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Is colorectal cancer a more aggressive disease in young patients? A population-based study from the Czech Republic

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ABSTRACT

Introduction: The incidence of colorectal cancer in young patients is increasing. The goal of this study was to investigate whether clinicopathological features and survival differed between young, middle-aged and elderly patients.

Methods: The Czech National Cancer Registry was searched to identify all cases of colorectal cancer between 1982 and 2014. Three subgroups of patients were created: young patients, defined as being between 18 and 40 years of age, middle-aged patients, defined as being between 41 and 74 years of age, and elderly patients, defined as being over the age of 75 years.

Results: A total of 192,241 patients diagnosed with colorectal cancer between the years 1982 and 2014 were included in the study. Out of these, 3,287 patients (1.7%) were between 18 and 40 years of age, 134,139 patients (69.8%) were between 41 and 74 years of age and 54,815 patients (28.5%) were 75 years of age or older. The young patients had a higher incidence of mucinous adenocarcinoma and signet ring cell carcinoma, more advanced disease and more rectal tumours than elderly patients. Nonetheless, young patients received treatment more frequently and had better cancer-specific survival than the older patients.

Conclusion: The better prognosis in young patients is presumably due to their better physiological reserve and lower incidence of comorbidities. Efforts should be made in younger patients to diagnose early and treat aggressively.

1. Introduction

Worldwide, colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer death [1]. Following the implementation of screening programs as well as a decline in cigarette smoking, the overall incidence of CRC has been decreasing [2,3]. However, despite the overall decrease in the incidence of CRC, the incidence in young patients has been found to be increasing. This observation is supported by studies based on the Surveillance Epidemiology and End Result (SEER) program data in the United States of America, as well as by studies from other developed countries, including Australia, Canada and Norway and a recent study based on cancer registries from 20 European countries [4–7]. In the Czech Republic the age-standardised incidence of CRC in patients under 40 years of age was 1.94 per 100,000 in the year 2017. The annual percentage increase among these patients was 1% between the years 1990 and 2015 [6]. The reason for the increasing CRC incidence in young patients remains unknown and is likely due to a combination of factors. It has been linked to the rising incidence of obesity and lack of physical activity in young people, both of which are known risk factors for CRC [5,8,9].

This alarming trend indicates that increased attention should be paid to young CRC patients. It has been hypothesised that CRC in young patients has a different biological behaviour than in older patients; with more frequent presentation at advanced stages and more aggressive histological features [10]. Despite these features, several population-

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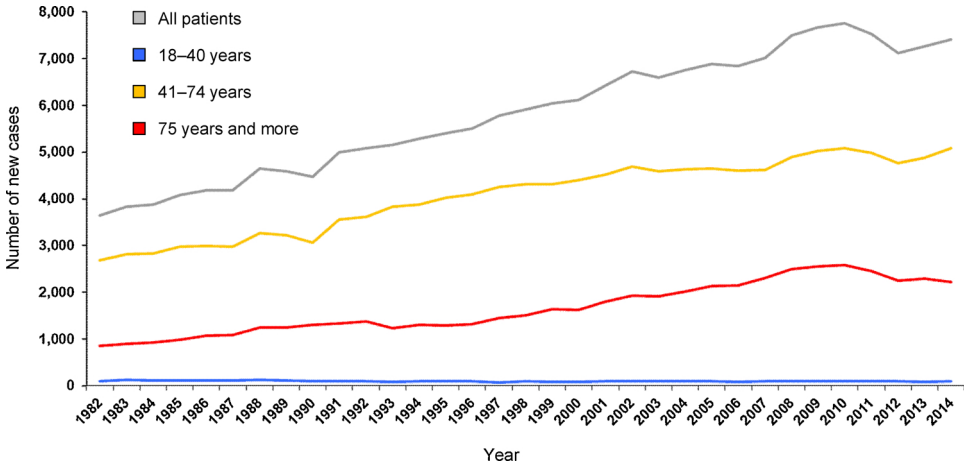


Fig. 1. Incidence of CRC over time in the total population and the selected age groups.

based studies show that younger patients have a better outcome than elderly patients [11–13]. The goal of our study was to investigate the clinicopathological features and survival data in young, middle-aged and elderly CRC patients using data from a national oncological database in the Czech Republic and to investigate prognostic factors.

