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Differences in treatment and survival in young and elderly patients with colorectal cancer

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ABSTRACT

INTRODUCTION. The incidence of colorectal cancer (CRC) in patients ≤ 40 years of age seems to follow an increasing trend worldwide. Previous studies have reported conflicting data on treatment intensity and survival in young patients with CRC. The aim of this study was to describe treatment and survival data in a national cohort of young Danish CRC patients in the 2001-2013 period and to compare these data with data on a national cohort of elderly patients with CRC.

METHODS. In a retrospective study design, we analysed data on pre-operative management, treatment and overall survival in a national cohort of 484 young (18-40 years) and 14,647 elderly (66-75 years) CRC patients. Cox regression models were used to calculate adjusted hazard functions of overall survival.

RESULTS. Surgical treatment did not differ markedly between age groups, but young patients received more oncological treatment and had a better stage-specific five-year overall survival than elderly patients. In an adjusted model, the hazard ratio for young patients with stage I-III disease was 0.67 (95% confidence interval (CI): 0.48-0.95) for colon cancer; 0.61 (95% CI: 0.37-0.99) for rectal cancer.

CONCLUSION. Despite more advanced clinical stages of disease, young CRC patients had a better survival than elderly CRC patients in this national cohort.

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TRIAL REGISTRATION. The project was approved by DCCG (2013-03), the Danish Data Protection Agency (2008-58-0035) and the Regional Scientific Ethical Committee for Southern Denmark (S-20130079).

Colorectal cancer (CRC) diagnosed in patients younger than 40 years of age remains relatively uncommon (approximately 1% of new cases in Denmark annually), but the incidence seems to be increasing in Denmark [1]. This causes concern as these young patients are neither covered by national screening programmes for asymptomatic patients nor by guidelines on urgent referral of symptomatic patients. It is well documented that young CRC patients often present with advanced disease, and recent data from Denmark have confirmed this [1]. However, despite higher stages in the young, it has also been debated whether the survival of young patients

with CRC is actually better [2-5], poorer [6-8] or comparable to that of older patients [9-12]. Most of the published studies are single-centre reports, and only few population-based studies are available.

The objective of this study was to develop a better understanding of the survival after CRC in the young patient, and to elucidate the relationship between age at diagnosis, cancer stage, treatment intensity and overall survival (OS) by comparing a national cohort of young CRC patients with a national cohort of CRC patients aged 65-75 years at diagnosis.

METHODS

Study population and reference group

This was a retrospective study of a national cohort comprising young patients and elderly patients aged 66-75 years with CRC diagnosed between 1 January 2001 and 31 December 2013. The main study populations are described elsewhere [1]; in brief, 521 young patients were identified in the Danish Colorectal Cancer Group (DCCG) database and in the Danish Cancer Register, whereas 15,588 elderly patients were identified only in the DCCG database.

National registers

The DCCG database is a national CRC database with prospectively collected data on patient demographics, perioperative management, surgical treatment and survival data for all patients with CRC in Denmark since 2001 [13]. The database is enriched with aggregated data on comorbidity and oncological treatment from the National Patient Registry and linked to the Danish Civil Registration System for monthly updates of survival and emigration data.

Surgical treatment

Patients with a procedure code including bowel resection or a procedure with a local resection (e.g., endoscopic polypectomies or transanal endoscopic microsurgery) were classified as cancer resection surgery, whereas patients with explorative procedures only (with or without stoma creation) or endoscopic decompression procedures (e.g., stent) were classified as “no cancer resection surgery”.

Oncological treatment

Information on oncological treatment in simplified form, *i.e.* whether or not the patient had been seen by an oncologist, received oncological treatment, and whether the latter was adjuvant or neoadjuvant, was collected in the DCCG database. National recommendations on oncological (and surgical) treatment of CRC have been in place in Denmark since 1998, and previous versions of guidelines (in Danish language) are available online [14].

