for all levels of comorbidity during the study period (Tables 6–8). Mortality decreased and survival increased most in patients with increasing level of comorbidity thus diminishing the gradient in outcome across patients with CCI = 0, CCI = 1, and CCI = 2, and CCI ≥3 with five-year relative survival rates in 2009–2012 of 67%, 60%, 68%, and 49%, respectively. However, the changes over time were not statistically significant in the minor group of patients with CCI ≥3.

Stage-specific mortality and survival improved significantly in the one- and five-year estimates for patients with stage I, III, and IV disease, and in one-year estimates for stage II (Tables 6–8). The relative improvements were most pronounced for patients with stage III and IV disease (Figure 4). The five-year relative survival rates in 2009–2012 were 98%, 88%, 80%, and 20% for stage I, II, III, IV, respectively.

Major improvements were observed for patients operated electively just as for colon cancer with a halving of the one-year mortality (Tables 6–8). The five-year relative survival improved 13 percent point during the study period and was 78% in 2009–2012. Mortality and survival also improved statistically significantly in the increasing proportion of patients not being operated with an increase in the five-year relative survival from 18% to 22%.

Trends over time in unadjusted, absolute stage-specific and overall survival also showed steadily increasing rates as for colon cancer (Figure 4). The five-year curves increased more than the one-year curves for stages II and III, especially from 2005–2006 and onwards.

Discussion

In this nationwide study we have demonstrated that mortality and survival have improved significantly for Danish patients with colon and rectal cancer during a 12-year period in which several national initiatives have been undertaken aiming to

Table 7. One- and 5-year absolute, age-adjusted survival for rectal cancer patients. Overall estimates (entire cohort) and stratified by gender, comorbidity level, cancer stage, and priority of surgery.