2. Patients and methods

2.1. Data source

The Czech National Cancer Registry is a nationwide population-based cancer registry founded in 1976 and maintained by the Institute of Health Information and Statistics of the Czech Republic. In the Czech Republic it is mandatory to report all cases of oncological diseases to this registry for the purposes of surveillance and research. TNM tumour staging has been reported consistently in the registry since 1982, which is why this year was selected to be the lower time cut-off point for the study.

2.2. Patient selection

We searched the registry for all cases of colorectal cancer in patients over the age of 18 years, irrespective of histopathological diagnosis, occurring between the years 1982 and 2014. We used codes from the tenth edition of the International Classification of Disease (ICD-10) to search for malignant disease of the cecum (C18.0), ascending colon (C18.2), hepatic flexure (C18.3), transverse colon (C18.4), splenic flexure (C18.5), descending colon (C18.6), sigmoid colon (C18.7), rectosigmoid junction (C19), rectum (C20), overlapping lesions of the colon (C18.8) and large intestine not otherwise specified (C18.9, C26.0). Patients with in-situ neoplasms, tumours of the appendix and patients without data regarding cancer stage were removed. Tumour location was divided into four groups: right colon (caecum to splenic flexure), left colon (descending colon to sigmoid colon), rectum (including rectosigmoid junction), and other (overlapping lesions of the colon and large intestine not otherwise specified). According to the first to third editions of the International Classification of Disease for Oncology histological types were divided into four groups according to: adenocarcinoma (8010/2, 8010/3, 8010/6, 8010/9, 8140/2, 8140/3, 8140/6, 8141/3, 8210/2, 8210/3, 8211/3, 8220/3, 8221/3, 8230/3, 8231/3, 8260/3, 8261/2, 8261/3, 8262/3, 8263/2, 8263/3), mucinous adenocarcinoma (8480/3, 8481/3), signet-ring cell adenocarcinoma (8490/3) and others (all remaining morphology codes). For the purpose of survival analysis, deaths due to CRC were defined as analysed events, whereas other death cases were censored. Colorectal cancer specific survival was monitored from the time of diagnosis to either the patient's death or the end of follow-up (last follow-up date: December 2014).

2.3. Data extraction

Data extracted from the database included age at diagnosis, gender, tumour location, TNM stage, histology, grade, primary treatment (any treatment, surgery, radiotherapy or chemotherapy) and the date and cause of death. We summarised these data for the total population and then created three subgroups of patients: young patients, defined as being between 18 and 40 years of age, middle-aged patients, defined as between 41 and 74 years of age, and elderly patients, defined as being 75 years of age or older. We then compared tumour and patient characteristics and survival data between these three groups.

2.4. Statistical analysis

Standard descriptive statistics were applied in the analysis; mean supplemented with standard deviation for continuous variables and absolute and relative frequencies for categorical variables. The statistical significance of differences between the two groups of patients was tested using the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. Survival estimates at given time points were computed using Kaplan-Meier methodology; statistical significance of their differences between groups of patients was tested using statistical test for comparison of survival estimates at fixed time points [14]. The influence of factors on patient mortality risk was monitored by both univariate and multivariate Cox proportional hazards model. All tests were computed with level of statistical significance $\alpha = 0.05$; statistical analysis was done using SPSS 24.0.0.1 (IBM Corporation, 2017).

