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Young onset colorectal cancer: Insights based on a population-based study from England

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Abstract

Aim: Young colorectal cancer patients are reported to have more aggressive disease, advanced stage at diagnosis and conflicting survival outcomes. The aim of the study was to analyse the demographics, clinicopathological features and prognosis of young colorectal cancer at a population-based level in England.

Methods: Retrospective review of all colorectal cancer patients using data from Public Health England collated from regional cancer registries in England between 2010 to 2014. Those aged 40 years and below were classified as young and those above 40 were classified as older.

Results: Overall, 167,501 patients had colorectal cancer. Of these, 3757 patients (2.2%) were young. Right-sided cancers were more common in younger patients (48.2% vs. 32.9%, $p<0.001$). Favourable histological grade (well or moderate) was present in 83.1% and 73.5% of young and older patients

respectively. The percentage of young and older patients being diagnosed at an early stage (1 & 2) ~~based on AJCC 7th edition~~ (40.6% vs. 42.9%) were similar. Overall five-year survival was better for younger patients (71.6% and 47.2%, p <0.001 in young and older colorectal cancer patients respectively). Additionally, five-year age and gender adjusted relative survival was significantly better for young patients, when compared with older patients diagnosed with colorectal cancer.

Conclusion: Young colorectal cancer patients have much better overall and relative survival compared to the older patients with colorectal cancer.

What does this paper add to the literature?

This is the largest in-depth analysis of young-onset colorectal cancer in England in a contemporary time-frame. We showed that young colorectal cancer patients have much better overall and relative survival compared to the older patients with colorectal cancer. Additionally, young patients with CRC in England do not present at later stages or have worse histopathological features as has been previously reported. Increased numbers of right sided colon cancer in the younger population might warrant further attention.

Manuscript

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in England(1). The overall incidence of CRC has declined over recent years with much of this decrease attributed to the removal of pre-malignant polyps via short wait referral pathways and the national screening program(2-3). However, epidemiological data have shown a worrying trend with a six-fold increase in younger patients diagnosed with CRC in England over the past three decades(4). The increasing incidence of young CRC is a global phenomenon with the American Cancer Society now recommending early screening of individuals starting at the age of 45(5,6).

The presentation, tumour biology and survival patterns of younger CRC patients are reported to be different from those of the older population(7–9). It has been reported that younger patients have more aggressive tumour biology, later cancer stage at presentation and variable survival outcomes(10). There is also considerable variation in the anatomical distribution of young colorectal cancer with conflicting reports from different parts of the world. Data from the American cancer registries have revealed a propensity for more left-sided CRC in young patients(11). In-depth population-based survival data of younger CRC patients from England is sparse with data limited to hospital case series(12,13).

The aim of this population-wide study was to establish whether there is a difference in survival outcomes between young and older patient populations in a contemporary cohort of CRC patients.

We also aim to describe demographic and clinicopathological characteristics and to determine if cancer in young patients differed significantly from older patients in terms of anatomical location, histopathological characteristics and cancer stage at diagnosis.

Materials and Methods

Study design

In this population-based retrospective study, anonymised data from all patients diagnosed with CRC in England between 2010 and 2014 were analysed. The dataset was collated by Public Health England (PHE) and was derived from eight regional cancer registries. The national cancer registration and analysis services (NCRAS), which is run by PHE is responsible to collect, register and analyse cancer data in England. There are robust mechanisms to ensure validity and completeness of data. Fewer than 0.1% of available data have serious errors.(14,15).

The diagnosis of CRC, treatment details and dates of diagnosis and death were based on the data entered into the cancer registries. Study approval was obtained from the University Hospitals Plymouth NHS Trust Audit, Research and Development department (CA 2018-19-152). This study did not require ethical review or individual patient consent as only anonymised, non-interventional data was collected. The online National Research Ethics Service decision tool was used to confirm this(16).

Patients diagnosed with CRC at the age of 40 years or younger were classified as young CRC and those diagnosed above the age of 40 years were classified as older. An age cut-off of 40 years was used because the majority of indications for urgent suspected CRC referral in the UK national guidelines use 40 years as a cut-off(17).

All patients diagnosed with colorectal adenocarcinoma were included in the study. Patients with neuroendocrine tumours and other synchronous malignancies were excluded. The dataset comprised of baseline demographics, stage of cancer at diagnosis, histopathological factors, socio-economic status and cancer registry region.