Statistical methods

Comparisons between groups were analysed with non-parametric test (Fisher's exact test or the χ^2-test) as appropriate. Missing or unknown values were excluded from the analysis. OS was defined as the time from diagnosis to death by any cause, and patients were censored if lost to follow-up (emigration) during the observation period. The minimum observation time for all patients was five years. The survival function of young and elderly patients was estimated with Kaplan-Meier curves, stage by stage, and the log-rank test was used to test for difference in five-year OS between groups. In addition, Cox regression models were used to adjust the five-year OS hazard function from the date of surgery to death for colon and rectal cancer patients with stage I-III disease. Gender, the Charlson comorbidity score, the American Society of Anesthesiologists (ASA) score, surgical treatment, oncological treatment, Union for International Cancer Control (UICC) stage and year

of diagnosis were predefined adjustment variables in the models. The year of diagnosis was grouped into four strata according to revisions of the national treatment guidelines issued by the DCCG. Results from both univariate and multivariate models are presented as hazard ratios (HR) with 95% confidence intervals (CI). p-values < 0.05 were considered statistically significant. All statistical analyses were performed in Stata IC 15.0 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA).

Trial registration: The project was approved by the DCCG (2013-03), the Danish Data Protection Agency (2008-58-0035) and the Regional Scientific Ethical Committee for Southern Denmark (S-20130079).

RESULTS

In the DCCG database, treatment data were available for 494 young CRC patients, and ten patients were excluded due to unknown stage of disease. In the elderly CRC patient group, 890 patients were excluded due to missing information about stage; thus 14,697 elderly patients remained for analysis.

The median age in the young CRC population was 36 years (range: 18-40 years); in the elderly group, 71 years (range: 66-75 years). Young patients with CRC had a more equal gender distribution, more advanced UICC stages, a lower ASA score and a lower Charlson comorbidity score than elderly CRC patients (**Table 1**).

TABLE 1 General patient demographics with comparison between young patients with colorectal cancer (CRC) and the elderly CRC cohort. The values are n (%).

	Young (N_y = 484)	Elderly (N_e = 14,697)	p-value
Cancer type			0.729
Colon	317 (65.5)	9,737 (66.3)	
Rectum	167 (34.5)	4,960 (33.7)	
Gender			0.004
Male	246 (50.8)	8,426 (57.3)	
Female	238 (49.2)	6,271 (42.7)	
Year of diagnosis			0.899
2001-2002	60 (12.4)	1,692 (11.5)	
2003-2005	102 (21.2)	3,076 (20.9)	
2006-2009	154 (31.8)	4,624 (31.5)	
2010-2013	168 (34.7)	5,305 (36.1)	
Cancer stage, Union for International Cancer Control			0.001
I	68 (14.0)	2,191 (14.9)	
II	117 (24.2)	4,760 (32.4)	
III	149 (30.8)	3,736 (25.4)	
IV	150 (31.0)	4,010 (27.3)	
American Society of Anesthesiologists score			< 0.0001
I	330 (68.2)	2,482 (16.9)	
II	116 (24.0)	7,801 (53.1)	
III-V	17 (3.5)	3,390 (23.1)	
Unknown[a]	21 (4.3)	1,024 (7.0)	
Comorbidity, Charlson Index			< 0.0001
0	428 (88.4)	9,153 (62.3)	
1-2	24 (5.0)	3,821 (26.0)	
≥ 3	32 (6.6)	1,723 (11.7)	

a) Data are omitted from statistical analysis.

Surgical treatment

For all patients, regardless of tumour localisation, no difference was seen in pre-operative management regime, such as multidisciplinary team conference and radiological examinations (**Table 2**).

TABLE 2 Differences in pre-operative management, surgical treatment and oncological treatment between young and elderly patients with colorectal cancer, shown for colon and rectal cancer separately. The values are n (%).