3. Results

A total of 192,241 cases of colorectal cancer were reported to the National Cancer Registry of the Czech Republic between the years 1982 and 2014. Of these, 3,287 patients (1.7%) between 18 and 40 years of age, 134,139 patients (69.8%) were between 41 and 74 years of age and 54,815 patients (28.5%) were 75 years of age or older. The total number of cases of CRC per year for the total population and in the selected age groups is shown in Fig. 1. Clinicopathological features of CRC in the total population are presented in Table 1.

3.1. Clinicopathological features

Significant differences ($p < 0.001$) were found between the age groups for all characteristics. In particular, there was a larger

Table 1
Clinicopathological features of all patients over 18 years old diagnosed with CRC in the Czech Republic between the years 1982 and 2014.

Clinicopathological features		All patients (N = 192,241)
Age	Mean ± SD, years	67.41 ± 11.24
Age groups	18–40 years	3,287 (1.7%)
	41–74 years	134,139 (69.8%)
	≥ 75 years	54,815 (28.5%)
Sex	Female	80,541 (41.9%)
	Male	111,700 (58.1%)
Tumour location	Right colon	57,740 (30.0%)
	Left colon	45,782 (23.8%)
	Rectum	82,870 (43.1%)
	Other[a]	5,849 (3.0%)
TNM stage	I	51,385 (26.7%)
	II	48,431 (25.2%)
	III	40,973 (21.3%)
	IV	51,452 (26.8%)
Histological type	Adenocarcinoma	158,377 (82.4%)
	Mucinous carcinoma	6,415 (3.3%)
	Signet ring cell carcinoma	442 (0.2%)
	Other	8,398 (4.4%)
	Unknown	18,609 (9.7%)
Tumour grade	Well differentiated	28,959 (15.1%)
	Moderately differentiated	82,175 (42.7%)
	Poorly differentiated	28,945 (15.1%)
	Undifferentiated	1,127 (0.6%)
	Unknown	51,035 (26.5%)
Treatment	Any treatment	153,301 (79.7%)
	Surgery	147,293 (76.6%)
	Radiotherapy	27,590 (14.4%)
	Chemotherapy	57,091 (29.7%)

[a] Includes overlapping lesions and lesions of the large intestine not otherwise specified.

proportion of males in the young (53.0%) and middle-aged (61.6%) groups compared with the elderly group (49.9%). Rectal tumours were more common in the young (42.5%) and middle-aged (45.4%) groups when compared to elderly group (37.4%) and tumours of the right colon were more common in the elderly group (36.3%). Advanced disease was more frequent in the young patients (50.2%) than in middle-aged (47.9%) and elderly patients (48.4%). Mucinous and signet ring cell carcinoma were more frequent histological findings in young patients (5.5% and 0.6%) compared to middle-aged (3.3% and 0.2%) and elderly (3.3% and 0.2%) patients. The young patients had a higher proportion of poorly differentiated and undifferentiated tumours (17.4% and 1.0%) than the middle-aged (15.3% and 0.6%) and elderly patients (14.4% and 0.6%). Young patients were more likely to receive treatment (90.8%) than the middle-aged (84.0%) and elderly patients (68.7%) as were the middle-aged more likely to receive treatment than the elderly patients. Clinicopathological features are summarised in Table 2.

3.2. Survival analysis

Cancer-specific survival rates, both overall and stage-specific, were significantly better in the young patients than in the elderly patients. The overall 1-, 3- and 5-year cancer-specific survival rates for the young patients were 80.2%, 61.4% and 55.6%, respectively. The overall 1-, 3- and 5-year cancer-specific survival rates for the middle-aged patients were 74.3%, 56.0% and 48.3%, respectively. The overall 1-, 3- and 5-year cancer-specific survival rates for the elderly patients were 58.3%, 40.7% and 33.4%, respectively. Survival data are summarised in Table 3 and Kaplan-Meier survival curves are shown in Figs. 2 and 3.

In the Cox proportional hazards model middle-aged and elderly age groups, male sex, advanced stage, mucinous and signet ring carcinoma, high tumour grade and not receiving treatment were all identified as negative prognostic factors. Univariate and multivariate Cox models are shown in Table 4.