Socio-economic deprivation was assessed based on the income domain of the 2010 Index of Multiple Deprivation based on the patient's residential postcode(18). Patients were scored on a scale of 1 to 5 with 1 being least deprived and 5 being most deprived. Cancer stage was based on the AJCC 7th edition TNM classification for CRC(19). Cancers were grouped based on anatomical location: right-sided colon cancer (cancers of the appendix, caecum, ascending colon, hepatic flexure and transverse colon: ICD-9 codes 153.0,153.1, 153.4 - 153.6 and ICD-

10 codes C18.0 - C18.4), left-sided colon cancer (cancers of the splenic flexure, descending colon, sigmoid colon and recto-sigmoid junction: ICD-9 codes 153.2, 153.3, 153.7, 154.0 and ICD-10 codes C18.5-C18.7 and C19) and rectal cancer (ICD-9 code 154.1, ICD-10 codes C20). Patients with colorectal cancer in England are usually managed based on the NICE guidelines.(20)

Statistical analysis

All percentages were calculated based only on the non-missing data; with the missing responses displayed in the tables for each variable. Chi-squared tests were used to assess the association between age groups and each demographic and clinical variable. Survival time was calculated as the time between the date of diagnosis and the date of death. Censored observations were included for patients that were alive when the data was extracted from the database (January 2020). Kaplan-Meier curves were used to visualise the differences in survival times between the young and older groups for each stage of disease and each category of deprivation. Log-rank tests were used to test the differences between 5-year survival rates across the age groups. Odds ratios and their 95% confidence intervals were calculated to compare the odds of each treatment in the two groups, the odds from the older CRC group were used in the denominator of all odds ratios reported. Hazard ratios were obtained for all demographic and clinical variables in the younger CRC cohort from a multivariable Cox proportional hazards model, with survival time as the outcome variable.

Post-hoc relative survival rates were calculated for the young group (40 and under) and each 10-year age band from 41 to 90. As explained by Dickman and Adami (2006), relative survival rates are calculated using an adjustment for the expected survival of each patient in the study according to their age and gender. The age and gender specific expected 5-year survival probabilities used to calculate relative survival were obtained from the InterPreT Cancer Survival website and they reflect the expected 5-year survival rate of the general population in England. Data from the reference population was only available for ages 40 to 90 years, anyone under the age of 40 years was assigned the expected survival probability of a 40-year-old to allow the calculation of conservative estimates.

Statistical analyses and data cleaning were carried out with the statistical programming software R version 4.0.2 (The R Foundation for Statistical Computing Platform).

Results

Between 2010 and 2014, 167,501 patients were diagnosed with CRC in England. Of these, 3757 patients (2.2%) were aged 40 and under **(Figure 1)**.

Demographics and socio-economic deprivation

The proportion of older CRC patients remained steady during the study period from 2010 to 2014 (***Figure 2***). However, there is evidence of an increase in proportion in the younger age group (14.4% of the total number of patients in the young group were diagnosed in 2010 and 23.7% were diagnosed in 2014). The male: female ratio was 0.95:1 in the younger cohort in comparison to 1.26:1 in the older CRC population ($p<0.05$) (***Table 1***). Young CRC patients were more likely to be from ethnic minority groups compared to older CRC patients (***Table 1***). The proportion of older patients diagnosed with CRC increased with increasing affluence (***Table 1***). However, this trend was reversed in young patients who showed a higher proportion of patients being diagnosed with higher levels of deprivation (***Supplementary figure 1***).

Figure 1: Age distribution of colorectal cancer patients between 2010 and 2014 in England (at time of diagnosis)