		Total period	Calendar period of rectal cancer diagnosis			
Absolute survival % (95% CI)	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012	p-value
All	0–1 year	81 (79–82)	78 (75–81)	81 (78–83)	83 (80–85)	0.001
	0–5 year	50 (49–51)	47 (45–49)	53 (51–55)	53 (47–60)	0.001
Gender						
Men	0–1 year	80 (78–82)	77 (74–81)	80 (77–84)	82 (79–85)	0.001
	0–5 year	48 (46–50)	46 (43–49)	50 (48–53)	52 (44–60)	0.001
Women	0–1 year	81 (79–83)	79 (75–83)	81 (78–85)	83 (79–87)	0.001
	0–5 year	53 (51–55)	49 (46–53)	56 (53–59)	56 (45–68)	0.001
Comorbidity level						
CCI = 0 (None)	0–1 year	82 (81–84)	80 (77–82)	83 (80–86)	85 (82–88)	0.001
	0–5 year	53 (51–54)	49 (47–51)	56 (54–58)	56 (49–64)	0.001
CCI = 1 (Low)	0–1 year	79 (75–84)	75 (66–85)	79 (72–86)	82 (75–89)	0.003
	0–5 year	43 (39–47)	40 (33–47)	45 (40–51)	53 (36–75)	0.040
CCI = 2 (Medium)	0–1 year	71 (67–76)	64 (55–75)	74 (67–82)	74 (67–80)	0.001
	0–5 year	39 (34–43)	34 (27–42)	41 (36–47)	59 (41–82)	0.015
CCI ≥3 (High)	0–1 year	63 (55–72)	47 (30–72)	62 (49–78)	69 (57–82)	0.024
	0–5 year	27 (20–35)	29 (16–50)	27 (18–38)	72 (32–100)	0.365
Cancer stage						
Non-metastatic, M0	0–1 year	92 (90–94)	90 (87–94)	92 (88–95)	93 (90–97)	0.001
	0–5 year	66 (64–68)	63 (60–66)	68 (65–70)	74 (65–84)	0.008
Metastatic, M1	0–1 year	55 (53–58)	50 (46–54)	55 (52–60)	58 (54–63)	0.001
	0–5 year	13 (11–14)	10 (8–13)	14 (12–16)	17 (11–25)	0.001
Unknown, Mx	0–1 year	69 (65–73)	64 (57–70)	74 (67–82)	71 (64–79)	0.013
	0–5 year	40 (37–44)	34 (29–39)	51 (45–58)	46 (28–73)	0.007
UICC cancer stage						
I	0–1 year	94 (91–98)	93 (86–100)	96 (89–100)	94 (89–100)	0.020
	0–5 year	79 (75–83)	77 (71–83)	80 (75–86)	81 (64–100)	0.024
II	0–1 year	92 (89–96)	92 (86–98)	91 (86–96)	94 (89–99)	0.001
	0–5 year	69 (66–73)	68 (63–73)	70 (65–75)	73 (58–90)	0.050
III	0–1 year	89 (86–93)	87 (82–93)	89 (84–95)	91 (86–97)	0.007
	0–5 year	53 (50–56)	49 (45–53)	56 (52–60)	66 (52–84)	0.001
IV	0–1 year	55 (53–58)	50 (46–54)	55 (52–60)	58 (54–63)	0.001
	0–5 year	13 (11–14)	10 (8–13)	14 (12–16)	17 (11–25)	0.008
Unknown	0–1 year	69 (67–72)	64 (59–69)	74 (69–79)	71 (67–76)	0.013
	0–5 year	40 (38–43)	34 (30–38)	51 (47–55)	46 (36–59)	0.007
Priority of surgery						
Elective	0–1 year	87 (86–89)	83 (80–86)	88 (85–90)	90 (88–93)	0.001
	0–5 year	57 (55–58)	52 (50–55)	60 (58–62)	64 (57–73)	0.001
Emergency/acute	0–1 year	45 (39–52)	45 (35–58)	40 (30–52)	51 (40–65)	0.187
	0–5 year	17 (13–23)	21 (14–30)	17 (10–25)	67 (27–100)	0.423
No surgery	0–1 year	51 (48–54)	46 (41–52)	52 (48–57)	51 (47–56)	0.035
	0–5 year	15 (13–17)	15 (12–18)	17 (14–19)	18 (11–29)	0.037

[1]The calendar year 2001 includes May–December, both included.
CCI, Charlson Comorbidity Index.

improve cancer therapy outcome. The five-year relative survival of colon cancer increased 5 percent points and was 63% in 2009–2012, and five-year relative survival of rectal cancer rose 6 percent points ending at 65% in 2009–2012. The largest improvements in five-year relative survival were observed in patients with stages III and IV disease with improvements of 12 and 6 percent points, respectively, in colon cancer, and even more in rectal cancer: 19 and 7 percent points, respectively.

Present estimates are based on data from the national clinical DCCG database with a patient coverage of at least 99% since 2010 and histological verifications of the great majority of patients, or clinical verification by surgeons in the residual few percent. We present more favorable survival rates as compared to those in the OECD Cancer Care [5] and OECD Health-at-glance [13] from 2013. Data in the OECD reports were retrieved from the Danish Cancer Registry, which includes patients who do not fulfill criteria to enter the DCCG database. Thus, patients with anal cancer and patients with other histological types of intestinal cancer like neuroendocrine tumors are not included in the DCCG database, but are so in the Cancer Registry. Furthermore, patients diagnosed with a late-stage cancer may not be fully verified, i.e. because of frailty, and patients with abdominal symptoms, suspicious of CRC, may thus be falsely notified as CRC to the Danish Cancer Registry. Similarly, patients with metastases or invasion to the colon or rectum from an unknown primary tumor, but mimicking CRC, may be registered as CRC in the Danish Cancer Registry.

The present results indicate that survival rates in CRC patients in Denmark now are quite comparable to rates observed in other Scandinavian countries. The Norwegian Colorectal Cancer Registry has very recently published results on rectal cancer showing a five-year relative survival of 63% in 2007–2010 [14].