4. Discussion

In this study we used data from the Czech National Cancer Registry to compare clinicopathological features and survival data in CRC patients of three different age groups: young (18–40 years), middle-aged

Table 2
Clinicopathological features in young (18–40 years), middle-aged (41–74 years) and elderly (≥75 years) patients.

Clinicopathological features		Young patients (N = 3,287)	Middle-aged patients (N = 134,139)	Elderly patients (N = 54,815)
Age	Mean ± SD, years	35.13 ± 4.61	63.00 ± 7.87	80.15 ± 4.21
Sex	Female	1,546 (47.0%)	51,549 (38.4%)	27,446 (50.1%)
	Male	1,741 (53.0%)	82,590 (61.6%)	27,369 (49.9%)
Tumour location	Right colon	968 (29.4%)	36,857 (27.5%)	19,915 (36.3%)
	Left colon	824 (25.1%)	32,729 (24.4%)	12,229 (22.3%)
	Rectum	1,396 (42.5%)	60,951 (45.4%)	20,523 (37.4%)
	Other[a]	99 (3.0%)	3,602 (2.7%)	2,148 (3.9%)
TNM stage	I	929 (28.3%)	36,851 (27.5%)	13,605 (24.8%)
	II	707 (21.5%)	33,057 (24.6%)	14,667 (26.8%)
	III	808 (24.6%)	28,862 (21.5%)	11,303 (20.6%)
	IV	843 (25.6%)	35,369 (26.4%)	15,240 (27.8%)
	Early disease (I + II)	1,636 (49.8%)	69,908 (52.1%)	28,272 (51.6%)
	Advanced disease (III + IV)	1,651 (50.2%)	64,231 (47.9%)	26,543 (48.4%)
Histological type	Adenocarcinoma	2,594 (78.9%)	112,344 (83.8%)	43,439 (79.2%)
	Mucinous adenocarcinoma	181 (5.5%)	4,451 (3.3%)	1,783 (3.3%)
	Signet ring cell carcinoma	20 (0.6%)	320 (0.2%)	102 (0.2%)
	Other	237 (7.2%)	6,034 (4.5%)	2,127 (3.9%)
	Unknown	255 (7.8%)	10,990 (8.2%)	7,364 (13.4%)
Tumour grade	Well differentiated	571 (17.4%)	20,735 (15.5%)	7,653 (14.0%)
	Moderately differentiated	1,207 (36.7%)	58,470 (43.6%)	22,498 (41.0%)
	Poorly differentiated	572 (17.4%)	20,505 (15.3%)	7,868 (14.4%)
	Undifferentiated	33 (1.0%)	780 (0.6%)	314 (0.6%)
	Unknown	904 (27.5%)	33,649 (25.1%)	16,482 (30.1%)
Treatment	Any treatment	2,986 (90.8%)	112,664 (84.0%)	37,651 (68.7%)
	Surgery	2,881 (87.6%)	108,534 (80.9%)	35,878 (65.5%)
	Radiotherapy	778 (23.7%)	23,424 (17.5%)	3,388 (6.2%)
	Chemotherapy	1,772 (53.9%)	50,028 (37.3%)	5,291 (9.7%)

All differences are statistically significant.
[a] Includes overlapping lesions and lesions of the large intestine not otherwise specified.

Table 3
One-, three- and five-year survival rates for the years 1982–2014 (N = 188,061).