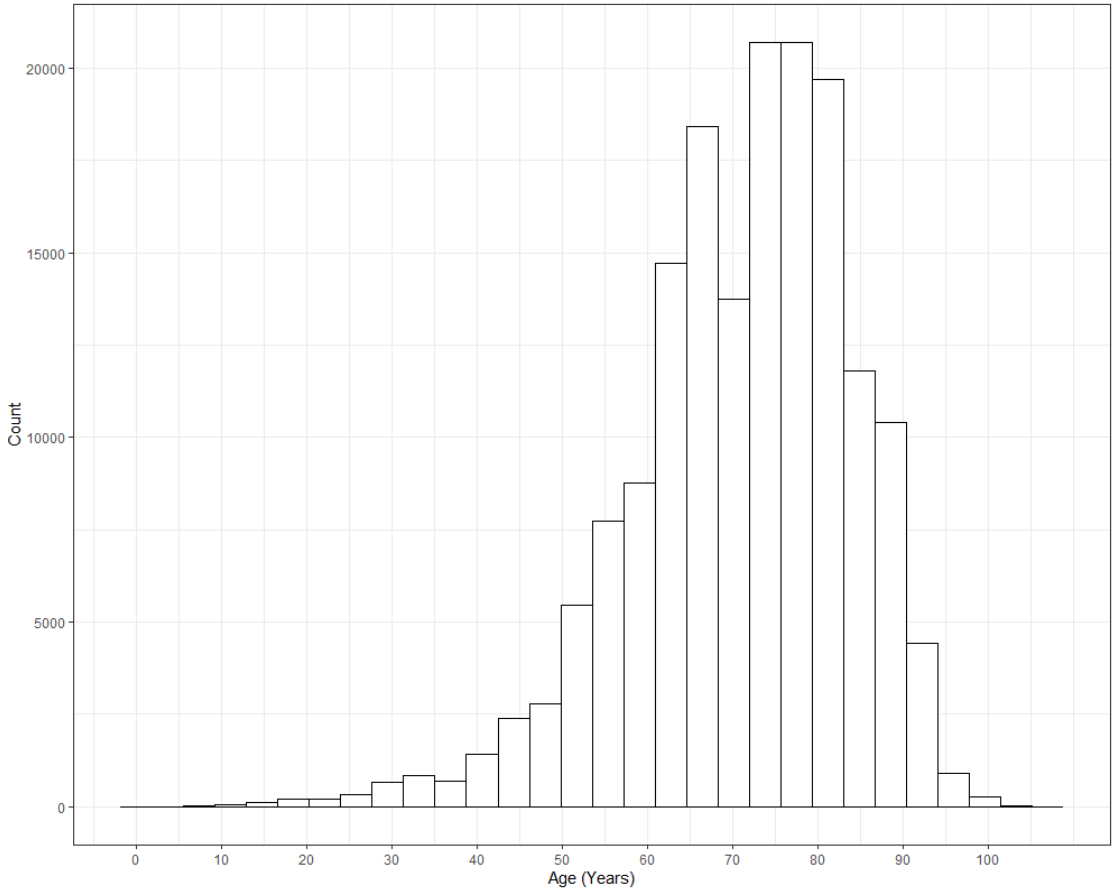

Figure 2: Temporal trends of young and older colorectal cancer patients between 2010 and 2014 in England

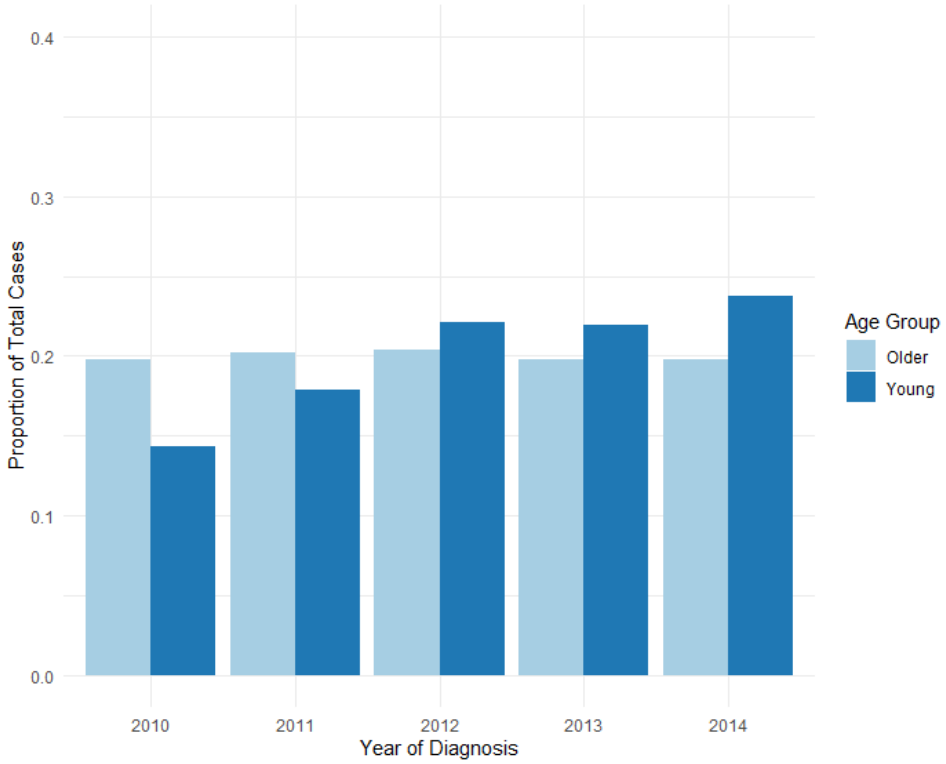

Figure 2 Legend: This figure displays the proportions of all patients in the study that were diagnosed each year between 2010 and 2014 for the young and older age groups.