Excess mortality the first 6–12 months after diagnosis in Denmark as compared to other countries, was previously (and repeatedly) demonstrated in cohorts diagnosed until the early 2000s [15,16]. This study on patients diagnosed 2001–2012 thus represents a breakthrough, documenting a substantial fall in one-year mortality. The largest decreases were obtained in comorbid patients, in patients operated upon electively, in

Table 8. One- and 5-year relative, age-adjusted survival for rectal cancer patients. Overall estimates (entire cohort) and stratified by gender, comorbidity level, cancer stage, and priority of surgery.

		Total period	Calendar period of rectal cancer diagnosis			
Relative survival % (95% CI)	Follow-up	2001[1]–2012	2001[1]–2004	2005–2008	2009–2012	p-value
All	0–1 year	83 (82–85)	81 (78–84)	84 (81–86)	85 (83–88)	0.001
	0–5 year	62 (60–64)	59 (56–61)	64 (62–67)	65 (57–73)	0.001
Gender						
Men	0–1 year	83 (81–85)	81 (77–84)	84 (80–87)	85 (82–88)	0.001
	0–5 year	61 (59–63)	59 (55–62)	63 (60–66)	64 (55–75)	0.004
Women	0–1 year	83 (81–86)	81 (77–85)	84 (80–88)	85 (81–89)	0.001
	0–5 year	63 (60–65)	59 (55–63)	66 (62–70)	65 (53–79)	0.001
Comorbidity level						
CCI = 0 (None)	0–1 year	85 (83–87)	83 (80–86)	86 (83–89)	87 (84–91)	0.001
	0–5 year	65 (63–67)	61 (58–64)	69 (66–72)	68 (59–77)	0.001
CCI = 1 (Low)	0–1 year	82 (78–87)	78 (69–88)	82 (75–89)	84 (78–91)	0.003
	0–5 year	53 (49–58)	49 (42–58)	55 (49–62)	65 (44–92)	0.030
CCI = 2 (Medium)	0–1 year	74 (69–79)	67 (57–78)	77 (69–85)	76 (69–83)	0.001
	0–5 year	48 (42–53)	42 (33–52)	51 (44–58)	72 (50–99)	0.009
CCI ≥3 (High)	0–1 year	65 (57–75)	49 (31–75)	64 (50–80)	71 (58–85)	0.018
	0–5 year	33 (24–43)	36 (20–62)	33 (22–46)	81 (36–113)	0.302
Cancer stage						
Non-metastatic, M0	0–1 year	95 (93–97)	94 (90–97)	95 (91–98)	96 (93–100)	0.001
	0–5 year	81 (78–83)	78 (74–82)	82 (79–86)	89 (78–101)	0.001
Metastatic, M1	0–1 year	57 (55–59)	52 (47–56)	57 (53–62)	60 (56–65)	0.001
	0–5 year	15 (14–17)	13 (11–16)	18 (15–20)	20 (13–30)	0.011
Unknown, Mx	0–1 year	72 (68–76)	66 (60–73)	77 (69–85)	74 (67–82)	0.008
	0–5 year	50 (46–55)	43 (37–49)	63 (55–71)	57 (34–89)	0.002
UICC cancer stage						
I	0–1 year	98 (94–101)	96 (89–104)	99 (93–103)	97 (92–103)	0.003
	0–5 year	97 (92–102)	95 (88–104)	98 (91–105)	98 (78–121)	0.008
II	0–1 year	96 (92–99)	95 (89–101)	94 (88–100)	97 (91–102)	0.001
	0–5 year	85 (81–89)	84 (78–91)	85 (79–91)	88 (71–109)	0.076
III	0–1 year	92 (89–96)	91 (85–97)	92 (87–98)	94 (89–100)	0.004
	0–5 year	65 (62–69)	61 (56–66)	68 (63–73)	80 (62–101)	0.001
IV	0–1 year	57 (55–59)	52 (47–56)	57 (53–62)	60 (56–65)	0.001
	0–5 year	15 (14–17)	13 (11–16)	18 (15–20)	20 (13–30)	0.011
Unknown	0–1 year	72 (69–75)	66 (61–71)	77 (72–82)	74 (69–79)	0.008
	0–5 year	50 (47–53)	43 (38–47)	63 (58–68)	57 (44–71)	0.002
Priority of surgery						
Elective	0–1 year	90 (88–92)	86 (83–89)	91 (88–94)	93 (90–96)	0.001
	0–5 year	70 (68–72)	65 (62–68)	73 (71–76)	78 (69–88)	0.001
Emergency/acute	0–1 year	46 (40–54)	47 (37–60)	41 (31–54)	53 (41–67)	0.210
	0–5 year	22 (16–28)	26 (18–37)	20 (13–31)	71 (29–106)	0.327
No surgery	0–1 year	52 (50–55)	48 (42–54)	54 (49–59)	53 (49–58)	0.056
	0–5 year	18 (16–21)	18 (14–23)	20 (17–24)	22 (13–35)	0.036