Survival rates		Age groups		
		18–40 years	41–74 years	≥75 years
One-year survival	All stages	80.2 (0.70)	74.3 (0.12)	58.3 (0.22)
	Stage I	96.3 (0.62)	90.9 (0.15)	78.5 (0.37)
	Stage II	92.4 (1.00)	86.4 (0.19)	71.5 (0.38)
	Stage III	87.7 (1.16)	80.6 (0.23)	62.2 (0.47)
	Stage IV	44.3 (1.74)	39.7 (0.27)	22.7 (0.36)
Three-year survival	All stages	61.4 (0.87)	56.0 (0.14)	40.7 (0.23)
	Stage I	85.5 (1.17)	79.2 (0.22)	62.9 (0.45)
	Stage II	76.9 (1.62)	70.8 (0.26)	53.7 (0.44)
	Stage III	64.9 (1.73)	58.5 (0.30)	39.3 (0.50)
	Stage IV	16.7 (1.36)	14.2 (0.20)	7.2 (0.24)
Five-year survival	All stages	55.6 (0.90)	48.3 (0.15)	33.4 (0.23)
	Stage I	79.7 (1.36)	71.7 (0.25)	53.6 (0.49)
	Stage II	71.2 (1.76)	62.4 (0.28)	44.7 (0.46)
	Stage III	57.1 (1.83)	48.1 (0.32)	30.7 (0.50)
	Stage IV	12.3 (1.22)	9.1 (0.17)	4.5 (0.21)

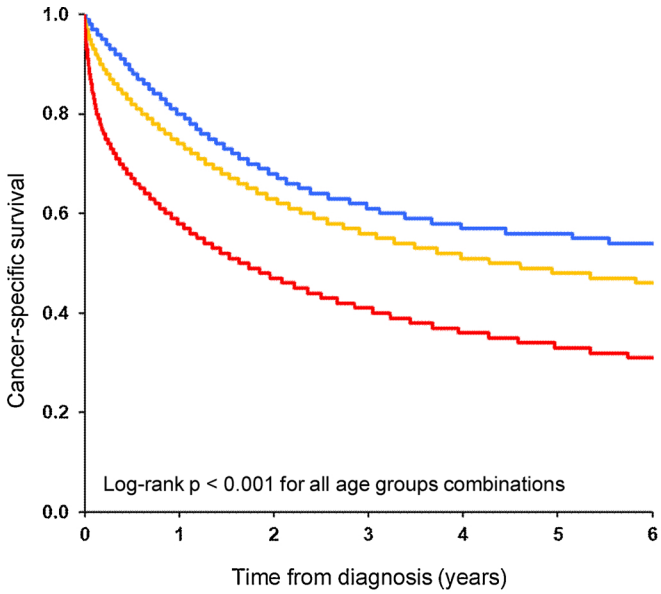
Values = % (SE%).
All differences are statistically significant.

(41–74 years) and elderly (75 years and over). Furthermore, we identified prognostic factors in the total cohort of patients. We showed that young patients have more aggressive histological features, more advanced disease and more rectal tumours than older patients. Nonetheless, young patients receive treatment more frequently and have better cancer-specific survival than older patients. We identified the middle-aged and elderly age groups, male sex, advanced disease, mucinous adenocarcinoma and signet ring cell carcinoma, high-grade tumours and absence of treatment to be negative prognostic factors.

A higher incidence of poor prognostic factors in young patients has been identified in both our study and other population studies. A study based on the Taiwan cancer registry by Chou et al. of 61,789 patients with CRC found mucinous and signet ring histological subtypes to be more frequent in young patients [15]. McMillan's study using data from 2,077 patients from 11 hospitals in Scotland demonstrated more advanced disease and more emergency presentations in younger patients [16]. Wang's population-based study from the SEER cancer registry included 279,623 patients with CRC diagnosed between 1988 and 2011 and showed that young patients were more likely to have mucinous and signet ring differentiation, higher tumour grades, more advanced stage and left-sided and rectal cancers [13]. Rodriguez's study from the Ontario cancer registry included 6,775 patients with colon cancer stages I to III. One hundred and seven (1.58%) of the patients were under the age of 40 years. Again, these patients had more left-sided cancers and higher T and N stages than the older patients [12]. A unique genetic background has been proposed to be responsible for these clinicopathological features and it follows on from this that early-onset CRC may be considered to be a separate clinical entity [17].