Table 1: Comparison of demographic data between young and older patients diagnosed with colorectal cancer in England 2010-2014. Percentages calculated based on non-missing data only.

	Young colorectal cancer (≤40 years) n (%)	Older colorectal cancer (>40 years) n (%)	P value
Sex			<0.001
Male	1 829 (48.7%)	91 332 (55.8%)	
Female	1 928 (51.3%)	72 412 (44.2%)	
Ethnicity			<0.001
Asian	212 (6.6%)	2 027 (1.4%)	
Black	127 (3.9%)	1 693 (1.2%)	
Caucasian	2 746 (85.0%)	137 538 (96.2%)	
Chinese	21 (0.7%)	323 (0.2%)	
Mixed	31 (1.0%)	357 (0.3%)	
Others	94 (2.9%)	1 105 (0.8%)	
Missing data	526	20 701	
Deprivation score			< 0.001
1 (Least deprived)	641 (17.8%)	34 053 (21.2%)	
2	701 (19.5%)	36 399 (22.6%)	
3	685 (19.1%)	34 242 (21.3%)	
4	804 (22.4%)	30 360 (18.9%)	
5 (Most deprived)	762 (21.2%)	25 874 (16.1%)	
Missing data	164	3 816	
Total	3 757	163 744	

Anatomical location, stage at diagnosis and histopathological features

Compared to older CRC patients, young patients were more likely to be diagnosed with right-sided colon cancer (***Figure 3***). The proportion of patients diagnosed with early stage (1 & 2) and late stage (3 & 4) cancers is depicted in ***Table 2***.

Young CRC patients were more likely to have well or moderately differentiated CRC compared to older patients (83.1% vs. 73.5%, p<0.001) (***Table 2***). Younger patients were also more likely to have signet ring and mucinous cancers.

Figure 3: Anatomical distribution of colorectal cancer in young and older patients diagnosed in England 2010-2014

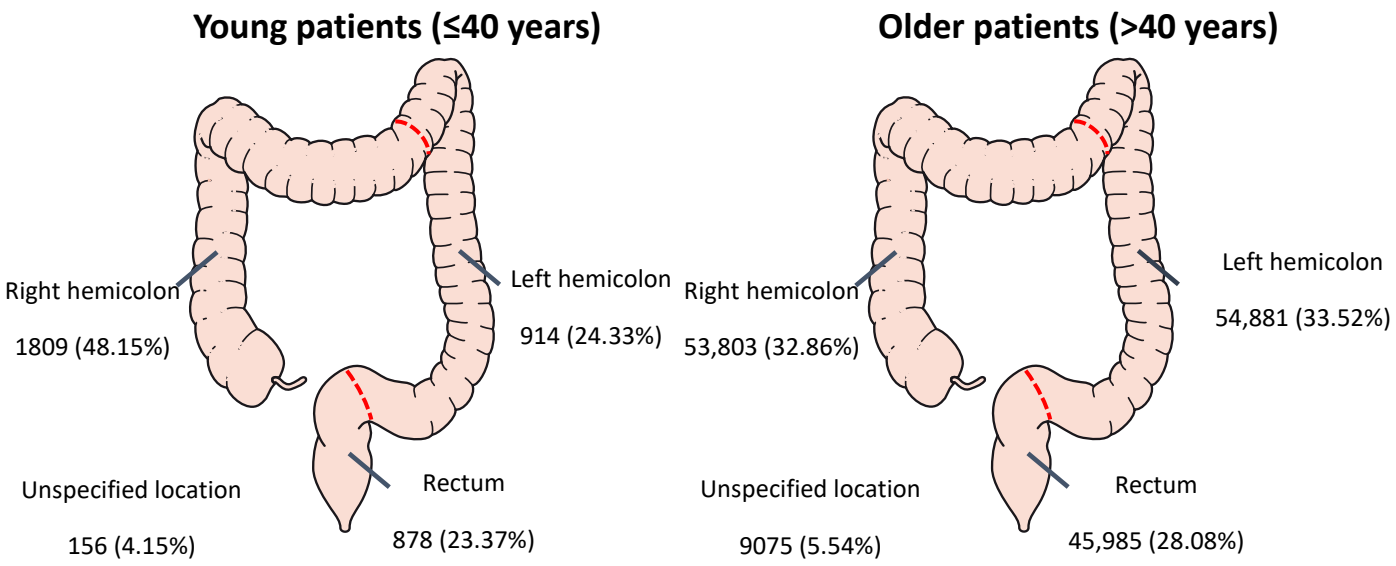

Figure 3 Legend: Figure constructed using images from Servier Medical Art. Licensed under CC BY 3.0.