	Colon cancer			Rectal cancer		
	young (N_{cy} = 317)	elderly (N_{ce} = 9,737)	p-value	young (N_{ry} = 167)	elderly (N_{re} = 4,960)	p-value
Discussed at multidisciplinary team conference?						
Yes	41 (38.0)	1,285 (36.3)	0.901	55 (91.7)	1,570 (89.1)	1.00
No	63 (58.3)	2,025 (57.2)		3 (5.0)	106 (6.0)	
Unknown[a]	4 (3.7)	233 (6.6)		2 (3.3)	86 (4.9)	
Patients diagnosed in 2001-2009[b]	209 (65.9)	6,194 (63.6)		107 (64.1)	3,198 (64.5)	
Computed tomography of the thorax and abdomen?						
Yes	96 (88.9)	3,105 (87.6)	0.986	56 (93.3)	1,616 (91.7)	1.00
No	8 (7.4)	257 (7.3)		3 (5.0)	107 (6.1)	
Unknown[a]	4 (3.7)	181 (5.1)		1 (1.7)	39 (2.2)	
Patients diagnosed in 2001-2009[b]	209 (65.9)	6,194 (63.6)		107 (64.1)	3,198 (64.5)	
Surgical treatment?						
Yes	304 (95.9)	8,835 (90.7)	0.005	153 (91.6)	4,384 (88.4)	0.411
No	12 (3.8)	779 (8.0)		14 (8.4)	506 (10.2)	
Unknown[a]	1 (0.3)	123 (1.3)		0	70 (1.4)	
If surgery						
Surgical priority:						
Elective	236 (77.6)	7,370 (83.4)	0.040	145 (94.8)	4,277 (97.6)	0.089
Emergent	63 (20.7)	1,463 (16.6)		7 (4.6)	106 (2.4)	
Unknown[a]	5 (1.6)	2 (0.0)		1 (0.6)	1 (0.0)	
Surgical approach:						
Laparotomy	227 (74.7)	6,082 (68.8)	0.031	103 (67.3)	2,924 (66.7)	0.875
Laparoscopy	77 (25.3)	2,753 (31.2)		50 (32.7)	1,459 (33.3)	
Unknown[a]	0	0		0	1 (0.0)	
Cancer resection surgery?						
Yes	286 (94.1)	8,385 (94.9)	0.662	144 (94.2)	4,104 (93.6)	0.646
No	12 (4.0)	401 (4.5)		8 (5.2)	270 (6.2)	
Unknown[a]	6 (2.0)	49 (0.6)		1 (0.6)	10 (0.2)	
All stages						
Seen by an oncologist?						
Yes	238 (75.1)	4,828 (49.6)	< 0.0001	128 (76.7)	2,790 (56.3)	< 0.0001
No	79 (24.9)	4,909 (50.4)		39 (23.3)	2,170 (43.7)	
If seen by an oncologist						
Oncological treatment?						
Yes, regardless of regime	218 (91.6)	3,994 (82.7)	< 0.0001	126 (98.4)	2,491 (89.3)	< 0.0001
No	20 (8.4)	834 (17.3)		2 (1.6)	299 (10.7)	

a) Missing or unknown data are omitted from statistical analysis.
b) Patients (% of entire cohort) with no data available.

Regarding colon cancer, significantly more young patients with colon cancer (yCC) had surgical treatment compared with the elderly patients with colon cancer (eCC); and the proportion of patients who underwent emergent surgery was slightly higher in yCC patients. A larger proportion of yCC patients had a laparotomy performed. For rectal cancer, no difference was seen between young rectal patients (yRC) and elderly rectal cancer (eRC) patients having surgical treatment or emergent surgery, and no difference was seen between the surgical approaches used in these patients. Furthermore, no differences were recorded in the proportion of patients having cancer resection surgery for either colon or rectal cancer (Table 2).

Oncological treatment – colon cancer

Three out of four yCC patients were seen by an oncologist, compared with only one out of two eCC patients. Almost nine out of ten yCC patients and eight in ten eCC patients received oncological treatment (Table 2). A total of 100 yCC patients (98%) and 2,034 (81%) eCC patients with stage III disease were seen by an oncologist ($p < 0.0001$), and 95 (95%) of yCC patients received adjuvant treatment compared with 1,758 (86%) in the eCC group ($p = 0.01$). A total of 94% yCC patients and 74% eCC patients with stage IV disease were seen by an oncologist ($p < 0.0001$), and 88% of the yCC patients and 83% of the eCC patients with stage IV received palliative oncological treatment.