[1]The calendar year 2001 includes May–December, both included.
CCI, Charlson Comorbidity Index.

patients with stage IV disease, and in rectal cancer patients not undergoing surgery. These decrements were translated into improved five-year outcome as well. Future studies are needed to elucidate whether or not the improvements have eliminated the survival gap separating Denmark from other comparable countries.

For many years, the 30-day post-operative mortality rate has been about double as high in Denmark as in other countries [17]. However, 30-day mortality after elective surgery has declined from 7.3% in 2001–2002 to 1.8% in 2013 [10]. In colon cancer, post-operative mortality after elective surgery dropped statically significantly after 2007 and was associated with implementation of laparoscopic surgery [18]. Worldwide, the proportions of patients who undergo laparoscopic resection of CRC are among the highest in Denmark, being 57% for colon cancer and 75% for rectal cancer in 2013 [10].

Expectedly, outcome for rectal cancer has improved as a consequence of the extensive and profound focus on the management of rectal cancer in both an international and national setting. First of all and probably most important has the implementation of total mesorectal excision (TME) been, resulting in a decrease of the local recurrence rate [19,20]. Introduction of TME has led to other actions with impact on short- and long-term outcome. Thus, surgery is now restricted to much fewer centers where the specialist surgeons become highly specialized in CRC surgery [21]. From 2001 to 2012 the number of Danish hospitals performing surgery for rectal cancer decreased from 47 to 15 [17], a process also enhanced through the national cancer plans. Other important elements in the management of rectal cancer include a more proper T-staging by use of magnetic resonance imaging (MRI), use of neoadjuvant chemo-radiotherapy in certain T3 and T4 tumors located in mid and lower rectum, and planning of treatment strategy at multidisciplinary team (MDT) meetings since mid-2000s. Our stage-specific analyses now prove that the five-year relative survival rates of non-metastatic rectal cancer, i.e. stage I + II + III, are in line with those of breast cancer patients with non-metastatic disease [22]. In our minds the better outcome of rectal cancer obtained over the past 12 years is a result of several elements orchestrated so very well together.

Optimized treatment strategies specific for colon cancer has not been introduced to the same extent as in rectal cancer.