Table 2: Histological grade, subtype and stage of cancer at diagnosis in young (≤40 years) and older patients diagnosed with colorectal cancer in England 2010-2014. (The percentages are calculated on the non-missing data only)

	Young colorectal cancer (≤40 years) n (%)	Older colorectal cancer (>40 years) n (%)	P value
Grade (differentiation)			<0.001
Well/moderate	2 598 (83.1%)	104 980 (73.5%)	
Poor/undifferentiated	529 (16.9%)	37 807 (26.5%)	
Unknown	630	20 957	
Histological subtype			<0.001
Adenocarcinoma	3 428 (91.3%)	155 239 (94.8%)	
Signet Ring cancer	286 (7.6%)	7 736 (4.7%)	
Mucinous cancer	42 (1.1%)	737 (0.5%)	
Unknown	2	32	
Stage at diagnosis			<0.001
1	457 (18.7%)	18 124 (16.4%)	
2	534 (21.9%)	29 144 (26.4%)	
3	750 (30.7%)	31 590 (28.6%)	
4	700 (28.7%)	31 429 (28.5%)	
Unknown	1 316	53 457	
Tumour location			< 0.001
Colon	2 879 (76.6%)	117 759 (71.9%)	
Rectum	878 (23.4%)	45 985 (28.1%)	

Treatment patterns in young and older patients with colorectal cancer

Significant variations in the use of surgery, chemotherapy and radiotherapy were noted between young and older patients. Young patients with stage 2 or 3 CRC were significantly more likely to undergo chemotherapy. In stage 4 (metastatic) cancer, young patients were

significantly more likely to undergo surgery, chemotherapy and radiotherapy compared to older patients (***Table 3***).

Table 3: The use of surgery, chemotherapy and radiotherapy in young and older patients diagnosed with colorectal cancer in England 2010-2014. The odds ratios show the odds in the younger group compared with the older group. These figures are obtained from the patients for which both treatment and staging information were available (out of a total of 3757 patients, treatment and staging information were available for 2273 in the young cohort. Out of a total of 163744 records in the older cohort, 92265 were available).

Stage	Total	Surgery	OR[1] (95% CI[2])	Chemotherapy	OR (95% CI)	Radiotherapy	OR (95% CI)
Stage 1							
Old	15025	14588 (97.1%)	-	1367 (9.1%)	-	2800 (18.6%)	-
Young	291	286 (98.3%)	1.71 (0.70,4.17)	22 (7.6%)	0.82 (0.53,1.27)	34 (11.7%)	0.58* (0.41,0.83)
Stage 2							
Old	24487	23501 (96.0%)	-	6256 (25.6%)	-	4423 (18.1%)	-
Young	501	475 (94.8%)	0.77 (0.51,1.14)	209 (41.7%)	2.09* (1.74,2.50)	85 (17.0%)	0.93 (0.73,1.17)
Stage 3							
Old	28600	26720 (93.4%)	-	17529 (61.3%)	-	8999 (31.5%)	-
Young	760	713 (93.8%)	1.07 (0.79,1.44)	606 (79.7%)	2.49* (2.08,2.97)	250 (32.9%)	1.07 (0.92,1.24)
Stage 4							
Old	24153	21914 (90.7%)	-	13797 (57.1%)	-	5759 (23.8%)	-
Young	721	671 (93.1%)	1.37* (1.03,1.83)	543 (75.3%)	2.29* (1.93,2.72)	201 (27.9%)	1.23* (1.05,1.46)

[1]OR = odds ratio, [2]CI = confidence interval, * = $p<0.05$

Survival from diagnosis

The median follow-up for patients was 4.3 years (interquartile range 0.8-7.1 years). Young patients with CRC were more likely to achieve 5-year overall survival (OS) than older patients (71.6% vs. 47.2%, $p<0.001$) (***Table 4***). Stage-stratified survival analysis revealed that young patients with stage I CRC had over 98% five-year survival and the stage-stratified survival between the two cohorts was significantly better for the younger patients regardless of stage at diagnosis (***Figure 5***). The effect of deprivation on overall survival was greater in older CRC patients, with young CRC patients having a similar 5-year survival between the least and most

deprived (72.8% vs. 70.6%, p=0.620) (***Table 4)***. Post-hoc relative survival rates (a measure of studying disease specific survival), were calculated for the young age group (≤40 years) and in 10-year age bands up to age 90 (***Table 5)***. When adjusting for the expected survival in each age group, the young group had better overall 5-year survival than all of the 10-year age bands.