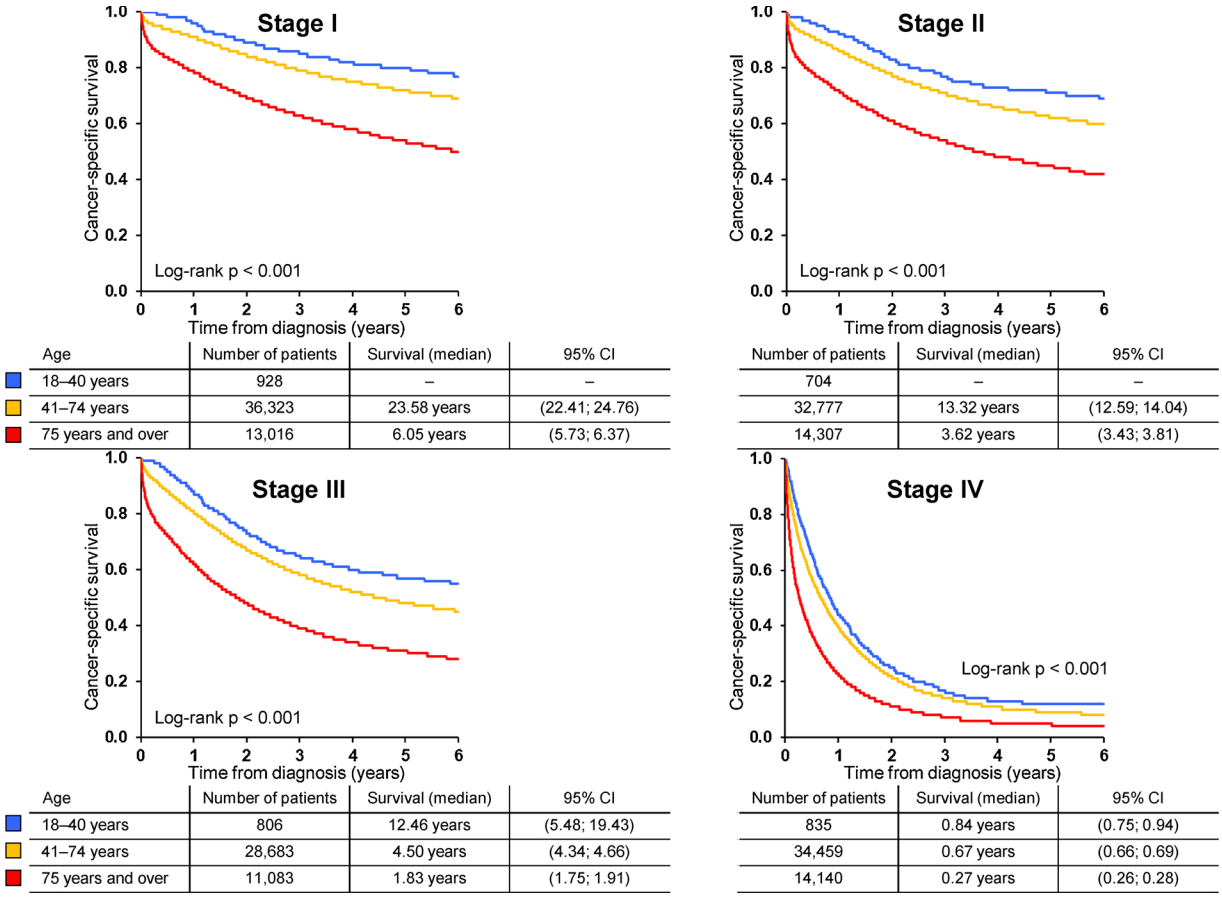
Our results show a proximal shift of tumour location when comparing young and elderly. Tumours were located in the right colon in 36.3% of the elderly patients compared with 29.4% in young patients. Rectal tumours were present in 42.5% of the young patients compared with 37.4% of the elderly patients. The difference in left colon tumours was smaller, yet still significant, with 22.3% in elderly patients and 25.1% in young patients. This trend has been found in other population studies [13,18].