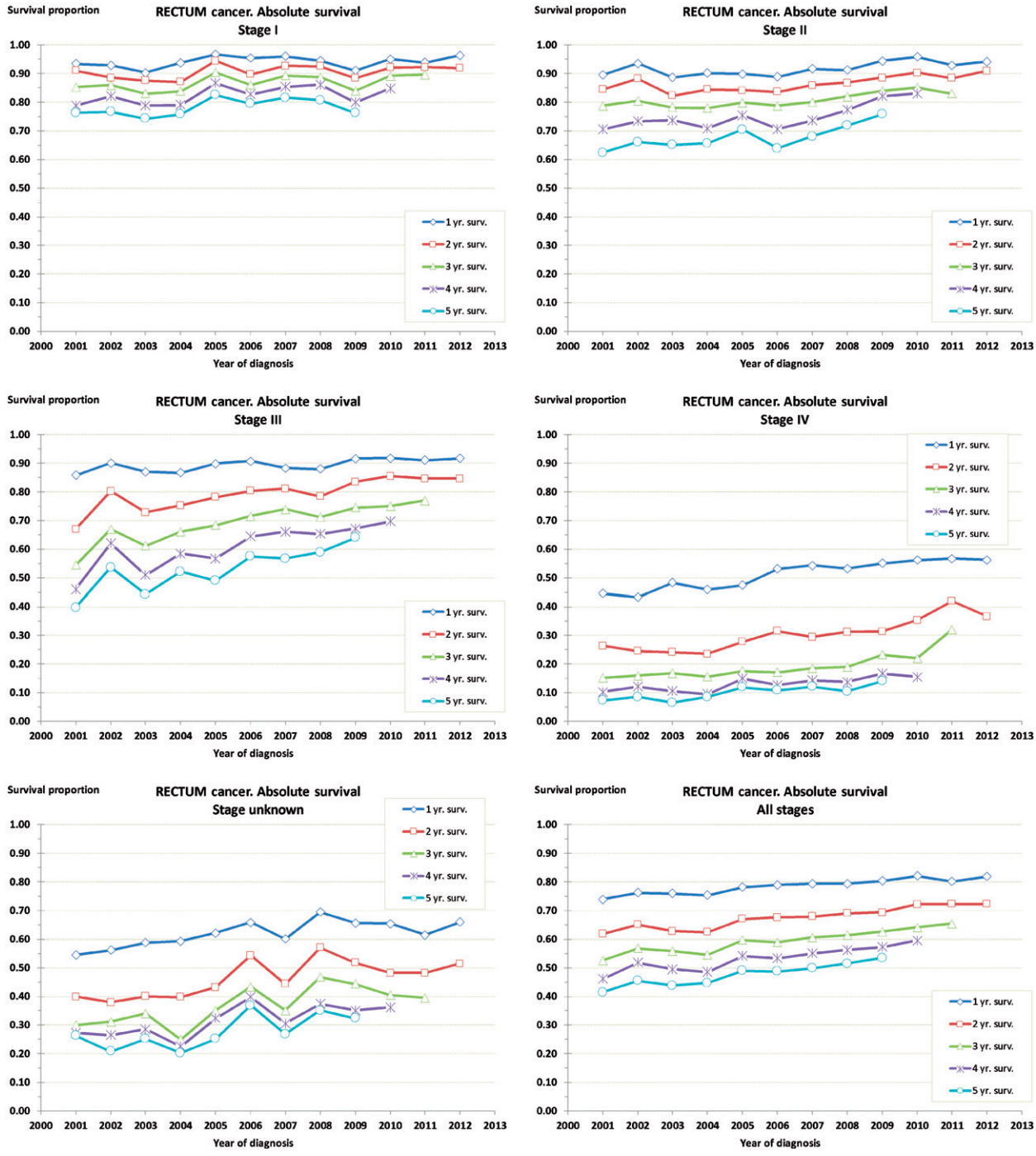

Figure 4. Trends in unadjusted, absolute survival proportions by year at diagnosis. Rectal cancer.

Nevertheless, the outcome of patients with colon cancer did improve. Explanations behind this may include implementation of laparoscopic surgery, concentration of surgical treatment with a reduction of the number of hospitals performing surgery for colon cancer from 50 in 2001 to 20 in 2012 [17], specialization, and MDT meetings for patients with advanced stages (albeit not yet introduced everywhere).