Analysis of the younger CRC cohort using a Cox regression model with survival time as the outcome variable showed that the only predictors of survival were tumour stage at diagnosis (hazard ratios: Stage 2 – 8.57, Stage 3 – 20.77, Stage 4 – 116.22) and signet ring carcinoma on histology (hazard ratio: 2.03) (**Supplementary table**).

Table 4: Five-year survival by stage at diagnosis, deprivation index, ethnicity and tumour location in young and older patients diagnosed with colorectal cancer in England 2010-2014

Five-year survival	Young colorectal cancer (≤40 years) % (95% CI)	Older colorectal cancer (>40 years) % (95% CI)	P-value
Overall	71.6% (70.2%, 73.1%)	47.2% (47.0%, 47.5%)	< 0.001
By stage at diagnosis			< 0.001
Stage 1	98.2% (97.0%, 99.5%)	79.2% (78.6%, 79.8%)	
Stage 2	89.1% (86.5%, 91.8%)	68.6% (68.1%, 69.1%)	
Stage 3	74.8% (71.7%, 77.9%)	55.1% (54.6%, 55.7%)	
Stage 4	20.1% (17.2%, 23.1%)	9.6% (9.3%, 10.0%)	
By deprivation index			< 0.001
Least deprived-1	72.8% (69.4%, 76.3%)	52.2% (51.7%, 52.8%)	
Most Deprived-5	70.6% (67.4%, 73.8%)	41.1% (40.5%, 41.7%)	
By ethnicity			< 0.001
Caucasian	71.2% (69.5%, 72.9%)	47.7% (47.5%, 48.0%)	
Asian	63.2% (56.7%, 69.7%)	55.5% (53.3%, 57.7%)	
Chinese	76.2% (56.0%, 94.4%)	60.4% (55.0%, 65.7%)	
Black	63.0% (54.6%, 71.4%)	47.4% (45.0%, 49.8%)	
Mixed	67.7% (51.3%, 84.2%)	53.2% (48.1%, 58.4%)	
Other	66.0% (56.4%, 75.5%)	53.1% (50.2%, 56.1%)	
By tumour location			< 0.001
Colon	74.4% (72.8%, 76.0%)	47.6% (47.3%, 47.9%)	
Rectum	67.1% (64.0%, 70.2%)	51.7% (51.2%, 52.1%)	

Table 5: 5-year relative survival rates in the young age group and 10-year age bands up to age 90 in England for male, female, and all patients.

5-year survival %	Observed Survival	Expected Survival	Relative Survival (95% CI)
Male			
≤40	70.4%	99.0%	71.1% (69.0%, 73.2%)
41 - 50	62.5%	98.3%	63.6% (62.0%, 65.2%)
51 – 60	62.2%	95.5%	65.1% (64.2%, 66.0%)
61 – 70	60.7%	89.1%	68.1% (67.4%, 68.8%)
71 – 80	46.1%	74.6%	61.8% (61.0%, 62.6%)
81 – 90	22.9%	48.7%	47.0% (45.7%, 48.2%)
Female			
≤40	72.8%	99.0%	73.5% (71.5%, 75.5%)
41 – 50	64.1%	98.8%	64.8% (63.2%, 66.5%)
51 – 60	65.2%	97.1%	67.1% (66.1%, 68.2%)
61 – 70	62.3%	92.5%	67.3% (66.5%, 68.1%)
71 – 80	49.6%	80.2%	61.9% (61.0%, 62.7%)
81 – 90	26.2%	55.5%	47.2% (46.1%, 48.3%)
Overall (Male and female)			
≤40	71.6%	99.0%	72.3% (70.9%, 73.8%)
41 – 50	63.3%	98.5%	64.2% (63.1%, 65.4%)
51 – 60	63.5%	96.2%	66.0% (65.3%, 66.7%)
61 – 70	61.3%	90.4%	67.8% (67.3%, 68.3%)
71 – 80	47.6%	76.9%	61.9% (61.3%, 62.4%)
81 – 90	24.6%	52.2%	47.1% (46.3%, 47.9%)

Figure 5: Kaplan-Meier curve of overall survival from diagnosis of colorectal cancer in young and older patients, stratified by stage at diagnosis