Oncological treatment – rectal cancer

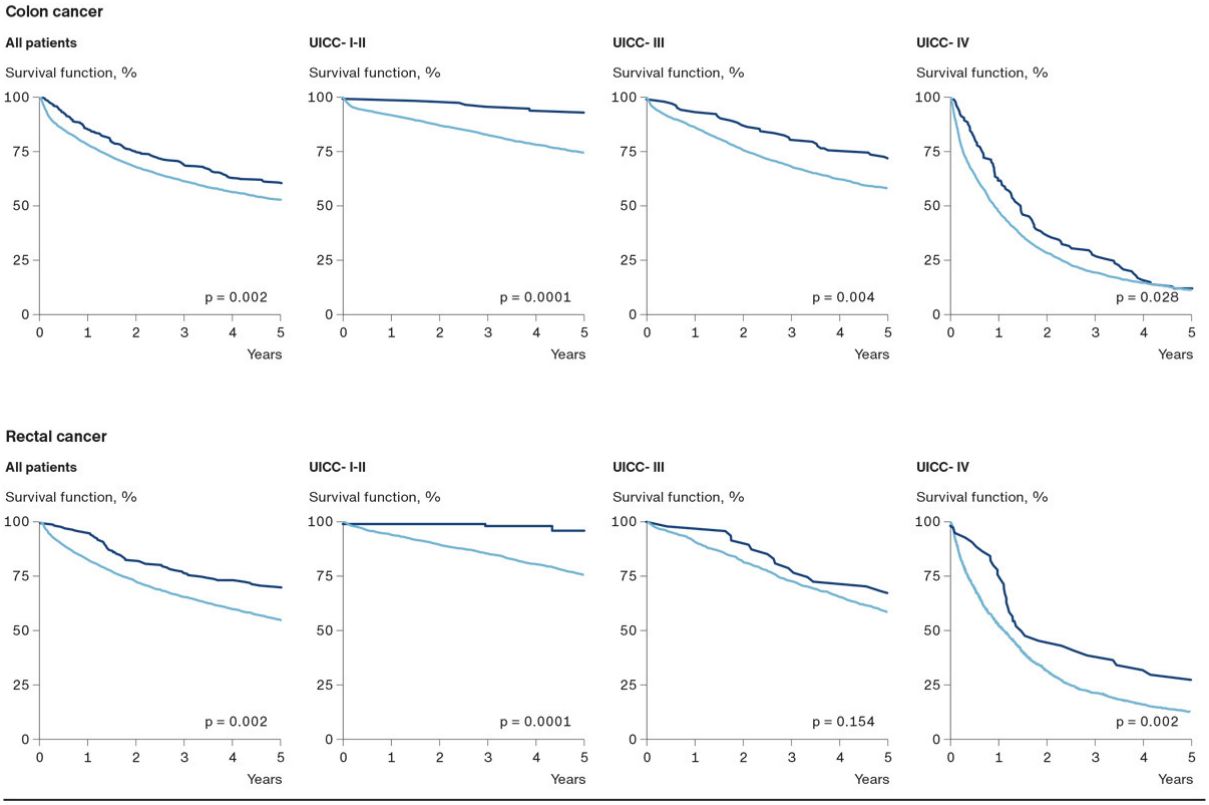
Similar to patients with colon cancer, 75% yRC patients and 56% eRC patients were seen by an oncologist. In all, 126 (98%) yRC patients received oncological treatment compared with 89% of the eRC cohort (Table 2). Almost equal proportions of rectal cancer patients had neo-adjuvant therapy regardless of age, but a slightly larger proportion of yRC patients with stage III disease had adjuvant treatment compared with eRC patients (84% versus 61%, p = 0.004). Nearly all yRC patients and one third of eRC patients with disseminated disease were seen by an oncologist (p = 0.001), with 96% yRC and 86% eRC patients receiving palliative oncological treatment.

Survival

Six (1.2%) young and 23 (0.2%) elderly patients with CRC were lost to follow-up due to emigration, and the median follow-up was 83 months (range: 0-212 months) in the young age group and 65 months (range: 0-213 months) in the elderly cohort.

Overall, 178 (36%) young CRC patients and 6,872 (47%) elderly CRC patients died within the five-year observational period. The five-year OS was better in yCC patients for all UICC stages (I: 100% versus 81%, p = 0.010; II: 91% versus 72%, p = 0.001; III: 73% versus 58%, p = 0.004; IV: 13% versus 11%, p = 0.028, all stages: 60% versus 53%, p = 0.002), and similar survival outcomes were seen in yRC patients (I: 100% versus 81%, p = 0.006; II: 95% versus 71%, p = 0.003; III: 68% versus 58%, p = 0.154; IV: 28% versus 12%, p = 0.002, all stages: 70% versus 55%, p = 0.0001) (**Figure 1**).