Comorbidity had negative impact on outcome in both colon cancer and rectal cancer with five-relative survival being almost half as high for patients with CCI $\geq$3 compared to patients with no comorbidity in 2001–2004. Surprisingly, we only observed improvements for patients with CCI levels up to two in colon cancer, whereas outcome improved in all CCI levels in rectal cancer, diminishing the gradient across the CCI levels over time. Discussion of rectal cancer patients at MDT and increasing awareness of the influence of comorbidity probably have resulted in referral to relevant medical specialists for optimization before treatment. Colon cancer patients are, as mentioned, not yet systematically put on MDT. Additionally, optimization of comorbidity may not always be possible in patients presenting as emergency patients.

Stage-specific analyses revealed pronounced improvements of patients with stage III and IV disease, irrespective of tumor location. These improvements do not seem to be caused by

stage migration because the stage distribution was stable in colon cancer, and in rectal cancer, a non-systematic change occurred with an increasing proportion of patients with stages I and IV. Explanations for the improvements include adjuvant chemotherapy in stage III colon cancer, which in randomized trials has shown survival increments of 5–15 percent points [23]. Regimens of 5-floururacil and leucoverin have been offered Danish patients since 1997 with addition of oxaliplatin since ultimo 2005. In stage III rectal cancer, adjuvant chemotherapy was not recommended before 2009 and could therefore not explain the improvements. Neither is neoadjuvant radiotherapy expected to contribute to the findings in stage III rectal cancer patients as this treatment has not shown significant effect on survival, but solely on reducing the risk of local recurrence [24]. Further, neoadjuvant radiotherapy has also been offered certain patients with stage II disease. However, we cannot rule out that neoadjuvant radiotherapy has made resectional surgery possible in some patients with locally advanced tumors. It is most natural to assign TME surgery, with dissection in the embryologic planes and removal of lymph nodes in the mesorectum, the improvement in outcome in node positive disease. In addition, during the study period the number of lymph nodes identified in the rectal specimens has increased from 10 to 26 per specimen [10]. The number of identified metastatic as well as non-metastatic lymph nodes in the specimens has been reported to increase overall survival [25,26]. In patients with stage IV disease the general treatment policy has become more aggressive over time including treatment with curative intent of hepatic metastases [27], pulmonary metastases [28], and peritoneal carcinomatosis [29]. Palliative treatment options have also been more advanced including local treatment of hepatic metastases, and most of all, systemic chemotherapy still becomes more effective with median survival in prospective trials increasing from 12 to 30 months [30].

Increasing proportions of patients were spared for surgical treatment during the study period, i.e. 15% and 19% for colon and rectal cancer patients, respectively, in 2009–2012. If surgery foremost was denied patients with short life expectancy, such a change certainly would contribute to the observed improvements of patients who underwent surgical treatment. In rectal cancer, the increasing opting out of surgery seems to be the right strategy resulting in improved survival in patients who do not have surgical treatment. In colon cancer, however, this altered treatment strategy had the opposite effect with poorer outcome in the recent period where more patients were spared for surgery. It seems that patients with rectal cancer may be well palliated by chemo- and radiotherapy, whereas chemotherapy is the only option in patients with colon cancer. However, the proportion of colon cancer patients, who underwent emergency surgery, also decreased and some of these patients may have been spared surgery. Another reason for the decreasing proportion of emergency surgery could be conversion to elective surgery by use of a bridge-to-surgery procedure with stent or a defunctioning stoma. These speculations need more data, and most optimally, in a prospective design. Whether or not it is advantageous to resect the primary tumor in stage IV colon cancer is currently being investigated in two randomized trials, CAIRO 4 and Synchronous [31].

The present population-based study documents major improvements of outcome for Danish patients with CRC during 2001–2012. Several disease- and stage-specific but also more general national treatment initiatives seem to have borne fruit. National register-based studies are very valuable to monitor the effects of such initiatives. Future studies will reveal the effect of other initiatives, such as implementation of complete mesocolic excision [32,33], among others.

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