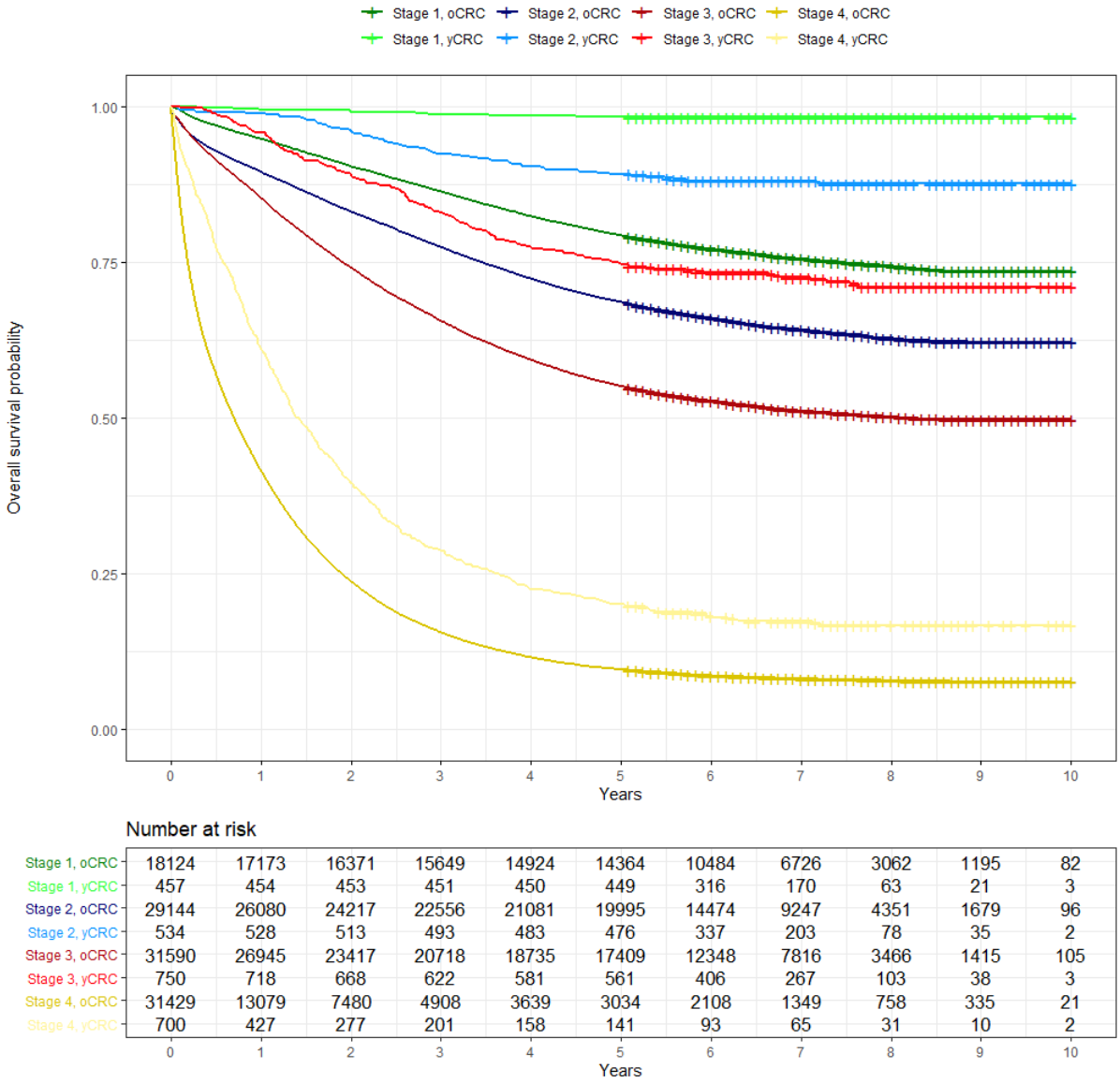

Figure 5 Legend: yCRC= young patients (aged 40 and below), diagnosed with colorectal cancer, oCRC= older patients(aged above 40 years) diagnosed with colorectal cancer.

Discussion

This population-based study is the largest clinicopathological and survival analysis of young patients diagnosed with colorectal cancer in England. In keeping with previous reports, There is an increase in the number of younger patients being diagnosed with colorectal cancer during the study period (4). According to these data, over 1 in 50 patients diagnosed with CRC (2.2%) are aged 40 or under. The importance of increasing awareness of colorectal cancer in young people cannot be overstated.