FIGURE 1 Union International Cancer Control (UICC) stage-specific overall survival from diagnosis until death by any cause with p-values calculated by the log-rank test. Young colorectal cancer (CRC) patients in dark blue and elderly CRC patients in light blue.



The adjusted HR in yCC stage I-III patients with cancer resection surgery was 0.67 (95% CI: 0.48-0.95, p = 0.023). An improved adjusted HR was also seen in yRC patients with stage I-III disease having cancer resection surgery,

0.61 (95% CI: 0.37-0.99, p = 0.048) (**Table 3**).

TABLE 3 Cox regression analysis regarding five-year overall survival for colon and rectal cancer patients with stage I-III disease.

	Colon cancer				Rectal cancer			
	univariate		multivariate		univariate		multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age								
Elderly: 66-75 yrs	1.00 (reference)				1.00 (reference)			
Young: 18-40 yrs	0.48 (0.35-0.67)	< 0.0001	0.67 (0.48-0.95)	0.022	0.43 (0.27-0.69)	0.001	0.61 (0.37-0.99)	0.048
Sex								
Female	1.00 (reference)				1.00 (reference)			
Male	1.27 (1.17-1.38)	< 0.0001	1.23 (1.13-1.34)	< 0.0001	1.26 (1.11-1.44)	0.001	1.18 (1.04-1.34)	0.012
Year of diagnosis								
2001-2002	1.00 (reference)				1.00 (reference)			
2003-2005	0.95 (0.83-1.09)	0.459	0.91 (0.79-1.04)	0.175	0.94 (0.77-1.13)	0.486	0.86 (0.71-1.04)	0.129
2006-2009	0.73 (0.64-0.84)	< 0.0001	0.74 (0.65-0.85)	< 0.0001	0.77 (0.64-0.92)	0.005	0.71 (0.58-0.86)	0.001
2010-2013	0.56 (0.49-0.64)	< 0.0001	0.58 (0.50-0.67)	< 0.0001	0.51 (0.42-0.61)	< 0.0001	0.49 (0.39-0.60)	< 0.0001
American Society of Anesthesiologists score								
I	1.00 (reference)				1.00 (reference)			
II	1.70 (1.48-1.95)	< 0.0001	1.49 (1.30-1.72)	< 0.0001	1.51 (1.27-1.79)	< 0.0001	1.38 (1.15-1.65)	0.001
III-V	3.48 (3.02-4.01)	< 0.0001	2.25 (1.93-2.62)	< 0.0001	2.98 (2.46-3.60)	< 0.0001	2.23 (1.82-2.74)	< 0.0001
Unknown	2.11 (1.65-2.70)	< 0.0001	1.60 (1.24-2.05)	0.0002	1.62 (1.02-2.58)	0.042	1.26 (0.79-2.02)	0.328
Comorbidity, Charlson Index								
0	1.00 (reference)				1.00 (reference)			
1-2	1.64 (1.49-1.80)	< 0.0001	1.45 (1.32-1.60)	< 0.0001	1.48 (1.29-1.69)	< 0.0001	1.40 (1.21-1.61)	< 0.0001
≥ 3	2.84 (2.51-3.20)	< 0.0001	2.35 (2.06-2.68)	< 0.0001	2.53 (2.07-3.10)	< 0.0001	2.29 (1.84-2.85)	< 0.0001
Surgical priority								
Elective	1.00 (reference)				1.00 (reference)			
Emergent	2.49 (2.25-2.76)	< 0.0001	2.07 (1.87-2.31)	< 0.0001	1.72 (1.01-2.91)	0.044	1.28 (0.75-2.18)	0.364
Surgical technique								
Minimal invasive	1.00 (reference)				1.00 (reference)			
Laparotomy	1.80 (1.63-1.99)	< 0.0001	1.21 (1.08-1.36)	0.001	1.64 (1.43-1.88)	< 0.0001	1.20 (1.02-1.41)	0.028
Oncological treatment?								
No	1.00 (reference)				1.00 (reference)			
Yes, regardless of regimes	1.00 (0.92-1.10)	0.914	0.68 (0.61-0.76)	< 0.0001	1.12 (0.99-1.26)	0.063	1.07 (0.94-1.21)	0.319
Cancer stage, Union for International Cancer Control								
I	1.00 (reference)				1.00 (reference)			
II	1.53 (1.32-1.78)	< 0.0001	1.44 (1.24-1.68)	< 0.0001	1.61 (1.36-1.90)	< 0.0001	1.52 (1.28-1.80)	< 0.0001
III	2.57 (2.22-2.98)	< 0.0001	3.02 (2.56-3.57)	< 0.0001	2.63 (2.24-3.09)	< 0.0001	2.55 (2.17-3.01)	< 0.0001

CI = confidence interval; HR = hazard ratio.