The difference in presentation with advanced disease in young and old patients was only 1.8% of young and old patients and although statistically significant, its clinical impact in our study is undoubtedly small. Larger differences have been seen in other studies, in McMillian's study 63% of patients under 45 presented with advanced disease, compared with 49% in patients aged 65–74 years [16]. In Rodriguez's study stage III disease was present in 58% of patients under 40 years of age compared to 41% in patients over 60 years of age [12]. The higher



Age	Number of patients	Survival (median)	95% CI
18–40 years	3,273	11.33 years	–
41–74 years	132,242	4.44 years	(4.34; 4.54)
75 years and over	52,546	1.69 years	(1.64; 1.74)

Fig. 2. Cancer-specific survival for all stages of CRC in young, middle-aged and elderly patients.



Age	Number of patients	Survival (median)	95% CI
18–40 years	928	–	–
41–74 years	36,323	23.58 years	(22.41; 24.76)
75 years and over	13,016	6.05 years	(5.73; 6.37)

Number of patients	Survival (median)	95% CI
704	–	–
32,777	13.32 years	(12.59; 14.04)
14,307	3.62 years	(3.43; 3.81)

Age	Number of patients	Survival (median)	95% CI
18–40 years	806	12.46 years	(5.48; 19.43)
41–74 years	28,683	4.50 years	(4.34; 4.66)
75 years and over	11,083	1.83 years	(1.75; 1.91)

Number of patients	Survival (median)	95% CI
835	0.84 years	(0.75; 0.94)
34,459	0.67 years	(0.66; 0.69)
14,140	0.27 years	(0.26; 0.28)

Fig. 3. Stage-specific, cancer-specific survival for young, middle-aged and elderly patients with CRC.

Table 4
Univariate and multivariate Cox models for the years 1982–2014.

Clinicopathological features		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age groups	18–40 years	1		1	
	41–74 years	1.34 (1.28; 1.41)	<0.001	1.19 (1.12; 1.27)	<0.001
	≥75 years	2.21 (2.10; 2.32)	<0.001	1.66 (1.55; 1.77)	<0.001
Sex	Female	1		1	
	Male	1.04 (1.02; 1.05)	<0.001	1.09 (1.07; 1.10)	<0.001
Tumour location	Right colon	1.		1	
	Left colon	0.86 (0.84; 0.87)	<0.001	0.96 (0.94; 0.98)	<0.001
	Rectum	0.98 (0.96; 0.99)	<0.001	1.03 (1.01; 1.05)	0.006
	Other[a]	1.40 (1.35; 1.45)	<0.001	1.09 (1.04; 1.15)	<0.001
TNM stage	I	1		1	
	II	1.35 (1.33; 1.38)	<0.001	1.46 (1.43; 1.50)	<0.001
	III	1.93 (1.89; 1.96)	<0.001	2.32 (2.27; 2.38)	<0.001
	IV	6.37 (6.26; 6.49)	<0.001	6.22 (6.08; 6.38)	<0.001
Histological type	Adenocarcinoma	1		1	
	Mucinous adenocarcinoma + signet ring cell carcinoma	1.20 (1.17; 1.24)	<0.001	1.10 (1.06; 1.15)	<0.001
Tumour grade	Well differentiated	1		1	
	Moderately differentiated	1.13 (1.11; 1.15)	<0.001	1.04 (1.02; 1.06)	<0.001
	Poorly differentiated and undifferentiated	1.76 (1.72; 1.80)	<0.001	1.44 (1.40; 1.47)	<0.001
Treatment	Surgery	1		1	
	No surgery	4.88 (4.81; 4.94)	<0.001	2.44 (2.39; 2.50)	<0.001
	Radiotherapy	1		1	
	No radiotherapy	1.33 (1.31; 1.36)	<0.001	1.04 (1.01; 1.06)	0.001
	Chemotherapy	1		1	
	No chemotherapy	1.60 (1.58; 1.62)	<0.001	1.67 (1.64; 1.70)	<0.001

CI = confidence interval.
[a] Includes overlapping lesions and lesions of the large intestine not otherwise specified.

rate of presentation of advanced disease has been attributed to diagnostic delay in young patients. In O'Connell's review on CRC in young patients an average diagnostic delay of 6.2 months was reported [19]. This believed to be partially due to overlooking the symptoms of CRC in young patients.