The overall, stage-stratified and relative (cancer specific survival based on age and gender), survival of young CRC patients in England is good; especially if diagnosed early (5-year overall survival 98.2% in stage 1 and 89.1% in stage 2). This is in keeping with population-based data from Canada and Australia(22,28). American studies have shown varied results in terms of survival ranging from worse to equivocal and better overall survival compared to older patients. The worse overall (all stages combined) survival in a few American studies have largely been attributed to later stage of diagnosis, nevertheless, the stage-stratified survival of young colorectal cancer in America has consistently shown favourable results (8,29). On the other hand, a few studies from Asia have tended to show worse overall and stage-stratified survival in younger patients (9,26). The relative survival analysis in this paper suggests that even after adjusting for the reference life expectancy between the groups, younger patients had better survival figures.

The most common site of CRC in young patients (aged 40 and below) is the right hemicolon (48.2% of all colorectal malignancies). This trend has been described in England previously, Exarchakou *et al reported a* 5.2% increase in right colon cancers between the years 1991 and 2010 with a dramatic 19.4% increase from 2010 to 2014; this is in contrast to data from America, Asia and Australia (3,11,21,22); thus highlighting the importance of complete visualisation of the colon when young patients present with worrying symptoms (23). However, it is also important to prevent unnecessary investigations in a population in whom most patients will have a benign cause for their symptoms. The quantitative faecal

immunohistochemical test (qFIT) could be used as a screening tool in younger patients with abdominal symptoms in the absence of overt rectal bleeding to select patients who would benefit with colonoscopy(24).

According to data from the Surveillance Epidemiology and End Results (SEER) database, young CRC patients present at a later stage and have more aggressive disease compared to older patients(25). However, this England-wide study found largely similar stage-wise distribution in younger and older patients.

The notion that younger patients have more aggressive histological subtypes is also not entirely supported by this study, as fewer young adults had poorly differentiated adenocarcinoma than the older population. When compared to literature, only 16.9% in the young population in England had poor grade of adenocarcinoma versus 27.3% in a similar cohort from the USA(25). The percentage of younger patients with mucinous and signet ring cancer was slightly higher than in older patients (8.7% vs. 5.2%); it is still considerably lower than historical cohorts where these histological subtypes accounted for up to 20% of young CRC patients(8,26,27).

In the older age group, there were fewer CRC patients from more deprived areas compared to the least deprived areas. Interestingly, this trend is reversed in young patients, with higher deprivation indices having a higher number of cases of CRC. Despite deprivation being associated with an increased incidence of CRC in young patients the effect of deprivation on 5-year survival was markedly less than in older patients. It is possible that deprivation affects all-cause mortality rather than CRC-specific mortality, which may explain why deprivation had a greater effect on 5-year survival in older patients.

A potential explanation for the improved outcomes of younger CRC patients in this contemporary dataset is that younger patients received more treatment than older patients (**Table 4**). This was especially evident in those with metastatic cancer, young patients had a significantly higher chance of receiving all forms of therapy compared to older patients. In addition, young CRC patients with stage 2 disease had twice the odds of receiving chemotherapy(30). This finding is consistent with a recent American population-based study, in which younger patients with stage 1 and 2 CRC received significantly more chemotherapy than older patients(29). However, more treatment does not necessarily translate to better

survival; earlier stage of diagnosis and better grade of cancers in this cohort probably play a significant role in explaining the overall better survival outcomes.

There are several study limitations. As with all retrospective registry-based studies, missing data can result in information and selection bias(31). However, the English cancer registries are amongst the most complete and therefore provide robust data.

Due to the large numbers in population studies, there is a known trend of the statistical tests to produce highly significant results (as observed in our study). However, statistical significance is not always equivalent to clinical significance.

These data are derived from English registries which may limit generalisability. Details regarding timing of therapy (neoadjuvant or adjuvant therapy) were not available; this needs to be factored in – especially when interpreting data of rectal cancer patients. Data on genetic analysis and familial syndromes was not available at a population-based level for patients diagnosed with CRC during the study period because routine testing for microsatellite instability and lynch syndrome was initiated only in 2017 in England.(32) Data on recurrence of cancer was not available and this may limit the ability to ascertain cancer specific outcomes, however we have controlled for this limitation by providing relative survival rates. There is a lack of international consensus on the definition of young CRC, different papers have used different age cut-offs, thereby making direct comparison between studies speculative at times.

Conclusion

In England, over one in 50 patients diagnosed with Colorectal cancer are aged 40 or under. Young colorectal cancer patients have much better overall and relative survival compared to the older patients with colorectal cancer. Young patients do not have more aggressive histopathological features than the older cohort as has been previously reported and almost half of young patients have right-sided malignancy.

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Disclosures

Mark Coleman and Sebastian Smolarek have served on the board of the funding charity; however, they declare no conflict of interest and the charity was not involved in the study design, data analysis or manuscript preparation in anyway.

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