DISCUSSION

This study described the relationship between age, cancer stage, treatment intensity and survival in patients with CRC. We report a better stage-specific five-year OS in both colon and rectal cancer (significant difference were not seen in stage III rectal cancer) for young CRC patients. Furthermore, young CRC patients recorded a better survival than elderly patients in the adjusted survival models taking patient and treatment characteristics into account. This is consistent with a recent population-based study from Canada that showed a superior OS and cancer-specific survival (CSS) in yCC (≤ 40-year-old) patients. Similar to our findings, their yCC patients more often had open surgery, and yCC patients in both stage II and III disease received more adjuvant chemotherapy than older patients (> 60 years) [15].

Our data showed that yCC patients with stage III disease more often received oncological treatment in line with the national guidelines than stage III-eCC patients did. For rectal cancer, no difference was seen in the proportion of patients having neo-adjuvant treatment. However, yRC patients were more likely to receive adjuvant treatment (especially in stage III). The reason why elderly patients - who were seen by an oncologist - did not receive treatment is difficult to investigate retrospectively. Obvious explanations may potentially be comorbidity, an unfavourable performance score or patient refusal. We did not have access to information on oncological agents, dosage and treatment duration, which is a limitation to our study. Such information might

have provided valuable insights since recent studies have suggested oncological overtreatment of young CRC patients with no survival benefit [16, 17].

Another limitation was the lack of histopathological data describing the aggressiveness of the tumour (grade of differentiation, tumour budding, venous invasion, perineural invasion, tumour perforation, etc.). These high-risk factors were considered as valuable prognostic tools and were used to determine if some patients (i.e. stage II colon cancer patients) should receive adjuvant chemotherapy in a revision of the national DCCG guidelines in late 2009. This means that the majority of the patients in our dataset lack this valuable information. However, others have investigated the role of tumour histology and survival in the young patient. Two larger population-based studies deserve mention. A Dutch population-based study showed that yRC patients had survival rates equal to those of middle-aged RC patients, and young age was a prognostic factor for improved survival when adjusting for tumour characteristics (tumour histology and grading) among other variables [18]. Similar results were reported in an American study using the Surveillance, Epidemiology, and End Results database with 6,700 CRC patients aged 20-40 years and 253,539 CRC patients aged over 50 (mean age 72) years. The young group had significantly larger proportions of adverse histological tumour type and tumour grading. Despite this, the multivariate Cox regression model showed poorer survival in the elderly group [19]. None of the mentioned studies encompassed other pathological risk factors included in the study model.

The major strength of this study is that we used a complete national cohort of young CRC patients. They were all identified in national registers whereby selection bias was minimized. Another major strength is that all patients received treatment in public hospitals since free tax-financed healthcare is universal in Denmark. National guidelines for treatment of CRC have been in place since 1998, even though we cannot rule out local variations in treatment regimes. The national screening programme for bowel cancer commenced in Denmark in 2014 for citizens aged 50-75 years, i.e. after our study period concluded. Potential stage migration in the reference population was thus avoided. Data on CSS are not available in the DCCG database. CSS data would have been interesting since we compared two groups of patients in different age spans where older age has an impact on OS. Relative survival is an alternative to OS, but the expected death rate per year in the general Danish youth population (18-40 years) in the study period was 0.59‰ (according to Statistics Denmark). Therefore, we assume that the OS curves for young CRC patients in this cohort may be interpreted as CSS. This is, of course, not applicable for the elderly cohort. Even so, we believe that our results are important since one of the objectives of this study was to supply the clinician with survival curves regarding the young CRC patient.

CONCLUSION

Our data show that young CRC patients had a better OS than elderly CRC patients, even when adjusting for surgical and oncological treatment and comorbidities. This information as well as the survival graphs published in this article may be helpful when counselling young Danish CRC patients.

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