The histological subtypes mucinous adenocarcinoma and signet ring cell carcinoma are generally considered poor prognostic factors. However, some controversy exists around the prognostic value of mucinous adenocarcinoma, particularly in its role as a prognostic factor in patients receiving preoperative chemoradiotherapy for rectal cancer [20]. In our study mucinous adenocarcinoma and signet ring cell carcinoma were identified in the univariate and multivariate Cox proportional hazards model as negative prognostic factors. They have been shown to be more resistant to chemotherapy. These subtypes were also more frequent in the young patients; a finding which has been made by other studies [13,15].

In our study a total of 1.7% of cases of CRC occurred in patients under the age of 40 years. This value is lower when compared with population-based studies from other countries. A study-based data from 18 SEER registries from the years 2000 and 2014 reported 2.6% of cases of CRC occurring in patients under 40 years of age [21]. Higher incidences have been reported from Asian countries. Chou's population-based study from Taiwan reported that 5.5% of cases occurred in patients under 40 years of age [15]. The highest incidences of early-onset CRC may be in South Asia, where several studies have reported proportions of CRC in young patients ranging from 38% to 52% [22–26]. Although these studies are subjected to selection bias, it seems likely that there may be a geographical variation in the incidence of early-onset CRC.

Some controversy exists in the literature regarding survival data of young compared to elderly patients, with some studies claiming a worse overall survival in young patients but a similar stage-specific survival and other studies claiming no significant differences in survival [27–31]. This controversy arises from small single institutional studies, with inconsistencies in cut-off values for young and old patients and selection bias. Population studies offer more reliable data. Our study confirms the finding of several recently published population-based studies that young patients, despite having biologically more aggressive tumours, have better survival than their elderly counterparts [12,13,15]. The worse survival in elderly patients is presumably due to their higher incidence of comorbidities and lower physiological reserve. As young patients are generally in a better state of health they are better candidates for more aggressive treatment, thus the higher rate of poor prognostic factors does not necessarily mean a worse outcome.

The mucin content of colorectal adenocarcinomas is known to increase after chemotherapy, and thus the patients who received neoadjuvant chemotherapy would have likely had a higher rate of mucinous adenocarcinoma [32]. Unfortunately, due to limitations in treatment data in the cancer registry we unable to account for this in our analysis. Other limitations included incompleteness of data, lack of details on treatment, lack of data on patient history and predisposing conditions (genetic syndromes, inflammatory bowel disease etc.).

5. Conclusions

Adverse histological features, higher grade and late presentation are hallmarks of CRC in the young. Despite this, evidence suggests these patients have better prognosis than elderly patients, which is presumably due to the better physiological reserve of young patients. Therefore, every effort should be made to diagnose CRC early and treat it aggressively in young patients.

Authorship contribution statement

Petr Kocián: Designing study, Preparation of manuscript.

Ivana Svobodová: Data retrieval and analysis, Statistics.

Denisa Krejčí: Data retrieval and analysis, Statistics.

Milan Blaha: Data retrieval and analysis, Statistics.

Robert Gürlich: Editing and approving manuscript, Clinical implications of the study.

Ladislav Dušek: Editing and approving manuscript, Reviewing the statistical analysis.

Jiří Hoch: Editing and approving manuscript, Clinical implications of the study.

Adam Whitley: Designing study, Preparation of manuscript, Coordinating the project.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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